ManagingAML

Complexities of Relapsed/Refractory AML: Aligning Strategies to Maximize Outcomes

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Welcome to *Managing AML*. I'm Dr. Nicholas Short from the University of Texas MD Anderson Cancer Center. In today's activity, I'll discuss the complexities of relapsed/refractory AML and how we can align strategies to maximize outcomes for these patients.

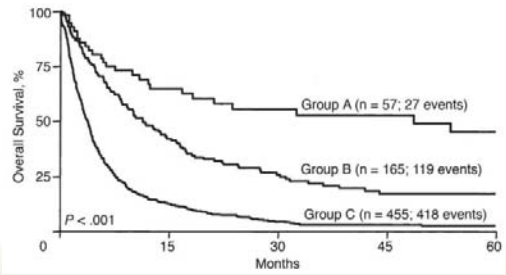
Faculty Disclosure

- Dr. Nicholas Short has relevant financial relationships from Amgen Inc. and Novartis AG, as well as relevant financial relationships related to consulting from AstraZeneca, Jazz Pharmaceuticals plc, and NGM Biopharmaceuticals. He has received research grant(s) from Astellas Pharma US, Inc. and Takeda Oncology.

These are my disclosures.

Outcomes in Relapsed or Refractory AML

- Outcomes poor for patients with R/R AML
  - Historical response rates with chemotherapy: 20-30%
  - Median OS <6 months, long-term survival in ~10%
- Predictors of survival after first relapse:
  - Age
  - Cytogenetics (core-binding factor)
  - Relapse-free interval
  - Prior HSCT
- Cure is exceptionally rare without HSCT



Breems DA, et al. *J Clin Oncol.* 2005;23(9):1969-1978.

The outcomes of relapsed/refractory AML are quite poor. When all we had was intensive chemotherapy, in different combinations, we could achieve response rates around 20% to 30%, but median survival, historically, has been less than six months, with only a small minority of patients experiencing long-term survival. There are some well-described predictors of survival after first relapse. These include age, with those patients who are younger doing better; cytogenetics, specifically those with core-binding factor leukemia do better in relapse. A longer relapse-free interval is associated with better outcomes, and also lack of a prior transplant because ultimately, our goal for these patients to have a potentially curative strategy is to get them to another transplant, and of course, those patients who have had prior transplant do much more poorly with a subsequent transplant.

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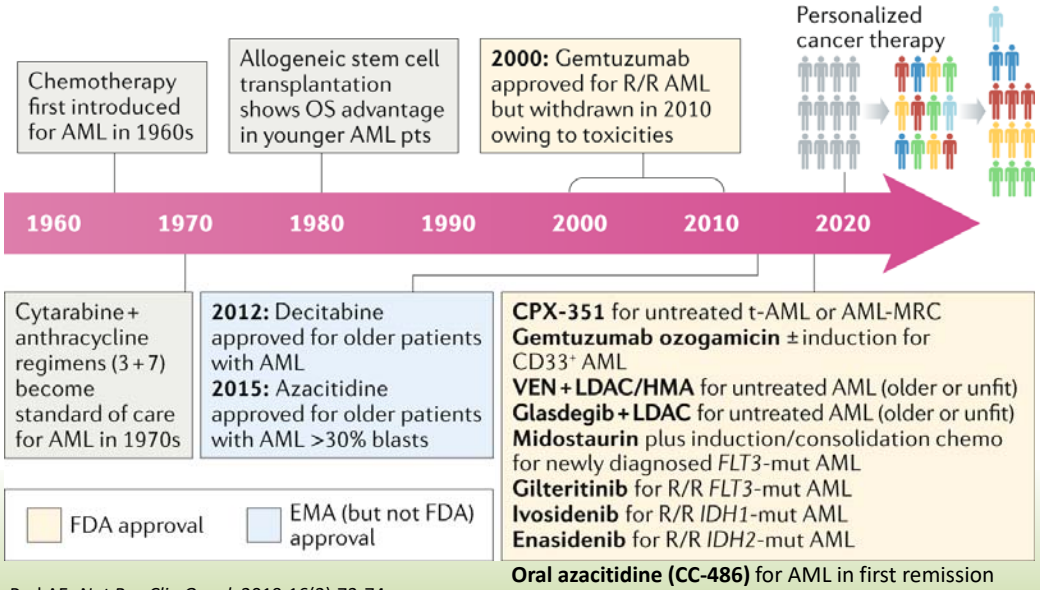
Timeline of AML Therapeutics



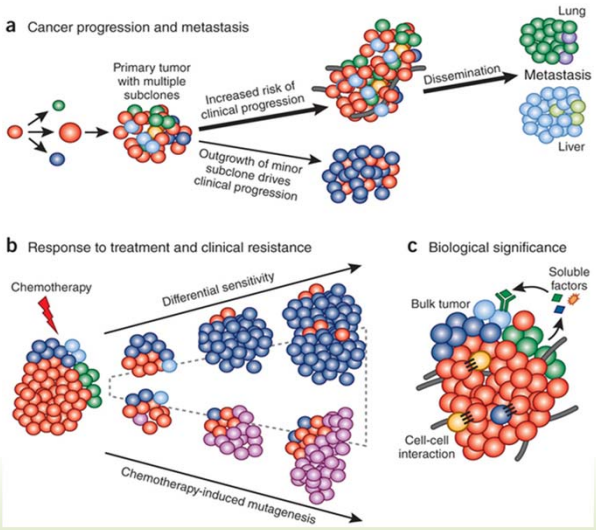
DiNardo CD, Perl AE. *Nat Rev Clin Oncol.* 2019;16(2):73-74.

Fortunately, though, in the last several years, really since 2017, there's been an explosion of approvals of various drugs in AML, both in the frontline setting and in the relapsed/refractory setting for patients with AML. We'll focus particularly on those that are now approved and used in common clinical practice for patients with relapsed/refractory AML.

Complexities of Relapsed/Refractory AML: Aligning Strategies to Maximize Outcomes

Relapsed AML Often Differs from the Original AML Clone

- AML is not a static disease
- New subclones may expand or emerge in response to selective pressure from therapy
- Repeat genomic analysis at relapse is imperative



Kleppe M, Levine RL. *Nat Med.* 2014;20(4):342-344.

