ManagingAML

New Uses for Hypomethylating Agents (HMAs)

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Hi, welcome to *Managing AML*. I'm Dr. Brian Jonas, Associate Professor at the University of California, Davis. Today I'll be discussing new uses for hypomethylating agents in AML and MDS. Let's begin.

Disclosures

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First, these are my disclosures.

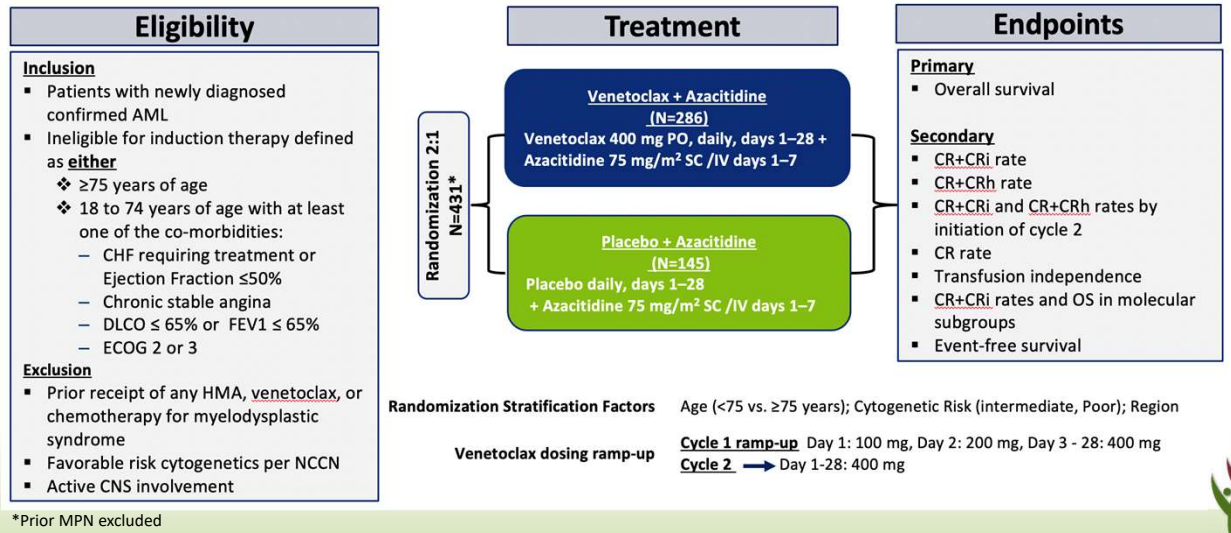
Learning Objectives

- Utilize HMA as part of a low-intensity therapeutic strategy in those unfit for intensive chemotherapy
- Investigate the role of HMAs in combination with BCL-2 inhibitors and small-molecule targeted therapies
- Explore the role of HMAs in maintenance therapy for AML
- Incorporate novel oral HMA into standard practice where appropriate

The objectives of the talk today are fourfold, we want to see how HMA are utilized as part of low-intensity therapeutic strategies in those unfit for intensive chemotherapy. Investigate the role of HMAs in combination with BCL2 inhibitors and small molecule or targeted therapies. Explore the role of HMAs in maintenance therapy for AML, and incorporate novel oral HMA into standard practice where appropriate.

New Uses for Hypomethylating Agents (HMAs)

VIALE-A Trial: Azacitidine plus Venetoclax vs Azacitidine for AML Ineligible for Induction



*Prior MPN excluded

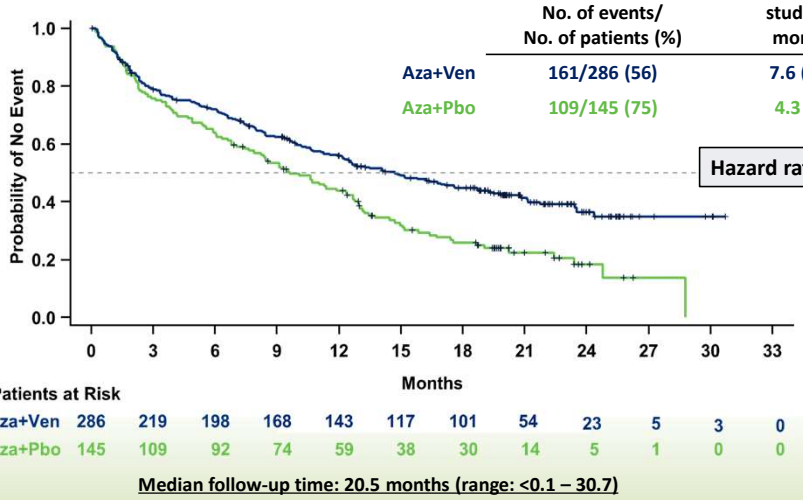
DiNardo C, et al. EHA 2020. Abstract LB2601.; DiNardo C, et al. *N Engl J Med*. 2020;383(7):617-629.

First, I'm going to discuss the azacitidine-venetoclax combination. This is the VIALE-A trial which led to the approval of this combination for patients with AML ineligible for induction. The main eligibility for this study was patients who are 75 or older with newly diagnosed AML, or those who were ineligible for induction chemotherapy, which were based on the old Ferrara criteria with some modifications.

You can see there on the left, including cardiac, lung, and other abnormalities including ECOG. Patients were randomized 2:1 to get azacitidine-venetoclax versus placebo-azacitidine. The primary endpoint was overall survival, with a number of other secondary endpoints including response rates.

