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CONGRESS COVERAGE: EHA 2021 – FOCUS ON LEUKEMIA AND MDS

June 25, 2021

Full Report

REPORT CONTENTS

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MEETING SNAPSHOT

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VIRTUAL CLOSED-DOOR ROUNDTABLE

DATE:
June 25, 2021

COVERAGE OF EHA 2021 CONGRESS – FOCUS ON LEUKEMIA AND MDS by key experts

INSIGHTS REPORT including postmeeting analyses and actionable recommendations

PANEL: Key experts in MDS and leukemia

> 5 from US
> 5 from Europe

MDS- and LEUKEMIA-SPECIFIC DISCUSSIONS on current and future treatment landscape and how newly presented data from EHA may impact treatment paradigms

PANEL CONSISTING OF 5 US AND 5 EUROPEAN LEUKEMIA EXPERTS

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Eunice Wang, MD
Roswell Park Comprehensive Cancer Center

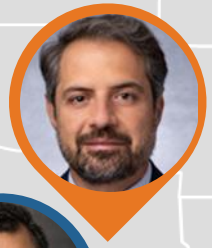
Daniel DeAngelo, MD, PhD
Dana-Farber Cancer Institute

Jae Park, MD
Memorial Sloan Kettering Cancer Center

Charles Craddock, CBE, FRCP (UK), FRCPath, DPhil
Queen Elizabeth Hospital

Gert Ossenkoppele, MD, PhD
Amsterdam University Medical Center

Nicola Gökbuget
Goethe University Hospital



CHAIR:
Elias Jabbour, MD
MD Anderson Cancer Center

Philippe Rousselot, MD, PhD
University of Versailles Saint-Quentin-en-Yvelines

Guillermo Garcia-Manero, MD
MD Anderson Cancer Center

Valeria Santini, MD
University of Florence

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MEETING AGENDA

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Time (CEST)	Topic	Speaker/Moderator
16.00 – 16.05	**Welcome and Introductions**	Elias Jabbour, MD
16.05 – 16.15	**Updates on MDS**	Valeria Santini, MD
16.15 – 16.40	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
16.40 – 16.50	**Newly Diagnosed AML Patients**	Gert Ossenkoppele, MD, PhD
16.50 – 17.15	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
17.15 – 17.25	***IDH1/2* and *FLT3* Mutations in Newly Diagnosed AML Patients**	Eunice Wang, MD
17.25 – 17.45	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
17.45 – 17.55	***FLT3* Mutations in Relapsed/Refractory AML Patients**	Daniel DeAngelo, MD, PhD
17.55 – 18.15	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
18.15 – 18.25	***IDH1/2* Mutations in Relapsed/Refractory AML Patients**	Guillermo Garcia-Manero, MD
18.25 – 18.45	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
18.45 – 18.55	**Updates in ALL**	Nicola Gökbuget, MD
18.55 – 19.25	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
19.25 – 19.30	**Summary and Closing Remarks**	Elias Jabbour, MD

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CONGRESS HIGHLIGHTS

UPDATES ON MDS

BENEFIT OF CONTINUING LUSPATERCEPT THERAPY IN PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES WHO DID NOT ACHIEVE RED BLOOD CELL TRANSFUSION INDEPENDENCE BY WEEK 25 IN THE MEDALIST STUDY

EPICS

GERMING, ET AL. 2021, EHA #EP915

STUDY POPULATION

> MEDALIST study: MDS patients with ≥15% ring sideroblasts or ≥5% with *SF3B1* mutation, <5% blasts in bone marrow, non-del(5q) MDS, refractory/intolerant to ESAs, or naive; average RBC transfusion burden ≥2 U/8 weeks; no prior treatment with disease-modifying agents (eg, IMiDs, HMAs); randomized to luspatercept (n = 153) or placebo (n = 76). This subanalysis: 68/153 patients who did not achieve RBC transfusion independence (TI) for ≥8 weeks by week 25 but continued treatment through week 48

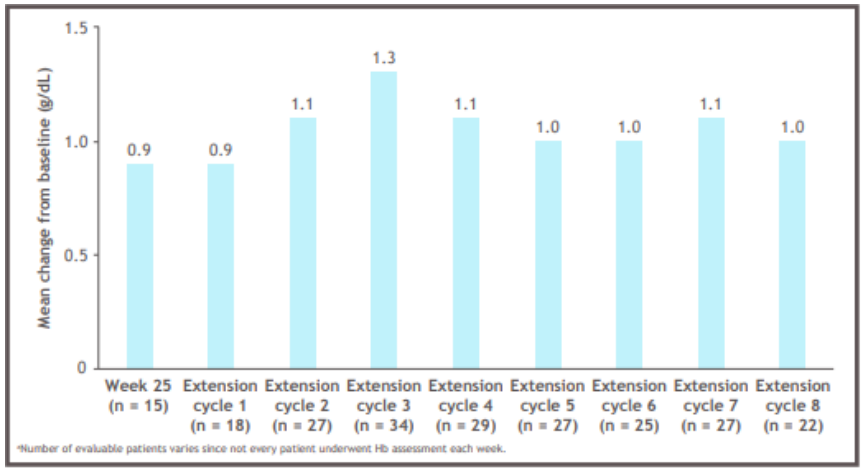
OUTCOME

> 16% (n = 11/68) of patients achieved RBC TI for ≥8 weeks
  - Of these, 3 patients achieved RBC TI for ≥16 weeks
  - Median time to achieving RBC TI for ≥8 weeks was 5 months

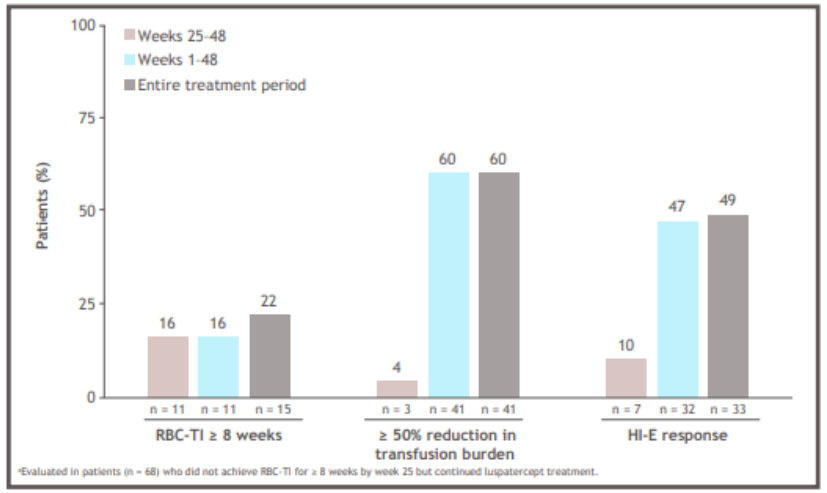
EXPERT CONCLUSIONS

Continuing luspatercept treatment beyond week 25 provides clinical benefit in late responders and decreases the transfusion load in patients

MEAN CHANGE FROM BASELINE IN HB LEVELS, WEEKS 25–48



RESPONSE INDICATORS ACROSS ANALYSIS PERIODS



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LUSPATERCEPT REDUCES RED BLOOD CELL TRANSFUSIONS IN PATIENTS WITH LOWER-RISK MDS REGARDLESS OF BASELINE TRANSFUSION BURDEN IN THE MEDALIST STUDY

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GARCIA-MANERO, ET AL. 2021, EHA #EP920

STUDY POPULATION

> Patients in MEDALIST had lower-risk MDS, were refractory, intolerant, or unlikely to respond to ESAs, and required regular RBC transfusions (≥2 units/8 weeks) in the 16 weeks prior to randomization. Of the 153 patients randomized to receive luspatercept, 87 (57%) were classified as having low baseline RBC transfusion burden (TB) and 66 (43%) as high baseline RBC TB

OUTCOME

> At week 25, patients receiving luspatercept had fewer mean cumulative RBC transfusion units and RBC transfusion visits than placebo across both baseline RBC TB categories

> Patients receiving luspatercept had a lower cumulative number of RBC transfusion units and a lower cumulative number of RBC transfusion visits through 144 weeks compared with placebo, particularly those with low baseline RBC TB

MEAN CUMULATIVE RBC TRANSFUSION UNITS THROUGH 24 WEEKS

	Luspatercept (N = 153)[a]	Luspatercept responders (N = 58)[a]	Luspatercept non-responders (N = 95)[a]	Placebo (N = 76)[a]
Low baseline RBC TB (< 6 units/8 weeks)	6.8 (5.6-8.4) n = 81[b]	2.7 (2.0-3.7) n = 49[b]	13.0 (11.4-14.9) n = 32[b]	13.2 (11.5-15.2) n = 38[b]
High baseline RBC TB (≥ 6 units/8 weeks)	17.2 (15.1-19.6) n = 47[b]	3.7 (1.8-7.4) n = 6[b]	18.9 (16.9-21.1) n = 41[b]	24.2 (21.3-27.4) n = 30[b]

[a]Number of patients in the intention-to-treat population.
[b]Number of patients with RBC transfusion data up to 24 weeks.

MEAN CUMULATIVE RBC TRANSFUSION VISITS THROUGH 24 WEEKS

	Luspatercept (N = 153)[a]	Luspatercept responders (N = 58)[a]	Luspatercept non-responders (N = 95)[a]	Placebo (N = 76)[a]
Low baseline RBC TB (< 6 units/8 weeks)	4.0 (3.3-4.8) n = 81[b]	1.7 (1.2-2.2) n = 49[b]	7.5 (6.5-8.6) n = 32[b]	7.2 (6.3-8.3) n = 38[b]
High baseline RBC TB (≥ 6 units/8 weeks)	9.4 (8.3-10.7) n = 47[b]	2.0 (1.0-4.0) n = 6[b]	10.3 (9.2-11.5) n = 41[b]	12.5 (11.0-14.2) n = 30[b]

[a]Number of patients in the intention-to-treat population.
[b]Number of patients with RBC transfusion data up to 24 weeks.

EXPERT CONCLUSIONS

Expected cumulative number of transfusions was lower in patients with high and low transfusion burden treated with luspatercept. This resulted in lower numbers of hospital visits. The response is maintained through 144 weeks; these results are very positive

EFFICACY OF IMETELSTAT IS INDEPENDENT OF MOLECULAR SUBTYPES IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER RISK MDS (LR-MDS) RELAPSED/REFRACTORY (R/R) TO ERYTHROPOIESIS STIMULATING AGENTS (ESA)

PLATZBECKER, ET AL. 2021, EHA #EP910

EPICS

STUDY POPULATION

> Patients with lower-risk MDS, RBC transfusion dependent, non-del(5q), and ESA R/R from the IMerge phase II/III study. Patients were screened to determine their karyotype, and correlation analyses between molecular profiles and clinical efficacy and hematologic improvement-erythroid response were performed

OUTCOME

> Of 31/38 patients with baseline mutation data, 28 (90.3%) patients had at least 1 mutation, among which 15 (53.6%), 8 (28.6%), and 5 (17.9%) patients had 1, 2, and ≥3 mutations, respectively
> Durable TI was observed in patients with 0–3 mutations, except *K666R*
> Patients with >3 mutations showed lower response

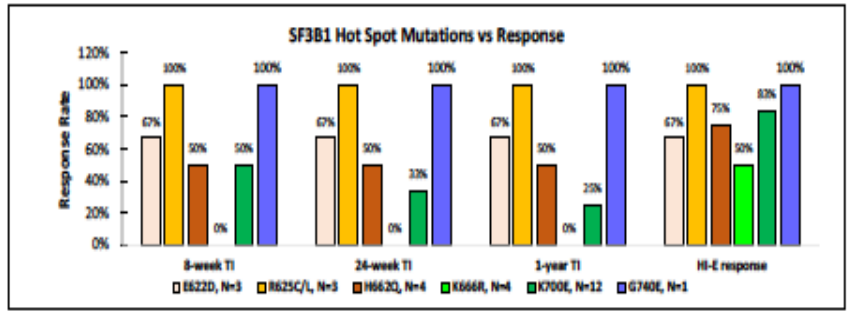
CONCLUSIONS

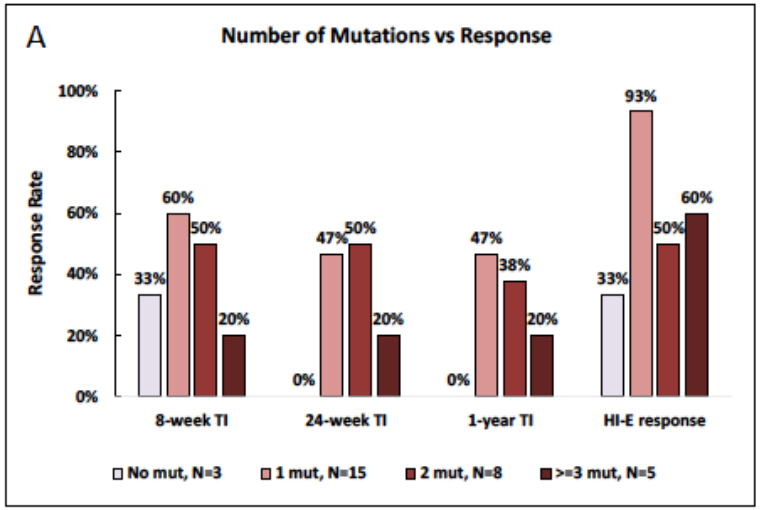
Imetelstat demonstrated clinical efficacy across different molecularly defined subgroups including in patients with poor prognosis in heavily transfused LR-MDS ESA R/R, who have limited treatment options

> Longer follow-up is need to understand whether the responding patients will respond to treatment for the long term

RESPONSE

Figure 6. HI-E response was seen in patients with different SF3B1 hot spot mutations, durable TI was observed in patients with all SF3B1 hot spot mutations except K666R





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IMETELSTAT DEMONSTRATES AN ACCEPTABLE SAFETY PROFILE IN MYELOID MALIGNANCIES

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MASCERENHAS, ET AL. 2021, EHA #EP1106

STUDY POPULATION

> Patients with myelofibrosis from IMbark/MYF201 trial and patients with lower-risk MDS from IMerge trial

OUTCOME

> Forty-one percent of patients with myelofibrosis had grade ≥3 (G≥3) thrombocytopenia and 32% had G≥3 neutropenia. Sixty-one percent of patients with lower-risk MDS had G≥3 thrombocytopenia and 55% had G≥3 neutropenia, respectively

> One patient on each study experienced imetelstat-related G3 AST increase that recovered with dose reduction. HEC reviews found no significant imetelstat-related liver injury

CONCLUSIONS

Imetelstat-related cytopenias are on-target effects that are based on the selective reduction of malignant cells through telomerase inhibition. They are of short duration, reversible, and have limited clinical consequences when managed with the dose-modification guidelines in the protocols. Patients in these 2 studies had no evidence of imetelstat-related liver injury

SAFETY PROFILE OF IMETELSTAT

Table 1: Characteristics of Cytopenias

	MYF2001 9.4 mg/kg q 3 weeks (n=59)		MDS3001 Part 1 7.5 mg/kg q 4 weeks (n=38)	
	G3/4 Thrombo-cytopenia	G3/4 Neutropenia	G3/4 Thrombo-cytopenia	G3/4 Neutropenia
Median duration	2.0 weeks	1.3 weeks	1.1 weeks	1.7 weeks
Median time to onset	9.0 weeks (~ 3 cycles)	9.0 weeks (~3 cycles)	4.0 weeks (~1 cycle)	4.7 weeks (~1 cycle)
Reversible within 4 weeks	47/65 events 72.3%	47/56 events 83.9%	86/95 events 90.5%	68/79 events 87.3%
Cytopenias leading to treatment discontinuation	6/59 (10%)	3/59 (5%)	6/38 (15.8%)	1/38 (2.6%)
Median time to first dose reduction	21.4 weeks (Cycle 6.5)		10.8 weeks (Cycle 3)	

Importantly, clinical consequences of cytopenias including grade ≥3 hemorrhagic events or febrile neutropenia occurred in <11% of pts (Table 2).

