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Conference Coverage: EHA 2023 – Focus on AML and MDS

Full Report

June 10, 2023

Report Contents

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Meeting Snapshot

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LIVE ROUNDTABLE MEETING

DATE:
June 10, 2023

DISEASE-STATE AND DATA PRESENTATIONS by key experts

INSIGHTS REPORT including postmeeting analyses and actionable recommendations

PANEL: Key experts in leukemia

> 6 from the US

MDS- AND AML-SPECIFIC DISCUSSIONS on therapeutic advances and their application in clinical decision-making

Panel Consisting of 6 US Leukemia Experts

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Jessica K. Altman, MD
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Alexander Perl, MD
Abramson Cancer Center, University of Pennsylvania

CHAIR:
Elias Jabbour, MD
University of Texas MD Anderson Cancer Center

Naval Daver, MD
University of Texas MD Anderson Cancer Center

Guillermo Garcia-Manero, MD
University of Texas MD Anderson Cancer Center

Rami Komrokji, MD
Moffitt Cancer Center

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Meeting Agenda

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Time (CEST)	Topic	Speaker/Moderator
18.30 – 18.35	Welcome and Introductions	Elias Jabbour, MD
18.35 – 18.45	**New Developments in First-Line Treatment of Myelodysplastic Syndromes (MDS)**	Guillermo Garcia-Manero, MD
18.45 – 19.05	Discussion	All
19.05 – 19.15	**New Developments in Treatment of Relapsed/Refractory (R/R) MDS**	Rami Komrokji, MD
19.15 – 19.35	Discussion	All
19.35 – 19.40	Key Takeaways for MDS	Rami Komrokji, MD, and Guillermo Garcia-Manero, MD
19.40 – 19.50	**Advances in Acute Myeloid Leukemia (AML): Newly Diagnosed**	Naval Daver, MD
19.50 – 20.15	Discussion	All
20.15 – 20.20	BREAK	
20.20 – 20.30	**Advances in AML: Newly Diagnosed Elderly and/or Unfit**	Alexander Perl, MD
20.30 – 20.50	Discussion	All
20.50 – 20.55	**Advances in AML: R/R AML**	Jessica K. Altman, MD
20.55 – 21.20	Discussion	All
21.20 – 21.25	Key Takeaways	Naval Daver, MD; Alexander Perl, MD; and Jessica K. Altman, MD
21.25 – 21.30	**Summary and Closing Remarks**	Elias Jabbour, MD

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Conference Highlights

New Developments in First-Line Treatment of MDS

KER-050 TREATMENT IMPROVED MARKERS OF ERYTHROPOIETIC ACTIVITY AND HEMATOPOIESIS OVER SIX MONTHS WHICH RESULTED IN HEMATOLOGICAL RESPONSES ACROSS A BROAD, LOWER-RISK MDS POPULATION

Aristoteles Giagounidis, et al. S166

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STUDY POPULATION

- Ongoing phase II study evaluating safety and tolerability of KER-050 in pts with low- to intermediate-risk MDS
- Pts aged 53–89 yr dosed at the recommended part 2 dose (RP2D; 3.75 mg/kg with titration to 5 mg/kg every 4 wk)
- RP2D population (N=59) included 31 (53%) high-transfusion-burden (HTB) pts and 42 (71%) ring sideroblast (RS)-positive pts

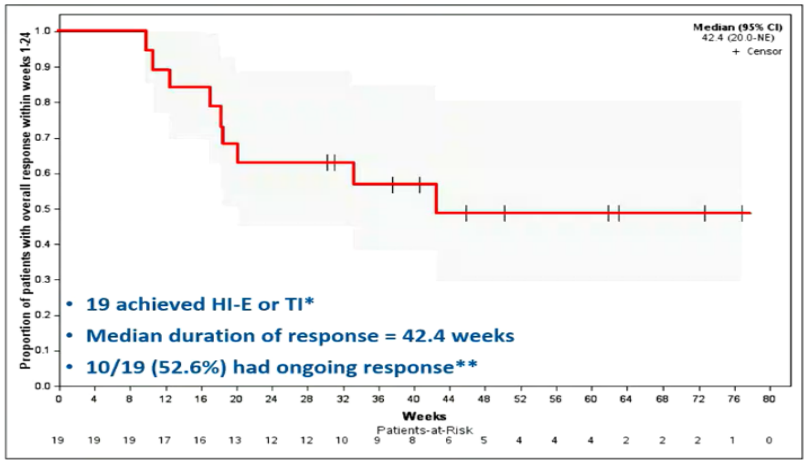
OUTCOME

- Mean treatment duration was 225 d; median doses received: 6 (1–22)
- The most frequent adverse events regardless of causality were fatigue (22%), nausea, diarrhea (19% each), epistaxis (17%), COVID-19, dyspnea (15% each)
- KER-050 treatment resulted in hematologic response across a broad population of pts with lower-risk MDS
- Similar rates of hematologic improvement-erythroid (HI-E) and transfusion independence (TI) were observed regardless of transfusion burden or RS status
- Data suggest that KER-050 elicited a durable response

Hematologic response in LR MDS

Response Endpoint	RP2D Participants[a]	
	All Evaluable	HTB Evaluable
Overall Response[b]	19/37 (51.4)	11/22 (50)
Modified IWG 2006 HI-E[c]	19/37 (51.4)	11/22 (50)
TI ≥ 8 weeks[d]	11/26 (42.3)	9/22 (40.9)
RS+	8/19 (42.1)	6/17 (35.3)
Non-RS	3/7 (42.9)	3/5 (60)

[a] Includes data for weeks 0-24 in RP2D participants with ≥24 weeks of treatment or who discontinued
[b] Defined as achieving modified IWG 2006 HI-E and/or TI
[c] Modified HI-E = mean increase in hemoglobin ≥1.5 g/dL (NT+LTB) or reduction in transfusion of ≥4 RBC units (HTB) over 8 weeks on-treatment compared to 8-week pre-treatment period
[d] TI-evaluable participants received at least 2 RBC units in the 8 weeks prior to treatment initiation



* During weeks 0-24 in RP2D participants with ≥24wk of treatment or who discontinued
**Participants with ongoing response censored at time of cutoff, denoted by vertical lines

EXPERT CONCLUSIONS

- *"The toxicity profile of this compound is minimal if you compare with other therapies that we give in this context"*
- *"We're starting to see response rates that are similar to what we have seen with luspatercept in first line, second line"*
- *"I think it would be difficult to do a randomized study and prove that one is better than the other"*

LUSPATERCEPT VERSUS EPOETIN ALFA FOR TREATMENT OF ANEMIA IN ESA-NAÏVE LOWER-RISK MYELODYSPLASTIC SYNDROME (LR-MDS) PATIENTS (PTS) REQUIRING RBC TRANSFUSIONS: DATA FROM THE PHASE-3 COMMANDS STUDY

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Matteo Giovanni Della Porta, et al. S102

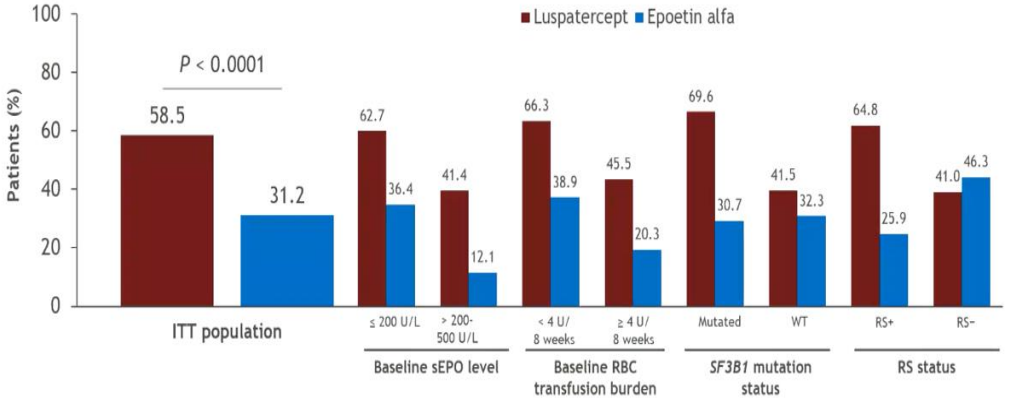
STUDY POPULATION

- Pts aged ≥18 yr with IPSS-R very low-, low-, or intermediate-risk MDS by WHO 2016; well balanced in terms of age, transfusion burden, IPSS risk
- RS-positive pts: 73% and 72% in luspatercept and placebo (PBO) arms, respectively
- Baseline RBC transfusions: 2–6 RBC units/8 wk for a minimum of 8 wk prior to randomization
- Composite primary endpoint (wk 1–24): RBC-TI for ≥12 wk with concurrent mean hemoglobin increase ≥1.5 g/dL

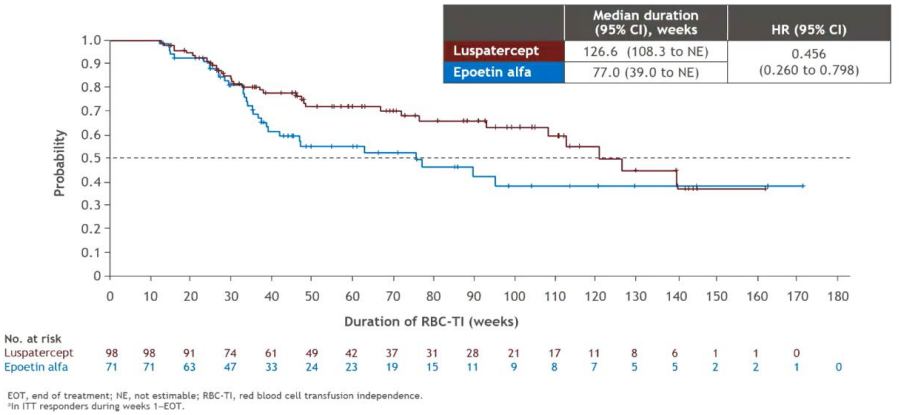
OUTCOME

- At data cutoff (Aug 2022), 58.5% of pts receiving luspatercept and 31.2% epoetin alfa achieved the primary endpoint (*P* <.0001) (**Fig A**)
- Median duration of response for luspatercept vs epoetin alfa (**Fig B**)
  - ITT population: 126.6 vs 77.0 wk; HR 0.456
  - RS positive: 120.9 vs 47 wk; HR 0.626
  - RS negative: Not Estimable vs 95.1; HR 0.492

A. Primary endpoint: luspatercept superior to epoetin alfa



B. Duration of RBC-TI ≥12 weeks longer with luspatercept



EOT, end of treatment; NE, not estimable; RBC-TI, red blood cell transfusion independence.
[a]In ITT responders during weeks 1–EOT.