New Uses for Hypomethylating Agents (HMAs)

VIALE-A Trial: OS and Other Outcomes



	No. of events/ No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), *P*<0.001

DoCR/CRi
Aza-Ven 17.5 mo (13.6-NE)
Aza-PBO 13.4 mo (5.8-15.5)

Safety
More hematologic toxicity, including neutropenia and febrile neutropenia, and mild GI toxicity

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

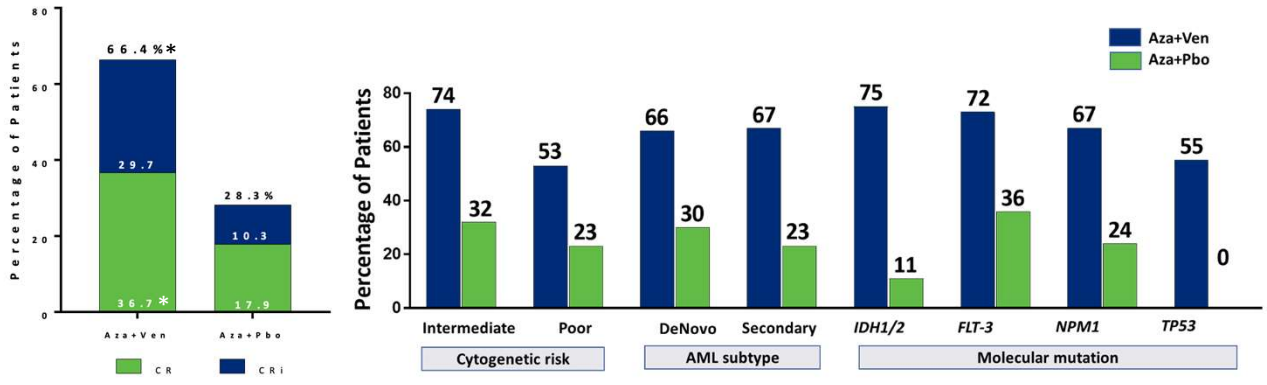
DiNardo C, et al. EHA 2020. Abstract LB2601.; DiNardo C, et al. *N Engl J Med*. 2020;383(7):617-629.

Here's the primary endpoint, which is overall survival. The study met this primary endpoint with aza-venetoclax, improving overall survival compared to azacitidine-placebo. The hazard ratio is 0.66, which was significant. The median survival was 14.7 months for aza-ven, versus 9.6 months for aza-placebo.

Some other endpoints are shown here, summarized here on this slide, including duration of remission, which was longer in the aza-venetoclax arm at 17.5 months compared to the aza-placebo arm. In terms of safety, there was more hematologic toxicity including neutropenia, febrile neutropenia with the aza-venetoclax combo, as well as some mild GI toxicity.

New Uses for Hypomethylating Agents (HMAs)

VIALE-A Trial: Response Rates



	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with *P*<0.001 by CMH test

DiNardo C, et al. EHA 2020. Abstract LB2601.; DiNardo C, et al. *N Engl J Med*. 2020;383(7):617-629.

In terms of response rates, you can see on the left side there, the CR/CRi rate was 66.4% for the aza-venetoclax arm. What's interesting about this combination is, you can see on the right, it is pretty active in all these different subgroups of AML, so whether or not the patients have intermediate- or poor-risk cytogenetics, de novo or secondary disease, or a number of molecular mutations such as IDH 1/2, FLT3, NPM1, and TP53. You can see the azacitidine activity is robust across the board. Now, in terms of the median time to response, the aza-venetoclax combination had a median time to CR/CRi of 1.3 months.

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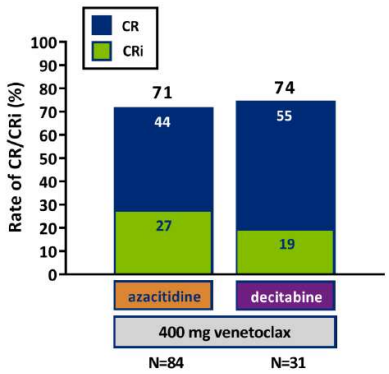
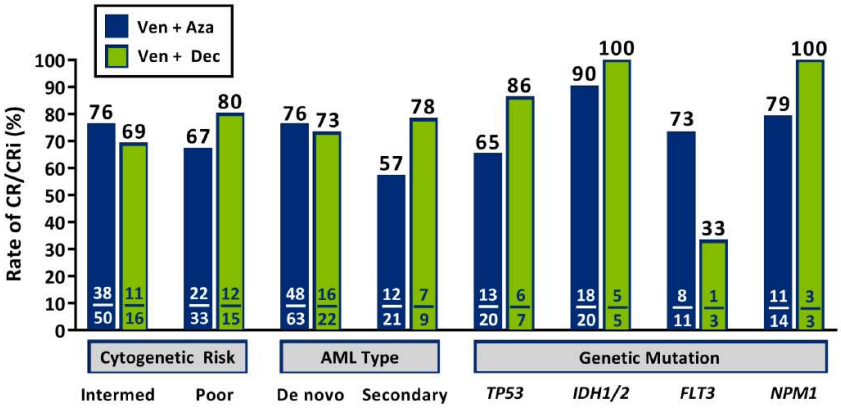
Phase 1b Trial: HMA + Venetoclax Response Rates





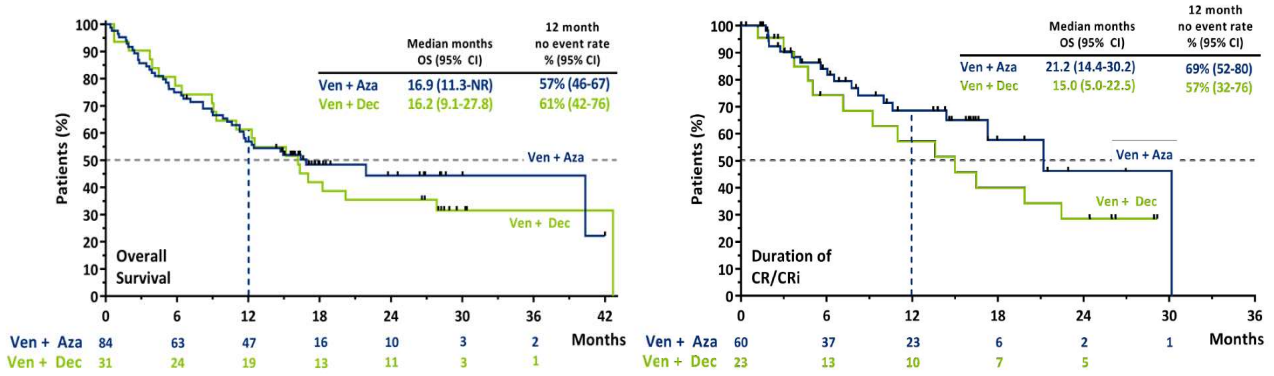
CR/CRi and MRD Negative:
48% AZA
39% DEC
10^{-3} at any time

Pollyea D, et al. *Blood.* 2018;132(1):285.; DiNardo C, et al. *Lancet Oncol*. 2018;19(2):216-228.; DiNardo C, et al. *Blood*. 2019;133(1):7-17.