Table 3: Non hematologic AE occurring in >20% of patients with either MF or MDS

	MYF2001 9.4 mg/kg q 3 weeks (n=59)	MDS3001 part 1 7.5 mg/kg q 4 weeks (n=38)
Nausea	20 (33.9%)	5 (13.2%)
Diarrhea	18 (30.5%)	7 (18.4%)
Abdominal pain	14 (23.7%)	3 (7.9%)
Fatigue	16 (27.1%)	6 (15.8%)
Asthenia	14 (23.7%)	6 (15.8%)
Pyrexia	13 (22.0%)	8 (21.1%)
Dyspnea	15 (25.4%)	4 (10.5%)
Back pain	7 (11.9%)	9 (23.7%)
Infusion related reactions	16 (27.1%)	5 (13.2%)

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PHASE II STUDY OF THE IDH2-INHIBITOR ENASIDENIB IN PATIENTS WITH HIGH-RISK IDH2-MUTATED MYELODYSPLASTIC SYNDROMES (MDS)

EPICS

VENUGOPAL, ET AL. 2021, EHA #S167

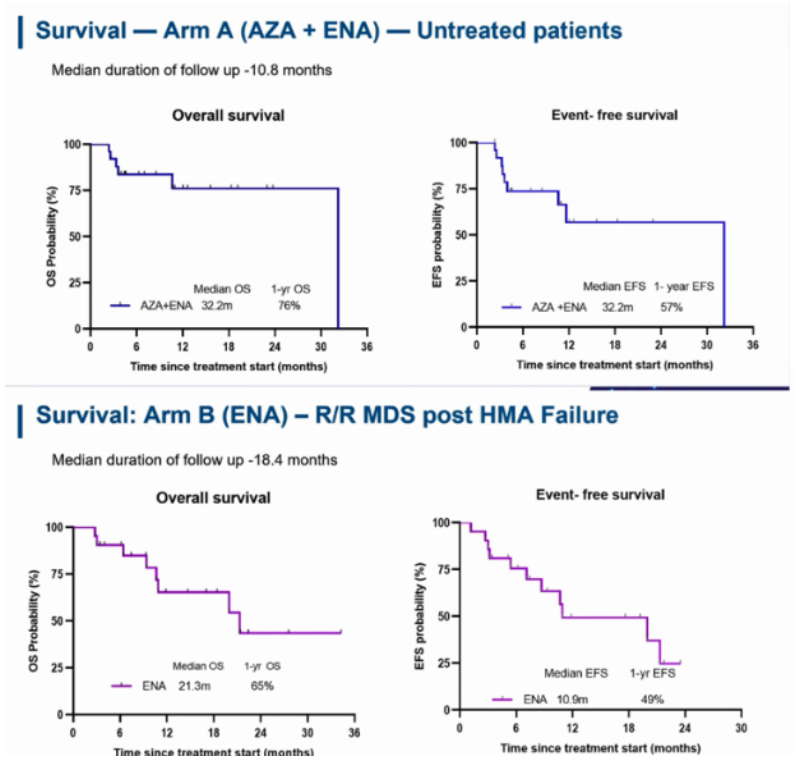
STUDY DESIGN

> Patients with *IDH2*-mutated higher-risk MDS randomized to azacitidine (AZA) + enasidenib (ENA; Arm A, n = 25) or ENA monotherapy (Arm B; n = 21). Median age Arm A and Arm B: 73 years

OUTCOME

	Response Evaluable (N = 46)	Arm A (Untreated) AZA + ENA (N = 25)	Arm B (HMA-failure) ENA (N = 21)
Overall response rate (ORR), n (%)	**30 (68)**	**21 (84)**	**9 (43)**
Complete remission (CR)	11 (24)	6 (24)	5 (24)
Partial remission (PR)	3 (7)	2 (8)	1 (5)
Marrow CR (mCR)	12 (26)	11 (44)	1 (5)
Hematological improvement (HI) only	4 (9)	2 (8)	2 (10)
No response (NR), n (%)	**16 (35)**	**4 (16)**	**12 (57)**
Stable disease (SD)	14 (30)	4 (16)	10 (48)
Progressive disease (PD)	2 (4)	0 (0)	2 (10)

SURVIVAL



EXPERT CONCLUSIONS

> The preliminary data are very interesting and the value of ORR in patients with HMA failure (43%) is considered very high
> The 21.3-month median OS in R/R patients treated with ENA after HMA failure is very good for these patients, who are known to have very poor survival of ~4–5 months

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LOWER RESIDUAL MUTATION LOAD FOLLOWING TREATMENT WITH PEVONEDISTAT+AZACITIDINE VERSUS AZACITIDINE ALONE: COMPARATIVE ANALYSIS OF STUDY ARMS IN P-2001, A RANDOMIZED PHASE 2 TRIAL

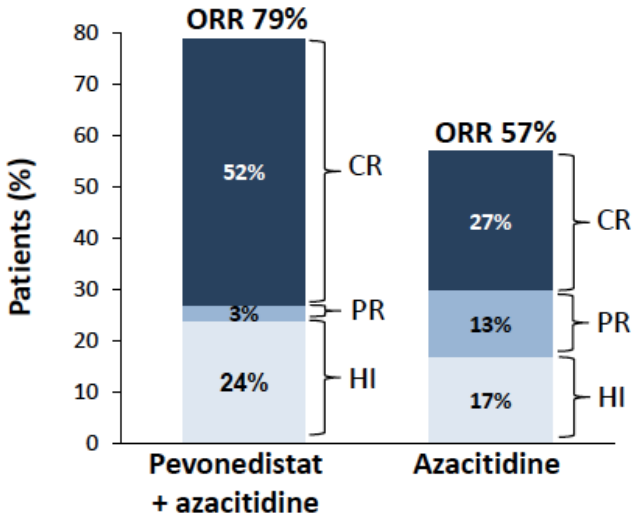
FRIEDLANDER, ET AL. 2021, EHA #S166

EPICS

STUDY POPULATION

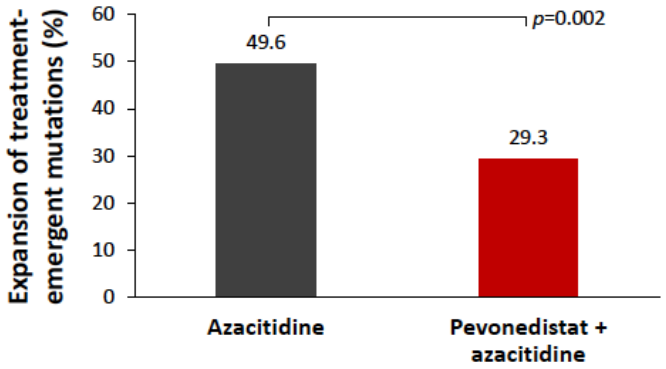
> Patients with higher-risk MDS or higher-risk CMML or low-blast AML who had no previous HMAs and were ineligible for allogeneic SCT; randomized to pevonedistat + AZA or AZA monotherapy

OUTCOME



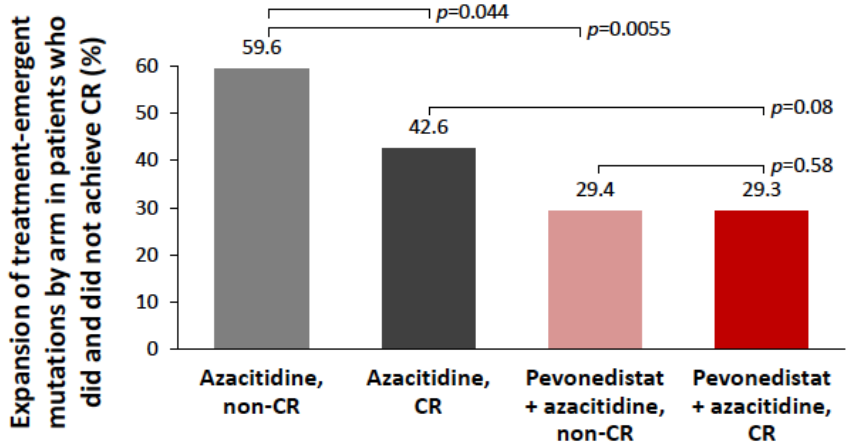
CLONAL EXPANSION OF TREATMENT-ENERGENT MUTATIONS

Pevonedistat + azacitidine was associated with significantly less expansion of treatment-emergent mutations than azacitidine alone[a]



	Azacitidine	Pevonedistat + azacitidine
Expanding, n	63	27
Non-expanding, n (data not shown)	64	65
P=0.002	0.496	0.293

Pevonedistat controlled clonal expansion in patients who did and did not achieve CR, mCR or CRi



Trend p-value=0.0008

EXPERT CONCLUSIONS

> Although the number of patients is small, the data from this subanalysis of P-2001 trial are considered very promising
> The ORR values in patients treated with pevonedistat + AZA are higher than those reported in previous studies
> It is very interesting to see that patients who did not achieve CR had a lower number of emergent mutations if treated with pevonedistat + AZA

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UPDATED SAFETY AND EFFICACY OF VENETOCLAX IN COMBINATION WITH AZACITIDINE FOR THE TREATMENT OF PATIENTS WITH TREATMENT-NAÏVE HIGHER-RISK MYELODYSPLASTIC SYNDROMES: PHASE 1B RESULTS

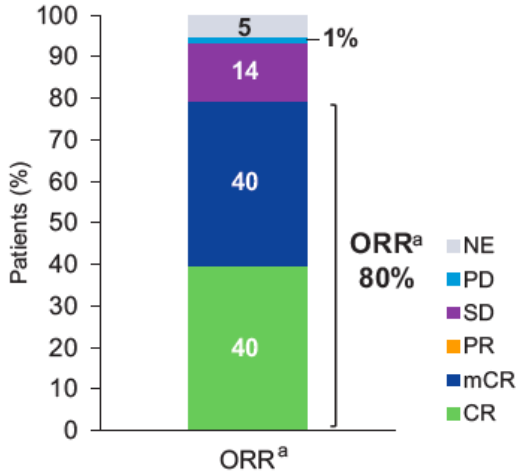
WEI, ET AL. 2021, EHA #EP917

EPICS

STUDY POPULATION

> Patients (≥18 years) with International Prognostic Scoring System intermediate-2 or high-risk MDS, bone marrow blasts <20% at baseline, and ECOG ≤2. Median age: 70 years

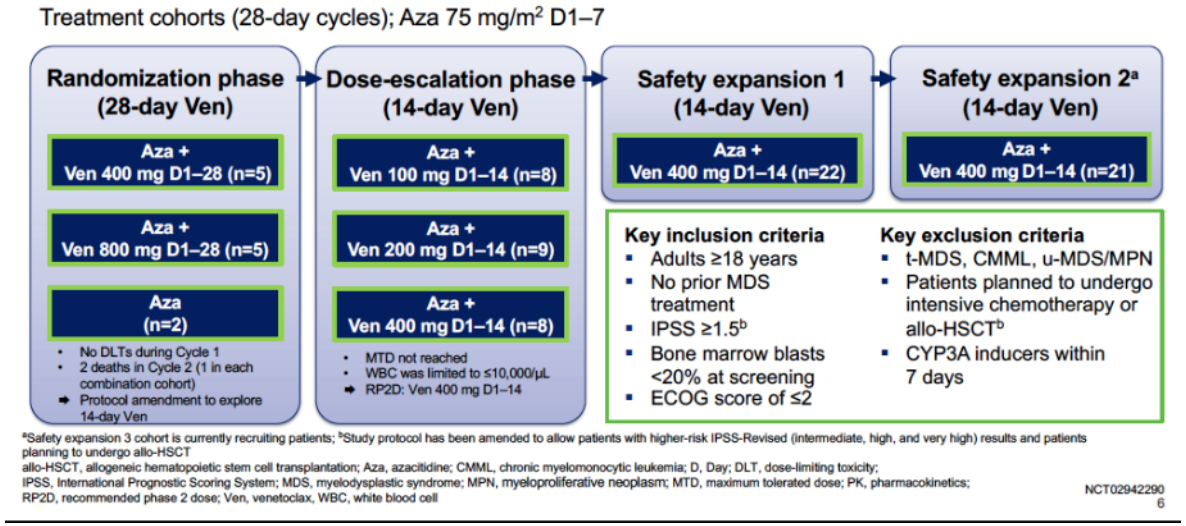
OUTCOME



OS, median (95% CI), months	
— CR	28.6 (27.5, NR)
— mCR	17.7 (11.3, NR)
— Other	9.3 (1.7, 21.2)

	n (% of N = 78)
Overall Response Rate[a]	62 (80%)
CR	31 (40%)
mCR	31 (40%)
mCR + hematologic improvement[b] n/N (%)	13/31 (42%)
Transfusion Independence Rate[c] n/N (%)	20/43 (46.5%)
[95% CI]	[31.2, 62.3]
	Months [95% CI]
Median time on study	23 [16.9, 24.5]
Overall Survival, median	28.2 [17.7, NE]
Overall Survival for CR, median[d]	28.6 [27.5, NE]
Duration of Response for CR, median	13.8 [8.9, NE]
Median time to CR, months (range)	2.6 (1.2–19.6)
Median time to mCR, months (range)	0.9 (0.7–4.6)

STUDY DESIGN



EXPERT CONCLUSIONS

The combination of venetoclax (VEN) + AZA was associated with rapid and durable responses in patients with disease mutation with poor prognosis (eg, *p53*, *ASXL1*, and *U2AF1*), and promising efficacy including remission rates and OS. The safety profile of this combination therapy is acceptable for patients with higher-risk MDS

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Discussion Summary

UPDATES ON MDS

ACHIEVING RBC TI IN PATIENTS WITH LOW-RISK MDS

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Effective reduction in RBC transfusions and number of hospital visits by continuing luspatercept treatment

The effects of luspatercept on lowering RBC transfusion numbers in low-risk MDS patients, including the late-responding patients treated after week 24, are considered very positive by the experts

- Many patients with low-risk MDS are expected to benefit from luspatercept treatment in the future
- Because of its recent approval, some experts are not yet certain how to best use luspatercept in their clinical practice. The majority will very likely use it in patients relapsing after ESA treatment and possibly in combination with lenalidomide or other ESAs, with the aim of increasing and prolonging responses
- At MD Anderson Cancer Center, patients with low-risk MDS are treated with low-dose HMA; it would be of interest to see whether early intervention with combination HMA + luspatercept prevents the transition from low- to high-risk MDS
  - One expert would not treat their indolent low-risk MDS patients unless they manifest disease progression; when an agent able to delay disease progression becomes available, the expert will definitely treat their patients with it
- It was discussed how long clinicians should wait to see a response from luspatercept before concluding that the therapy is not beneficial
  - The clinical approach of one expert is to wait at least 5 months before declaring therapy failure. In some circumstances, this expert may decide to increase the dose of luspatercept and wait a few more months before finally concluding that there is no response
- For some experts, the cost of luspatercept is still high and the agent may not yet be available in daily clinical practice