EXPERT CONCLUSIONS

- *"I think the power of these data is not the response, it's actually the quality of the response, meaning the duration"*
- *"I don't know in a patient with a low EPO level who is RS negative, if I would utilize it* [luspatercept]*"*
- *"Now, we have a randomized phase III international trial doubling the response rate, doubling the duration of response"*

LUSPATERCEPT RESTORES EFFECTIVE ERYTHROPOIESIS AND PROVIDES SUPERIOR AND SUSTAINED CLINICAL BENEFIT VS EPOETIN ALFA: BIOMARKER ANALYSIS FROM THE PHASE 3 COMMANDS STUDY

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Uwe Platzbecker, et al. P693

STUDY POPULATION

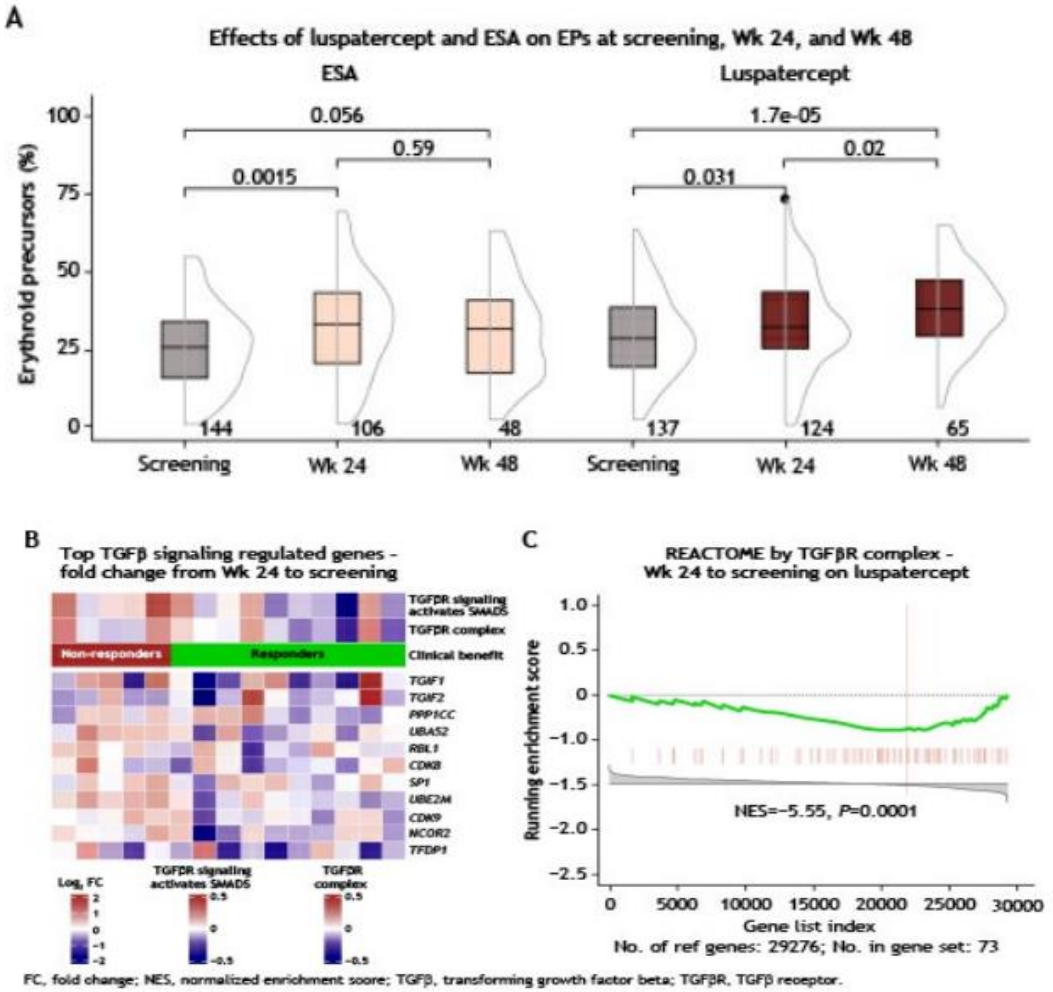
> Erythropoiesis-stimulating agent (ESA)-naive pts with LR MDS from the COMMANDS phase III study

OUTCOME

> Cytomorphology analysis showed a significant increase of erythroid precursors (EPs) at wk 24 compared with baseline in both luspatercept and ESA arms (*P* <.05) (**Fig A**)
> Gene set enrichment analysis on BMMC RNA-Seq revealed that upregulation of genes expressed in both early and late EPs at baseline was favorable for response to luspatercept (normalized enrichment score [NES] >2, padj ≤0.01) and enrichment of late EPs in the ESA arm was unfavorable (NES <-2, padj=0.006) (**Fig B)**
> Luspatercept treatment led to downregulation of TGFβ signaling (NES=−5.55, padj=0.01 vs 0.56 in ESA) (**Fig C**)

CONCLUSION

> Luspatercept is the first and only therapy to demonstrate superiority in a head-to-head study against ESAs and brings a paradigm shift in the treatment of LR-MDS-associated anemia



FC, fold change; NES, normalized enrichment score; TGFβ, transforming growth factor beta; TGFβR, TGFβ receptor.

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PHASE 1/2 STUDY OF ORAL DECITABINE/CEDAZURIDINE IN COMBINATION WITH VENETOCLAX IN TREATMENT-NAÏVE HIGHER-RISK MYELODYSPLASTIC SYNDROMES OR CHRONIC MYELOMONOCYTIC LEUKEMIA

Alex Bataller, et al. S172

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STUDY POPULATION

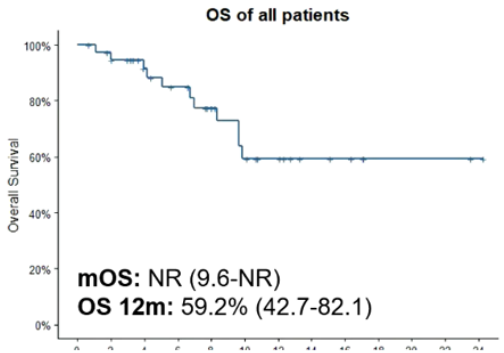
> Pts aged 27–94 yr with confirmed diagnosis of treatment-naive HR MDS or CMML (IPSS intermediate-2 or high) and bone marrow blasts >5%
> High frequency of *ASXL1* (48.7%) *and TP53* mutations (20.5%)

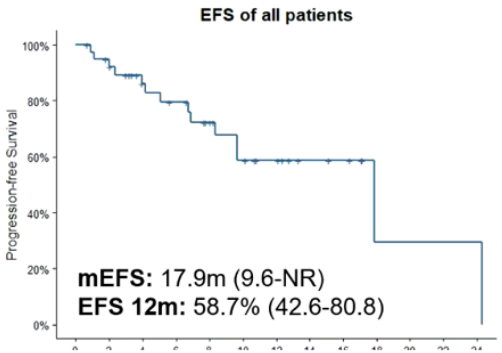
OUTCOME

> Mortality at 4 wk and 8 wk: 0% and 3%, respectively
> Most frequent G3–4 AEs were thrombocytopenia (85%), neutropenia (74%), and febrile neutropenia (21%)
> After first cycle, 80% of pts required reduced VEN dose
> Median number of cycles given was 2 (1–13)
> ORR was 94.9%, with 35.1% complete remission (CR), 29.7% marrow CR (mCR) with hematologic improvement, and 29.7% mCR alone
> In pts with cytogenetic abnormalities at diagnosis, 53.8% achieved cytogenetic response
> A high proportion of pts (48.7%) went on to transplant

Efficacy

	Full cohort (n=39)	Phase 1 (n=9)	Phase 2 (n=30)
ORR, n (%) CR mCR mCR mCR + HI	37 (94.9) 14 (35.9) 23 (59) 11 (28.2) 12 (30.8)	9 (100) 6 (66.7) 3 (33.3) 2 (22.2) 1 (11.1)	28 (93.3) 8 (26.7) 20 (66.7) 9 (30) 11 (36.7)
Cytogenetic response, n (%)	14/26 (53.8)	4/5 (80)	10/21 (47.6)
Cycles to first response, n (range)	1 (1-2)	1 (1-1)	1 (1-2)
Cycles to best response, n (range)	1 (1-6)	1 (1-6)	1 (1-4)
Cycles received, n (range)	2 (1-13)	6 (2-13)	2 (1-8)
HSCT, n (%)	19 (48.7)	5 (55.6)	14 (46.7)





EXPERT CONCLUSIONS

> *"My impression is that it's a little bit more myelosuppressive than IV. . . . I don't think you need the full dosing* [of VEN] *to have this activity"*
> *"Those patients who went to transplant are doing really well posttransplant"*
> *"This could provide a total oral approach that could be quite effective in both high-risk MDS and AML"*

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Discussion Summary

New Developments in First-Line Treatment of MDS

New Developments in First-Line Treatment of MDS (1/4)

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LR MDS

KER-050

- KER-050 is mechanistically very similar to sotatercept, with some variation in structure. Dr Garcia-Manero confirmed that it is becoming apparent that the TGFβ pathway is important in the later stages of erythropoiesis. He added that KER-050 may also have an anti-inflammatory type of mechanism that may be important in early-stage MDS or in clonal cytopenia of unknown significance
- Dr Garcia-Manero mentioned that KER-050 does not demonstrate an advantage over luspatercept, and added that it would be difficult to perform a randomized study to ascertain whether one compound has an advantage over the other
- The experts agreed that the role of KER-050 is unclear

Luspatercept

- The primary endpoint in the phase III COMMANDS trial, RBC-TI for ≥12 weeks with concurrent mean hemoglobin increase ≥1.5 g/dL, is considered a “solid endpoint” by the experts
- Dr Garcia-Manero highlighted that the power of the data lies in the response duration with luspatercept- vs epoetin alfa-treated patients, and in RS-negative patients: “*In effect, these people are transfusion independent for an extra year*”
- Experts believe the RS-positive patients are driving the positive data, since >70% of patients are RS positive in each arm of the trial. In RS-negative and *SF3B1*-mutated patients, the response is comparable with epoetin alfa, although the duration of response is longer
- Experts agreed that the COMMANDS trial data support a shift in the treatment of LR MDS-associated anemia, with luspatercept moving to up-front therapy, especially for ESA-naive, LR, RS-positive patients

New Developments in First-Line Treatment of MDS (2/4)

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LR MDS

Luspatercept (cont.)

- Dr Komrokji noted that luspatercept will become the new erythropoietin, and he assumes that the intention is to get it as up-front therapy for all comers
  - However, there was discussion among the experts whether luspatercept should be used for RS-negative patients, also considering the cost implications; it was agreed that further data would be valuable
  - Dr Garcia-Manero commented that community physicians will not care about RS or *SF3B1* status: ”*This is a drug that is given every 3 weeks. It doubles the response rate. In the community, no one is going to care about RS”*
  - The experts agreed that the ease of administration of luspatercept, with every-3-weeks dosing, will facilitate its use by community physicians
- The potential issues of medical insurance coverage for all comers vs RS-positive patients were noted, and it was agreed that this will be “*an interesting discussion”* between physicians and insurers
- Dr Garcia-Manero believes that in the future, luspatercept will be studied in combination with other compounds and its use will expand into different therapeutic areas, eg, renal failure, solid tumors, and myelofibrosis
  - Dr Komrokji commented that in RS-negative patients, the combination of ESA + luspatercept could be an option
- Dr Garcia-Manero commented that, *“The mechanism of action for this compound is not clear, so we are going to see a lot more data”.* He noted that the mutational burden has an impact on therapy

New Developments in First-Line Treatment of MDS (3/4)

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HR MDS

Total oral therapy: oral decitabine-cedazuridine in combination with VEN

> Dr Garcia-Manero commented that while this is a pilot phase I/II study, the data are positive, and while the combination does not look better than AZA-VEN, it is not inferior and may provide a total oral approach in HR MDS (and AML)
  - Dr Komrokji agreed that a total oral therapy is “very appealing,” and a good induction for transplant

Dose reduction

> The experts agreed that while the concept of total oral therapy is good, the optimal dosing needs to be determined
  - They discussed the possibility of reducing the dose of VEN (currently 400 mg; 14 days) on the basis of French data and monotherapy/combination therapy, as well as the feasibility of reducing the decitabine-cedazuridine dose
  - Dr Komrokji commented that the full dosing of VEN is not necessary for activity; for example, 7 days instead of 14 days of VEN would reduce myelosuppression
    - Dr Altman stated that she would be agreeable to this approach in the context of a trial
  - Dr Jabbour noted that the schedule could be 7 days VEN induction and possibly 5 or 3 days of VEN for consolidation
> Dr Garcia-Manero mentioned that there may be an effect of a patient’s weight or ethnicity on the PK profile of the drugs (he shared a patient case from his own experience) and confirmed that there are studies evaluating the impact of weight on drug PK profiles
> Experts agreed that a lower-dose schedule is important, especially for physicians in the community setting