Now, I bring this side up, which is actually data from the Phase IB trial which also looked at decitabine-venetoclax. On the left there you can see with the purple label, the CR/CRi rate for decitabine-venetoclax on the Phase IB trial was 74%. Now, similar to the data I just showed you for VIALE-A, you can see on the right there that the responses are robust across all the same subcategories of AML, both for azacitidine combos and for decitabine-venetoclax combos. You can see the azacitidine combos are in blue and the decitabine combos are in green. This activity is very similar between azacitidine-venetoclax and decitabine-venetoclax.

New Uses for Hypomethylating Agents (HMAs)

Phase 1b Trial: HMA + Venetoclax OS and DoR

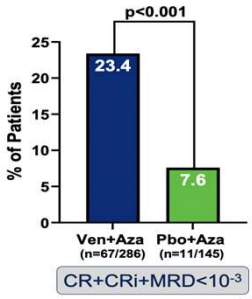


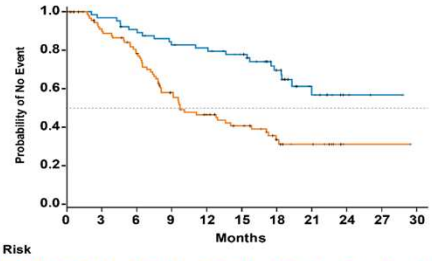
Pollyea D, et al. *Blood.* 2018;132(1):285.; DiNardo C, et al. *Lancet Oncol*. 2018;19(2):216-228.; DiNardo C, et al. *Blood*. 2019;133(1):7-17.

In terms of survival and duration of remission, this is also data from that Phase IB trial, but I wanted to point out here was the overall survival shown on the left side is similar to the aza-venetoclax arm to the decitabine-venetoclax arm. On the right side, which is the duration of remission, also similar outcomes for the aza combo versus the decitabine combo.

New Uses for Hypomethylating Agents (HMAs)

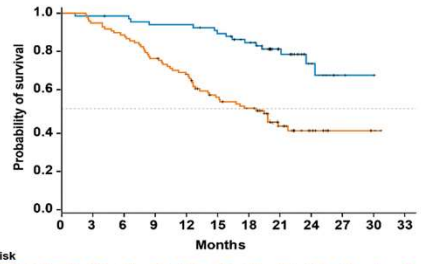
VIALE-A Trial: MRD Response, DoR and OS





Patients at Risk

CR+CRi+MRD<10-3	67	63	58	52	50	44	30	14	3	1	0
CR+CRi+MRD≥10-3	97	80	67	46	34	27	14	9	1	1	0



Patients at Risk

CR+CRi+MRD<10-3	67	66	65	62	62	58	52	30	13	2	1	0
CR+CRi+MRD≥10-3	97	92	86	74	64	49	42	21	10	3	2	0

Duration of remission	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median DoR, months (95% CI)
CR+CRi+MRD<10-3	22	81.2 (69.3, 88.9)	69.6 (55.9, 79.8)	NR (19.3 – NR)
CR+CRi+MRD≥10-3	54	46.6 (35.6, 56.8)	33.5 (22.9, 44.5)	9.7 (8.0 – 15.8)

Overall survival	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median OS, months (95% CI)
CR+CRi+MRD<10-3	15	94.0 (84.7, 97.7)	84.6 (73.3, 91.4)	NR (24.4 – NR)
CR+CRi+MRD≥10-3	52	67.9 (57.6, 76.2)	50.1 (39.6, 59.8)	18.7 (12.9 – NR)

Timing of MRD response: 25% achieved MRD negative response after C1, 52% after C4, 79% after C7 and the remaining 21% after C7.
OS by treatment cycles: there was no impact of time to MRD negative response on OS

Pratz K, et al. ASCO 2021. Abstract 7018.; Pratz K, et al. EHA 2021. Abstract S137.

Now, going back to the VIALE-A trial, which again was the Phase III study, looking at aza-venetoclax versus aza-placebo. We recently reported an analysis of MRD responses and outcomes at ASCO and EHA this year. On the left, you can see that 23% of patients on the VIALE-A study is of interim, achieved MRD negativity. In the middle column, you can see that the duration of remission was much longer for patients with MRD negativity compared to those that did not have MRD negativity. On the right, the overall survival curves also show longer survival for patients who are MRD negative versus MRD positive. Now, these are not powered to formally evaluate the differences between the two, which is why there's not a formal statistical comparison. In terms of the timing of MRD response, another thing I thought was interesting about this data was that 25% of patients achieved the MRD negative response after cycle 1. Basically, the other 75% was afterwards. Another 25% or so after cycle 4, another 25% or so after cycle 7, and the remaining 20% to 25% afterwards. The other thing that was interesting was that there was no impact on overall survival for a later achievement of MRD negativity compared to an earlier achievement at that endpoint.

Allogeneic HCT is Feasible in Patients Treated with Venetoclax-based Regimens

- **10%** (31/304) of patients received allo-HCT
  - Phase 1 trials of Ven-HMA and Ven-LDAC
- Median time on study drug for patients that had HCT 3.7 mo (range 0.9-20)
- **68%** (21/31) of patients remained alive at 12 months post-allo-HCT
- **55%** (17/31) of all patients that had allo-HCT had posttransplant remission of ≥12 months
  - **71%** (12/17) of those patients remained in remission for ≥2 years

Best response prior to SCT, n (%)	SCT Patients n = 31
CR/CRi	**26 (84)**
CR	16 (52)
CRi	10 (32)
CRh	6 (19)
MLFS	2 (6)
RD	3 (10)

Pratz K, et al. ASH 2019. Abstract 264.