Clinical efficacy of imetelstat in low-risk MDS patients carrying different mutations

Imetelstat is able to modify MDS disease by decreasing the mutational burden. Recent subanalysis of a previous clinical trial showed that patients carrying 0–3 mutations continued to respond to imetelstat. Patients with >3 mutations had shorter response

- The experts consider the results of this subanalysis very promising despite the small number of analyzed patients.
- It will be important to see the OS data from a longer follow-up of this subanalysis to confirm the benefits of imetelstat
- The myelosuppressive effect of imetelstat showed in this safety analysis can be interpreted as evidence of disease modification

MOVING FROM MONOTHERAPY HMA TO COMBINATION THERAPY FOR PATIENTS WITH HIGH-RISK MDS

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Addition of ENA to HMA for patients with high-risk, *IDH2*-mutated MDS

- The phase II study's preliminary data showing 43% ORR in patients with HMA failure are perceived as very positive and promising for the future
- The 21.3-month median OS in R/R patients treated with ENA after HMA failure is seen as highly positive, as these patients are known to have very poor survival of about 4–5 months
- Both ENA and VEN have shown efficacy on MDS with *IDH2* mutation. The experts may consider treating their patients with one of the agents first, and with the other at disease relapse. However, there was no clarity on which would be used first

Adding pevonedistat (PEVO) to AZA resulted in lower clonal expansion both in patients who achieved and patients who did not achieve CR

- Treatment with PEVO + AZA resulted in significantly less expansion of treatment-emergent mutations in patients with high-risk MDS
- Even patients who did not reach CR showed lower clonal expansion rates when treated with PEVO + AZA vs AZA alone
- The preliminary results on the benefits of PEVO + AZA are considered very promising, as this combination therapy may greatly increase the survival of high-risk MDS patients with disease relapse after ESA treatment
- Additional data are needed to understand whether there is benefit and which specific subgroup of patients experience the most benefit from PEVO + AZA combination

A FUTURE FOR CHEMO-FREE REGIMEN AS BRIDGE TO TRANSPLANT FOR PATIENTS WITH HIGH-RISK MDS?

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VEN in combination with AZA demonstrated very good efficacy in newly diagnosed high-risk MDS patients even when they harbored poor-prognostic mutations

VEN added to AZA resulted in 80% ORR of newly diagnosed high-risk MDS patients (updated results from a phase Ib study)

- Although the patients recruited in the study were not eligible for transplant, after treatment with VEN + AZA, about a quarter of them underwent transplant, proving the efficacy of this treatment
- The experts agreed that VEN + AZA represents a less toxic treatment that can be used as bridge to transplant for patients who have >10% blasts. For the future, the experts hope to use a chemo-free treatment for these patients before they undergo transplant, and VEN is considered a very promising agent that could be used instead of chemotherapy, as it is expected to decrease the number of blasts faster than AZA alone and with less myelotoxicity
- Importantly, VEN + AZA was effective also in patients with *p53*-mutated MDS, who are considered poor responders. However, the experts clarified that not all *p53* mutations are the same and some clones may respond to VEN + AZA better than others
- VEN is expected to be a game-changer in the treatment of MDS, and the experts look forward to additional data on the benefits of this treatment

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CONGRESS HIGHLIGHTS

NEWLY DIAGNOSED AML PATIENTS

MEASURABLE RESIDUAL DISEASE RESPONSE IN ACUTE MYELOID LEUKEMIA TREATED WITH VENETOCLAX AND AZACITIDINE

PRATZ, ET AL. 2021, EHA #S137

EPICS

STUDY POPULATION

> Patients ≥18 years and unfit for intensive chemotherapy from the VIALE-A study to evaluate the prognostic impact of MRD <10^{-3} on outcomes

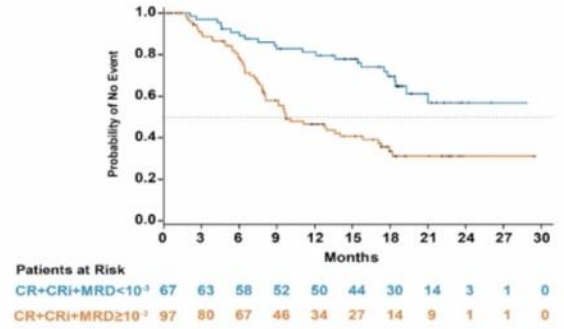
OUTCOME

In patients with AML who achieved CRc with lower-intensity VEN + AZA

> MRD <10^{-3} response resulted in longer DOR, EFS, and OS than patients who had MRD ≥10^{-3}
> MRD response was a significant predictor of OS
  - OS benefit was similar in patients who achieved an MRD response at any time on treatment
  - Median OS in patients without an MRD response was 18.7 months, longer than median OS for the overall population

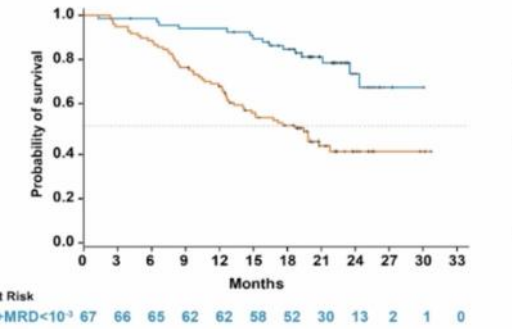
RESPONSE

Duration of remission



Duration of remission	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median D months (95
CR+CRi+MRD<10⁻³	22	81.2 (69.3, 88.9)	69.6 (55.9, 79.8)	NR (19.3 –
CR+CRi+MRD≥10⁻³	54	46.6 (35.6, 56.8)	33.5 (22.9, 44.5)	9.7 (8.0 – 1

Overall survival



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)

EXPERT CONCLUSIONS

MRD response in patients treated with VEN and AZA is valuable and warrants further investigation to establish its role in clinical management

APTITUDE HEALTH®

SEQUENTIAL NCRI AML TRIALS SHOW CONSISTENT BENEFIT FOR RIC TRANSPLANT IN CR1 FOR OLDER PATIENTS >60YEARS THAT IS INDEPENDENT OF MRD STATUS AFTER FIRST INDUCTION

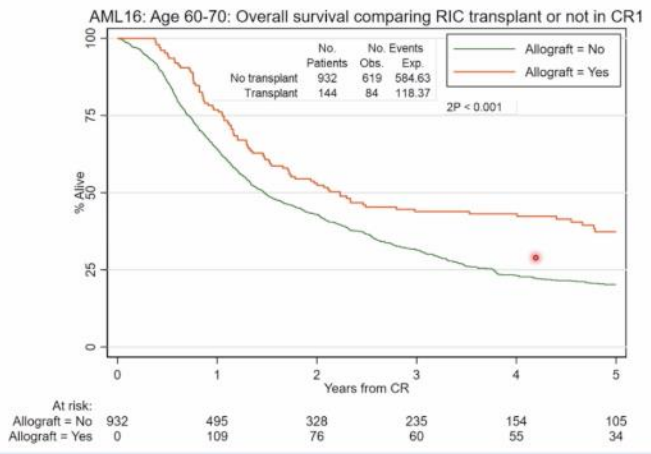
RUSSELL, ET AL. 2021, EHA #S130

STUDY POPULATION

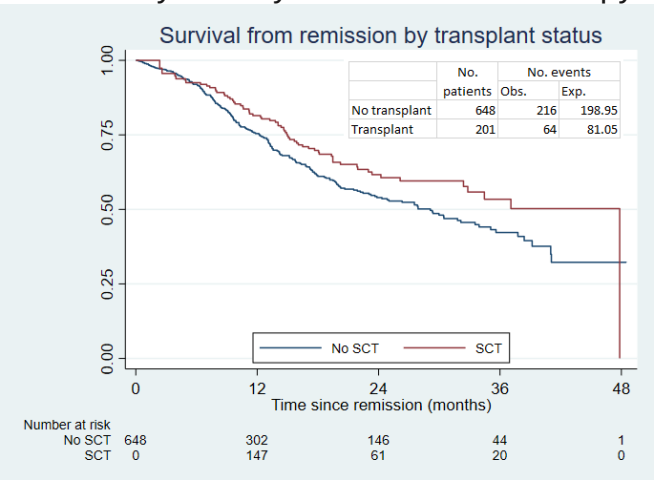
- In AML16, 932 patients in CR1 aged 60–70 (inclusive; median 65 years) were studied, with reduced-intensity conditioning (RIC) transplant given to 144 (15%); median follow-up for survival from CR = 60 months
- In AML18, 648 patients in CR1 aged 60–74 (median 65 years) were studied, with RIC transplant given to 201 (31%); median follow-up of survival from CR = 45 months

OUTCOME

AML16. Overall Survival from CR1
Mantel-Byar analysis RIC v Chemotherapy



AML18: Overall Survival from CR1
Mantel-Byar analysis RIC v Chemotherapy



EXPERT CONCLUSIONS

- Two consecutive trials in >1500 older AML patients >60 years demonstrated consistent benefit for RIC transplant in first remission
- This benefit is independent of their post-course 1 MRD status
- For post-course 1 MRD-positive patients, the benefit of transplant appeared greater in those who converted to MRD-negative remission post-course 2, although benefit for those remaining MRD-positive patients cannot be excluded
- The overall improvement in outcome in MRD-positive patients seen in AML18 compared with AML16 may reflect the increased uptake of RIC transplant and the use of post-remission treatment intensification

SURVIVAL OUTCOMES FROM THE QUAZAR AML-001 TRIAL WITH ORAL AZA FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA IN REMISSION BY DISEASE SUBTYPE, CYTOGENETIC RISK, AND NPM1 MUTATION STATUS AT DIAGNOSIS

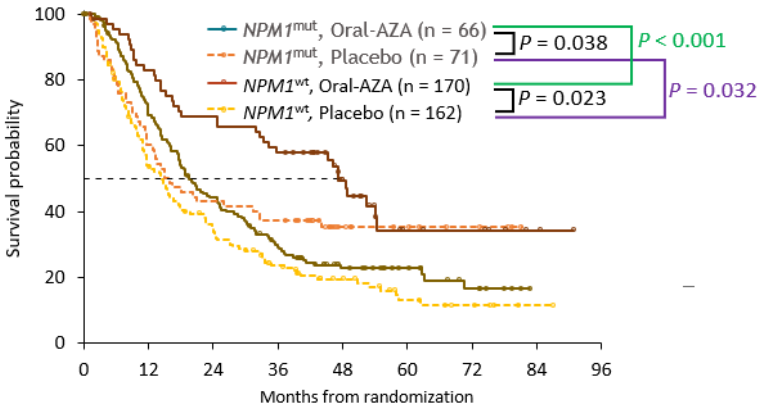
DÖHNER, ET AL. 2021, EHA #S131

STUDY POPULATION

- Patients age ≥55 years, with de novo or secondary AML, ECOG PS ≤3, intermediate- or poor-risk cytogenetics, and not candidates for HSCT
- Patients had attained first CR/CRi after induction ± consolidation ≤4 months before randomization
- Overall, 137 patients had *NPM1* mutation, and 66 patients had *FLT3*-ITD and/or *FLT3*-TKD mutations at AML diagnosis

OUTCOME

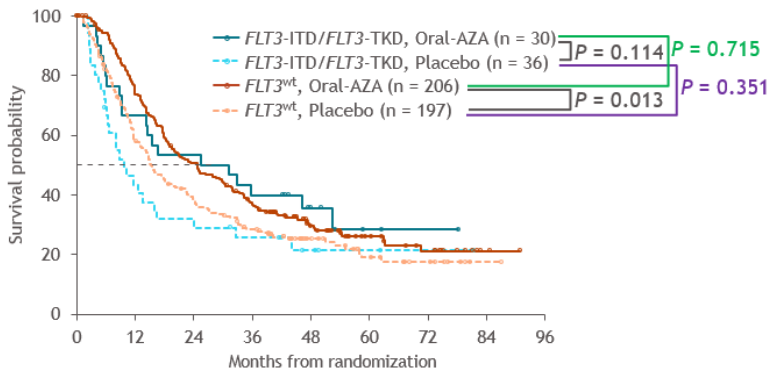
OS by *NPM1* mutation status at diagnosis



Median OS, months

NPM1^{mut}, Oral-AZA	47.2	*NPM1*^{wt}, Oral-AZA	19.6
NPM1^{mut}, Placebo	15.9	*NPM1*^{wt}, Placebo	14.6

OS by *FLT3* status at diagnosis



Median OS, months

FLT3-ITD/TKD, Oral-AZA	28.2	*FLT3*^{wt}, Oral-AZA	24.7
FLT3-ITD/TKD, Placebo	9.7	*FLT3*^{wt}, Placebo	15.2

CONCLUSIONS

- *NPM1* mutational status at AML diagnosis was prognostic, and predictive of a survival benefit for patients in remission treated with oral AZA
  - Median OS in patients with *NPM1*-mutated AML treated with oral AZA was 47.2 mo vs 15.9 mo in the placebo arm
- *FLT3*-ITD/TKD mutations at diagnosis appeared to have a negative prognostic influence in the placebo arm
- Treatment benefit with oral AZA vs placebo was observed in patients in remission with *FLT3*-ITD/TKD mutations
- Multivariate analyses confirmed the independent prognostic influence of *NPM1* and *FLT3* mutations, and oral AZA showed improvement in OS independent of these mutations

PRELIMINARY RESULTS OF V-FAST, A PHASE 1B MASTER TRIAL TO INVESTIGATE CPX-351 COMBINED WITH TARGETED AGENTS IN NEWLY DIAGNOSED AML

EPICS

PULLARKAT, ET AL. 2021, EHA #EP442

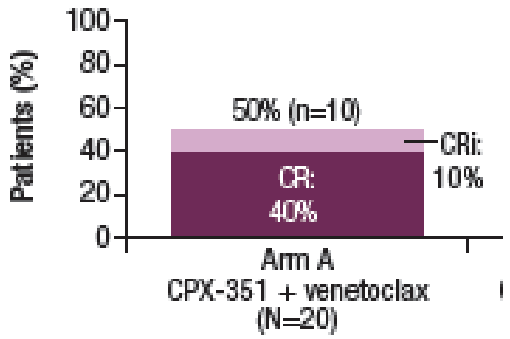
STUDY POPULATION

> Patients aged 18–75 years, newly diagnosed AML, ability to tolerate intensive chemotherapy; ECOG 0–2

OUTCOME

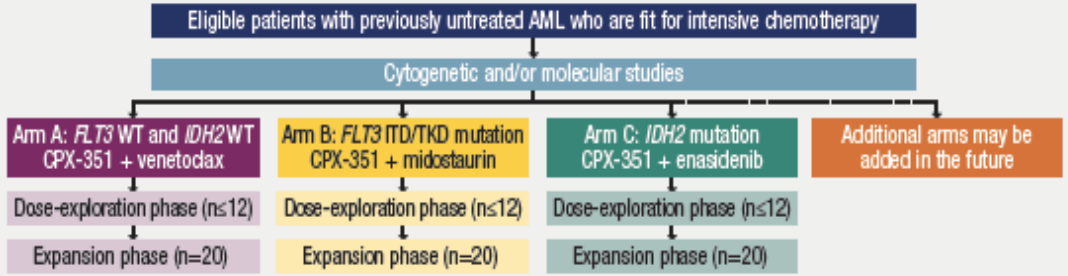
> In Arm A (CPX-351 + VEN) the recommended phase II dose was determined to be dose level 1
> One of 6 patients in the dose-exploration phase experienced DLTs of grade 4 neutropenia and thrombocytopenia that extended beyond day 49; no dose adjustments were required

Figure 3. Remission rates.