New Developments in First-Line Treatment of MDS (4/4)

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HR MDS

_TP53_ mutation

> Patients with *TP53* mutations had a high rate of response, but the response was not long-lasting. In wildtype *TP53*, Dr Garcia-Manero commented that the response looks "*pretty amazing*"; there were good responses in patients with *ASXL1* mutation

Frontline therapy in HR MDS with _IDH1/2_ mutation

> Dr Garcia-Manero commented from his own experience that triplet therapy with oral decitabine, VEN, and ivosidenib/enasidenib is "*extremely powerful and extremely well tolerated*"

> Dr Altman stated that the choice of therapy should depend on the patient's goals; if the goal is to get to transplant, a triplet would be a good option

> Dr Komrokji noted that he would like to see IDH inhibitors explored in LR MDS

Patients with _TP53_ mutation

> Dr Komrokji commented that there is promising efficacy with AZA + magrolimab combination for *TP53*-mutant patients; however, the phase III data (ENHANCE trial) are eagerly awaited and if positive, this regimen will become the backbone of treatment

> He commented that *TP53*-mutant patients should be included as one group in clinical trials, rather than being included with other patient groups

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Conference Highlights

New Developments in Treatment of R/R MDS

CONTINUOUS TRANSFUSION INDEPENDENCE WITH IMETELSTAT IN HEAVILY TRANSFUSED NON-DEL (5Q) LOWER-RISK MYELODYSPLASTIC SYNDROMES RELAPSED/REFRACTORY TO ERYTHROPOIESIS STIMULATING AGENTS IN IMERGE PHASE 3

Uwe Platzbecker, et al. S165

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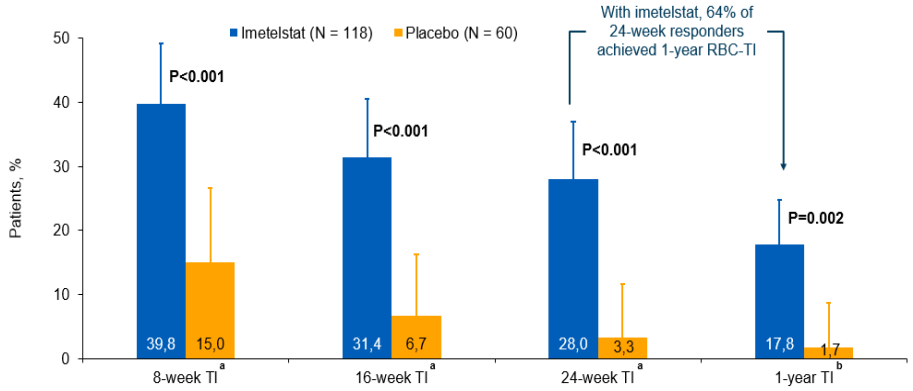
STUDY POPULATION

> Heavily red blood cell (RBC) transfusion-dependent (TD), ESA R/R or ESA ineligible non-del(5q) LR MDS pts naive to len-HMA were randomized 2:1 to receive imetelstat 7.5 mg/kg (n=118) or PBO (n=60) every 4 wk

OUTCOME

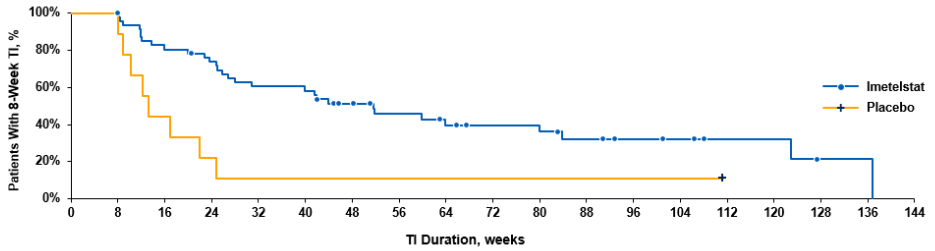
> Primary endpoint was met: 47 pts (39.8%) vs 9 pts (15.0%) receiving imetelstat vs PBO achieved 8-wk TI; *P* <.001 **(Fig A)**
> The rate of 8-wk TI was also significantly higher with imetelstat vs PBO across subgroups, including in RS-negative pts
> Median TI duration (95% CI) was 51.6 (26.9–83.9) wk with imetelstat vs 13.3 (8.0–24.9) wk with PBO; *P* <.001 **(Fig B)**
> Baseline cytogenetic abnormalities were reported in 22.0% in the imetelstat group and 21.7% in the PBO group
  – Cytogenetic responses (CR) seen with imetelstat vs PBO: 19% vs 8% complete CR; 15% vs 8% partial CR
> Grade 3–4 thrombocytopenia and neutropenia were the most frequently reported AEs, most often reported during cycles 1–3; no fatal hematologic AEs

A. Long-term duration of RBC TI observed with imetelstat vs PBO



B. 8-week RBC-TI responders have significantly longer duration of TI vs PBO

8-Week TI Responders	Imetelstat (N = 47)	Placebo (N = 9)	HRa (95%CI)	P-Value
Median duration of RBC-TI, weeks (95% CI)	51.6 (26.9–83.9)	13.3 (8.0–24.9)	0.23 (0.09–0.57)	<0.001



Patients, N																			
Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0				

EXPERT CONCLUSIONS

> *". . . even at 24 weeks you are seeing one-third of the patients becoming transfusion independent, regardless of their transfusion burden at baseline . . . so, this is really good"*
> *"My take . . . is that they should really look at this drug in HR disease"*

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DISEASE MODIFYING ACTIVITY OF IMETELSTAT IN PATIENTS WITH HEAVILY TRANSFUSED NON-DEL (5Q) LOWER-RISK MYELODYSPLASTIC SYNDROMES RELAPSED/REFRACTORY TO ERYTHROPOIESIS STIMULATING AGENTS IN IMERGE PHASE 3

Valeria Santini, et al. S164

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STUDY POPULATION

> Heavily RBC TD, ESA R/R or ineligible non-del(5q) LR-MDS pts naive to len-HMA were randomized 2:1 to receive imetelstat 7.5 mg/kg (N=118) or PBO (N=60) every 4 wk

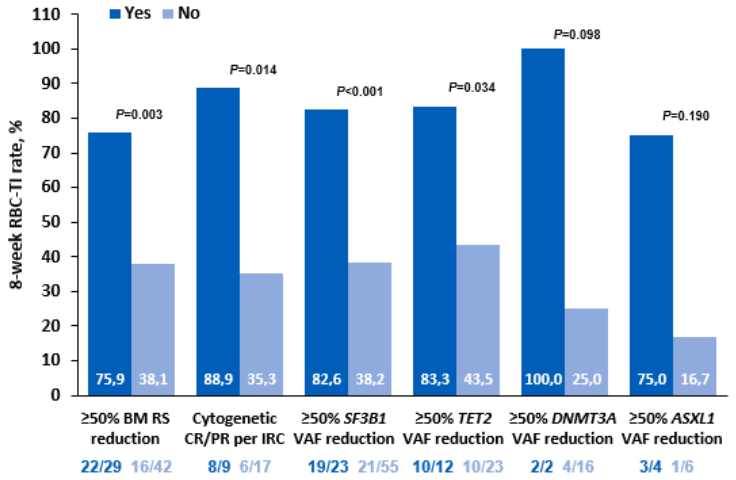
OUTCOME

> A ≥50% *SF3B1* VAF reduction was associated with durable RBC TI rates and longer RBC TI duration
> Imetelstat-treated pts demonstrated a higher rate of ≥50% VAF decreases in *SF3B1, TET2, DNMT3A,* and *ASXL1* mutations compared with PBO
> 30% of pts with *SF3B1* mutation had ≥50% VAF reduction and 40% with *ASXL1* mutation
> 8-wk and 24-wk TBC TI correlated with reductions in RS cells, cytogenetic responses, and VAF reduction in pts treated with imetelstat

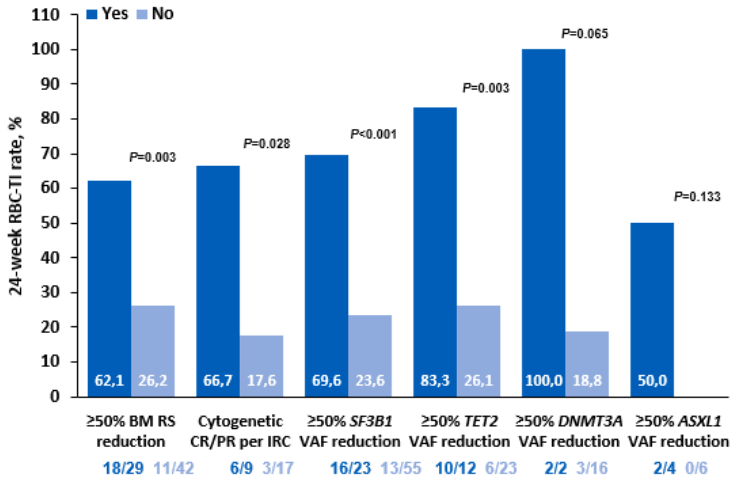
EXPERT CONCLUSIONS

> *"Potentially, as you get more mature data, this could be a drug that impacts overall survival"*
> *"So, this drug is not only having an impact on transfusion burden, but it is also disease modifying"*

8-Week RBC-TI Correlations



24-Week RBC-TI Correlations



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HIGHER *MDMX* EXPRESSION WAS ASSOCIATED WITH HYPOMETHYLATING AGENT RESISTANCE AND WORSE SURVIVAL IN MYELODYSPLASTIC SYNDROME PATIENTS, INFERRING IT A POTENTIAL THERAPEUTIC TARGET

Yu-Hung Wang, et al. S171

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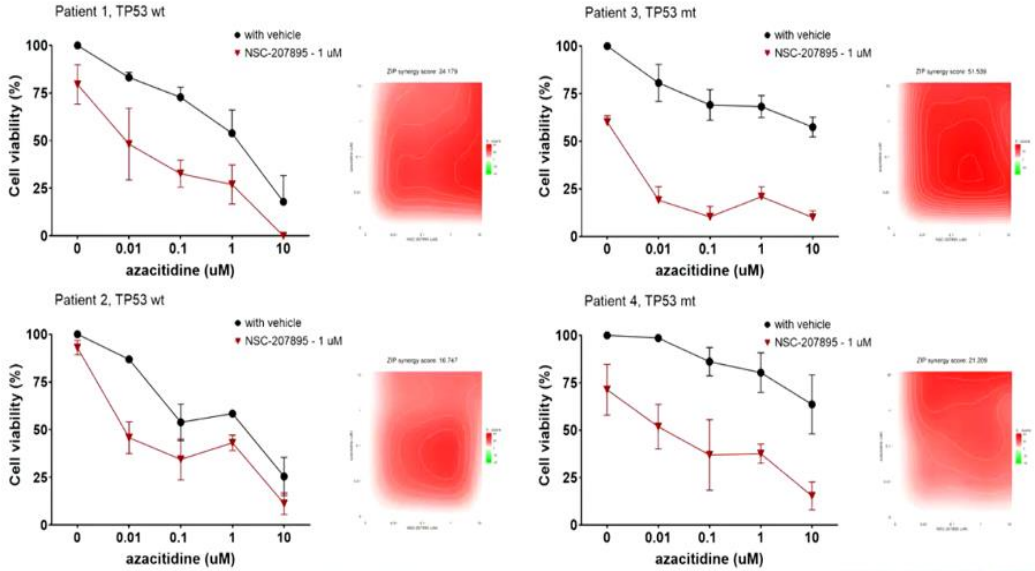
STUDY POPULATION

> MDS pts (N=340) treated at the National Taiwan University Hospital from 1997–2019 who had adequate samples at diagnosis for DNA and RNA sequencing; median age: 68.3 yr

OUTCOME

> High *MDMX* expression was associated with complex karyotypes and *ASXL1* mutations. *MDMX* expression was significantly higher in MDS pts with excess blasts vs those without excess blasts, and healthy donors (*P* <.001)
> Among 290 pts with unmutated *TP53*, high-*MDMX* pts invariably had significantly poorer OS and leukemia-free survival than low-*MDMX* pts (29.1 mo vs 91.3 mo; *P*<.001, and 21.4 mo vs 70.3 mo; *P*<.001, respectively)
> In high- vs low-*MDMX* pts, the rates of primary resistance to HMA were significantly higher (59.5% vs 22.7%; *P* <.001)

Pharmacologic inhibition of *MDMX* synergizes with azacitidine



CONCLUSIONS

> Further studies are required to ascertain the mechanism by which high *MDMX* expression results in higher resistance to HMA
> The potential for synergy with HMA of other compounds mediating *MDMX/MDM2/p53* and clinical applicability require investigation

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*The abstract was presented but not discussed.