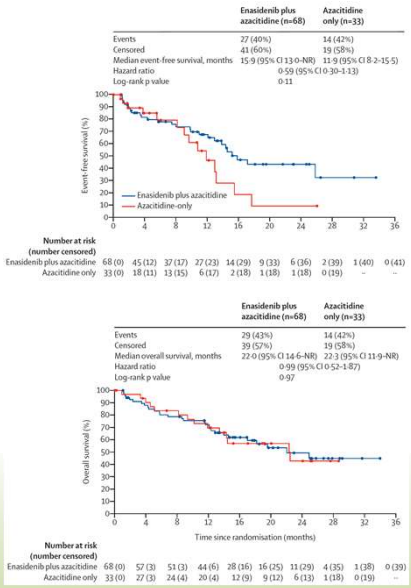
Another question that comes up is, "Can we take patients on azacitidine-venetoclax or decitabine-venetoclax, or low-dose cytarabine-venetoclax combinations to transplant?" This was analysis from a pool data from the Phase I trials of both the one that I was showing, the venetoclax-HMA, as well as the venetoclax low-DAC trial, and was presented by Dr. Pratz, et al., at ASH now almost two years ago. In this analysis, they found that 10% of patients on these Phase I trials went to transplant. The median time on study drug before transplant was 3.7 months. What was interesting was 68% of patients remained alive at 12 months post-transplant; 55% of patients had a post-transplant remission of greater than or equal to 12 months, and 71% of those were more than two years. This data suggests that taking patients to transplant is feasible with these venetoclax-based combinations.

New Uses for Hypomethylating Agents (HMAs)

Enasidenib plus Azacitidine vs Azacitidine for Treatment Naïve IDH2-mutated AML Ineligible for Induction

Endpoint	Enasidenib + Aza (n = 68)	Aza (n = 33)	*P* Value
ORR, % (95% CI)	74 (61-84)	36 (20-55)	.0003
CR, % (95% CI)	37 (42-67)	12 (3-28)	<.0001
CR/CRh, n (%)	39 (57)	6 (18)	.0002
CRi/CRp, n (%)	6 (9)	6 (18)	--
MLFS, n (%)	3 (4)	0	--
Time to First Response, Mo	1.9 (1.1-3.9)	3.6 (1.9-4.4)	--
Time to CR, Mo	5.4 (3.8-7.6)	4.4 (3.8-5.6)	--
Duration of Response, Mo	24.1 (95% CI 10-NR)	9.9 (95% CI 5.5-13.6)	--
Duration of CR, Mo	NR (95% CI 7.7-NR)	12.7 (95% CI 11.7-NR)	--

Currently not approved by the FDA
DiNardo C, et al. *Lancet Oncol*. 2021;22(11):1597-1608.



Moving to other HMA combinations that are beginning to be reported, this one is not yet approved by the FDA. This is enasidenib, which is an IDH2 inhibitor plus azacitidine versus azacitidine for treatment-naive IDH2 mutated AML, ineligible for induction. It was just published in the journal *Lancet Oncology* by DiNardo, et al. In this study, the azacitidine-enasidenib arm, which you can see on the left of the table, had increased overall response rate and CR rate and CR/CRh rate compared to azacitidine alone. All of those were statistically significant. There was also a shorter time to first response and a longer duration of response and a longer duration of complete remission, which you can see also there on the left-hand side of the table. Now, the event-free survival which is shown on the curve to the right was longer with the enasidenib-azacitidine combination, although this did not reach statistical significance. The overall survival was similar between the two arms.

New Uses for Hypomethylating Agents (HMAs)

Ivosidenib plus Azacitidine for Treatment Naïve IDH1-mutated AML Ineligible for Induction

Response Category	Response (n = 23)
CR + CRh, n (%) [95% CI] ▪ Median time to CR/CRh, mo (range) ▪ Median duration of CR/CRh, mo (95% CI)	16 (69.6) [47.1-86.8] 2.8 (0.8-11.5) NE (12.2-NE)
CR, n (%) [95% CI] ▪ Median time to CR, mo (range) ▪ Median duration of CR, mo (95% CI)	14 (60.9) [38.5-80.3] 3.7 (0.8-15.7) NE (9.3-NE)
CRh, n (%)	2 (8.7)
ORR, n (%) [95% CI] ▪ Median time to response, mo (range) ▪ Median duration of response, mo (95% CI)	18 (78.3) [56.3-92.5] 1.8 (0.7-3.8) NE (10.3-NE)

Response Category	Response (n = 23)
Best response by IWG, n (%) ▪ CR ▪ CRi/CRp ▪ MLFS ▪ SD ▪ NA	 14 (60.9) 2 (8.7) 2 (8.7) 4 (17.4) 1 (4.3)

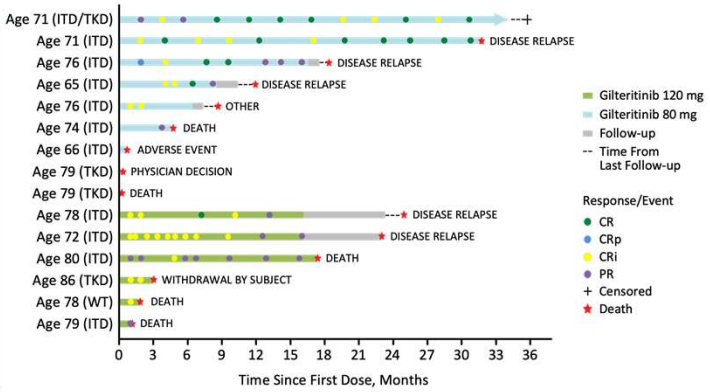
Currently not approved by the FDA
DiNardo C, et al. *J Clin Oncol*. 2021;39(1):57-65.

Now, ivosidenib, which is IDH1 inhibitor, has also been studied in combination with azacitidine for treatment-naive IDH1-mutated AML ineligible for induction. This was recently published in the *Journal of Clinical Oncology.* This is also a combination that is not FDA-approved. It looks promising like the enasidenib combination. In this case, you can see relatively a small data set of 23 patients, but the CR/CRh rate was almost 70%. The median time to this response was 2.8 months and the median duration of a CR/CRh response was not reached. The CR rate was 61%, which you can see in the next group down. Most of those CR/CRhs where actually full CRs. The overall response rate including other endpoints like CRi or MLFS was 78.3% with this combination.