STUDY DESIGN

V-FAST study design.



EXPERT CONCLUSIONS

Preliminary data of CR in high-risk patients treated with CPX-351 + VEN are considered very positive

APTITUDE HEALTH®

PROGNOSTIC IMPACT OF MINIMAL RESIDUAL DISEASE ASSESSMENT IN ELDERLY PATIENTS WITH SECONDARY ACUTE MYELOID LEUKEMIA. A COMPARISON BETWEEN CPX-351 AND INTENSIFIED FLUDARABINE-BASED REGIMENS

GUOLO, ET AL. 2021, EHA #EP459

EPICS

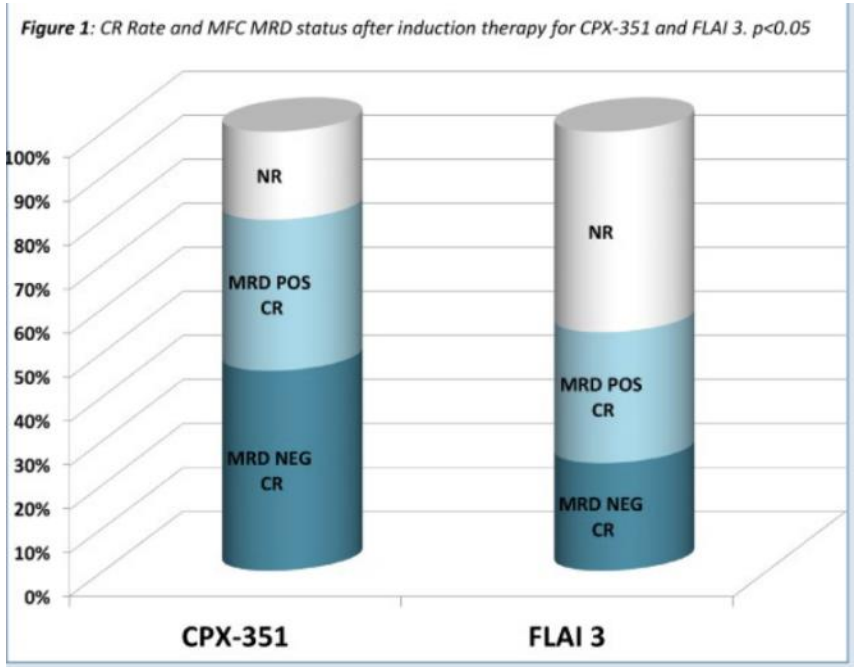
STUDY POPULATION

- 136 elderly patients (>60 years; median 67 years), treatment-naive s-AML or t-AML
- CPX-351: 35 patients
- Fludarabine–high-dose ara-C ± gemtuzumab ozogamicin (FLAI 3): 72 patients

CONCLUSIONS

- MRD showed significant prognostic value in terms of OS in all treatment groups

CR RATE AND MRD STATUS AFTER INDUCTION THERAPY



Multiflow cytometry MRD-negativity rate of 16/28 (57%) and 25/55 (45%) in CR patients who received CPX-351 or FLAI, respectively (*P* <.05)

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EPICS

Discussion Summary

NEWLY DIAGNOSED AML PATIENTS

MRD IS CONSIDERED A PROGNOSTIC FACTOR IN AML AND FUTURE CLINICAL TRIALS MAY HAVE MRD NEGATIVITY AS STUDY ENDPOINT

EPICS

AML patients achieving MRD negativity have a better prognosis

According to the experts, the data presented at EHA 2021 confirm the prognostic value of MRD

- Both early and late responders treated with VEN + AZA in the VIALE-A study showed increased OS, DOR, and EFS when their MRD levels were $<10^{-3}$
- The percentage of elderly patients with secondary AML achieving MRD negativity was higher when treated with CPX-351 compared with those treated with FLAI 3 (57% vs 47%). This resulted in longer OS for CPX-351–treated patients
- Clinical trials have shown that patients who are MRD negative before transplant have better outcomes

- The experts speculated that future clinical studies will likely adopt MRD negativity as a primary study endpoint, although it will be necessary to first obtain approval from regulatory authorities
- Some experts believe that in the future, patients with low-risk AML who achieve MRD negativity may avoid transplant. However, more data are needed to conclude that this is a sound clinical approach
- Importantly, achievement of MRD negativity does not overcome the poor-prognostic factor of high-risk AML

MAINTENANCE THERAPY IS NOT THE STANDARD OF CARE IN AML

EPICS

Maintenance therapy can be used in patients with targetable mutations (eg, *FLT3*), but is not the current standard in AML treatment

Although the QUAZAR study showed the benefits of maintenance therapy with oral AZA in patients who underwent induction and short consolidation, the experts agreed that maintenance therapy is not the current standard in AML

- Some experts noted that patients in the QUAZAR study were not eligible for transplant and could not be cured. Therefore, the treatment with oral AZA cannot be considered a maintenance therapy, but rather an alternative treatment for patients not eligible for any other treatment option

FLT3 inhibitors are used by some experts as maintenance therapy for patients with *FLT3*-mutated AML

- It was noted that patients treated with FLT3 inhibitors may relapse due to emergence of new clones that are resistant to this targeted therapy. However, as not enough data are available, it is difficult to predict which patients will relapse and which will not
- There was consensus among the experts on not using HMA as maintenance therapy for AML patients who do not have targetable disease (eg, *FLT3* or *IDH* mutations). Their clinical experience has shown that HMAs are not well tolerated by patients and therefore are not good options to prolong treatment after transplant as maintenance therapy. Very often the patients are not able to continue the treatment, as confirmed by clinical trials that show very high dropout rates for these patients
  - Only 1 expert, from MD Anderson Cancer Center, reported the off-label use of HMA for maintenance treatment of their patients

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EPICS

CONGRESS HIGHLIGHTS

IDH1/2 AND *FLT3* MUTATIONS IN NEWLY DIAGNOSED AML PATIENTS

UPDATED PHARMACODYNAMIC AND SURVIVAL OUTCOMES FROM THE AG221-AML-005 TRIAL OF ENASIDENIB (ENA) PLUS AZACITIDINE (AZA) IN PATIENTS WITH MUTANT IDH2 NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA (ND-AML)

DINARDO, ET AL. 2021, EHA #EP465

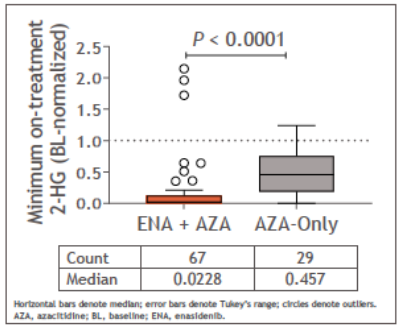
EPICS

STUDY POPULATION

> Patients ≥18 years with *IDH2*-mutant AML and ineligible for intensive chemotherapy, randomized to EMA + AZA vs AZA only

MAXIMUM REDUCTIONS FROM BASELINE IN 2-HG AND *IDH2* VAF

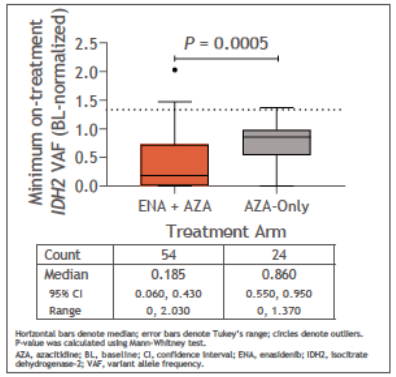
Figure 3. Maximum reductions from baseline in 2-HG concentrations on-study



	ENA + AZA	AZA-Only
Count	67	29
Median	0.0228	0.457

Horizontal bars denote median; error bars denote Tukey's range; circles denote outliers.
AZA, azacitidine; BL, baseline; ENA, enasidenib.

Figure 5. Maximum reductions from baseline in *IDH2* variant allele frequency on-study

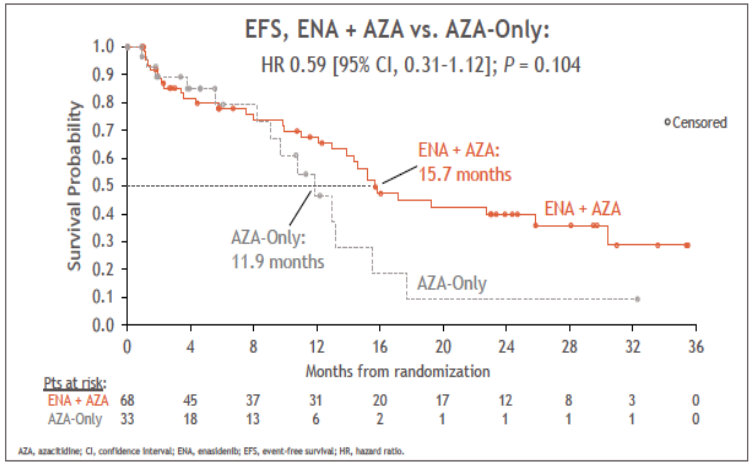


	ENA + AZA	AZA-Only
Count	54	24
Median	0.185	0.860
95% CI	0.060, 0.430	0.550, 0.950
Range	0, 2.030	0, 1.370

Horizontal bars denote median; error bars denote Tukey's range; circles denote outliers.
P-value was calculated using Mann-Whitney test.
AZA, azacitidine; BL, baseline; CI, confidence interval; ENA, enasidenib; IDH2, isocitrate dehydrogenase-2; VAF, variant allele frequency.

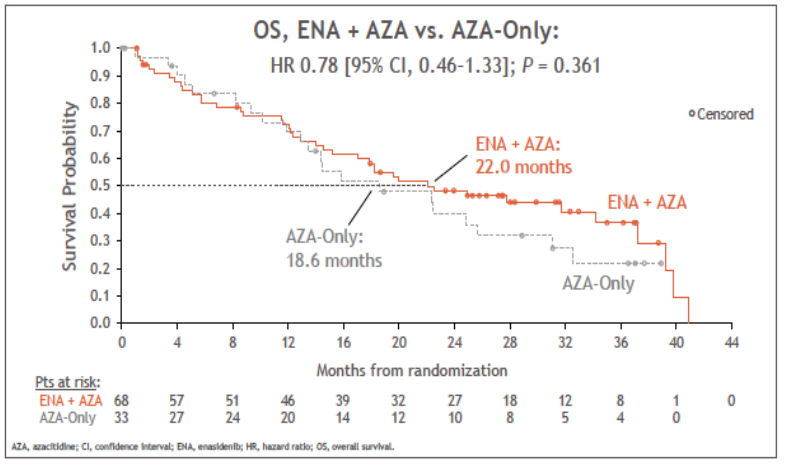
EFS AND OS

Figure 7. Event-free survival (Aug 2020 cutoff)



AZA, azacitidine; CI, confidence interval; ENA, enasidenib; EFS, event-free survival; HR, hazard ratio.

Figure 8. Overall survival (Aug 2020 cutoff)



AZA, azacitidine; CI, confidence interval; ENA, enasidenib; HR, hazard ratio; OS, overall survival.

EXPERT CONCLUSIONS

> OS is promising
> ENA + AZA reduced 2-hydroxyglutarate (2-HG) and *IDH2* variant allele frequency (VAF) more than AZA alone
> Changes in *IDH2* VAF were greater in responding patients
> Half of all patients are alive at 2 years

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EFFICACY AND SAFETY OF ENASIDENIB AND AZACITIDINE COMBINATION IN PATIENTS WITH IDH2 MUTATED ACUTE MYELOID LEUKEMIA NOT ELIGIBLE FOR INTENSIVE CHEMOTHERAPY

EPICS

VENUGOPAL, ET AL. 2021, EHA #EP471

STUDY POPULATION AND TREATMENT

- *IDH2*-mutant patients (newly diagnosed and R/R AML)
- Prior ENA and HMA therapy allowed
- Treatment: ENA 100 mg qd + AZA 75 mg/m^2 × 7 days ± VEN or FLT3 inhibitor therapy
- Endpoints: ORR, safety, and OS

OUTCOME

Seven *IDH2*-mutant R/R AML patients received ENA + AZA + VEN triplet therapy (no prior VEN)

- CR/CRi = 86% (33% MRD negative by flow)
- 6-month OS = 70%
- One patient to alloSCT
- Median follow-up 11.2 mo → mOS not reached

Table: 2 Response rates

	ND N= 7	R/R N=19
Overall response rate (ORR), n (%)	7 (100)	11 (58)
Complete remission (CR) MRD neg CR	5 (72) 5 (100)	5 (28) 2/5 (40)
CRi	2 (28)	6 (32)
Not evaluable	0	1 (5)
No response	0	7 (37)
Median number of cycles (range)	3 (1-8)	4 (1-17)
Time to best response, months (range)	1.6 (1.0-4.2)	1.8 (0.8-5.4)

SURVIVAL OUTCOME

Figure:1 Survival outcomes in pts with ND AML

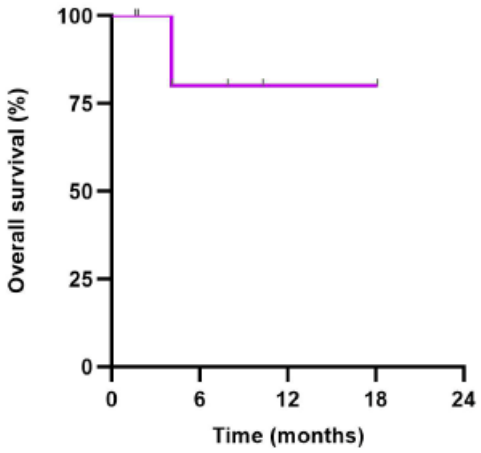
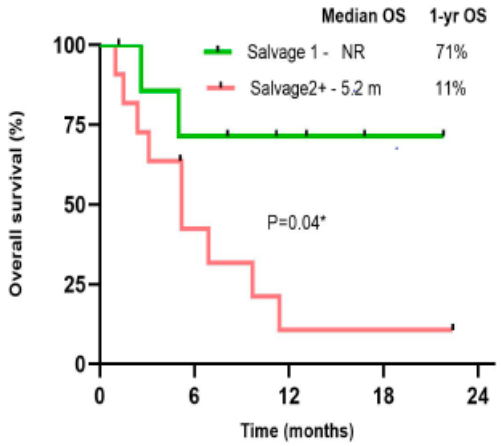


Figure:2 Survival outcomes in pts with first relapse vs ≥ 2 relapses



CONCLUSIONS

- ENA + AZA is an effective therapy for *IDH2*-mutant AML, with 100% CR/CRi in ND AML patients and 58% in RR AML
- Patients treated in first relapse had significantly superior OS than ≥2 relapses
- ENA + AZA + VEN may be an effective combination in RR AML even in patients with prior HMA or ENA therapy

APTITUDE HEALTH®

QUIZARTINIB WITH DECITABINE AND VENETOCLAX (TRIPLET) IS HIGHLY ACTIVE IN PATIENTS WITH FLT3-ITD MUTATED ACUTE MYELOID LEUKEMIA

EPICS

YILMAZ, ET AL. 2021, EHA #EP430

STUDY POPULATION

- Patients with newly diagnosed AML ineligible for intensive chemo and patients with R/R AML who received ≤5 prior treatments
- ECOG ≤2, QTcF <450 msec prior to therapy
- All patients underwent day 14 bone marrow, and VEN (400 mg/day) was put on hold in patients with bone marrow (BM) blasts ≤5% (or marrow aplasia). Patients with day 14 BM blasts >5% continued VEN for 21 days during cycle 1

Treatment

- Decitabine (DEC) 20 mg/m^2 IV × 10 days (cycle 2 onward × 5 days)
- Quizartinib (QUIZ) 30 or 40 mg qd
- VEN 400 mg qd

EXPERT CONCLUSIONS

Despite the small number of patients (only 4 in frontline setting), the triple combination of QUIZ + DEC + VEN was very active in newly diagnosed and heavily pretreated AML with *FLT3* mutations

OUTCOME

Response Rates*, N (%) / Outcomes	R/R (n=17)	Frontline (n=4)
CRc	12 (70)	4 (100)
CR	3 (18)	2 (50)
CRi	9 (52)	1 (25)
MRD		
Flow Cytometry (-)	5/12 (42)	3/4 (75)
FLT3 PCR (-)	5/10 (50)	4/4 (100)
Day 14 BM blasts ≤5%	8 (47)	4 (100)
30-day mortality	0 (0)	0 (0)
60-day mortality	1 (6)	0 (0)
Bridge to ASCT	6 (35)	2 (50)

*Response assessment by modified IWG criteria – Cheson et al. J Clin Oncol. 2003 Dec 15;21(24):4642-9

With a median follow-up of 7.2 months, the median OS was not reached in the frontline cohort and was 7.1 months in R/R cohort (figure 2).