One thing that's important to note is that when thinking about a patient with AML who's experiencing a first relapse or a first or later relapse, is that the AML that's present at relapse may be very different than the AML that was initially diagnosed. There can be various reasons for this but essentially, sometimes this can be a small sub-clone that was resistant that then emerges later on. It can have very different characteristics than the initial leukemia or sometimes new mutations if therapy-related mutations even can develop over the course of therapy. It's very important to repeat any genomic testing at the time of relapse because we can be surprised sometimes and see new targetable mutations in the relapse clone. We can't entirely rely on the genomic profiling that was conducted at the initial diagnosis.

Standard Treatment Options for R/R AML

- Intensive chemotherapy (eg, FLAG-Ida, MEC, CLAG, HiDAC)
- HMA or LDAC ± venetoclax (off label)*
- Gemtuzumab ozogamicin
- Targeted agents
  - Gilteritinib (*FLT3*)
  - Ivosidenib (*IDH1*)
  - Enasidenib (*IDH2*)

Always repeat mutation testing at the time of relapse!

If remission is achieved, follow with HSCT ASAP

*This regimen has not been approved by the FDA.

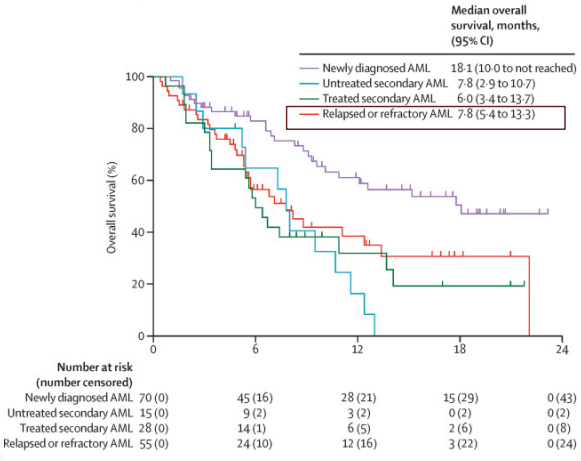
That leads us to a discussion of some of the standard treatment options that we currently have for relapsed/refractory AML. What's commonly used in clinical practice would include intensive chemotherapy, and there's a number of different regimens, none of which has been shown to be better than the other. Common regimens include FLAG-Ida, MEC, high-dose AraC-based regimens. Physicians often use hypomethylating agents or low-dose AraC. Now, these are often combined with venetoclax, but again, this is off-label use, but this is commonly done in clinical practice, and I'll show you some of the data to support this. Gemtuzumab ozogamicin is an approved drug in the setting. That being said, it's not particularly effective and I don't think is the best option for most patients in this setting. I think what we've really seen, and again, an expansion with this recent FDA approval are drugs in the relapsed/refractory setting that target specific mutations.

We have gilteritinib for patients with FLT3 mutations, or ivosidenib and enasidenib for patients with IDH1 or IDH2 mutations, respectively. Again, this highlights, now that we have these effective drugs in the relapsed/refractory setting, this highlights the importance of repeating mutation testing at the time of relapse.

Complexities of Relapsed/Refractory AML: Aligning Strategies to Maximize Outcomes

Decitabine x 10d + Venetoclax in R/R AML

- 55 patients with R/R AML (median of 2 prior therapies; 1/3 with prior HSCT)
- Decitabine x 10 days + venetoclax 400 mg on days 1-28 (cycle 1) and days 1-21 (cycles 2+)*
- CR rate: 24%; CR/CRi rate: 42%; CR/CRi/MLFS rate: 62%
- Median CR/CRi duration: 16.8 months



*This regimen has not been approved by the FDA

DiNardo CD, et al. *Lancet Haematol.* 2020;7(10):e724-736.

These are some data supporting the use of a hypomethylating agent in combination with venetoclax in the relapsed/refractory setting. Again, hypomethylating agent plus venetoclax is approved therapy for patients who are newly diagnosed, older, unfit for intensive chemotherapy, and this is off-label use of venetoclax. Again, but what we've seen is very promising outcomes with this combination in the relapsed/refractory setting.

This is a study looking at 55 patients with relapsed/refractory AML a median of two prior therapies, one-third of whom had prior transplants. Relatively heavily pretreated population. With this combination of 10 days of decitabine in combination with venetoclax, in this study about a quarter of patients achieved a complete remission, increasing nearly to over 40%, if you include CR and CRi and then if you include MLFS, nearly two-thirds of patients achieved a response. The median duration of responses has been quite impressive with a median duration of CR/CRi of 16.8 months. Now, the survival of patients with relapsed/refractory disease is still poor because still, a significant proportion of these patients don't respond. That said, the median overall survival in this study was 7.8 months in the relapsed/refractory setting, certainly superior to what we've seen in similar historical populations. I think a reasonable regimen to consider for patients who have relapsed/refractory AML, particularly those who have not had prior exposure to venetoclax in the frontline setting.

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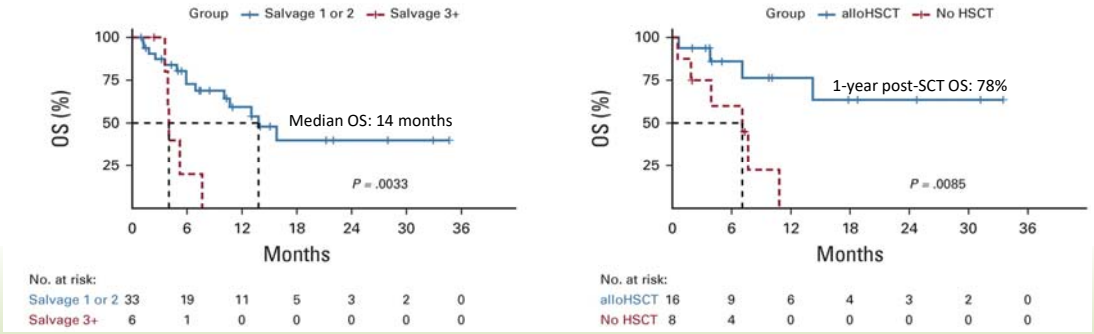
FLAG-Ida + Venetoclax in R/R AML

- 39 patients with R/R AML (69% in S1; 15% in S2; 15% in S3+)
- FLAG-Ida + venetoclax 400 mg daily on days 1-14 (induction) and days 1-7 (consolidation), up to 6 cycles*
- CR rate: 44%; CRc rate: 67%



*This regimen has not been approved by the FDA

DiNardo CD, et al. *J Clin Oncol.* 2021 (in press).