New Uses for Hypomethylating Agents (HMAs)

LACEWING: Phase 3 Trial of Gilteritinib, Gilteritinib plus Azacitidine or Azacitidine Alone for Treatment Naïve FLT3-mutated AML Unfit for Induction

Characteristic	Safety Cohort (N=15)
Age, y	
Median (range)	75 (65–86)
≥75, n (%)	9 (60)
Female, n (%)	8 (53)
Race, n (%)	
Asian	2 (13)
White	11 (73)
***FLT3* mutation status, n (%)**	
ITD alone	10 (67)
TKD alone	3 (20)
ITD/TKD	1 (7)
Wild type	1 (7)
ECOG PS ≤1 at screening, n (%)	6 (40)



CRc rate 67% (CR 33%) in the safety cohort.
Med DoCRc 10.4mo (0.95-NR)
Hematologic AEs most common

Wang E, et al, ASH 2020. Abstract 27.

Another combination that's been explored is gilteritinib, which is a FLT3 inhibitor in combination with azacitidine. Here's preliminary data from the LACEWING trial. This is a Phase III trial of gilteritinib-azacitidine, or azacitidine alone for treatment-naive FLT3-mutated AML unfit for induction. This was reported by Eunice Wang at ASH in 2020 and updates are expected this year. This is the safety cohort of 15 patients that were treated with gilteritinib-azacitidine. None of these is comparative data. This is just the gilteritinib-aza arm. You can see there, the swim lane plot on the right, overall the CRc rate was 67%, and 33% achieved the full CR. The median duration of CRc was 10.4 months, and the most common AEs were hematologic. This showing some preliminary promise with the safety cohort.

New Uses for Hypomethylating Agents (HMAs)

Other Novel HMA Combinations in Development

Combination	Population	Outcomes	Reference
Magrolimab plus Azacitidine	1L AML and higher risk MDS	AML – 64% ORR (41% CR), mDoR NR, mOS NR AML TP53 – 71% ORR, 48% CR, mDoR 9.9, mOS 18.9mo MDS – 92% ORR (50% CR)	Sallman et al, ASH 2019 Abstract 569. Sallman et al, ASH 2020 Abstract 330.
Eprenetapopt plus Azacitidine	1L AML and MDS with TP53 mutations	AML – 88% ORR, 50% CR, mDoR 7mo MDS – 88% ORR, 61% CR, mDoR 7.3mo	Sallman et al, ASH 2019 Abstract 676.
Sabatolimab plus Decitabine	1L higher risk MDS and AML	AML – ORR 47%, CR 35% MDS – ORR 61%, CR 33.3% Aza arm as well	Brunner et al, ASH 2020 Abstract 657.
Pevonedistat plus Azacitidine vs Aza	1L higher risk MDS/CMML and low-blast count AML	mOS 21.8 mo vs 19mo (NS) mEFS 21mo vs 16.6mo (NS) MDS – ORR 79%, 52% CR, mOS 23.9mo, mEFS 20.2mo	Sekeres et al, Leukemia 2021.

I apologize for the busy slide, but there's a number of other novel HMA combinations in development. Magrolimab, which is an anti-CD 47 antibody, plus azacitidine. Eprenetapopt, which is also known as APR-246, and I hope I didn't mispronounce that, plus azacitidine. Sabatolimab, which is an anti-TIM3 antibody, plus decitabine. Pevonedistat, which is a NEDD8-activating-enzyme inhibitor, plus azacitidine. These are being studied mostly in the first-line, as you can see there within the second column in AML and in some cases, in MDS as well. The APR-246 is a p53-stabilizing drug, so this one is only for patients with p53 mutations, which you can see in the second line.

The magrolimab-aza trial, again, that's a CD-47 antibody, which blocks this "don't eat me signal," and leads to the destruction of the disease cells through the macrophages and monocytes. This has an outcome, for AML of 64% overall response rate with a median duration or remission not reached, median overall survival not reached. What's interesting is this compound looks active in p53-mutated AML with a 71% overall response rate, 48% complete remission rate, and a median duration of remission of 9.9 months, and median overall survival of 18.9

months.

In MDS where it's also being explored, 92% overall response rate was seen including a 50% CR rate. For the APR-246 plus aza, there was a 88% overall response rate both in AML and MDS, with 50% to 60%, CR rates, and median duration remissions of about seven months. Quite promising for that p53 subset. The TIM3 antibody plus decitabine combination had a 47% response rate in AML and a 61% response rate in MDS. The pevo-aza combination had a 21.8-month median overall survival compared to 19 with azacitidine alone, 21 months versus 16.6 months compared to aza alone for EFS. These were not significant. However, looking at the MDS subset, the overall response rate was 79% with a 52% CR rate, median overall survival of 23.9 months, and median EFS of 20.2 months. Appears to be promising in the MDS subset in particular.

New Uses for Hypomethylating Agents (HMAs)

Recent Phase 3 HMA Combination Trial Press Releases

- **AGILE** – 8/2/21 – P3 trial of ivosidenib-Aza vs Aza in treatment naïve IDH1-mutated AML – met its primary endpoint of EFS and secondary endpoints of OS, CR, CRh and ORR
- **LACEWING** – 12/21/20 – P3 trial of gilteritinib-Aza vs Aza in treatment naïve FLT3-mutated AML – failed to meet primary endpoint of OS
- **PANTHER** – 9/1/21 – P3 trial of pevonedistat-Aza vs Aza in treatment naïve MDS, CMML and low-blast count AML – failed to meet primary endpoint of EFS
- **Eprenetapopt** – 12/28/20 – P3 trial of eprenetapopt-Aza vs Aza in HMA naïve TP53-mutated MDS – failed to meet primary endpoint of CR rate