MYELODYSPLASTIC NEOPLASMS (MDS) CLASSIFICATION FROM WHO 2017 TO WHO 2022 AND ICC 2022: AN EXPANDED ANALYSIS OF 7017 PATIENTS ON BEHALF OF THE INTERNATIONAL CONSORTIUM FOR MDS (ICMDS)

Rami S. Komrokji, et al. S170

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BACKGROUND AND AIMS

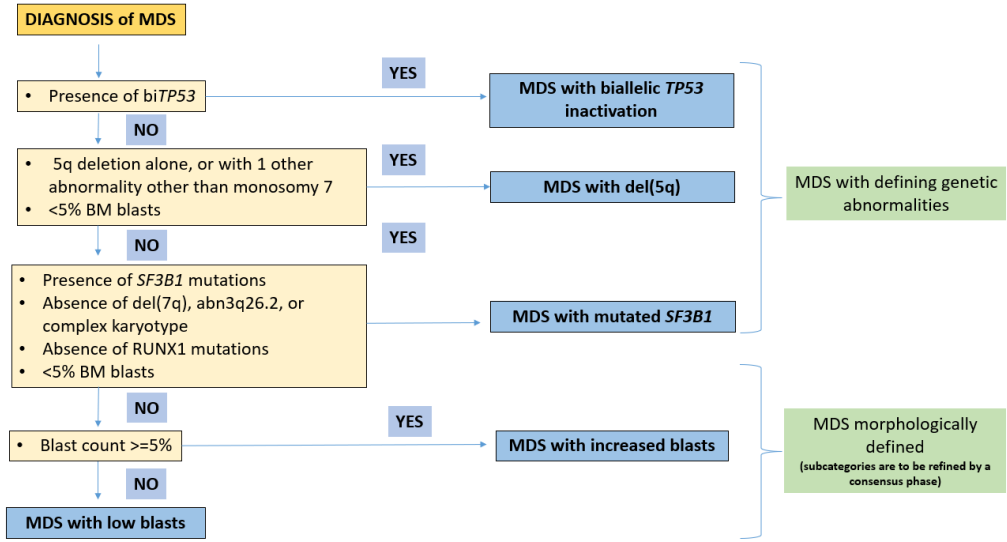
- In 2022, two new classifications for myeloid neoplasms were published: the World Health Organization (WHO) and International Consensus Classification (ICC)
- The aims were to validate and compare these 2 classifications in a large international cohort of MDS pts and to provide data-driven evidence for future harmonization

OUTCOME

- MDS-*SF3B1* mutated group accounted for 12–13% of all MDS cases and demonstrated favorable outcome: median OS and LFS exceeded 8 yr
- Pts with MDS-del5q had good prognosis
- *TP53*-mutated MDS pts had the shortest survival
- Pts with MDS-RS *SF3B1* wildtype had similar outcomes to MDS low blasts
- Increased myeloblasts are associated with worse outcome but the exact cutoff is not clear

EXPERT CONCLUSIONS

- *"I think it's very clear that there are 3 clearly defined genetic groups: MDS SF3B1, they are good; MDS-del(5q) [the intermediate]; and the bad, the biallelic TP53 MDS"*
- *"I think this is beautiful in its simplicity"*



Conceptual classification of MDS

Chronic phase MDS

- MDS-*SF3B1*
- MDS-del5q
- MDS-LB

Accelerated phase MDS

- MDS-EB (5-19% myeloblasts) (cutoff to be refined)
- Bi-allelic *TP53* MDS
- MDS-f

AML-MDS related (AML-MR)

- ≥20% myeloblasts (cutoff to be refined) with prior history of MDS or AML with MDS defining cytogenetic abnormalities or gene mutations.

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Discussion Summary

New Developments in Treatment of R/R MDS

New Developments in Treatment of R/R MDS (1/3)

EPICS

R/R MDS

Inclusion of RS-positive patients in the IMERGE (and COMMANDS) trial

> Dr Perl questioned the preponderance of RS-positive patients in the trials, which he noted is different than a real-world patient population
  - Dr Komrokji outlined 2 reasons for this
    - A bias in the patients being recommended to enroll in trials due to a perceived benefit of the drugs in these patients
    - Since RS-positive patients tend to live longer, they are enriched in clinical practice

Imetelstat in LR MDS R/R to ESA

> The experts agreed that the data from the IMERGE phase III trial indicate imetelstat is beneficial in heavily transfusion-dependent patients

> They agreed that the data suggest that imetelstat impacts not only transfusion burden, but it is also disease modifying
  - Dr Komrokji speculated that imetelstat could impact OS

> Myelosuppression was acknowledged as a potential issue with imetelstat
  - Dr Komrokji (a co-author on both imetelstat abstracts [S164 and S165]) confirmed that the myelosuppression is dose dependent
  - Dr Jabbour suggested that a clinical trial is needed to identify the best dose and schedule, especially if up-front use is planned. Dr Komrokji clarified that imetelstat will probably not be positioned as up-front therapy, at least not until data about disease modification, decreasing burden, and responses have matured from clinical trials. He confirmed that in the R/R setting, the myelosuppression is manageable

New Developments in Treatment of R/R MDS (2/3)

EPICS

R/R MDS

Imetelstat in LR MDS R/R to ESA (cont.)

- The experts believe that once approved, imetelstat will be positioned as second line after luspatercept failure in LR MDS patients, and will be the SOC in both RS-negative and RS-positive MDS
  - It was agreed that luspatercept does well in terms of hematologic improvement if there are more than 2 mutations, but it does not impact allele burden and there is no reversal of disease course
  - Dr Komrokji commented that in his view, imetelstat will become the “go-to” rather than HMAs in LR MDS. He stated that HMA should be “moved away completely from the low risk” settings
- Experts agreed that imetelstat would be appealing for use in HR MDS patients, although they acknowledged that the combination with VEN would be very myelosuppressive. Other potential combinations would need to be studied

Mechanism of action

- Dr Garcia-Manero expressed doubt that imetelstat is only a telomerase inhibitor, and commented that additional mechanisms of action still need to be deduced

Imetelstat use in community practice

- The experts discussed the feasibility of imetelstat use by community physicians
  - Dr Komrokji commented that the rate of febrile neutropenia was not high, some investigators easily managed neutropenia with G-CSF, and there was no mortality. He added that the challenge will be the one-third of the LR MDS patients who have thrombocytopenia at baseline
  - The experts agreed that community physicians are experienced with AZA; therefore, this will not be an issue for them

New Developments in Treatment of R/R MDS (3/3)

EPICS

R/R MDS

Promising new agents

> Dr Komrokji highlighted 2 agents, post-HMA failure, that are worth following in spliceosome and splicing mutation subsets:
  - Emavusertib, targeting *IRAK4*
    - Single-agent activity in MDS spliceosome patients (also in AML spliceosome and AML *FLT3* patients)
  - SX-682, first-in-class CXCR1/2 inhibitor
    - Activity seen more in patients with splicing mutations

MDS classification from WHO 1017 to WHO 2022 and ICC 2022

> Three clearly defined genetic groups: *SF3B1* (best outcome), deletion 5q, and biallelic *p53*
  - Chronic phase MDS: *SF3B1*, deletion 5q, low blasts
  - Accelerated phase MDS: excess blasts (5-9% myeloblasts), biallelic *TP53,* MDS with fibrosis
  - AML (≥20% myeloblasts (cutoff to be refined), prior history of MDS or AML with MDS defining cytogenetic abnormalities or gene mutations

Molecular testing in the community

> Up-front testing for *IDH* mutation is improving in the community because the platforms now include testing for *IDH*; however, it does not necessarily guide treatment
  - Dr Komrokji commented that *"beautiful data*" have been presented on the concordance of peripheral blood and bone marrow testing, which means that community physicians, who may be reluctant to repeat bone marrow biopsies for molecular data, can use peripheral blood assays to effectively guide targeted therapy decisions

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Conference Highlights

Advances in AML: Newly Diagnosed

FLAG-IDA COMBINED WITH GEMTUZUMAB OZOGAMICIN (GO) REDUCED MRD LEVELS AND IMPROVED OVERALL SURVIVAL IN *NPM1* MUT AML INDEPENDENT OF *FLT3* AND MRD STATUS, RESULTS FROM THE AML19 TRIAL

EPICS

Nigel Russell, et al. S134

STUDY POPULATION

> The NCRI AML19 trial randomized pts (n=1475; median age 51.5 yr) with newly diagnosed AML or MDS-EB2 between FLAG-IDA and DA 3+10
> Of these, 1031 (18–60 yr; median age 51.5 yr) were also randomized to receive gemtuzumab ozogamicin (GO). No *FLT3* inhibition was used
> Previously, a survival benefit with FLAG-IDA–GO was reported in *NPM1*-mut pts (n=307; 5-yr OS 82% vs 64%, HR 0.50, CI 0.31-0.81; *P* <.005)
> Aim was to analyze the impact of FLAG-IDA–GO on PC2 MRD and outcome of post-induction therapy in *NPM1*-mut AML with and without *FLT3* mutation

OUTCOME

> The OS benefit for FLAG-IDA–GO was seen in *NPM1*-mut AML in both *FLT3*-mut (HR 0.32, 95 CI: 0.17-0.62) and *FLT3*-wt pts (HR 0.75, 95% CI: 0.37-1.51) with statistically significant heterogeneity (**Fig 1A**)
> For PB PC2 MRD-positive pts, those randomized to FLAG-IDA–GO produced a trend towards better OS vs DA-GO (74% vs 51% at 3 yr, HR 0.52, 95 CI: 0.17-1.57) (**Fig 1B**)
> For PC2 PB MRD-negative pts, survival was superior in pts treated with FLAG-IDA–GO (OS 90% vs 78% at 3 yr, HR 0.43, 95 CI: 0.22-0.87) (**Fig 1B**)