Also, venetoclax has also been evaluated in combination with intensive chemotherapy in the relapsed/refractory setting. I mentioned that FLAG-Ida is a common regimen used in this setting. This is a study looking at the combination of FLAG-Ida with venetoclax for relapsed/refractory AML, again currently still off-label use of venetoclax. This is a study conducted in 39 patients with relapsed/refractory AML. In this cohort, a majority of them were in first salvage. FLAG-Ida was used at standard doses in combination with venetoclax for two weeks during induction and then decrease to seven days in consolidation. The CR rate was 44%, and two-thirds of patients achieved some form of response. Very high response rates with this combination.

Not surprisingly, those patients treated in first or second salvage had superior outcomes. The median survival for those patients is 14 months, which is significantly better than what we've seen again with historical cohorts. Now, for those patients treated in much later salvages, the outcomes were still very poor. You can see on the right side, that's showing the outcomes post-transplant, so we still know that we need to transplant all of these patients if they are fit to undergo the procedure. Those patients who did not undergo transplant, unfortunately, all of them relapsed and died within one year after their salvage therapy. However, those patients who received FLAG-Ida plus venetoclax and then went on to transplant had a one-year post-transplant survival of 78%, which is really quite remarkable in the relapsed/refractory setting.

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FLT3 Mutations in AML

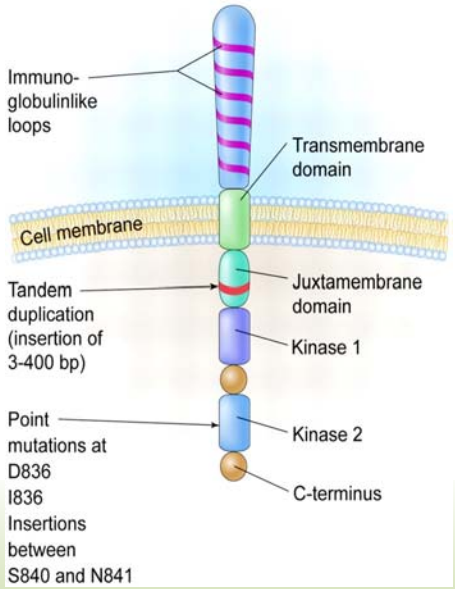


Figure adapted from Litzow MR. *Blood.* 2005.

- Incidence
  - *FLT3*-ITD in 20-25%
  - *FLT3*-TKD in 5-10%
- Downstream effects
  - Promotion of cellular proliferation and survival
  - Inhibition of differentiation
- Impact of therapy
  - Indications for HSCT in CR1
  - Incorporation of *FLT3* inhibitors

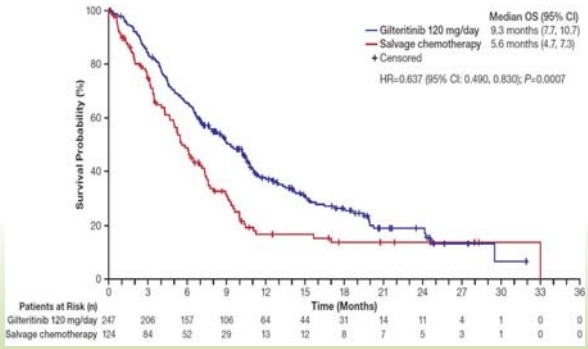
Moving on now to talk about some of the targeted therapies that we have approved for relapsed/refractory AML. FLT3 mutations are one of the most common mutations in AML. In the frontline setting, ITD mutations, internal tandem duplication mutations, are seen in up to a quarter of patients and tyrosine kinase domain mutations, or TKD mutations, are present in up to 10% of patients. These have impacts in the frontline setting for risk stratification and also selection of patients who should undergo transplant in first remission. In both the frontline and in the relapsed/refractory setting, the presence of these mutations is important because now we have FLT3 inhibitors, we have midostaurin approved in the frontline setting, and now gilteritinib in the relapsed/refractory setting.

ADMIRAL Study: Gilteritinib in R/R *FLT3*-Mutated AML

- 371 patients with relapsed *FLT3*-mutated AML randomized to:
  - Gilteritinib 120 mg/day (n=247)
  - Salvage chemotherapy (n=124)
- Response rates

Response	Gilteritinib	Chemotherapy
CR, n (%)	52 (21)	13 (11)
CRc, n (%)	134 (54)	27 (22)
CR/CRh, n (%)	84 (34)	19 (15)