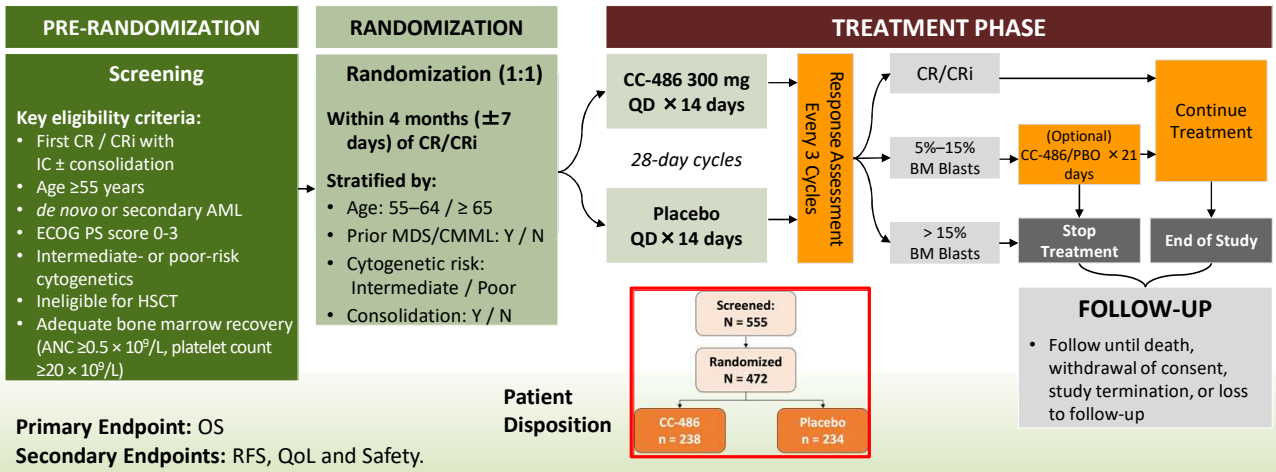
https://www.astellas.com/us/news/5306.;
https://ir.aprea.com/news-releases/news-release-details/aprea-therapeutics-announces-results-primary-endpoint-phase-3.;
https://www.takeda.com/newsroom/newsreleases/2021/takeda-provides-update-on-phase-3-panther-pevonedistat-3001-trial/.;
https://www.servier.us/servier-announces-positive-topline-data-from-the-global-phase-3-study-of-tibsovo.

Now, tempering some of the enthusiasm I just presented were some recent Phase III HMA combination trial press releases. Now, press releases, of course, are those exact things, they're press releases, so we do need to actually see the actual data before we can draw more conclusions, but I just wanted to mention these. The AGILE trial, which had a press release in August of this year, this is the Phase III trial of ivo-aza versus aza alone. This study apparently has met its primary endpoint of EFS and secondary endpoints of overall survival and CR rate and overall response rate. Obviously, we're eagerly awaiting the actual data from that study. LACEWING had a press release at the end of 2020 that showed that it did not meet its primary endpoint of overall survival. The PANTHER trial, which was pevo-aza versus aza did not mean its primary endpoint of EFS. The APR-246 compound, which was discussed late last year as well in a press release, that did not meet its primary endpoint of CR rate. Now, again, I think what's important about these press releases is to hold on to our final judgments until we see the actual data from these trials, either presented at conferences or in the journals because there may be subgroups that benefit or other data that we can glean from these.

New Uses for Hypomethylating Agents (HMAs)

QUAZAR AML-001 Trial: Maintenance CC-486 (Oral Azacitidine) for AML

International, multicenter, placebo-controlled, double-blind, randomized, phase 3 study that enrolled patients from 148 sites in 23 countries (NCT01757535)



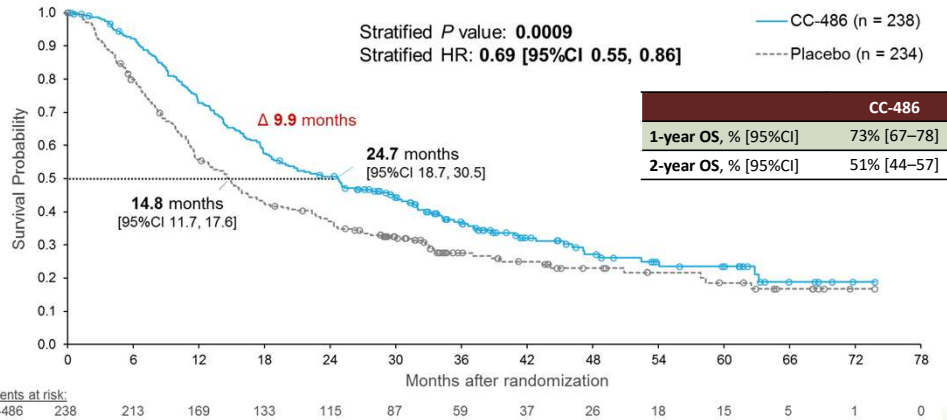
Wei A, et al. ASH 2019. Abstract LBA 3.; Wei A, et al. *N Engl J Med.* 2020;383(26):2526-2537.

Okay, I want to move on now to oral HMA options. This is the QUAZAR AML-001 with maintenance CC-486, which is also known as oral azacitidine for AML. This was an international multi-center placebo-controlled, double-blind, randomized Phase III study in many countries and in many sites. Basically, it took patients with AML in first remission, either CR or CRi, who had had induction chemotherapy plus or minus consolidation. They had to be ineligible for transplant for whatever reason. They had to be within four months of achieving their CR. These patients were randomized 1:1 to receive either 14 days per month or per 28 days of CC-486 300 milligrams daily or placebo for 14 days daily. The primary endpoint was overall survival and the secondary endpoints included relapse-free survival, quality of life, and safety. As you can see patients were basically treated until they either progressed or they couldn't tolerate treatment. They were followed in the usual way until death or withdrawal consent study determination lost to follow up. One thing I'll point out is that for patients who did have an increase in blasts between 5% and 15%, they could actually increase their CC-486 to 21 days out of 28 days.

New Uses for Hypomethylating Agents (HMAs)

QUAZAR AML-001 Trial: Outcomes

- Median follow-up: 41.2 months



	CC-486	Placebo	Difference
1-year OS, % [95%CI]	73% [67–78]	56% [49–62]	17% [8–26]
2-year OS, % [95%CI]	51% [44–57]	37% [31–43]	14% [5–23]

Secondary Endpoints:

- Superior RFS with median 10.2 vs 4.8mo, HR 0.65, *P* < 0.0001
- GI AEs and neutropenia were more common with CC-486 and in some led to dose modifications or discontinuation

Data cutoff: July 15, 2019
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 *vs.* placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.
95%CI, 95% confidence interval; HR, hazard ratio.