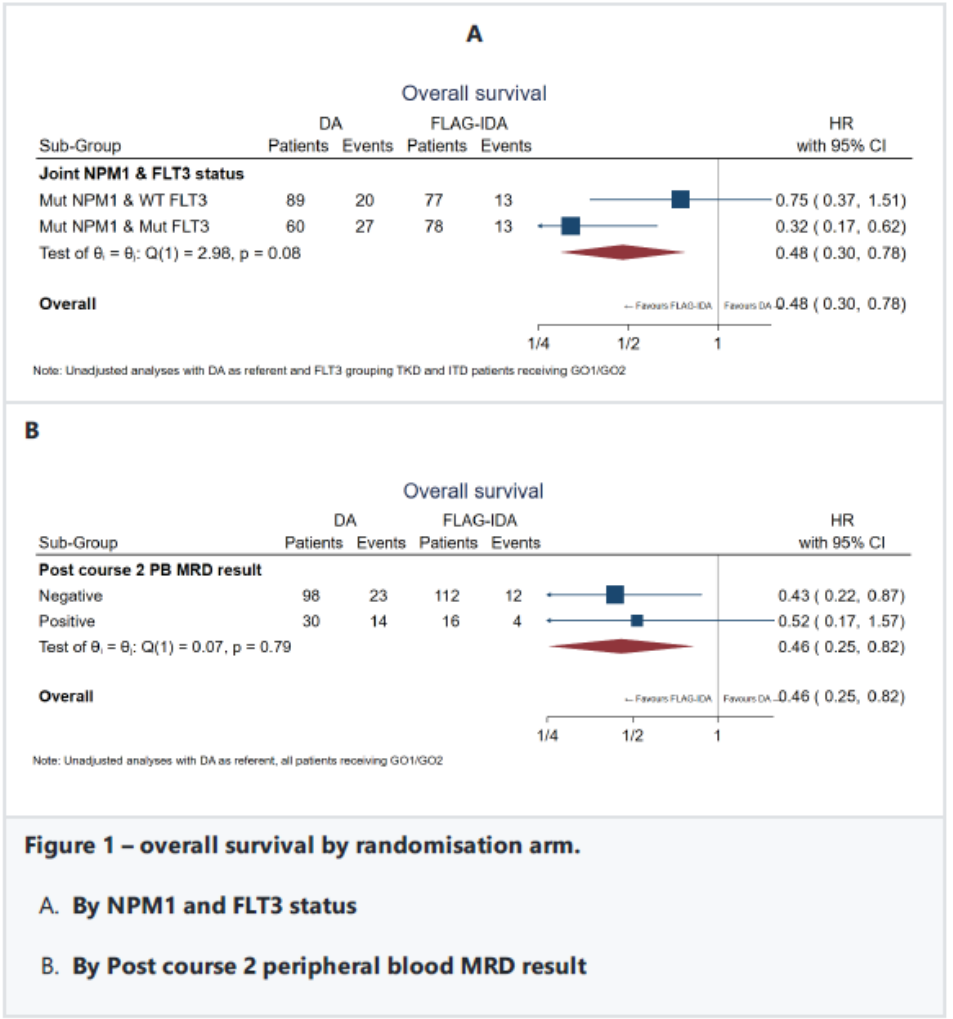


Figure 1 – overall survival by randomisation arm.

A. **By NPM1 and FLT3 status**

B. **By Post course 2 peripheral blood MRD result**

EXPERT CONCLUSIONS

> *"Whether you were MRD positive or negative, FLAG-IDA [GO] was the superior regimen"*
> *"We are already doing this, for isolated NPM1-mutated patients. We are using FLAG-IDA–GO; we allow both [FLAG-IDA–VEN]"*

PRELIMINARY RESULTS OF QUIWI: A DOUBLE BLINDED, RANDOMIZED CLINICAL TRIAL COMPARING STANDARD CHEMOTHERAPY PLUS QUIZARTINIB VERSUS PLACEBO IN ADULT PATIENTS WITH NEWLY DIAGNOSED FLT3-ITD WILD-TYPE AML

Pau Montesinos, et al. S130

EPICS

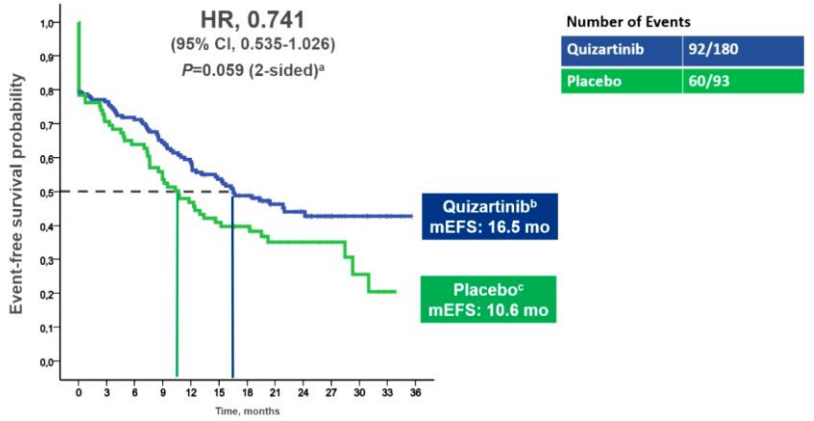
STUDY POPULATION

- Pts aged 18–70 yr (median: 57 yr) with newly diagnosed *FLT3*-ITD–wt AML, and fit for intensive chemotherapy centrally screened for *FLT3*-ITD prior to randomization (N=284)
- Pts randomized to Quiz (n=180) or PBO (n=93), both in combination with standard induction and consolidation 3+7 chemotherapy
- Dose of Quiz higher than in QuANTUM-First, at 60 mg/d × 14 d

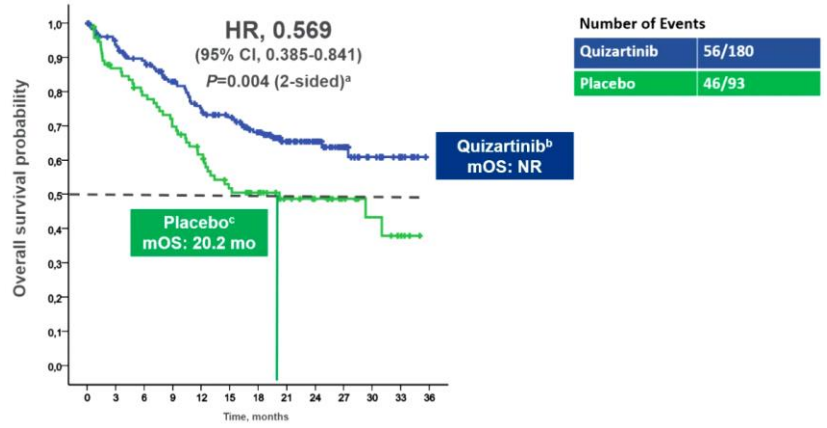
OUTCOME

- At data cutoff (Feb 2023), median follow-up was 17 mo
- Median EFS was 16.5 mo with Quiz vs 10.6 mo with PBO (HR, 0.741, 95% CI: 0.535-1.026; 2-sided *P*=.059) (**Fig 1A**)
- Median OS was not reached with Quiz vs 15 mo with PBO (HR 0.558, 95% CI: 0.373-0.834; *P*=.004), and the 2-yr OS was 63.5% with Quiz vs 47% with PBO (**Fig 1B**)
  - 50 of 180 pts died in the Quiz arm, and 45 of 93 with PBO
- Disease-free survival was not reached with Quiz vs 15.4 mo with PBO (HR 0.643, 95% CI: 0.411-1.005; *P*=.050)
- CR/CRi rate after 2 cycles was 76.7% in the Quiz arm and 76.4% in the PBO. CR/CRi with MRD negativity after 2 cycles was achieved in 41.5% in the Quiz arm and 41.6% with PBO

1A. Event-free survival



1B. Overall survival



EXPERT CONCLUSIONS

- *"This is at least as big as the benefit on QuANTUM-First"*
- *"I think this can be practice changing, but we need a confirmatory phase III study"*

BMT-CTN 1506 (MORPHO): A RANDOMIZED TRIAL OF THE FLT3 INHIBITOR GILTERITINIB AS POST-TRANSPLANT MAINTENANCE FOR FLT3-ITD AML

Mark J. Levis, et al. LBA2711

EPICS

STUDY POPULATION

- Pts with *FLT3*-ITD AML in first remission after receiving no more than 2 cycles of induction therapy with HCT planned within 12 mo of achieving remission. Median age: 53 yr (range 18–78) randomized 1:1 to gilteritinib (120 mg/d) or PBO after HCT
- Stratification: pre-HCT MRD, conditioning regimen, and time from HCT to randomization
- The aim was to determine whether post-HCT maintenance with gilteritinib benefits *FLT3*-ITD AML pts and to determine whether MRD should be used to guide decision on who should be treated with post-HCT gilteritinib

OUTCOME

- Primary endpoint of RFS was not met at the primary analysis (HR 0.679; 95% CI: 0.459-1.005; 2-sided *P*=.0518)
- The data demonstrate a correlation between MRD and survival in post-HCT therapy in *FLT3*-ITD AML

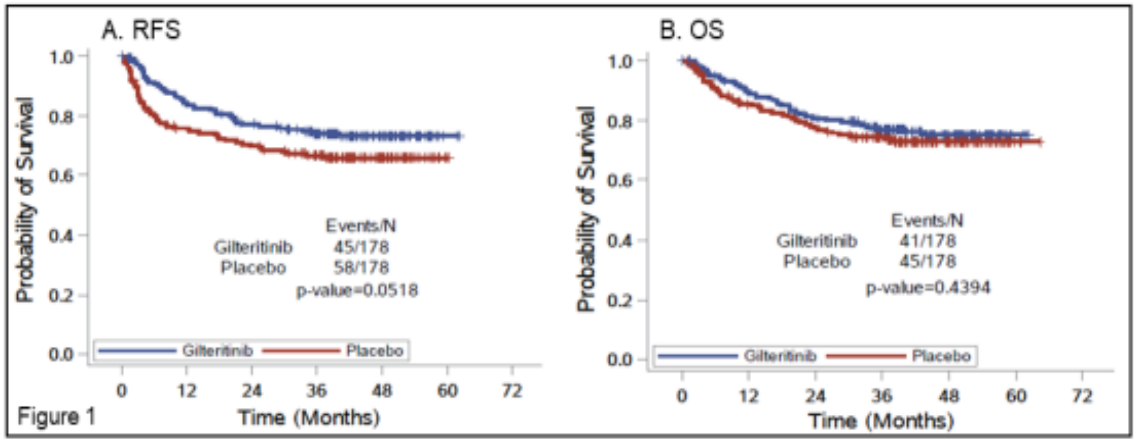


Figure 1

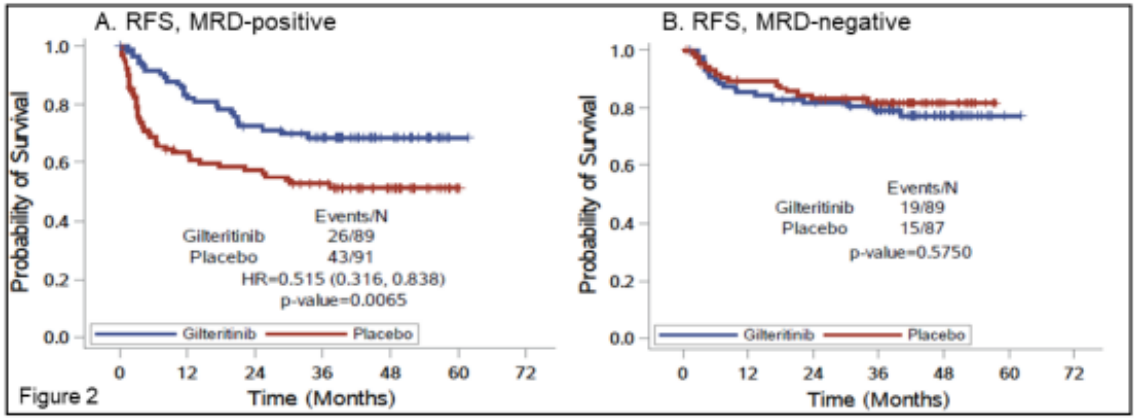


Figure 2

EXPERT CONCLUSIONS

- *"The curve that I think we all care about is if you're MRD positive, anything above* 1×10^{-6} *is curve A at the bottom [RFS, MRD positive]"*
- *"If you see this, MRD positive* 1×10^{4} *pretransplant, I'm going to give [the patient] gilteritinib; I don't care about the P* value *[P=.00518]"*