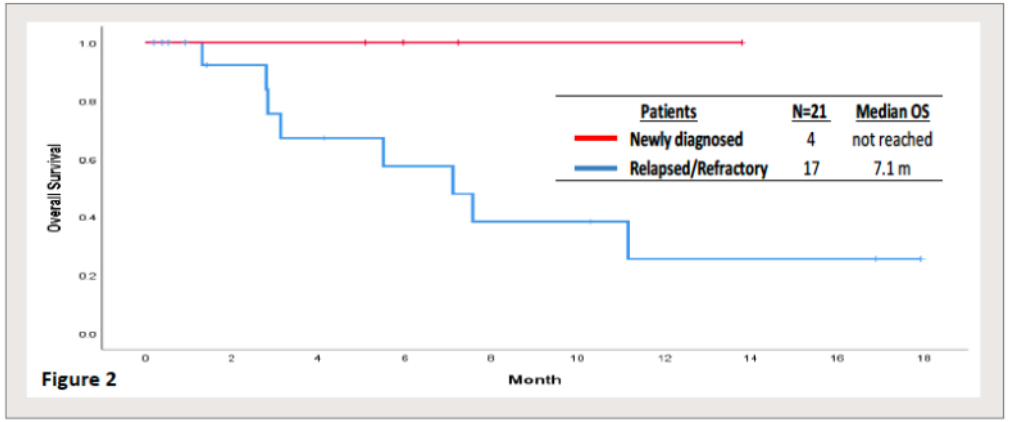


Figure 2

All frontline patients were alive at the last follow-up; 3 in CR and 1 relapsed disease on salvage therapy. Of 12 CRc pts in the R/R cohort, 7 are alive (5 CR, 2 relapse), and 5 died (4 from relapse, 1 death in CR from sepsis) (figure 3).

APTITUDE HEALTH®

A PHASE 1 STUDY OF GILTERITINIB IN COMBINATION WITH INDUCTION AND CONSOLIDATION CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED AML: FINAL RESULTS UPDATE

EPICS

PRATZ, ET AL. 2021, EHA #EP437

STUDY POPULATION

> 80 patients enrolled (median age 59 years); 44 patients had *FLT3*-mutant AML
> Median follow-up 35.8 months

OUTCOME

Efficacy

> CRc rate 89.5% (CR 71.1%, CRh 18.4%)
> 1-yr survival 85.9%
> 2-yr survival 72.3%
> 60-day mortality 0%
> Mutational clearance 84.6%

Safety

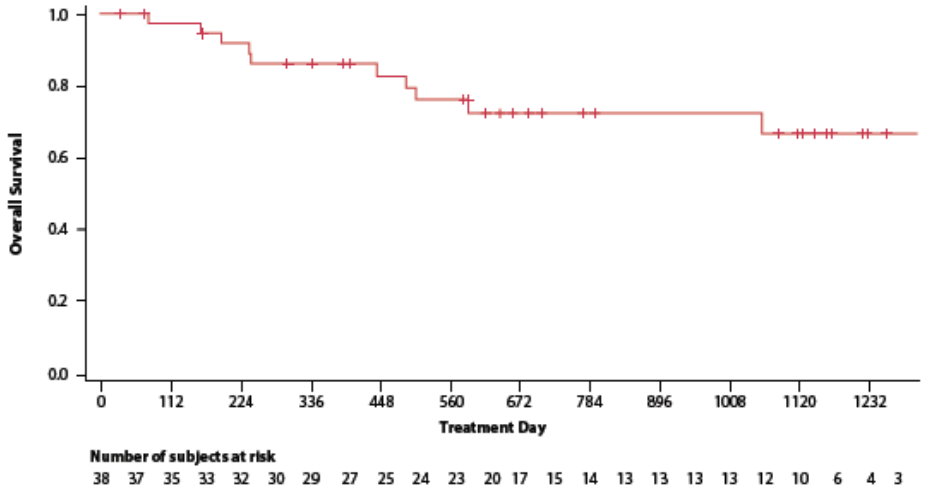
> Grade ≥3 AEs: ALT (13.9%), pneumonia (13.9%), sepsis (11%), bacteremia (11%)

EXPERT CONCLUSIONS

> Gilteritinib + intensive chemo was well tolerated
> Antileukemic activity seen in *FLT3*-mutant AML
> Anthracycline choice or gilteritinib schedule: no impact on efficacy
> High mutational clearance with gilteritinib 120 mg in patients who achieved CRc

OS AND *FLT3*-ITD CLEARANCE

Figure 2. Overall Survival Probability in Patients With *FLT3*$^{mut+}$ AML Who Received Gilteritinib 120 mg/day (N=38)



Abbreviations: AML, acute myeloid leukemia; *FLT3*$^{mut+}$, FMS-like tyrosine kinase 3 mutation–positive.

Table 5. *FLT3* ITD Clearance[a] by Ultra-Sensitive NGS Assay

Mutational clearance status	End of induction (n=12)	Beginning of consolidation (n=8)	Beginning of maintenance (n=13)
Cleared[b]	4 (33.3)	3 (37.5)	11 (84.6)
Not cleared[c]	8 (66.7)	5 (62.5)	2 (15.4)

APTITUDE HEALTH®

MIDOSTAURIN PLUS INTENSIVE CHEMOTHERAPY VERSUS INTENSIVE CHEMOTHERAPY IN FLT3 MUTATED ACUTE MYELOID LEUKEMIA. A RWE STUDY

EPICS

DE LA FUENTE, ET AL. 2021, EHA #EP447

STUDY POPULATION

- 385 previously untreated *FLT3*-mutant AML patients (PETHEMA AML registry); age ≥18 years
- Treatment: midostaurin + intensive chemotherapy (IC; n = 54) vs IC (n = 331)
- Patients who died within 7 days were excluded

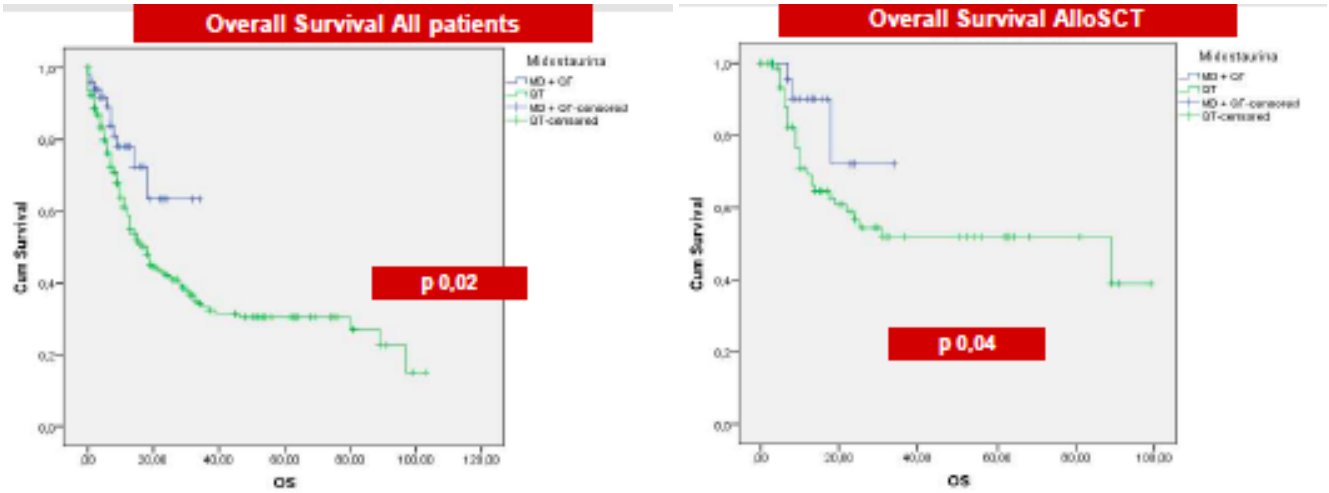
OUTCOME

1st Line in FLT3 Mutated AML

Midos Plus Intensive Chemo versus Intensive Chemo

Total 385 patient		
Total 385 p	Midos+IC (54)	IC (331)
CRR (CR after 1 or 2 Inductions)	86%	66%

OS



EXPERT CONCLUSIONS

- OS significantly longer in midostaurin + IC vs IC only (not reached vs 19 mo; *P* = .022)
- Survival at 24 months was longer in the midostaurin + IC arm: 79.2% vs IC only 54.2% (*P* = .026)
- A higher number of patients in the midostaurin + IC arm were consolidated in CR1 with alloSCT, with significantly longer OS

APTITUDE HEALTH®

EPICS

Discussion Summary

IDH1/2 AND *FLT3* MUTATIONS IN NEWLY DIAGNOSED AML PATIENTS

IDH INHIBITOR TREATMENT COMBINATIONS FOR AML WITH *IDH* MUTATIONS

EPICS

Patients with *IDH2*-mutated AML can be treated with IDH2 inhibitor ENA, with VEN, or with a combination of these 2 agents and with AZA as backbone

Different combination therapies can be used to treat patients with *IDH2*-mutated AML

- ENA + AZA decreased the level of IDH2 biomarkers in treated patients (AG221-AML-005 trial) and may improve their EFS and OS
- Clinical trials have demonstrated the efficacy of VEN + AZA in *IDH*-mutated AML patients
- The triple combination of ENA + AZA + VEN was used to treat patients with *IDH2*-mutated AML not eligible for intensive chemotherapy. This triplet was shown to be highly effective in both newly diagnosed and R/R patients who achieved MRD negativity

The experts discussed the most optimal use of these agents – should they be used in combinations or sequentially?

- One expert considers the 2 treatments equally effective and may make their choice on the basis of patient fitness. Patients with intermediate risk and able to tolerate possible myelosuppressive effects are treated with AZA + VEN. ENA is then used as maintenance therapy after 1 or 2 cycles of VEN + AZA, especially when patients are frail and elderly and not able/not willing to continue treatment with AZA that often requires hospital visits
- ENA + AZA is the preferred treatment for outpatients because of its convenient administration
- The triple combination ENA + AZA + VEN may be used for a greater response in patients who can tolerate this treatment

Treatment with IDH inhibitors induces a decrease in *IDH*-mutated clones; does the change in IDH clone levels provide information on patient prognosis?

- For some experts, when patients are elderly (eg, ≥80 years) and treated with IDH inhibitors, there is no requirement to routinely test them for IDH clones if they are responding to therapy. Knowing the level of IDH clones in responding patients will not translate into a change of treatment; therefore, retesting is considered unnecessary
- The experts prefer not to treat patients who become transfusion independent and have acceptable quality of life when treated with IDH inhibitors, unless they develop disease relapse

FLT3 INHIBITORS FOR FRONTLINE TREATMENT OF AML WITH *FLT3* MUTATIONS

EPICS

Efficacy of FLT3 inhibitors in frontline and use of transplant

- Gilteritinib in combination with induction and consolidation chemotherapy demonstrated high mutational clearance of *FLT3* mutations in patients who achieved CRc (phase I study)
- Although the presented results of gilteritinib in frontline are considered very promising, the experts will continue to send their *FLT3*-mutated AML patients to transplant
  - The number of patients recruited in the phase I trial is still very low and more-robust data are needed before concluding that the frontline treatment with gilteritinib + chemotherapy will allow patients to avoid transplant
  - One expert sends their patients to transplant when they have *FLT3*-ITD, low-level *NPM1*-mutated AML. The choice of transplanting these patients with low allelic ratio is guided by the expert's clinical experience with patients relapsing if not receiving transplant, and by the evidence that treatment with FLT3 inhibitors followed by transplant is very effective and can prevent disease relapse
  - The majority of experts agreed on sending to transplant patients with low-VAF *NPM1*-mutated AML, who are treated with chemotherapy (eg, 7+3 or FLAG-idarubicin) in combination with FLT3 inhibitors and achieve MRD negativity. The presented preliminary data are considered not sufficient to preclude curative therapy as transplant if it can be delivered safely and effectively

- The triple combination of FLT3 inhibitor QUIZ with VEN and decitabine was shown to be very effective for *FLT3*-mutated AML patients
  - The results are considered very positive, although patients who suffer QT prolongation may not tolerate this treatment well
  - The promising combination of VEN + FLT3 inhibitors led the experts to speculate on a possible chemotherapy-free treatment for *FLT3*-mutated AML patients who may not tolerate intensive chemotherapy

APTITUDE HEALTH®

EPICS

CONGRESS HIGHLIGHTS

FLT3 MUTATIONS IN RELAPSED/REFRACTORY AML PATIENTS

EFFICACY AND SAFETY OF VENETOCLAX IN COMBINATION WITH GILTERITINIB FOR RELAPSED/REFRACTORY FLT3-MUTATED ACUTE MYELOID LEUKEMIA: UPDATED ANALYSES OF A PHASE 1B STUDY

EPICS

ALTMAN, ET AL. 2021, EHA #S135

STUDY POPULATION

- R/R AML; wild-type or *FLT3* mutated (dose escalation) and *FLT3* mutated (dose expansion); ≥1 prior line of therapy
- WBC count ≤25 × 10^9/L at start of study drug
- ECOG PS 0–2