Wei A, et al. ASH 2019. Abstract LBA 3.; Wei A, et al. *N Engl J Med.* 2020;383(26):2526-2537.

This study met its primary endpoint of improved overall survival. You can see the median overall survival of 24.7 months for the CC-486 arm compared to 14.8 months for the placebo arm. An absolute difference of nearly 10 months. This was significant with a hazard ratio of 0.69. Putting it into another way, the one-year survival of CC-486 was 73% versus 56% for placebo at two years, 51% versus 37%.

In terms of other endpoints, there was a superior relapse-free survival with a median of 10.2 months versus 4.8 months, and a hazard ratio of 0.65. That was significant. GI side effects and neutropenia were more common with CC-486 and in some cases led to dose modifications or discontinuation.

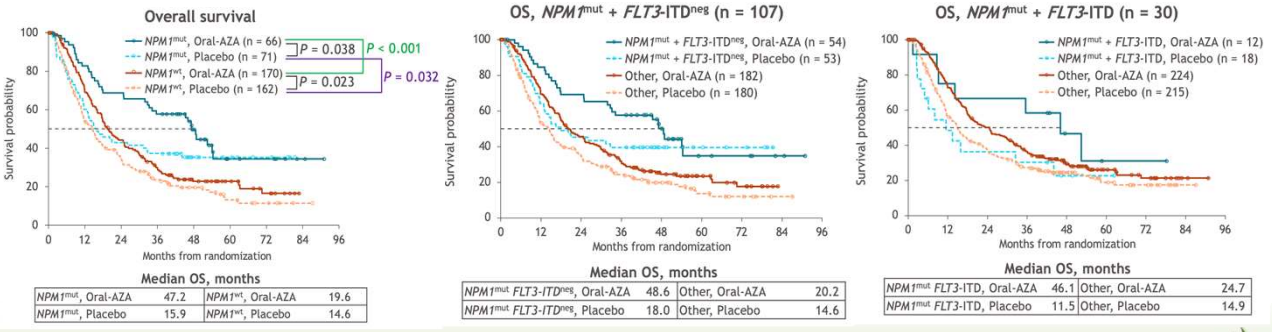
New Uses for Hypomethylating Agents (HMAs)

QUAZAR AML-001 Trial: Effects of NPM1 and FLT3-ITD Mutations

NPM1 mutational status at AML Dx was prognostic for OS and RFS, and predictive of a survival benefit for pts treated with Oral-AZA (vs. PBO).

Presence of *FLT3*-ITD at Dx had a negative prognostic influence, as suggested by differences in OS results in the PBO arm

Oral-AZA prolonged OS vs. PBO in pts with *NPM1*^{mut} + *FLT3*-ITD^{neg} (48.6 vs. 18.0 mo, respectively), and in pts with both *NPM1*^{mut} + *FLT3*-ITD (46.1 vs. 11.5 mo)



Döhner H, et al. EHA 2021. Abstract S131.

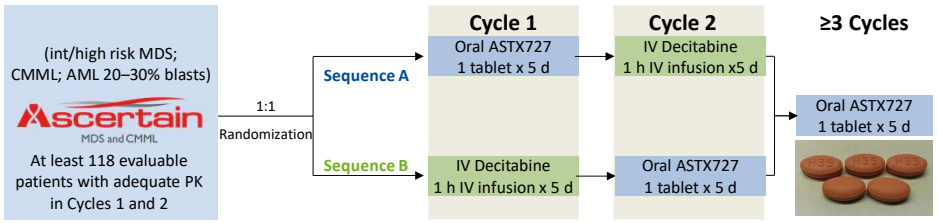
This is an update of new data from the study or subgroup analysis from the same QUAZAR trial. This was reported at the European Hematology Association meeting this past June by Dr. Döhner, et al. This was looking at the effects of NPM1 mutations and FLT3-ITD mutations in the QUAZAR dataset. What they found was that NPM1 mutational status at diagnosis was prognostic for overall survival and relapse-free survival, and was predictive of a survival benefit for patients who received CC-486 versus placebo. For patients with NPM1 mutation, you can see that the median overall survival is 47.2 months.

Now, the presence of a FLT3 mutation at diagnosis had a negative prognostic influence. In the setting of the NPM1 mutation, you can see the curve on the left, which is the NPM1 mutation plus FLT3-negative, had a median overall survival, 48.6 months. On the far-right curves, you can see that the NPM1 mutation plus a FLT3-ITD mutation, there was still pretty impressive survival with the combination, the oral azacitidine producing a median overall survival of 46.1 months. The presence of the NPM1 mutation really imparted a favorable outcome to the patients on this study. I should point out that the CC-486 is approved by the FDA for maintenance therapy in AML.

New Uses for Hypomethylating Agents (HMAs)

ASTX727-02 Trial of Decitabine-Cedazuridine (DEC-C) in MDS/CMML: Randomized Crossover Trial

- Current HMA treatment poses significant patient burden due to 5–7 days per month of parenteral administration in a clinic setting
- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver
- Cedazuridine is a novel, potent, and safe CDA inhibitor



Major entry criteria
- Candidates for IV decitabine
- ECOG PS 0–1
- Life expectancy of ≥3 months
- Adequate Organ Function
- One prior cycle of HMA is allowed

Primary endpoint
- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints
- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

Garcia-Manero G, et al. ASH 2019. Abstract 846.

This is the other oral HMA, which is the combination of decitabine and cedazuridine or DEC-C as some people like to call it, which is approved by the FDA for MDS and CMML. This was based on the studies I'm going to show you here, including this ASTX727-02 trial, and this is a randomized crossover trial. I think most people are aware that the IV HMA pose some burdens to patients, especially these are older patients, oftentimes that have to come in 5-7 days a month to receive IV therapy. There's also a problem, however, with the oral HMA and that they are degraded by cytidine deaminate (CDA) in the gut and the liver. That's why this combination of decitabine-cedazuridine was created, which cedazuridine is a CDA inhibitor. This allows the decitabine to be absorbed and get into the bloodstream and exert its effect.