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IMPACT OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN FIRST COMPLETE REMISSION PLUS FLT3 INHIBITION WITH QUIZARTINIB IN ACUTE MYELOID LEUKEMIA WITH FLT3-ITD: RESULTS FROM QUANTUM-FIRST

Richard Schlenk, et al. S137

STUDY POPULATION

- Pts aged 18–75 yr with newly diagnosed AML screened for *FLT3*-ITD prior to starting standard induction treatment
- Pts randomized to Quiz (40 mg/d, on d 8–21) or PBO. Pts achieving complete remission (CR) or CR with incomplete hematologic recovery (CRi) received up to 4 cycles of high-dose cytarabine + Quiz (40 mg/d) or PBO and/or allo-HCT followed by up to 3 yr of Quiz continuation tx (30-60 mg/d) or PBO

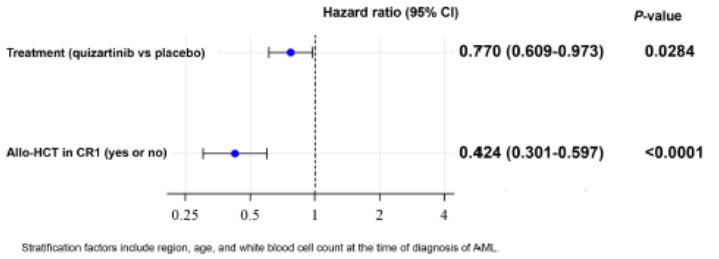
OUTCOME

- Quiz (HR 0.770, 95% CI: 0.609-0.973; *P*=.0284) and allo-HCT in CR1 (HR 0.424, 95% CI: 0.301-0.597; *P* <.0001) were favorable factors for OS (**Fig 1**)
- Pts with CR1 on Quiz had longer OS regardless of allo-HCT status (**Fig 2**)
- In pts undergoing allo-HCT in CR1 pre–allo-HCT *FLT3*-ITD MRD status (cutoff 10−4) was both prognostic and predictive; OS was longer with Quiz vs PBO, particularly in pts with pre–allo-HCT MRD-positive status (**Fig 3**)

EXPERT CONCLUSIONS

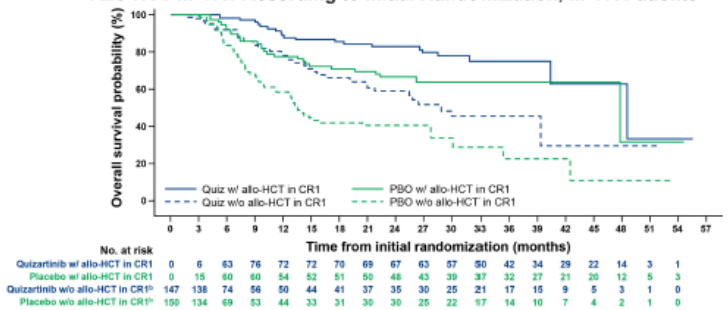
- *"If you're MRD positive pretransplant, you get Quiz, you see the survival advantage posttransplant. If you're MRD negative, you get Quiz, it doesn't help"*
- *"So, now you have 2 studies showing that MRD can predict who benefits from transplant"*

Figure 1. Post Hoc Analysis of OS with Allo-HCT in CR1 as Time Dependent Variable in All Randomized Patients



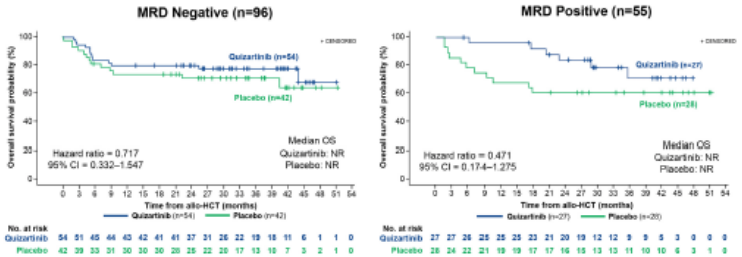
Stratification factors include region, age, and white blood cell count at the time of diagnosis of AML.

Figure 2. Post Hoc Analysis Illustrating the Time-Dependent Effect on OS of Allo-HCT in CR1 According to Initial Randomization, in CR Patients



Analysis using the Simon Makuch plot which takes into account the timing of allo-HCT occurrence, meaning that once a patient undergoes allo-HCT, the patient switches from the 'w/o allo-HCT' category to the 'w/ allo-HCT' category.
a"W/o allo-HCT in CR1' refers to CR patients without allo-HCT in the study or CR patients with allo-HCT outside CR1.

Figure 3. Post Hoc Analysis of OS in Patients Undergoing Allo-HCT in CR1 by Latest Pre-Allo-HCT *FLT3*-ITD MRD Status (Cutoff 10^{-4})



Analysis using Kaplan-Meier plots.
Note that of the 157 patients (84 in the quizartinib arm and 73 in the placebo arm) who underwent allo-HCT in CR1, 151 with MRD data were analyzed (81 in the quizartinib arm and 70 in the placebo arm).

GEMTUZUMAB-BASED INDUCTION CHEMOTHERAPY COMBINED WITH MIDOSTAURIN FOR FLT3 MUTATED AML. UPDATED TOXICITY AND INTERIM SURVIVAL ANALYSIS FROM THE NCRI AML19V2 "MIDOTARG" PILOT TRIAL*

Nigel Russell, et al. P484

EPICS

STUDY POPULATION

> In the NCRI AML19 v2 trial, pts aged 18–60 yr with newly diagnosed AML were randomized to receive with DA 3+10 plus single- or two doses of GO (DAGO1; DAGO2)

> Patients with a confirmed *FLT3*-ITD or *FLT3*-TKD could enter the "Midotarg" pilot and receive midostaurin (m) after completion of chemotherapy. Midostaurin was also given following the second induction (DA 3+8 without GO) and 2 courses of HDAC consolidation and as maintenance for 12 cycles in nontransplanted patients

OUTCOME

> Overall response (CR + CRi) was achieved in 82% (DAGO1m) and 91% (DAGO2m)

> Median follow-up is 15 mo. Estimated OS at 18 mo was 82% (**Fig 1A**) and was 81% and 84% for DAGO1m and DAGO2m, respectively. This compares favorably with 18-mo OS of 72% in pts treated with DAGO alone in AML19v1 (**Fig 1B**) (68% DAGO1; 76% DAGO2)

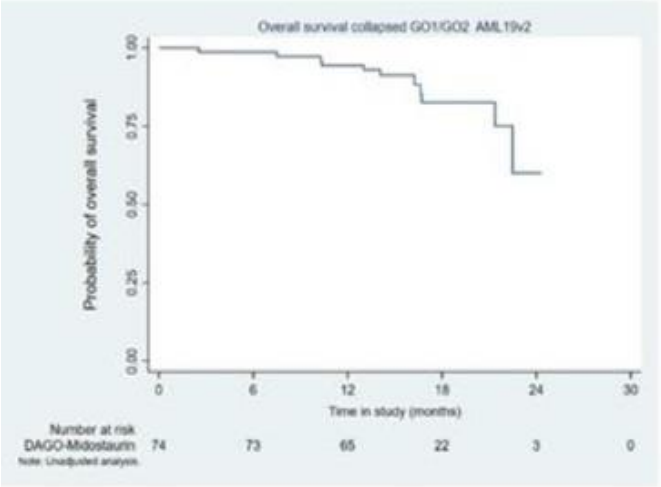
> In *NPM1*-mut pts, post-course 2 PB MRD negativity was 75% and 86% with DAGO1m and DAGO2m, respectively. This compares favorably with 61% and 74% in 65 evaluable pts with DAGO1 and DAGO2 without midostaurin on study AML 19v2

CONCLUSIONS

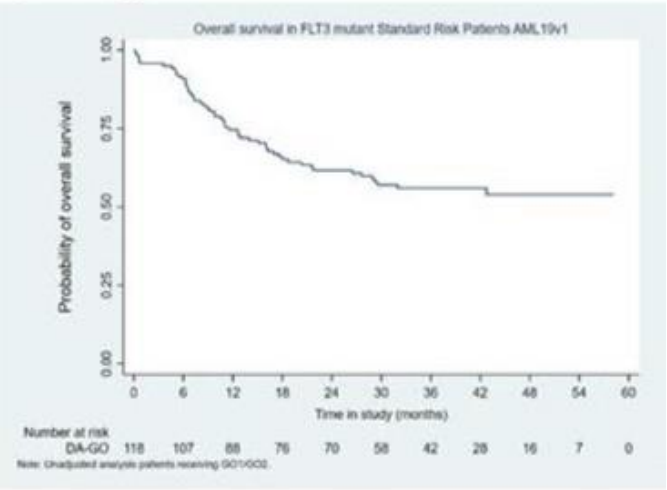
> The addition of midostaurin to DAGO1 and DAGO2 chemotherapy was well tolerated and safe in both young and old pts with *FLT3*-mut AML, with promising survival (>80% at 18 months). Further follow-up is planned

> DAGO2 gave a higher proportion of PB MRD negativity post-course 2 than DAGO1 in pts with *NPM1* mutations, which is associated with a greatly reduced risk of relapse and death

1A. Overall survival



1B. Overall survival



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*The abstract was not discussed.

NEXT-GENERATION SEQUENCING-BASED MEASURABLE RESIDUAL DISEASE MONITORING IN ACUTE MYELOID LEUKEMIA WITH FLT3 INTERNAL TANDEM DUPLICATION TREATED WITH INTENSIVE CHEMOTHERAPY PLUS MIDOSTAURIN*

Frank G. Rücker, et al. S135

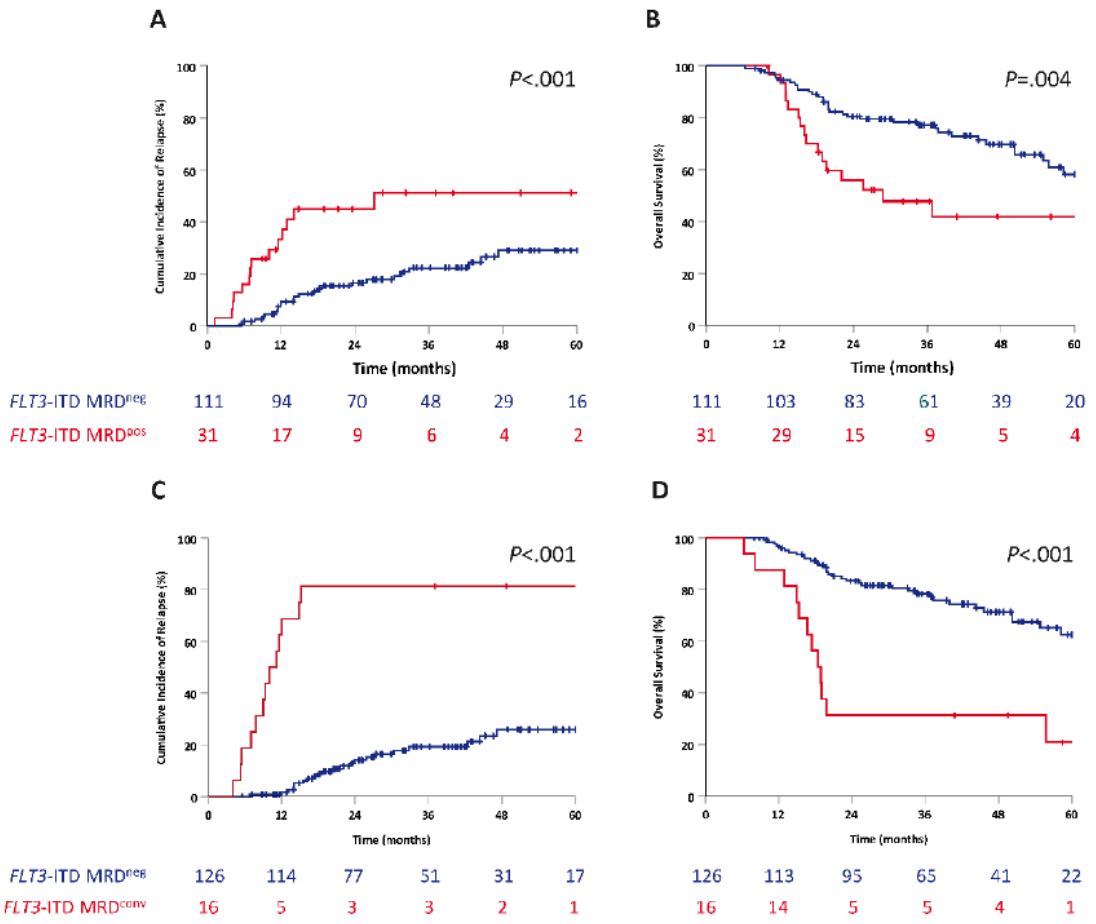
EPICS

STUDY POPULATION

> Pts aged 18–70 yr with *FLT3*-ITD–positive AML enrolled on the AMLSG 16-10 trial (NCT01477606) combining intensive chemotherapy + midostaurin (mido) followed by mido maintenance
> Aim was to evaluate the impact of the MRD status in adult pts with *FLT3*-ITD-positive AML enrolled on the AMLSG 16-10 trial