OUTCOME

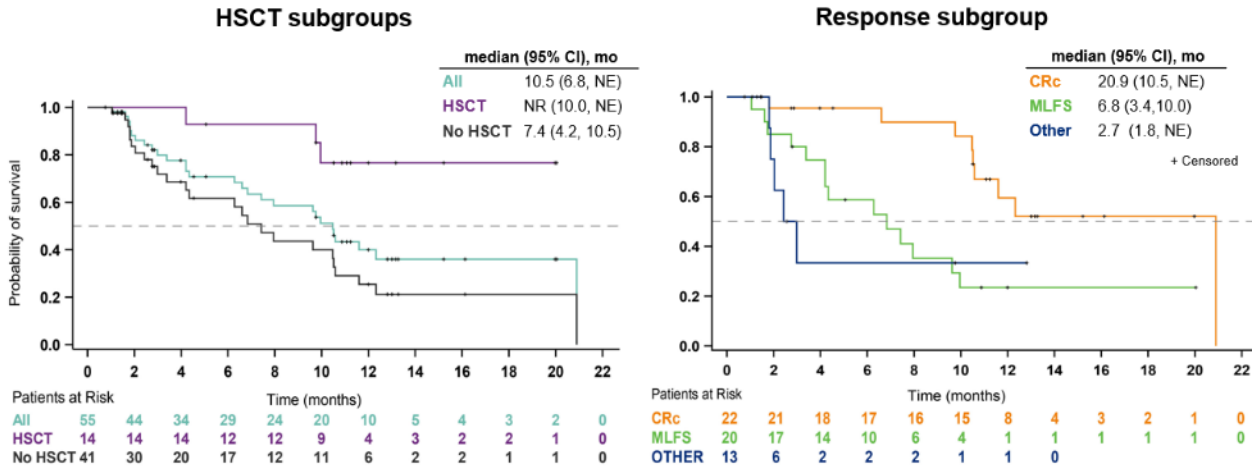
EFFICACY

	FLT3+ Patients with Prior TKI (N=35)	All FLT3+ Patients (N=55[a])
mCRc, n (%)	28 (80.0)	42 (76.4)
CR+CRp+CRi	12 (34.3)	22 (40.0)
MLFS	16 (45.7)	20 (36.4)
Time to mCRc (months), median (range)	0.9 (0.7, 4.2)	0.9 (0.7, 4.6)

SAFETY

n (%)	Ven N=56	Gilt N=56
Any AE leading to discontinuation[b]	7 (12.5)	6 (10.7)
Any AE leading to dose reduction[c]	4 (7.1)	4 (7.1)
Any AE leading to dose interruption	30 (53.6)	28 (50.0)

OS IN ALL *FLT3*-MUTATED PATIENTS



Median (range) duration of follow-up: 12 months (0.8–20.9)

CONCLUSIONS

- These updated analyses show that VEN + gilteritinib achieved high rates of mCRc in patients with heavily pretreated and prior TKI-exposed R/R *FLT3*-mutated AML, with encouraging molecular clearance rates
- Cytopenias were prominent but manageable

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FOLLOW-UP OF PATIENTS WITH FLT3-MUTATED RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA IN THE PHASE 3 ADMIRAL TRIAL

EPICS

PERL, ET AL. 2021, EHA #EP438

STUDY POPULATION AND AIM OF THE STUDY

> Patients with *FLT3*-mutated R/R AML from the ADMIRAL trial

Aim

> Follow-up of ADMIRAL to assess long-term survivors, HSCT outcomes, and gilteritinib safety beyond 1 year

CONCLUSIONS

> Patients with R/R *FLT3*-mutated AML continue to benefit from long-term therapy with gilteritinib years after randomization, with a high proportion of them living without relapse for ≥2 years after receiving HSCT followed by gilteritinib maintenance therapy
> Among all patients who underwent HSCT during the trial, pre-HSCT remission rates and post-HSCT survival were similar across arms
> Post-HSCT gilteritinib maintenance therapy may relate to the low relapse rate in the gilteritinib arm
> The safety profile of gilteritinib was stable at 2 years, with no new or significant safety signals

OS OUTCOMES

Figure 2. Overall Survival in R/R FLT3mut+ AML Patients (ITT Population; N=371)

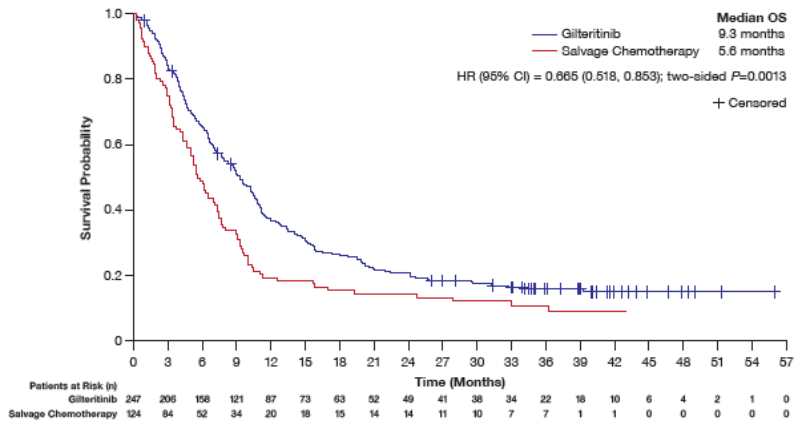
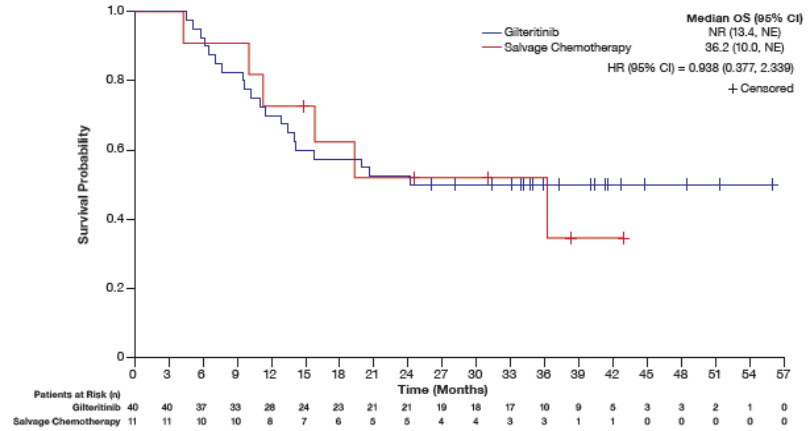


Figure 4. Overall Survival in *FLT3*$^{mut+}$ R/R AML Patients Who Underwent HSCT

A. Patients Who Achieved CRc Before HSCT



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CLINICAL OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA TREATED WITH GILTERITINIB WHO RECEIVED PRIOR MIDOSTAURIN OR SORAFENIB

PERL, ET AL. 2021, EHA #EP448

EPICS

STUDY POPULATION

> Retrospective analysis of clinical outcomes in patients with R/R AML previously treated with TKIs midostaurin or sorafenib, before receiving 120 or 200 mg gilteritinib in the CHRYSALIS trial, or before receiving 120 mg gilteritinib in the ADMIRAL trial

CONCLUSIONS

> Patients with *FLT3*-mutated R/R AML who received prior midostaurin or sorafenib achieved high remission rates with gilteritinib

> High response rates with 120 or 200 mg gilteritinib after prior TKI therapy were observed in heavily pretreated patients in the CHRYSALIS trial

> Higher response rates with gilteritinib than with salvage chemotherapy were observed in prior TKI-treated patients in the ADMIRAL trial

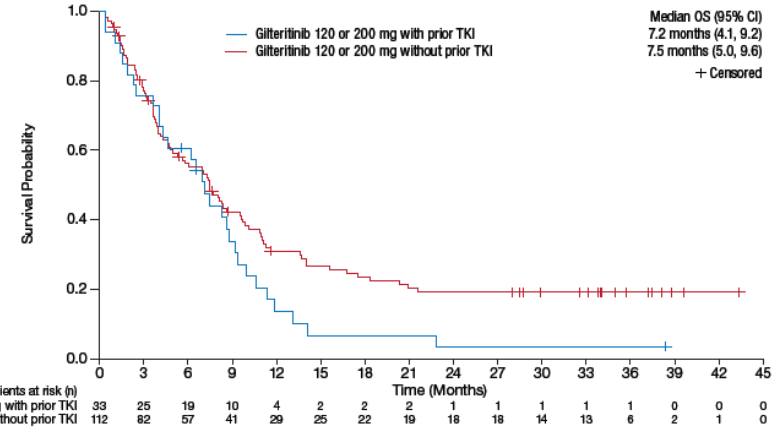
> Remission after prior TKI therapy was achieved in patients with *FLT3*-ITD, *FLT3*-TKD, or both *FLT3*-ITD and -TKD mutations

> Among patients who received prior midostaurin or sorafenib in the ADMIRAL trial, survival was longer in patients treated with gilteritinib than in those treated with salvage chemotherapy

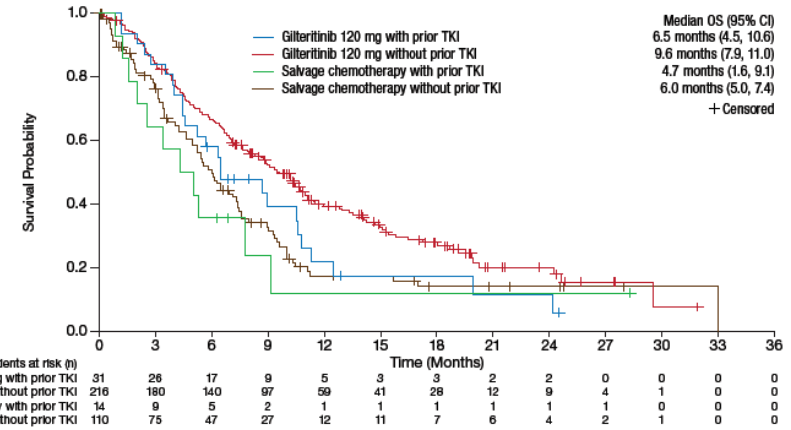
OS BY TKI STATUS

Figure 1. Overall Survival by Prior TKI Status

A. CHRYSALIS Trial



B. ADMIRAL Trial



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OUTCOMES IN GILTERITINIB-TREATED FLT3-MUTATED R/R AML PATIENTS WHO UNDERWENT TRANSPLANTATION

MAEDA, ET AL. 2021, EHA #EP441

EPICS

STUDY POPULATION

> Patients with *FLT3*-mutated R/R AML treated with gilteritinib who underwent HSCT during the ADMIRAL trial

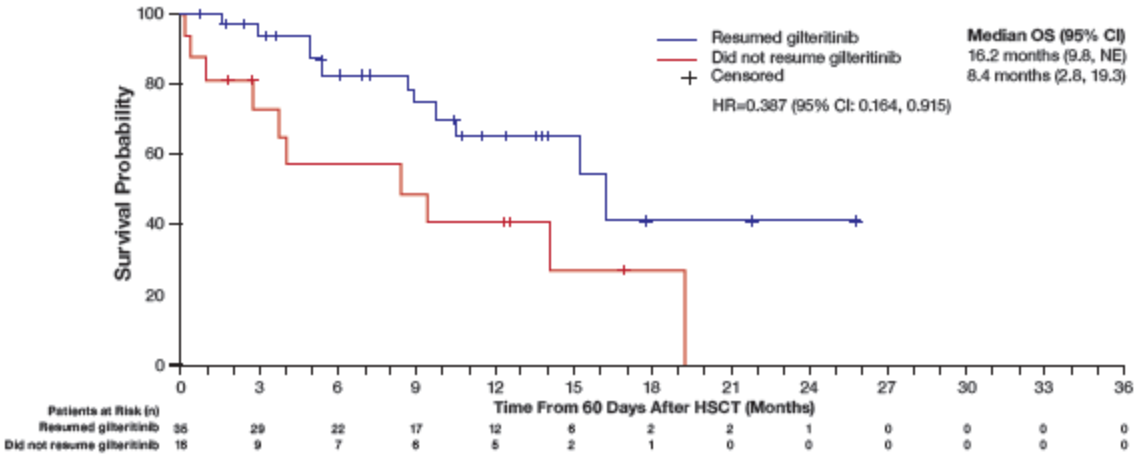
EXPERT CONCLUSIONS

Among patients with R/R *FLT3*-mutated AML who received gilteritinib and underwent HSCT during the ADMIRAL trial, those who resumed gilteritinib therapy after HSCT had better clinical outcomes than those who did not

> Patients who resumed gilteritinib had longer OS than those who did not
> Pretransplant remission rates were higher in patients who resumed gilteritinib compared with those who did not
> Because only patients without relapse 60 days after HSCT were included in this analysis, a potential bias in favor of patients who resumed gilteritinib after HSCT may exist
> No new safety signals during the post-HSCT period were identified in patients who resumed gilteritinib therapy

OS

Figure 2. Overall Survival in R/R *FLT3*$^{mut+}$ AML Patients Without Relapse for 60 Days After HSCT



Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; mut+, mutated; NE, not estimable; OS, overall survival; R/R, relapsed or refractory.

APTITUDE HEALTH®

EPICS

Discussion Summary

FLT3 MUTATIONS IN RELAPSED/REFRACTORY AML PATIENTS

GILTERITINIB SINGLE AGENT AND IN COMBINATION WITH VEN: A GAME-CHANGER IN R/R *FLT3*-MUTATED AML

EPICS

Gilteritinib superior to salvage chemotherapy for the treatment of R/R *FLT3*-mutated AML

The benefits of long-term therapy with gilteritinib were confirmed by the ADMIRAL trial updates

> According to one expert, in relapsed settings, salvage options with good efficacy are rare. The updated data from ADMIRAL are seen as very positive, as they confirm gilteritinib as a good treatment option in these settings
> Patients with R/R *FLT3*-mutated AML not eligible for transplant are usually treated with gilteritinib single agent by the experts

Gilteritinib in combination with VEN is considered a game-changing therapy

Preliminary data from a phase Ib study showed very positive response rates in R/R *FLT3*-mutated AML patients treated with the combination of gilteritinib + VEN

> Gilteritinib + VEN combination is sometimes used as off-label treatment in *FLT3*-mutated, young AML patients eligible for transplant by an expert from the US. This combination is considered better-indicated when the main treatment goal is to double morphologic remission in the patient before they go to transplant
> For the phase Ib study, it will be important to show data on the MRD status of the patients prior to transplant, and the related outcomes
> All the experts agreed this combination treatment will have a positive impact on future clinical practice for R/R *FLT3*-mutated AML patients

The experts discussed possible use of triple-combination therapy with gilteritinib + VEN + HMA to treat R/R *FLT3*-mutated AML patients

> This triple combination is currently not used outside clinical trials, and only 1 expert has used it to treat a patient who had very severe AML
> The triple combination may theoretically result in 100% of patients responding, assuming patients are able to tolerate the regimen, compared with ~80% response in patients treated with gilteritinib + VEN, if the phase Ib study data are confirmed in a bigger patient population. However, the experts will accept the slightly lower response rate if this allows them to use a chemo-free regimen (gilteritinib + VEN) to treat their patients
> Data from randomized trials are needed to confirm the possible benefits of the chemo-free regimen gilteritinib + VEN

APTITUDE HEALTH®

EPICS

CONGRESS HIGHLIGHTS

IDH1/2 MUTATIONS IN RELAPSED/REFRACTORY AML PATIENTS

A PHASE 3 STUDY OF ENASIDENIB (ENA) VERSUS CONVENTIONAL CARE REGIMENS (CCR) IN OLDER PATIENTS WITH LATE-STAGE MUTANT-IDH2 (MIDH2) RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA (R/R AML)