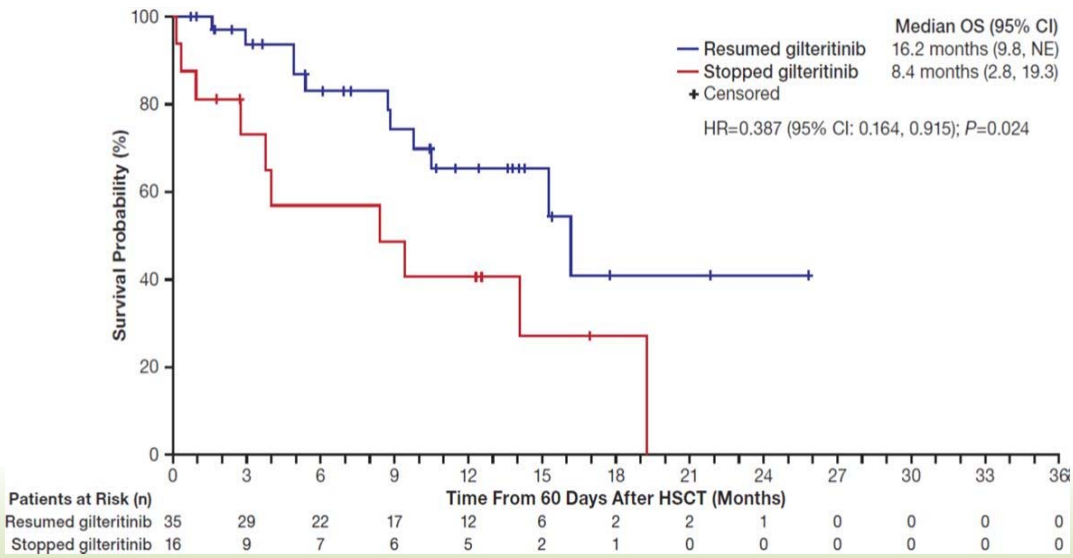
- Overall survival



Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

The ADMIRAL study was the large Phase 3 study that led to the approval of gilteritinib in patients with relapsed/refractory FLT3-mutated AML. This is again, a randomized study of patients with relapsed FLT3-mutated AML who received either gilteritinib at a dose of 120 milligrams daily or salvage chemotherapy, and this was at a 2:1 randomization. Response rates were significantly improved, regardless of what type of response we were evaluating, were improved with gilteritinib over chemotherapy. CR rate was 20% with gilteritinib, which was approximately double that of chemotherapy. If you look at either CR, CRh, or CRc rates, these are common composite response rates in clinical trials. You can see that both of those were more than doubled within gilteritinib, with over half of patients who received gilteritinib achieving a CRc, which is a composite CR rate, that also includes MLFS, so basically blasts less than 5%. Gilteritinib was associated with improvement of overall survival with a median survival of 9.3 months, compared to only 5.6 months for patients who received salvage chemotherapy. It's important to note though that gilteritinib, while it significantly improved the median survival, if you look at the tail of the curves, unfortunately, we have not yet seen a significant improvement in long-term survival or cure rates between these two approaches.

Outcomes Superior with Gilteritinib Post-HSCT



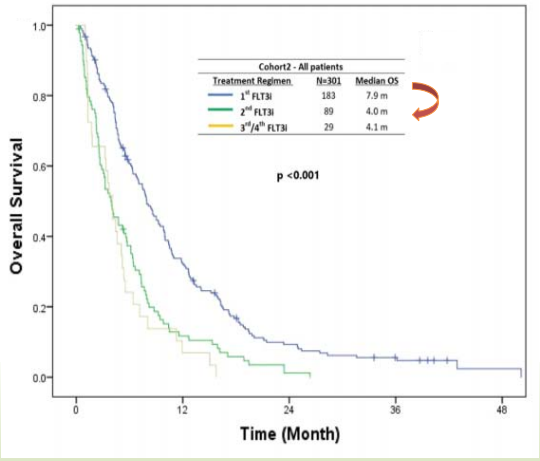
Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

One question that often comes up is, what should we be doing after we send these patients to transplant? In this study, they did allow for patients to receive gilteritinib after transplant. Those patients who were able to resume gilteritinib post-transplant had a median survival of 16.2 months, which was significantly better than those who did not receive any post FLT3 inhibitor maintenance. Together this study suggests that we should be using gilteritinib for patients who have relapsed FLT3-mutated AML. We should be sending them to transplant whenever possible, and then we should be resuming the gilteritinib post-transplant for those patients who are suitable.

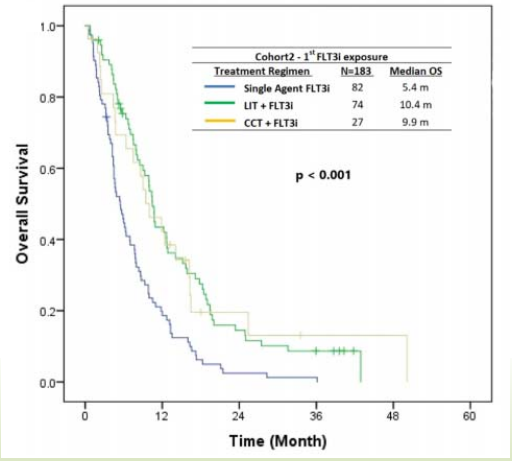
Impact of Previous *FLT3* Inhibitor Exposure and Combination Therapy in R/R *FLT3*-Mutated AML

Outcomes of *FLT3* inhibitor-based regimens superior with:

First use of *FLT3* inhibitor



Combination with chemotherapy



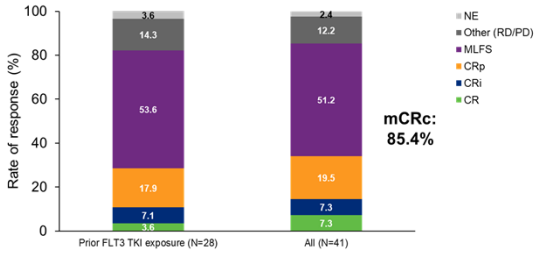
Yilmaz M, et al. *J Hematol Oncol.* 2020;13:132.

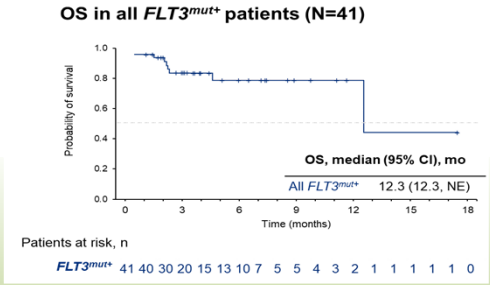
What about sequencing these FLT3 inhibitors, and what are some of the predictors for outcomes for patients with relapsed/refractory FLT3-mutated AML? One thing that we've seen, and this is from a retrospective study, is that outcomes for patients with FLT3-mutated AML in the relapsed/refractory setting are superior when they're receiving their first FLT3 inhibitor and also when these are combined, rather than given as a single agent. You can see on the left side, those patients who had relapsed/refractory FLT3-mutated AML and received their first FLT3 inhibitor in the salvage setting had a median survival in this retrospective cohort of about eight months. This drops sharply to a median survival of only approximately four months for those patients who are receiving later lines of FLT3 inhibitor therapy. Also, when evaluating how should we be giving these FLT3 inhibitors. Now, the FDA-approval is for gilteritinib as a single agent. That said, in clinical practice, many of us do combine gilteritinib with other agents, either chemotherapy or hypomethylating agents. This retrospective study also supports that the use of combination therapy, the median survival for patients who received a FLT3 inhibitor in combination with some form of either low-intensity or more intensive chemotherapy was 10 months, compared to those who received a FLT3 inhibitor as a single agent, the median survival was only five months.