OUTCOME

> Median follow-up was 3.9 yr. Achievement of MRD negativity at C2 predicted lower 4-yr cumulative incidence rates of relapse (CIR; 4-yr CIR 29% vs 51%; *P* <.001) and death (4-yr OS 70% vs 42%; *P*=.004) **(Fig 1A and B**), also for pts undergoing HCT CR1 (4-yr CIR 16% vs 40%; *P*<.001; 4-yr OS 74% vs 48%; *P*=.014)
> During follow-up,16 pts converted from MRD negative to MRD positive and 13/16 pts relapsed within a median time of 7 d (range, 0–197 d), translating into a significantly increased relapse risk (2-yr CIR, 81% vs 14%; *P* <.001) and inferior OS (2-yr OS, 31% vs 83%; *P*<.001) (**Fig 1C and D**)



CONCLUSIONS

> NGS-based *FLT3*-ITD MRD monitoring allows for the identification of pts at high risk of relapse and death
> Combining mido with intensive chemotherapy led to MRD negativity at C2 and EOT in a high proportion of pts; at C2, MRD negativity was the strongest independent favorable prognostic factor for relapse risk and OS
> Concurrent *NPM1* mut correlated with deeper molecular responses and higher rates of MRD negativity

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*The abstract was not discussed.

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EPICS

Discussion Summary

Advances in AML: Newly Diagnosed

Advances in AML: Newly Diagnosed (1/3)

EPICS

Latest Updates

FLAG-IDA combined with gemtuzumab ozogamicin (GO) in isolated *NPM1*-mutated AML

> Experts agreed that FLAG-IDA + GO is the way forward for patients with isolated *NPM1*-mutated AML

> The experts agreed that the results showing that for patients who are PB PC2 *NPM1* MRD negative, FLAG-IDA–GO treatment appears to be sufficient with no further consolidation therapy necessary are very convincing

> Dr Daver confirmed that he is already using FLAG-IDA–GO in this population, but prefers FLAG-IDA–VEN, which results in equally good survival benefit, and is another favorable option.

> Dr Daver summarized, acknowledging that patients with *FLT3* mutation are now a separate group, that *"in isolated NPM1-mutated AML without a FLT3 mutation, adding GO to FLAG-IDA, giving 2 cycles, 82% survival, pretty good"*

Standard chemotherapy + quizartinib in patients with *FLT3*-ITD–wildtype AML

> Experts agreed that the OS improvement seen with the addition of quizartinib to standard chemotherapy in the phase II QUIWI trial is compelling; with a confirmatory phase III study, the data could be practice changing

> The experts discussed the pros and cons of standard chemotherapy + quizartinib vs FLAG-IDA–VEN in the *FLT3*-wildtype population

  – A pro is the preliminary results of the multicenter QUIWI trial, showing OS improvement with the combination

  – A con is that there is less clinical evidence for standard chemotherapy + quizartinib vs FLAG-IDA–VEN, which has 5 confirmatory trials demonstrating positive efficacy and tolerability

– Dr Komrokji commented that the molecular signature of the patients should be considered

– Dr Perl noted that data were presented looking at adverse-risk cytogenetics and "*those patients were exactly the same in their survival whether they got Quiz or not, so there is probably a mechanism here; we don't know who they are"*

> The experts agreed that a clinical trial evaluating FLAG-IDA–VEN vs FLAG-IDA–QUIZ vs FLAG-IDA–GO would be valuable

> Dr Daver noted that there was no difference in the response data in the trial, no difference in the MRD negative rate, so it seems that it is the quizartinib maintenance phase that is driving the benefit. He added, "*I think the FDA need to see this"*

Advances in AML: Newly Diagnosed (2/3)

EPICS

Latest Updates

Gilteritinib as posttransplant maintenance for *FLT3*-ITD–mutated AML: MORPHO

- Experts noted that data from the phase III MORPHO trial are among the first to support the effectiveness of measurable residual disease (MRD)-based posttransplant maintenance therapy, and on the basis of the data, they support maintenance gilteritinib in patients who are MRD positive after transplant
- For patients whose MRD does not reach 1×10^{-6}, Dr Daver and Dr Altman commented that they would "*err on the side of giving gilteritinib*," especially since there is no negative effect on RFS the agent. Dr Perl added that there was some additional toxicity with gilteritinib, *"so while there is a downside to giving it [gilteritinib], it isn't huge"*
- Dr Altman noted that in the study, ". . . *the MRD analysis came from the first pull of the aspirate. I don't know that that gets done in the community. There was some data presented at this meeting that there is concordance between the aspirate and the peripheral blood, but until we see more of that related to FLT3… if things are done exactly [as they are done] at our institutions, first pull, good-quality samples, yes, I would feel very comfortable giving gilteritinib"*
- The advisors agreed that 2 years of gilteritinib maintenance, even if a patient becomes MRD negative while on maintenance therapy, is appropriate
- Experts noted that currently there is no label for any compound as maintenance therapy; however, Dr Perl added that there is a label for a patients with R/R AML with a *FLT3* mutation, and medical insurance will cover this

MRD positivity pretransplant may predict which patients with *FLT3*-ITD–mutated AML benefit from maintenance therapy

- Experts noted that there are now 2 studies (MORPHO and QuANTUM-First) showing that pretransplant MRD-positive patients benefit from posttransplant maintenance therapy with a FLT3 inhibitor

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Conference Highlights

Advances in AML: Newly Diagnosed Elderly and/or Unfit

PHASE II STUDY ON VENETOCLAX PLUS DECITABINE FOR ELDERLY (≥60 <75YEARS) PATIENTS WITH NEWLY DIAGNOSED HIGH-INTERMEDIATE RISK AML ELIGIBLE FOR ALLO-SCT: MIDTERM UPDATE OF VEN-DEC GITMO STUDY

EPICS

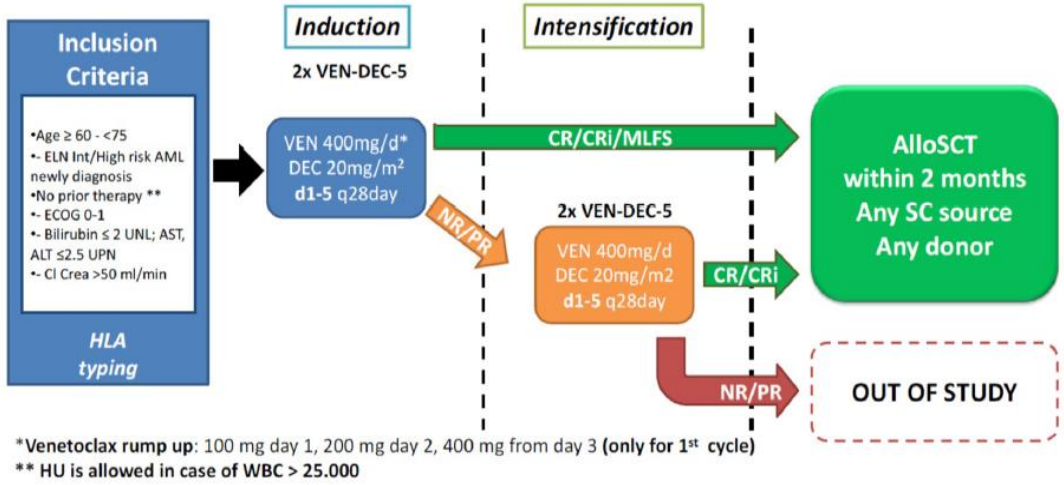
Domenico Russo, et al. P502

STUDY POPULATION

> Elderly (≥60 to <75 yr), fit AML pts (N=94)
> Primary endpoint: proportion of elderly AML pts who receive allo-SCT in CR with the “chemo-free” combination VEN-DEC (>15%)

OUTCOME

> At data cutoff, 75 pts had completed at least 2 C and were evaluable for response
> CR in 49 pts after 2 C (65.3%); of the remaining patients, 4 (15%) achieved CR after 2 additional cycles
> Median time to response was 67 d (range, 49–175). A total of 8/94 (9%) pts had died before transplant (in 3 cases for disease progression)
> The primary endpoint was met: 41/94 (43.6%) pts had successfully undergone allo-SCT, and 12 pts awaited transplant



EXPERT CONCLUSION

> *“‘It’s hard from the data presented to tell who these patients are”* [more demographic and genomic data needed]

UPDATED RESULTS OF VEN-A-QUI STUDY: A PHASE 1-2 TRIAL TO ASSESS THE SAFETY AND EFFICACY OF TRIPLETS FOR NEWLY DIAGNOSED UNFIT AML PATIENTS: AZACITIDINE OR LOW-DOSE CYTARABINE WITH VENETOCLAX AND QUIZARTINIB

Bergua Burgues, et al. S132

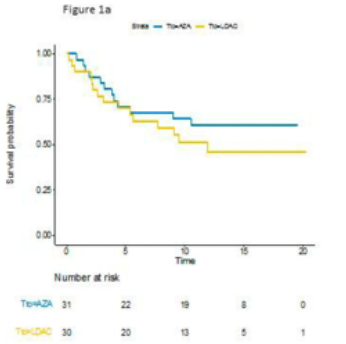
EPICS

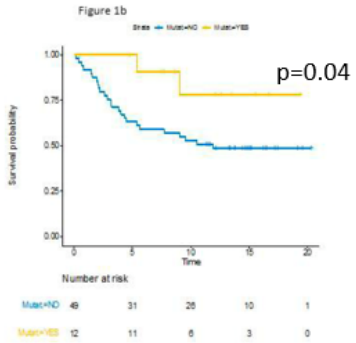
STUDY POPULATION

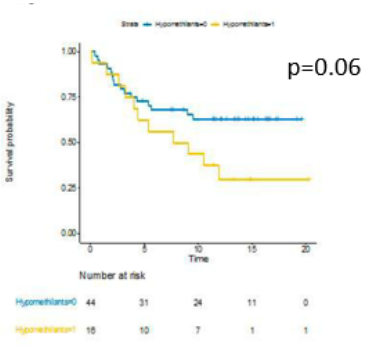
- Newly diagnosed AML pts >70 yr or unfit pts >65 yr
- Pts with previous antecedents of myeloproliferative disease, MDS; prior treatment with HMA allowed
- Randomization 1:1 QUIZ + VEN-AZA or VEN-LDAC
- *FLT3*-ITD–positive pts included (n=12)