Here you can see the schema of this ASCERTAIN trial. Basically, what patients on this trial, they had MDS or CMML that were higher-risk or intermediate or higher risk that were a candidate for a standard HMA therapy. They were randomized to get either oral decitabine-cedazuridine in cycle 1 followed by IV in cycle 2, or IV in cycle 1 followed by oral in cycle 2, and then from cycle 3 onwards everyone got the oral combination.

The primary endpoint, here was an interesting primary endpoint, not one you typically see in trials, was actually the total 5-day decitabine area under the curve equivalence. This primary endpoint is actually a pharmacokinetic primary endpoint.

New Uses for Hypomethylating Agents (HMAs)

ASTX727-02 Primary Endpoint: 5-day Decitabine AUC Equivalence

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

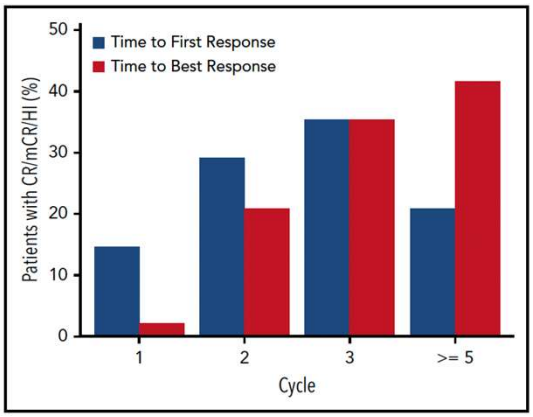
Garcia-Manero G, et al. ASH 2019. Abstract 846.

The study met its primary endpoint. There was the 5-day decitabine area under the curve, equivalence was 99%. The confidence interval of 93% to 106%. You can see they're summarized above and below in the text. This basically showed that after five days, the amount of decitabine detectable on the blood was more or less the same if you took the IV versus the oral formulation.

New Uses for Hypomethylating Agents (HMAs)

ASTX727-01-B: DEC-C Responses in MDS/CMML

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR mCR with HI	18 (22) 6 (7)	14-33 3-16
HI HI-E HI-N HI-P	13 (16) 8 (10) 2 (2) 11 (14)	9-26 4-19 0-9 7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52



- Comparable safety was seen between IV decitabine and PO DEC-C

Garcia-Manero G, et al. *Blood.* 2020;136(6):674–683.

Now, this is the ASTX727-01-B trial, also same population of patients, MDS, CMML patients. Here are some more robust response rate data, and you can see the oral decitabine-cedazuridine combination had a CR rate of 21%, a marrow CR rate of 22%, an overall response rate of 60%. The responses were improved over time. You can see on the right, the time to first response, many patients needed up to 3 cycles to see their first response, and the time the best response improved over time. We're seeing with later numbers of cycles five or more. You can see there on the red curves.

There was a comparable safety between the IV decitabine and the oral decitabine-cedazuridine combination. Taken together, these studies show that the equivalent that taking the oral decitabine-cedazuridine combination for five days led to very similar outcomes to IV decitabine, as well as almost identical amounts of decitabine in the blood. Therefore, it was approved as a potential treatment option for patients with MDS and CMML.

New Uses for Hypomethylating Agents (HMAs)

Future Directions

- Evaluation of HMA-venetoclax containing triplet regimens for treatment naïve AML unfit for induction
  - Aza-Ven plus ivosidenib – NCT03471260
  - DEC-C-Ven plus gilteritinib – NCT05010122
  - Aza-Ven plus magrolimab – NCT05079230
  - Aza-Ven plus pevonedistat – NCT04266795
  - Aza-Ven plus uproleselan (E-Selectin inhibitor) – NCT04964505
  - Aza-Ven plus sabatolimab (Anti-TIM-3 Ab) – NCT04150029
- Evaluation of HMA-venetoclax doublets with oral HMA for treatment naïve AML unfit for induction
  - CC-846 – NCT04102020, VIALE-M trial
  - DEC-C – NCT04657081

https://clinicaltrials.gov

Another busy slide, but that's because there's so much to do now. There's a lot of future directions to think about. I think one of the things that are being examined pretty aggressively right now is triplet regimens for the treatment of naive AML unfit for induction. These are based on a backbone of HMA-venetoclax with addition of a third drug. There's a number of trials out there right now. Basically, all those promising new drugs are being tested in these combinations. I've laid them all out here. Now, this is not an exhaustive list. There is additional triplet trials with other promising drugs that are being explored. If you spend a few minutes on *ClinicalTrials.gov,* you can find a lot of these other trials, but these are just a few to highlight. For example, ivosidenib, gilteritinib, magrolimab, pevonedistat, uproleselan, which is an E-selectin inhibitor, sabatolimab, which is an anti-TIM3 antibody, as I mentioned before. All these are being evaluated as triplets.

There's also, of course, evaluation of doublet therapies HMA-venetoclax with substitution of the oral HMA for treatment-naive AML patients unfit for induction. CC-486 has a version of that, as well as decitabine to cedazuridine. Because right now, it's not really feasible, in my opinion at least, to substitute the oral HMA for the IV HMA that you would normally use in these combinations. I think these trials are very important to show that the oral formulations produce equivalent outcomes and safety in the setting of these venetoclax combinations.

New Uses for Hypomethylating Agents (HMAs)

Summary

- Standard of care for AML and MDS and uses of HMA are evolving
- HMA plus venetoclax is a standard of care for those unfit for intensive chemotherapy
- CC-486/oral Azacitidine is a maintenance option for AML
- Oral DEC-C is an option for treatment of intermediate or higher risk MDS and CMML
- Clinical trials continue to advance new therapeutic approaches, including novel HMA combinations, HMA-Ven triplets, and oral HMA-Ven doublets, among others

To summarize, the standard of care for AML and MDS and uses of HMA are evolving, I would say, rapidly. HMA-venetoclax is a standard of care for those unfit for intensive chemotherapy, CC-486 or oral azacitidine is a maintenance option that's approved for AML. Oral decitabine-cedazuridine combinations is also an option for treatment at intermediate- or higher-risk MDS and CMML approved by the FDA for this indication. Of course, clinical trials continue to advance new therapeutic approaches, including novel HMA combinations, HMA-venetoclax triplets, and oral HMA venetoclax doublets among others.

To close, I wanted to thank everyone for viewing this activity and for the opportunity to present.