Together this shows we should be using FLT3 inhibitors as soon as possible. The first exposure to FLT3 inhibitor patients had the best outcome, and it may be better to combine these with some other backbone of chemotherapy or hypomethylating agent.

Gilteritinib + Venetoclax in Relapsed/Refractory *FLT3*-Mutated AML

- 43 patients treated (ITD, n=35; TKD, n=6; ITD+TKD, n=2); 65% with prior *FLT3* inhibitor exposure
- Venetoclax 400 mg/day + gilteritinib 120 mg/day
- mCRc (CR+CRp+CRi+MLFS) in 35/41 (85%)
- Median duration of response: not reached
- Median OS: 12.3 months (not reached in ITD patients)





Daver N, et al. ASH 2020. Abstract 333.

What is the future going to look like for treatment of FLT3-mutated AML? I think it will be combinations. One exciting combination that's been reported is this entirely oral combination of gilteritinib with venetoclax in relapsed/refractory FLT3-mutated AML. This is a study that evaluated 43 patients with FLT3-mutated AML in the relapsed/ refractory setting, most of whom had an ITD mutation, about two-thirds of whom had a prior FLT3 inhibitor exposure. We do expect those patients typically, as I mentioned, will not typically respond as well to subsequent therapies. The regimen was venetoclax and gilteritinib given continuously. The marrow CR rate, basically patients who achieved at least a blast count less than 5%, was extremely high, 85% in this study. Now, most of these responses were just an MLFS, so in other words, these patients didn't have count recovery. You can still see about 35% of patients had some amount of count recovery and 7% of patients achieved a complete remission. At the last update at ASH in 2020, the median duration of response was not reached, and the median survival was 12 months in the entire population and was not reached in the ITD patients. Overall, this looks better than what we see with gilteritinib as a single agent, and we'll have to see what the longer-term follow-up of this study shows.

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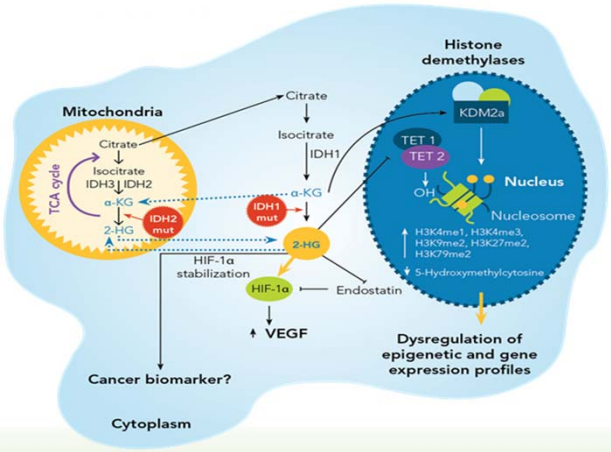
IDH Mutations in AML



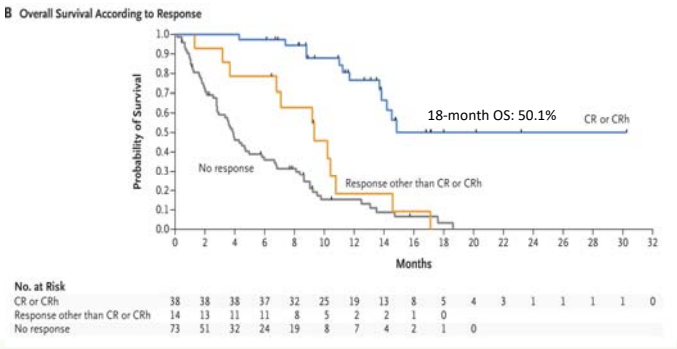
- *IDH*: critical enzymes of the citric acid cycle
- *IDH* mutations produce 2-HG→ alteration of DNA methylation and block of differentiation
- Incidence
  - 5-15% (*IDH1*)
  - 10-20% (*IDH2*)
- More common in older patients
- Approved agents
  - Ivosidenib (*IDH1*)
  - Enasidenib (*IDH2*)

Prensner JR, Chinnaiyan AM. *Nat Med.* 2011;17:291-293.

As I mentioned, we also have inhibitors for IDH mutations. IDH is a critical enzyme of the citric acid cycle. IDH mutations lead to a block of differentiation leading to the disease phenotype. IDH mutations are a bit less common than FLT3 mutations, but they're still present in a significant minority of patients. About 5% to 15% of patients have an IDH1 mutation, a slightly higher, 10% to 20%, have an IDH2 mutation, and these are more common in older patients. We'll discuss some of the approved IDH inhibitors in this context, ivosidenib for IDH1 mutations and enasidenib for IDH2 mutations.

Ivosidenib for Relapsed/Refractory IDH1-Mutated AML

- 179 patients with relapsed/refractory IDH1-mutated AML
- Ivosidenib dose: 500 mg daily
- ORR: 42%; CR rate: 22%
- Median OS: 8.8 months
- Grade ≥3 adverse events
  - QTc prolongation (8%)
  - Differentiation syndrome (4%)



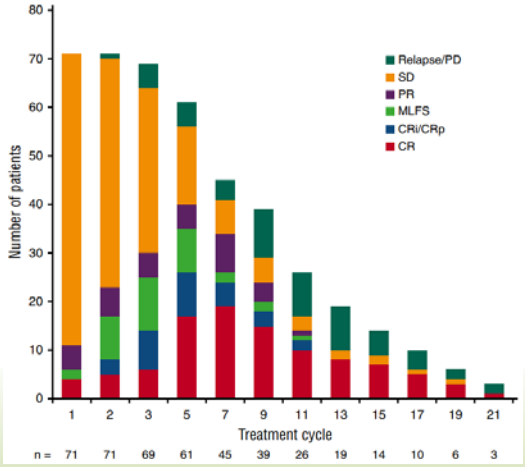
DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398.

Ivosidenib is approved for the treatment of relapsed/refractory IDH1-mutated AML. This is based on a large Phase 2 study where the overall response rate was approximately 40%. The CR rate was approximately 20%, and median overall survival in this study was 8.8 months. If we look specifically at those patients who responded to the treatment, the 18-month overall survival was reported as 50%. Very good durable responses for those patients who do achieve initial response.