DINARDO, ET AL. 2021, EHA #EP457

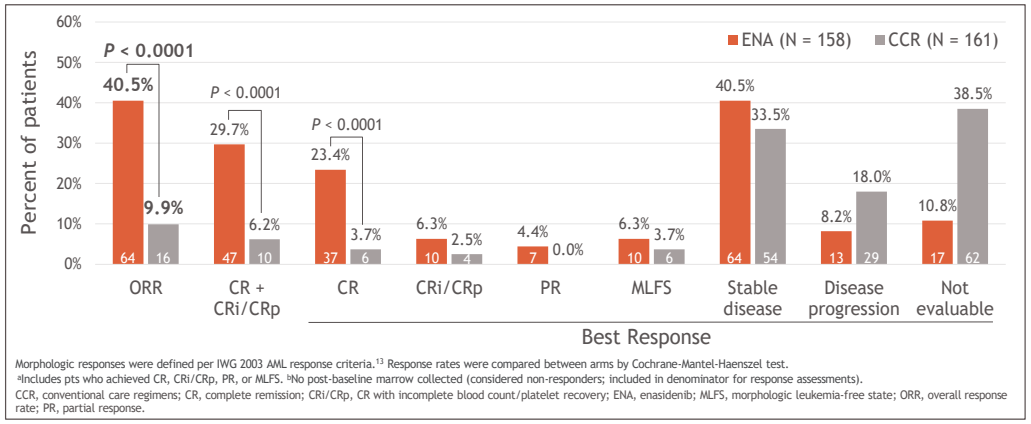
EPICS

STUDY POPULATION

> Patients ≥60 years; mutated *IDH2* AML; 2–3 prior AML treatments; ECOG PS 0–2

OUTCOME

Figure 3. Clinical responses



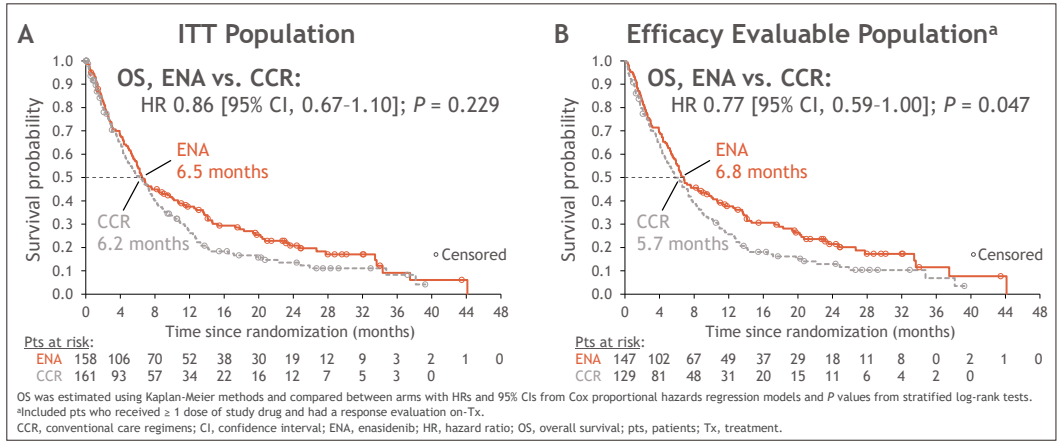
Morphologic responses were defined per IWG 2003 AML response criteria.[13] Response rates were compared between arms by Cochrane-Mantel-Haenszel test.
[a]Includes pts who achieved CR, CRi/CRp, PR, or MLFS. [b]No post-baseline marrow collected (considered non-responders; included in denominator for response assessments).
CCR, conventional care regimens; CR, complete remission; CRi/CRp, CR with incomplete blood count/platelet recovery; ENA, enasidenib; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial response.

EXPERT CONCLUSIONS

> Single-agent IDH2 inhibition with ENA does not change the natural history of *IDH2*-mutated R/R AML
>
> – Dichotomy between response and OS?

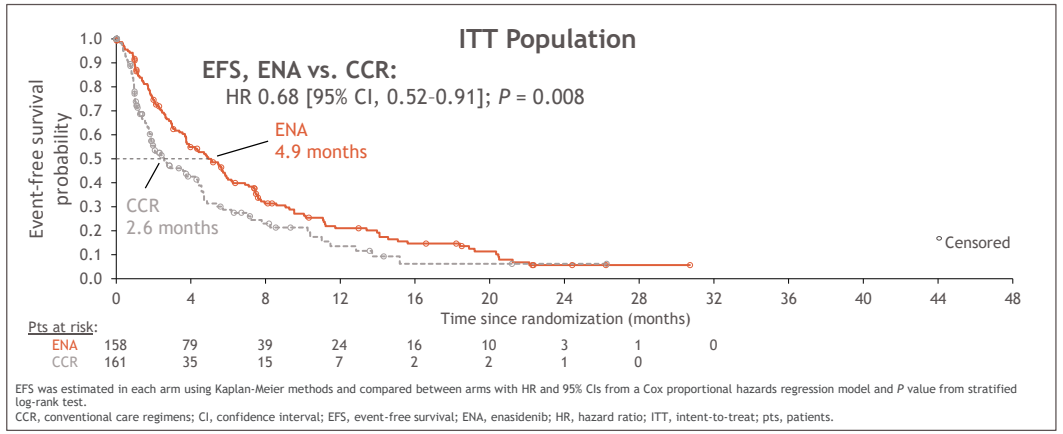
OS AND EFS

Figure 4. Overall survival



OS was estimated using Kaplan-Meier methods and compared between arms with HRs and 95% CIs from Cox proportional hazards regression models and *P* values from stratified log-rank tests.
[a]Included pts who received ≥ 1 dose of study drug and had a response evaluation on-Tx.
CCR, conventional care regimens; CI, confidence interval; ENA, enasidenib; HR, hazard ratio; OS, overall survival; pts, patients; Tx, treatment.

Figure 5. Event-free survival



EFS was estimated in each arm using Kaplan-Meier methods and compared between arms with HR and 95% CIs from a Cox proportional hazards regression model and *P* value from stratified log-rank test.
CCR, conventional care regimens; CI, confidence interval; EFS, event-free survival; ENA, enasidenib; HR, hazard ratio; ITT, intent-to-treat; pts, patients.

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A PHASE IB/II STUDY OF IVOSIDENIB WITH VENETOCLAX +/- AZACITIDINE IN IDH1-MUTATED MYELOID MALIGNANCIES

LACHOWIEZ, ET AL. 2021, EHA #S136

EPICS

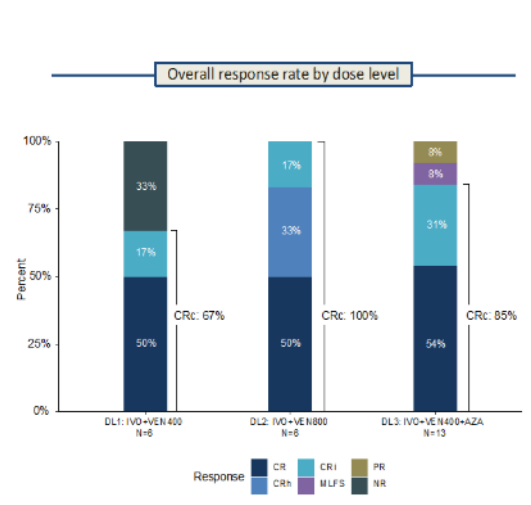
STUDY POPULATION

> Patients with *IDH1*-mutated, newly diagnosed or R/R AML; MDS or MPN with ≥10% blasts; ECOG PS ≤2; adequate renal/hepatic function

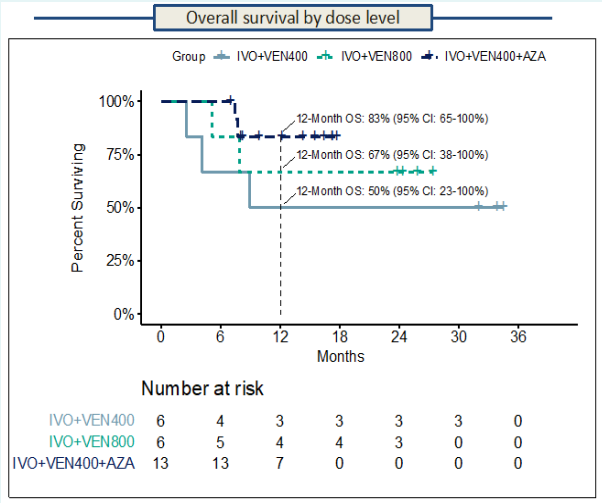
OUTCOME

> Coadministration of IVO + VEN resulted in 53% decrease in mean VEN steady state AUC and 47% decrease in C_{max}

ORR by dose level



OS by dose level



TREATMENT CHARACTERISTIC

Treatment characteristics

Variable*	All (N=25)	Dose Level #1 (N=6)	Dose Level #2 (N=6)	Dose Level #3 (N=13)
Time to response	27 (14-78)	29 (23-55)	28 (14-78)	27 (25-58)
Time on treatment	4.4 (3.7-NR)	8.2 (2.2-NR)	5.4 (3.9-NR)	4.3 (3-NR)
Cycles received	5 (1-38)	9 (2-38)	6 (3-30)	4 (1-17)
Off treatment	17 (68)	4 (67)	5 (83)	8 (62)
No response	1 (4)	1	-	-
Progression	7 (28)	2	3	2
Death	1 (4)	2	-	-
Transplant	8 (32)	-	2	6
On study Treatment	8 (32)	2 (33)	1 (17)	5 (38)

* Time to response reported in days. Time on treatment reported in months, (95% CI). All other variables reported as N (%) or median (range)

Dose Level #**1**: IVO + VEN 400

Dose Level #**2**: IVO + VEN 800

Dose Level #**3**: IVO + VEN 400 + AZA

EXPERT CONCLUSIONS

> Combinations of IDH1 inhibitor IVO and BCL-2 inhibitor VEN + HMA is effective

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EPICS

Discussion Summary

IDH1/2 MUTATIONS IN RELAPSED/REFRACTORY AML PATIENTS

USE OF IDH INHIBITORS TO TREAT R/R *IDH*-MUTATED AML PATIENTS

EPICS

IDH inhibitors used in combination treatments for R/R *IDH*-mutated AML patients are considered more beneficial than when used as single agents

Treatment of R/R *IDH*-mutated AML patients with ENA monotherapy did not show a benefit in OS, although the treated patients had better clinical responses and better EFS when compared with the conventional care regimen

> For some experts, IDH inhibitors are less effective when used as single drugs in R/R AML settings
> Experts from EU are not able to combine IDH inhibitors with other drugs (eg, VEN), as combination treatments are not yet approved by regulatory authorities. Therefore, these experts are currently using ENA monotherapy to treat R/R *IDH*-mutated AML patients

The combination of IDH1 inhibitor IVO + VEN ± AZA was shown to be highly effective in a phase Ib/II study

> One expert noted that the overall response appears to be higher in patients receiving doublet IVO + VEN 800 mg vs patients receiving triplet IVO + VEN 400 mg + AZA. In addition, there are differences among the patient population of each dose-level arm. These factors may make it difficult to select the optimal treatment dose for a phase II trial
> Another expert noted that VEN + AZA treatment was shown to be effective also in R/R *IDH*-mutated AML patients. It would be interesting to compare the results from the dose-level arms of the study with regard to VEN + AZA effects

The benefits of ENA are also currently being studied in MDS patients

> The experts believe there is an unmet need for targeted therapies for MDS patients, and urge pharmaceutical companies to invest in additional clinical studies in this disease area

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CONGRESS HIGHLIGHTS

UPDATES IN ALL

UPDATED RESULTS OF THE GIMEMA LAL2116, D-ALBA TRIAL, FOR NEWLY DIAGNOSED ADULTS WITH PH+ ALL

CHIARETTI, ET AL. 2021, EHA #S112

EPICS

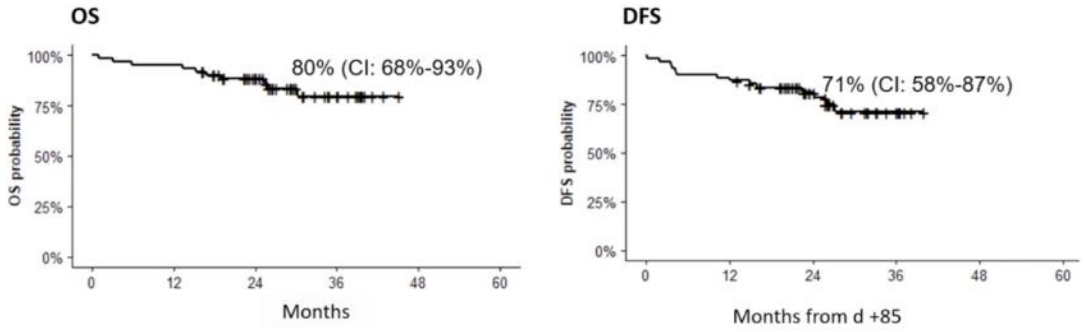
STUDY POPULATION

> Newly diagnosed Ph-positive ALL patients; no upper age limit

OUTCOME

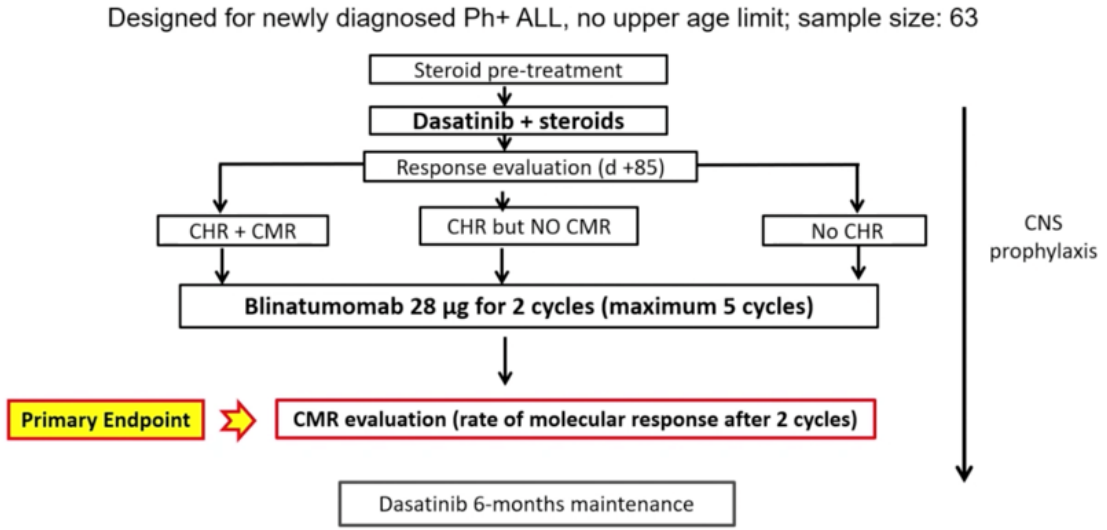
D-ALBA: updated molecular responses

	No molecular response (%)	CMR		PNQ		Overall molecular response (%)
Day 85	42/59 (71)	6/59	10%	11/59	19%	17/59 (**29**)
After cycle I	20/55 (36)	19/55	34%	16/55	29%	35/55 (**64**)
After cycle II	22/55 (40)	23/55	41%	10/55	18%	33/55 (**60**)
After cycle III	12/40 (30)	20/40	50%	8/40	20%	28/40 (**70**)
After cycle IV	7/36 (19)	17/36	47%	12/36	33%	29/36 (**81**)
After cycle V	8/29 (19)	16/29	55%	5/29	17%	21/29 (**72**)