It's important to be aware of the adverse events that can be seen with ivosidenib. In a small minority of patients, you can see QTC prolongation. It is important to monitor EKGs for QTC intervals for patients on this drug. We could see that with all IDH mutations is the potential for differentiation syndrome. This is just based on the mechanism of action of the drug. This is very similar to what we see sometimes with ATRA and arsenic for patients with APL, you can see an elevation of the white count, pulmonary infiltrates. This is managed the same way as ATRA syndrome, again in APL with dexamethasone, sometimes hydroxyurea for very high white counts, and then sometimes temporary cessation of the drug for patients with very clinically significant differentiation.

Enasidenib for Relapsed/Refractory *IDH2*-Mutated AML

- 176 patients with relapsed/refractory *IDH2*-mutated AML
- Enasidenib given at 50-650 mg daily (expansion cohort: 100 mg daily)
- ORR: 40%; CR rate: 19%
- Median OS: 9.3 months
- Grade ≥3 adverse events
  - Indirect hyperbilirubinemia (12%)
  - Differentiation syndrome (6%)



DiNardo CD, et al. *Blood.* 2017;130(6):722-731.

This is data from the Phase 2 study that led to the approval of enasidenib for IDH2-mutated AML. You'll note that actually the outcomes for enasidenib are very similar to what was seen with ivosidenib. An overall response rate of about 40%, CR rate around 20%, median survival somewhere around nine months. I would point out the pattern of responses that we see with these IDH inhibitors. The same applies for ivosidenib, but you can see that actually as you get on the figure on the right, this shows that as you continue to give cycles of enasidenib therapy, in this case, you see increasing rates of response. In other words, it takes a while for some of these responses to occur. An important principle when you're giving patients these IDH1, or IDH2 inhibitors is not to stop just because they have stable disease after one or two cycles. That's very common. Certainly, if they have progressive disease, it's reasonable to move on to another therapy, but it can take some time to achieve the maximum response. Sometimes it can take six or more cycles to achieve your maximum response. It's important to continue to give these agents as long as patients are achieving at least stable disease. As far as adverse events with enasidenib, one common thing that's observed is indirect hyperbilirubinemia. This is often not clinically significant and just something that can be monitored. As I mentioned, in about 5% of patients with both of these drugs, we can see a clinically significant differentiation syndrome.

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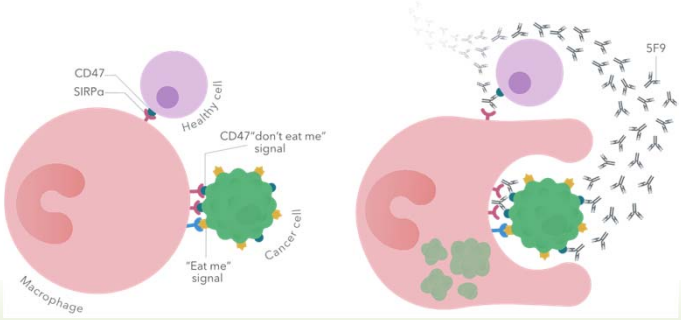
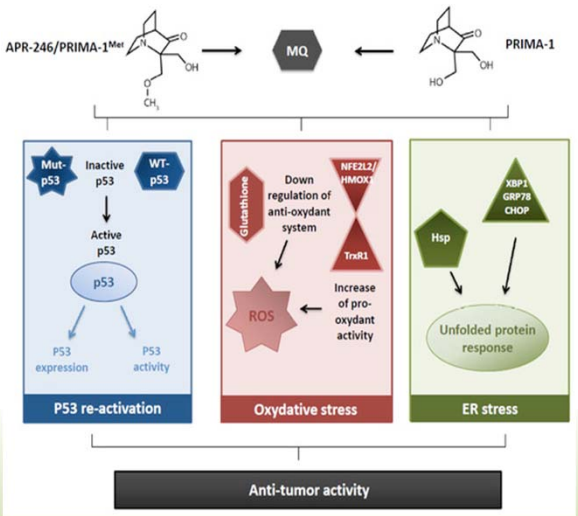
Emerging Agents Active in *TP53*-Mutated AML

Magrolimab (anti-CD47 mAb)

Macrophage checkpoint inhibitor



APR-246



There are several emerging agents that may have activity in TP53-mutated AML. This is very exciting because, first of all, patients with TP53-mutated AML have extremely poor outcomes and historically, we've always felt that these mutations were not targetable. However, we have two drugs that are in clinical trials. One is magrolimab. This is an anti-CD47 monoclonal antibody. Essentially, it's a checkpoint inhibitor for macrophages that stimulate the macrophages to ingest the malignant AML cells.

APR-246 is a drug that has been in clinical trials. This is a drug where the mechanism of action is not entirely understood. However, it's thought to be part of the mechanism may be that it can convert mutant p53 isoforms into more wild-type conformations, essentially then, leading to active p53 proteins. The mechanism of action is still not entirely understood.*

*On August 3, 2021 the FDA placed a clinical hold on APR246 on myeloid malignancy programmes of the drug plus azacitidine. Until the clinical hold is resolved, participant recruitment has been suspended.
https://www.clinicaltrialsarena.com/news/aprea-fda-clinical-hold/

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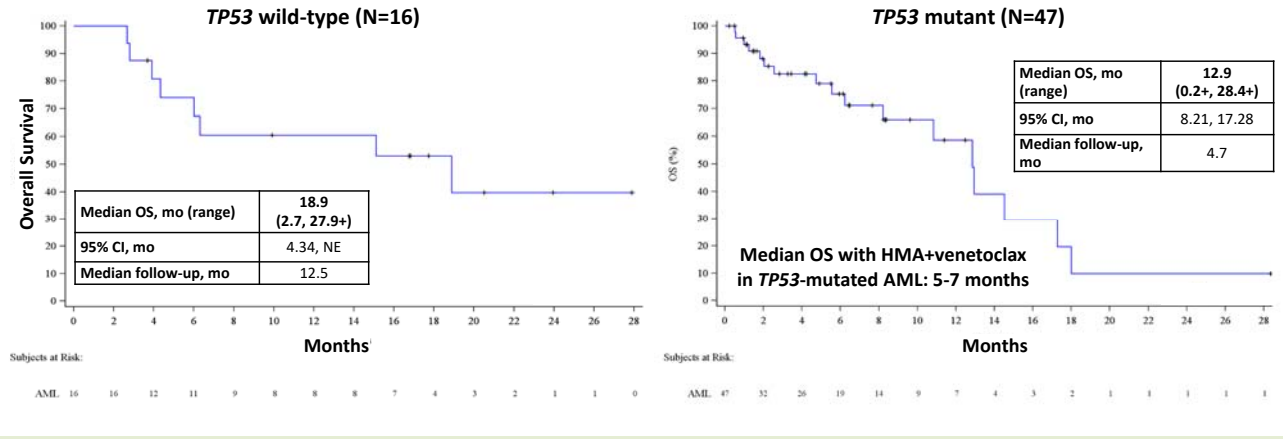
Azacitidine + Magrolimab in Newly Diagnosed *TP53*-Mutated AML



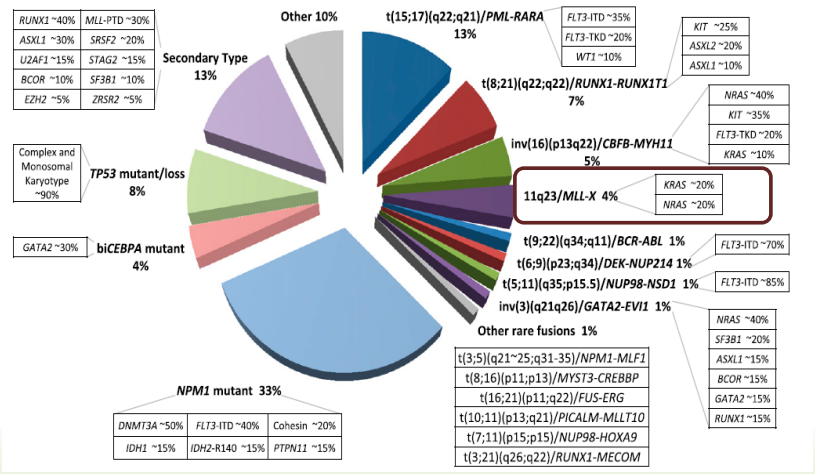
Sallman D, et al. ASH 2020. Abstract 330.

As I mentioned, magrolimab, in particular, is in a number of clinical trials and has shown some exciting data so far. Even though we're talking about relapsed/refractory AML, these are some data in newly diagnosed TP53-mutated AML just to show the potential promise of this drug in this setting. If you look at the curve on the right, these are patients specifically with TP53 mutated AML in the frontline setting who are receiving azacitidine plus magrolimab.

In the last update from ASH this last year in 2020, the median overall survival in this population of older patients with TP53-mutated AML was 12.9 months. It is important to note that if we look at the outcomes that are expected with hypomethylating agent plus venetoclax, we typically get median survival rates of around six months in this setting. It's hard to compare these two studies, but that being said, very promising data of azacitidine and magrolimab in the frontline setting of TP53-mutated AML. There's a number of studies also evaluating this drug now in the relapsed/refractory setting.

Complexities of Relapsed/Refractory AML: Aligning Strategies to Maximize Outcomes

KMT2A (MLL)-Rearranged AML



Frequency of MLL-r

Up to 70% of infant leukemia

About 15% of pediatric AML

About 5-10% of adult AML

- ✓ High-risk AML
- ✓ AML driver
- ✓ Poor prognosis (5-year OS: 5-20%)
- ✓ No approved inhibitor

Grimwade D, et al. *Blood*. 2016;127:29-41.; Issa GC, et al. *Leukemia.* 2021 (in press).

Another promising area where we don't yet have an approval, but I think that are very exciting drugs and clinical trials ongoing is in the area of KMT2A, or formerly known as MLL-rearranged AML. KMT2A rearrangements, which is present on the 11q23, are present in about 5%-10% of adult AML. This is a very high-risk disease genotype. It is associated with a poor prognosis, with long-term survival typically less than 20%. No currently approved targeted therapy for these patients.

Phase I Study of SNDX-5613 (Menin Inhibitor) in R/R Acute Leukemias

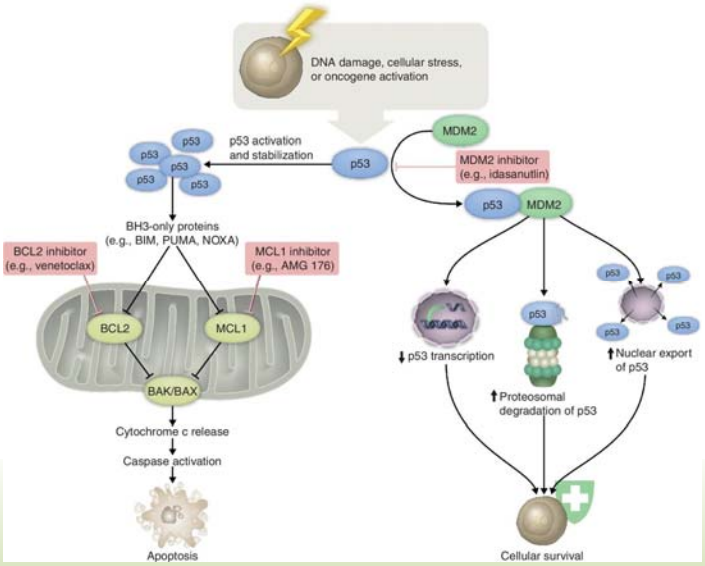
- 43 patients with R/R AML
  - MLLr, n=26; *NPM1*-mutated, n=9; others, n=8
  - AML, n=34, ALL, n=8, MPAL, n=1
  - Median 3 prior therapies (range, 1-11)
- Overall response rate: 15/31 (48%) in MLLr/*NPM1*-mutated patients
  - Response in 13/24 (54%) with MLLr
  - Response in 2/7 (29%) with mutated-*NPM1*
- MRD negativity achieved in 10/15 (67%) of responders

Syndax AUGMENT-101 Data Update (4/20/21)

We have some initial data reported with a couple of different compounds. These are some data from a menin inhibitor. Menin inhibitors are small molecule inhibitors that target this MLL or KMT2A rearrangement. They are being studied in a number of different types of leukemia. This is a study of this particular molecule in patients with different types of relapsed/refractory acute leukemia; 43 patients were treated at the most recent update back in April of 2021. Most of whom had MLL rearrangement, most of whom had AML. These patients were very heavily pretreated with a median of three prior therapies. The overall response rate was 48%, with 15 out of 31 evaluable patients responding. Importantly, we're seeing activity of these menin inhibitors not only in MLL rearranged patients, but also in NPM1-mutated patients. The response rate in those patients who were MLL rearranged was 54%, with 13 of 24 evaluable patients responding. We also do see clinical activity of the single-agent therapy in patients with mutated NPM1 relapsed/refractory AML. Notably, also 2/3 of the responding patients achieved MRD negativity, suggesting that although we don't have long-term data, we're hoping that these will be durable responses. A very exciting area in AML therapy and one that may lead to approvals in the future.