Median follow-up: 28.81 ms (0.9-45.16)

D-ALBA STUDY DESIGN



EXPERT CONCLUSIONS

> Favorable results from D-ALBA were confirmed
> Allograft has so far not impacted OS or DFS. Of note, the allograft population was enriched for MRD-positive cases
> Values for the conversion rate per cycle of treatment are missing in the presented data

APTITUDE HEALTH

INTERIM RESULTS OF A PHASE II STUDY OF BLINATUMOMAB PLUS PONATINIB FOR PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

SHORT, ET AL. 2021, EHA #S113

EPICS

STUDY POPULATION

> Newly diagnosed or R/R Ph-positive ALL patients treated with chemotherapy-free combination of blinatumomab and ponatinib

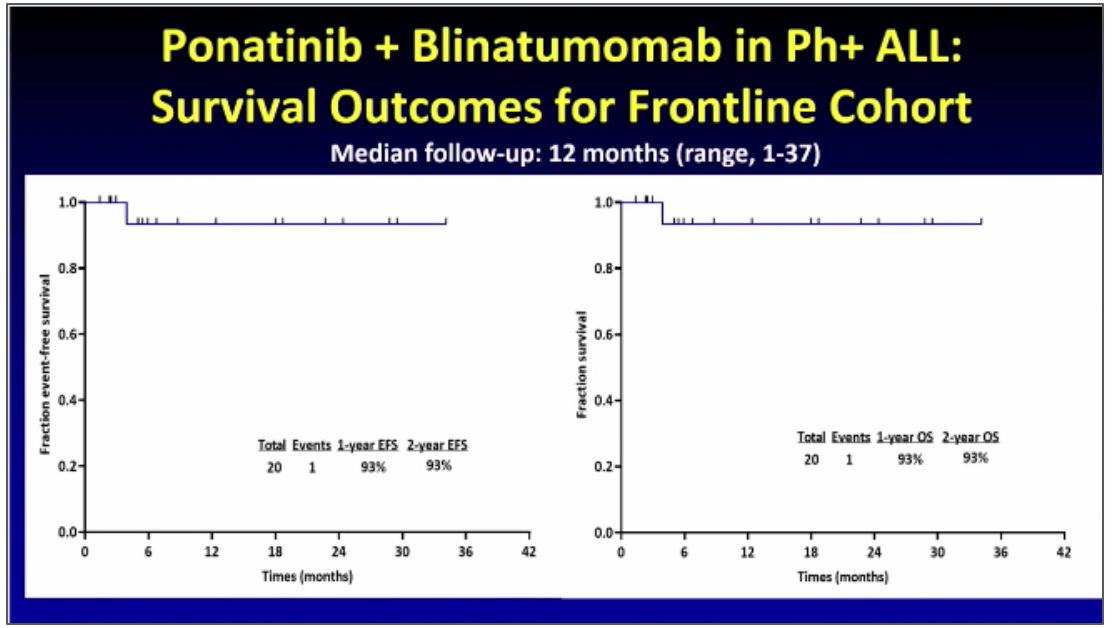
OUTCOME

Ponatinib + Blinatumomab in Ph+ ALL: Response Rates

Response, n/N (%)	All N = 35	Frontline Ph+ ALL N = 20	R/R Ph+ ALL N = 10	CML-LBC N=5
CR/CRp*	27/28 (96)	14/14 (100)	8/9 (89)	5/5 (100)
CR	25 (89)	13 (93)	8 (89)	4 (80)
CRp	2 (7)	1 (7)	0	1 (20)
MMR	30/33 (91)	20/20 (100)	7/8 (88)	3/5 (60)
CMR	26/33 (79)	17/20 (85)	7/8 (88)	2/5 (40)
Early death	0	0	0	0

* 6 frontline pts and 1 salvage pt in MRD+ CR at start

SURVIVAL OUTCOMES



EXPERT CONCLUSIONS

> Favorable results, but small cohort and short follow-up
> Molecular response superior to that in the D-ALBA study, but the time point of the response rate measurements is missing

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PRELIMINARY RESULTS OF THE GIMEMA LAL2317 SEQUENTIAL CHEMOTHERAPY-BLINATUMOMAB FRONT-LINE TRIAL FOR NEWLY DIAGNOSED ADULT PH-NEGATIVE B-LINEAGE ALL PATIENTS

BASSAN, ET AL. 2021, EHA #S114

EPICS

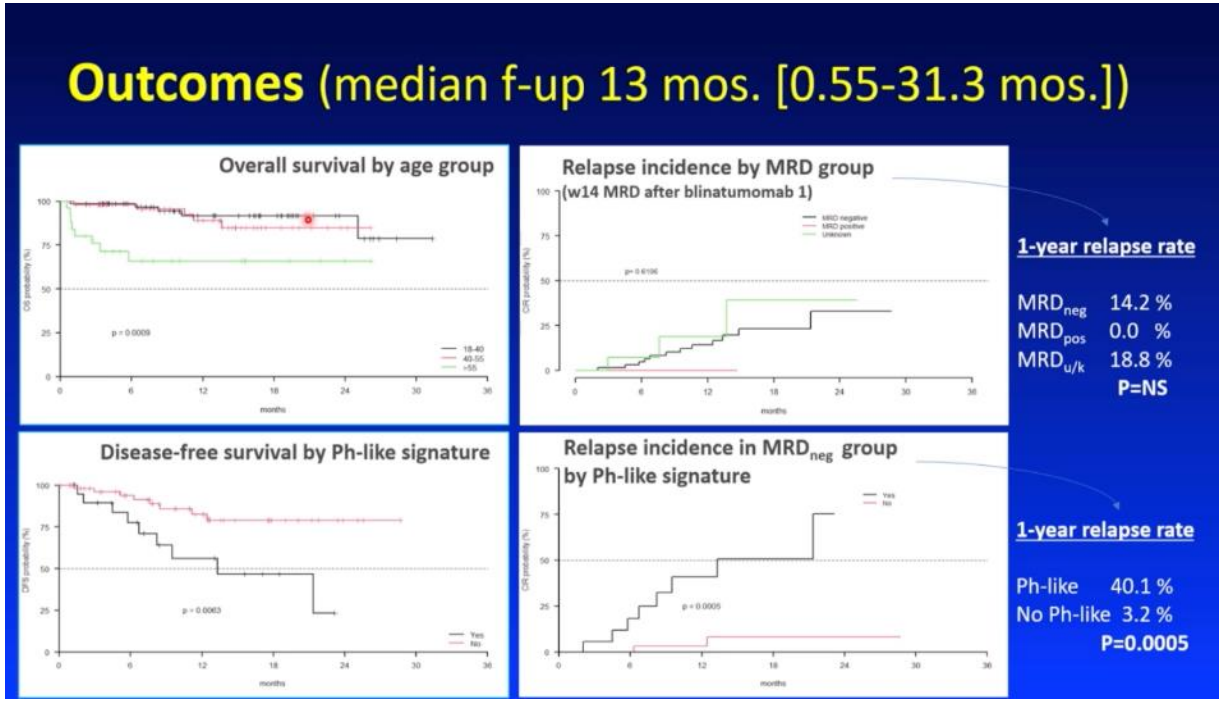
STUDY POPULATION

> Ph-negative ALL patients, 18–65 years old; risk-stratified according to SCT indication (very high risk, high risk, standard risk) treated with BLINA (cycle 1: after early consolidation; cycle 2: after late consolidation)

EXPERT SUMMARY AND CONCLUSIONS

> Favorable interim results with short follow-up
> Missing information on whether any of the patients in the study received transplant
> Ph-like ALL: good response to BLINA, but overall outcomes unfavorable

OUTCOME



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A PHASE II STUDY OF BLINATUMOMAB FOR THE TREATMENT OF MEASURABLE RESIDUAL DISEASE-POSITIVE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

SHORT, ET AL. 2021, EHA #EP367

EPICS

STUDY POPULATION AND TREATMENT

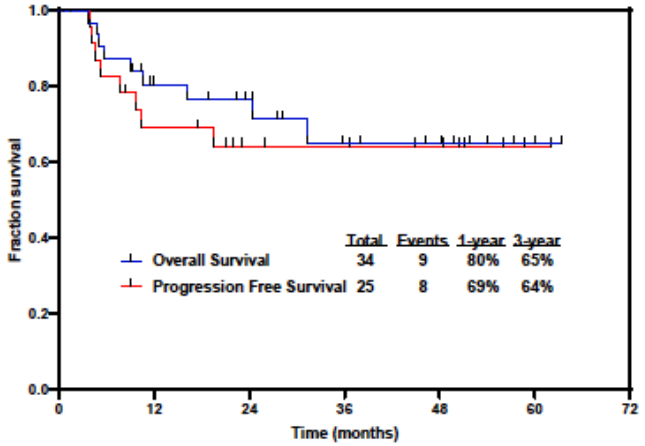
- Ph-positive/negative ALL and MRD positive in first-line treatment or after relapse treated with 1–5 cycles of BLINA followed by allogenic SCT or up to 4 maintenance cycles with BLINA every 3 months
- TKI treatment was added after BLINA treatment for Ph-positive ALL patients

OUTCOME

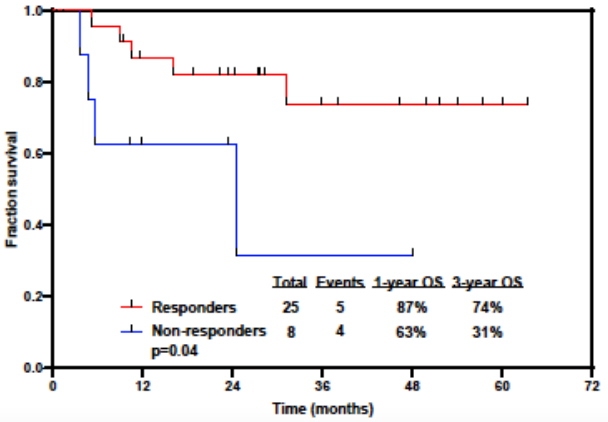
MRD Responose rates	N=33
Totral	25 (76%)
After 1 cycle	92%
Ph- ALL (n = 18)	84%
Ph+ ALL (n = 13)	64%
CR1	68%
CR2	100%
SCT after MRD response (n =23)	8 (35%)
Relapse localisation	4 BM; 1BM+CNS 1 extramedullary

OS

Overall survival and progression-free survival (entire cohort)



Overall survival by MRD response



EXPERT CONCLUSIONS

- Confirmed excellent efficacy of BLINA in MRD-positive disease
- First data in Ph-positive ALL
- The sensitivity of flow cytometry is not very high and may not be the best method to measure MRD

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Discussion Summary

UPDATES IN ALL

A FUTURE CHEMO-FREE REGIMEN FOR PH-POSITIVE ALL PATIENTS?

EPICS

Intensive chemotherapy vs chemo-free regimen

The D-ALBA study updates confirm the benefits of treating newly diagnosed Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) patients with dasatinib + steroids followed by blinatumomab (BLINA)

- For some experts, these data suggest that in the future, selected ALL patients may be treated with lower-dose chemotherapy or with a chemo-free regimen
- For other experts, it is important to be cautious in decreasing or removing chemotherapy, especially for young patients; ongoing trials are showing that young Ph-positive patients treated with low-dose chemotherapy have a high risk of relapse
- One European expert is already using a dose-reduced induction therapy for their Ph-positive ALL patients, together with imatinib treatment. When patients are still MRD positive, the expert switches imatinib with a different tyrosine kinase inhibitor (TKI) to improve their molecular response. However, after viewing the presented data from D-ALBA, the expert is considering the use of TKI in combination with BLINA to treat these patients
- The experts agreed that longer follow-up of the D-ALBA study will provide better insight on whether chemo-free regimens will be adopted in the future

WILL TRANSPLANT STILL BE NECESSARY FOR PH-POSITIVE ALL PATIENTS?

EPICS

Transplant vs maintenance therapy

Results from a phase II study of BLINA + ponatinib (PONA) followed by maintenance therapy with BLINA show very good response in treated patients

- For one expert from MD Anderson Cancer Center, these data suggest that patients receiving this treatment may avoid transplant and could instead be treated with BLINA maintenance therapy. In their institution, results supporting this possible clinical approach were previously demonstrated in patients treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone + ponatinib followed by maintenance therapy. Only very few of the treated patients had disease relapse
- The rest of the experts prefer to send their Ph-positive ALL patients to transplant when in complete remission, as for them the presented data are not sufficient to conclude that transplant can be avoided and patients can remain in disease remission. Conversely, patients not receiving transplant often relapse
  - One expert from the US commented that although they would like to avoid an intensive chemo regimen and transplant for their patients, the available clinical data are not sufficient to help identify which patients may benefit from a transplant-free approach. Because of this lack of certainty, the expert is currently still sending their patients to transplant, although they may delay the transplant in elderly patients who are responding to maintenance treatment with TKI (eg, D-ALBA study)
  - For another expert, maintenance treatment with the same drug used upfront (eg, BLINA) may generate molecular resistance in treated patients. Therefore, the expert would prefer to send their patients to transplant
- Data from a randomized trial comparing patients receiving maintenance therapy vs patients receiving transplant will be necessary to better understand which clinical approach is more effective and which types of patients can benefit from it

CAR T THERAPY FOR ADULT PATIENTS WITH ALL

EPICS

No consensus on the benefits of chimeric antigen receptor T-cell therapy (CAR T) in adult ALL patients

- The experts agreed there are not yet many data on the use of CAR T in adult ALL patients. Therefore, it is very challenging to conclude whether these patients benefit from CAR T treatment and what the actual place for and advantages of this methodology are
- It was noted that the available data on CAR T for adult ALL patients are mainly from retrospective studies where different types of CAR T were used. This makes clear conclusions on the benefits of this therapy difficult

- The experts discussed whether CAR T therapy should be used as bridging therapy to transplant or in relapsed settings after transplant
  - One expert from the US would prefer inotuzumab to CAR T as bridging therapy to transplant. In patients previously treated with inotuzumab and with disease relapse, the expert would consider using CAR T or BLINA, depending on the disease burden
  - The possible benefits of treating patients with BLINA before receiving CAR T therapy are unclear, as the preliminary data currently available are from pediatric patients. However, one expert from the US will not preclude the use of CAR T in patients who previously received BLINA
  - According to another expert, it is important to highlight that available data show that CAR T therapy is less effective in relapsed settings
- To better understand the benefits of CAR T treatment before transplant, it would be interesting to set up a randomized study comparing BLINA vs CAR T in patients who are not in immediate need of transplant. However, according to the experts, it may not be realistically possible to run this type of study

A FUTURE ROLE FOR TARGETED THERAPY IN ALL?

EPICS

Future use of targeted therapy in ALL

The experts speculated on the possible use of targeted therapy for treatment of ALL

- One expert commented that in T-cell ALL, different targeted therapies are currently being investigated in newly diagnosed and relapsed settings
- Another expert reported that an ongoing clinical trial is investigating the possible benefits of venetoclax in ALL patients
- Although some investigations are ongoing, at present there are no data on any targeted therapy with relevant efficacy in ALL

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