Complexities of Relapsed/Refractory AML: Aligning Strategies to Maximize Outcomes

Alternative Approaches to Targeting Apoptosis in AML

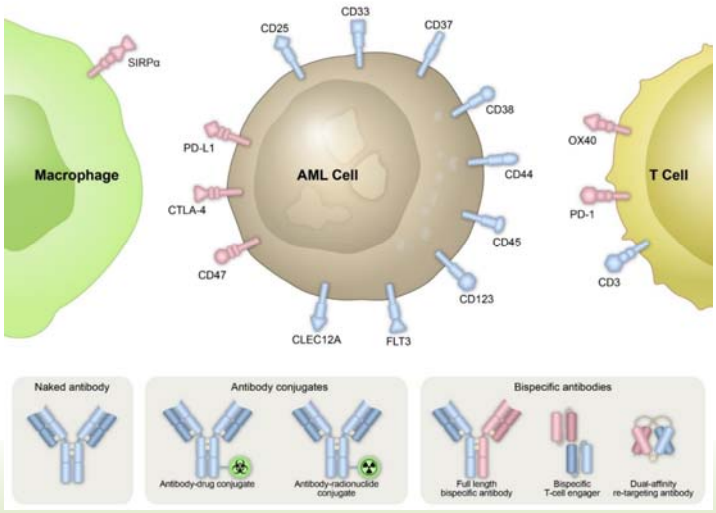


- MDM2 inhibitors: only active if *TP53* wild type
- Mcl-1 inhibitors
  - Direct: AMG-176, AMG-397, S64315
  - Indirect: CKD9 inhibitors, pevonedistat

Short NJ, et al. *Cancer Discov.* 2020;10(4):506-525.

Just discussing some of the other investigational therapies that are being evaluated in AML, we know that targeting apoptosis is very effective in AML based on the approval of venetoclax. There are several other agents that work in these apoptosis pathways that are being evaluated in clinical trials. These include MDM2 inhibitors, which work in an upstream to BCL2, which is the target of venetoclax, but ultimately, stimulate the apoptotic pathway. Also, venetoclax is a small molecule inhibitor of BCL2, which is an anti-apoptotic protein. We also have MCL1, which is another anti-apoptotic protein. We now have a number of drugs in clinical trials that are working to inhibit this MCL1, either directly or indirectly. There are a number of molecules in clinical development, which are what we consider as indirect MCL1 inhibitors but have the same downstream activity of stimulating that apoptotic pathway.

Monoclonal Antibody Targets in AML



- Gemtuzumab ozogamicin: anti-CD33 ADC
- Flotetuzumab: CD3-CD123 DART
- XmAb1405: CD3-CD123 bispecific Ab
- IMGN632: anti-CD123 ADC
- Iomab-B: anti-CD45 radiolabeled Ab
- Nivolumab: anti-PD1 Ab
- Magrolimab: anti-CD47 Ab

Short NJ, et al. *Cancer Discov.* 2020;10(4):506-525.

There are also a number of monoclonal antibodies that are in clinical development. Gemtuzumab ozogamicin, as I mentioned, is already approved. This is an anti-CD33 antibody-drug conjugate. There are a number of other either antibody-drug conjugates, or bi-specific antibodies against CD33 or CD123. We're also exploring radionucleotide antibodies as well as checkpoint inhibitors, which have shown a lot of promise in solid tumors, but their development has lagged behind so far in acute leukemias. There are a number of studies looking at nivolumab as well as I mentioned, magrolimab, which is a checkpoint inhibitor, but for macrophages.

Conclusions

- Outcomes of R/R AML have improved with the development of targeted therapies and (preliminarily) with use of venetoclax-based salvage regimens
- Repeat molecular profiling at the time of relapse is imperative to identify targetable mutations (eg, *FLT3, IDH1, IDH2*)
- Many novel agents are in development that target other genomic abnormalities (eg, *TP53, NPM1, KMT2A* rearrangements) or surface proteins (eg, antibody constructs)
- Rapid molecular profiling and clinical trial enrollment is key to further improving outcomes for these patients

In conclusion, the outcomes of patients with relapsed/refractory AML have been steadily improving as we've developed new drugs. We've had a number of FDA approvals of these targeted therapies, particularly for FLT3 mutated AML and IDH1, or IDH2 mutated AML. Preliminarily, we have good data supporting the potential use of venetoclax-based salvage regimens in the relapsed/refractory population, although this is still off-label use because we don't have an approval in this setting quite yet. Again, I want to emphasize the importance of repeating molecular profiling for patients with relapsed/refractory AML because we have these very good targeted therapies. In a small subset of patients with relapsed disease, we have the way we do see the emergence of these targetable mutations. There's also a number of other novel agents in development that may target specific genomic lesions. As I mentioned, magrolimab for TP53, and then we have these menin inhibitors that may target NPM1-mutated AML or these KMT2A rearrangements that historically have been very difficult to treat. We have a number also of antibody therapies that target a number of surface proteins. There's a wide variety of different antibody constructs that are in clinical development right now.

Importantly, in final conclusion, I think it's important to note that clinical trial and relevant enrollment is really key to improve further improving outcomes for these patients and to lead to future FDA approvals that can be used across the board. Very important that when particularly in the relapsed/refractory setting, which can be a very challenging disease to treat that patients are enrolled for clinical trials whenever possible. I thank you for your attention.