OUTCOME

- QUIZ dose was escalated up to 60 mg in the VEN-AZA arm and up to 40 mg in VEN-LDAC arm
- DLTs in the LDAC arm included prolonged myelosuppression, particularly thrombocytopenia, and 1 pt had a CNS hemorrhage; no DLTs in the VEN-AZA arm
- 61 pts treated; median age 74 yr (70–88)
- No difference in OS between VEN-LDAC + QUIZ vs VEN-AZA + QUIZ
- *FLT3*-ITD–positive pts had an apparent OS benefit; pts with prior HMA had poorer outcomes







EXPERT CONCLUSIONS

- *"The big question is what is the right dose? Quizartinib has been tested at a lot of different doses, and the magic answer is somewhere between 40 and 60 mg, which seems to be tolerable and avoids the major side effect, which is QT prolongation"*
- *"This is the first demonstration of multicenter triplet therapy, which is important, just to see the feasibility"*

A RANDOMISED ASSESSMENT OF THE SEQUENTIAL ADDITION OF THE KINASE INHIBITOR QUIZARTINIB TO INTENSIVE CHEMOTHERAPY IN OLDER ACUTE MYELOID LEUKAEMIA (AML) PATIENTS: RESULTS FROM THE NCRI AML18 TRIAL

Steven Knapper, et al. S131

EPICS

STUDY POPULATION

> Pts from NCRI AML18 ≥60 yr fit for intensive therapy (N=464), received a first course that was DA +/- GO and were then randomized to Quiz 14 mg/d × 14 days (vs no Quiz) added in the second course of induction (DA or FLAG-IDA) and a single course of consolidation (DA, mini-FLAG-IDA, or IDAC) in older AML, regardless of *FLT3*-ITD status

> There was a second randomization to a shorter vs longer Quiz (short-Quiz = 40mg/day for 14 days after chemotherapy cycles 2 and 3 and for an additional 28 days following recovery from final course; long-Quiz = as for short Quiz but for an additional 12 x 28-day maintenance cycles)

OUTCOME

> Remission status at time of Quiz randomization: CR 68%, CRi (9%), flow MRD positive 43%, MRD negative 57%

> 96 pts (22%) were *FLT3*-ITD positive and 23 *FLT3*-TKD positive; 2 (<1%) had both mutations

> Addition of Quiz and duration of maintenance Quiz (when adjusted for HSCT) had no effects on OS in the overall study population

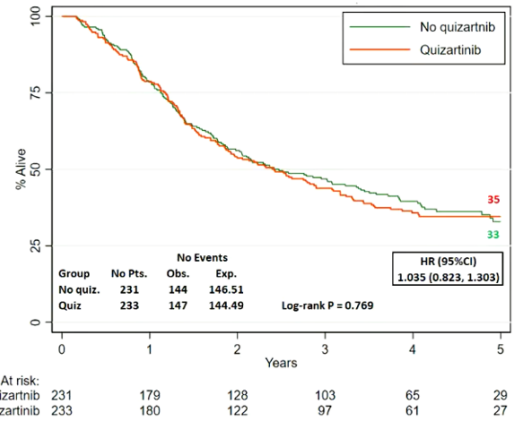
> The addition of Quiz to C2 and 3 of induction chemotherapy at a dose of 40 mg/d was well tolerated

> The subgroup analysis of *FLT3*-mut pts showed a trend toward OS benefit, consistent with the data from QuANTUM-First trial

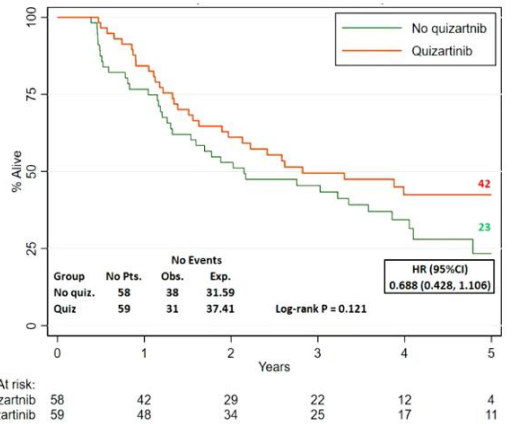
- Benefit with Quiz in FLT3-mutated patients was most apparent with short exposures to the drug rather than “long Quiz” maintenance therapy

Primary endpoint: Overall survival

All patients: Quizartinib vs No Quizartinib



***FLT3* mutated: Quizartinib vs No Quizartinib**



EXPERT CONCLUSION

> *“There was no difference between the short and long quizartinib when they censored the data for transplant, but I think that’s a little artificial, because the whole benefit might be in posttransplant maintenance, and if you censor at the time of transplant, you’ll never see that”*

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Discussion Summary

Advances in AML: Newly Diagnosed Elderly and/or Unfit

Advances in AML: Newly Diagnosed Elderly and/or Unfit (1/5)

EPICS

Latest Updates

VEN-decitabine: phase II GITMO study – midterm update

- High-intensity chemotherapy is the current standard pretransplant induction strategy for elderly, fit patients (60–75 years) with newly diagnosed high- to intermediate-risk AML
  - There is increasing movement to using VEN-AZA, a reasonable alternative induction therapy; remission rates are similar to chemotherapy
- The study's primary endpoint was considered to demonstrate a clinically meaningful benefit, with 44% of elderly, fit AML patients (60–75 years) in complete response with VEN-decitabine able to proceed to transplant
  - This high proportion of patients proceeding to transplant is considered encouraging
  - This high proportion is higher than in cooperative group studies or the CPX-351 pivotal trial
- In Dr Perl's practice, they have moved away from intensive chemotherapy as standard in this group, favoring AZA-VEN. He added that a randomized comparison of intensive chemotherapy vs VEN-HMA is currently enrolling in the UK, which will collect similar data but with a control arm, and he tries to enroll all eligible patients so that they can potentially receive this regimen
  - Dr Perl commented that it is "*nice to see that the majority of older patients who respond to the regimen are proceeding to transplant*"

Advances in AML: Newly Diagnosed Elderly and/or Unfit (2/5)

EPICS

Latest Updates

VEN-decitabine: phase II GITMO study – midterm update (cont.)

- The experts discussed the pros and cons of intensive therapy for newly-diagnosed elderly patients and the importance of patient fitness for transplant
  - Experts noted that one key advantage of VEN-DEC over intensive chemotherapy is that it contributes not only to remission rates, but also has a low burden of adverse events, which can enable more patients to be fit enough for transplant
  - A key advantage for daunorubicin and cytarabine induction therapy is in patients for whom prior HMA had failed, since a good therapy option is not available for these patients
    - In contrast, Dr Komrokji opined that if the patient had already received ≥6 cycles of AZA for MDS, the response to daunorubicin and cytarabine would be very low; therefore, he would use CLAG-M. However, he noted that the offset to this option is the toxicity
    - Dr Altman commented that VEN-HMA would be a good choice if the patient had received only limited prior treatment. She might try FLAG-IDA–VEN if the patient is young and very fit, but her choice would depend on the goal for the patient (balancing potential for long-term disease control vs burden of toxicities)

Advances in AML: Newly Diagnosed Elderly and/or Unfit (3/5)

EPICS

Latest Updates

Quizartinib + VEN-AZA or VEN-LDAC: VEN-A-QUI phase I/II trial

- Dr Perl highlighted that quizartinib is currently investigational; however, in Japan the label has been expanded to include both R/R and front line. He confirmed that QUANTUM-First is expected to lead to a new US label in AML in a few months
- The data were considered promising, particularly in *FLT3*-ITD–mutated patients; those who had received prior HMA did not do as well. Dr Perl noted that this is the first demonstration of multicenter triplet therapy, which is important to show the feasibility of the regimen
- The experts concurred that the combination is very myelosuppressive
- Dr Perl noted that the investigators were uncertain whether the regimen could be considered a low-intensity therapy
- Dr Perl acknowledged that it is uncertain whether a survival advantage, as seen in QuANTUM-First, is dependent on *FLT3*-ITD mutation. He noted that a similar HR was seen in patients without *FLT3*-ITD in QuANTUM-First, which was surprising, and added that there is a current debate about whether to further explore FLT3 inhibitors in *FLT3*-ITD–wildtype patients

Advances in AML: Newly Diagnosed Elderly and/or Unfit (4/5)

EPICS

Latest Updates

Quizartinib + intensive chemotherapy in older AML patients: NCRI AML18 trial

> Experts agreed that the data are similar to those from QuANTUM-First, at least in the *FLT3*-ITD–positive population, and there was also an apparent advantage in the wildtype population, with the caveat of censoring for transplant

> While OS was somewhat better in the quizartinib arm in the *FLT3*-ITD–positive patients, experts did not consider it impressive; however, the elderly patients in QuANTUM-First also did not do so well. Therefore, the major OS benefit of adding a *FLT3* inhibitor in AML occurs in younger patients, so alternatives may be preferable for older patients

– Experts recommend that triplets vs intensive chemotherapy be investigated in in older AML patients, because there is no SOC, and even with VEN-AZA vs AZA there was no survival advantage for the addition of VEN

> The experts discussed the possible treatment decisions for a hypothetical case of a 65-year-old, fit patient with *FLT3*-mutated disease

  – The decision was considered tricky, with a choice of intensive chemotherapy, FLT3 inhibitor, and transplant, or triplet therapy with AZA-VEN and FLT3 inhibitor

  – The experts agreed that the rationale for intensive chemotherapy is to make the patient ready for transplant, although Dr Altman added that on day 1, it may not be known if there is a donor available for the patient

  – For patients who cannot go to transplant, the question is whether a triplet can give the same durability as intensive chemotherapy and FLT3 inhibitor even if it is inferior, the benefit in loss of early mortality might still compensate for that. Dr Daver stated that it would

    • Dr Komrokji added that patients on intensive chemotherapy + FLT3 inhibitor generally do not do so well without transplant; patients will relapse

  – Dr Daver concluded that he would choose the triplet therapy in this situation, preferring gilteritinib as the FLT3 inhibitor, although acknowledging that once the data are available, quizartinib will likely be as good

Advances in AML: Newly Diagnosed Elderly and/or Unfit (5/5)

EPICS

Latest Updates

Gilteritinib + HMA-VEN in older patients with *FLT3* mutation

- Dr Daver confirmed that his practice of giving 7 days of AZA, 14 days of VEN, and 14 days of concomitant gilteritinib in the first cycle works very well
  - In subsequent cycles, the VEN is reduced to 10 or 7 days, and gilteritinib maintained as a continuous dose of 80 mg/day
- The experts discussed in which patients intensive chemotherapy is given, and there was no consensus approach
  - Dr Perl confirmed that he uses intensive chemotherapy in younger patients, and for older patients, he would use it for those who are 60–70 years old and very fit, and rarely to patients who are >70 years, outside of a study
  - For older, unfit patients, Dr Komrokji confirmed that he gives triplet; Dr Perl would not use triplet front line outside of a clinical trial, preferring HMA-VEN for a *FLT3*-ITD–positive patient (as long as he can control the patient's counts), and if the patient has a good remission, he would "*get the patient to a transplant,"* if possible. If there is persistence of a *FLT3*-ITD mutation, he switches to VEN-gilteritinib
- Dr Daver outlined an ongoing study that also involves Dr Perl and Dr Altman, which is a planned de-escalation. The regimen is 2–3 cycles of triplet therapy (AZA-VEN-gilteritinib), and if there is deep molecular remission, an option of AZA-gilteritinib for a few months, then an option of gilteritinib alone. He added that the idea is evaluate whether it is possible to make it a shorter treatment, and move to single-agent gilteritinib in 6–8 months, without losing efficacy

Triplet therapy for older patients with *IDH1* mutation

- The experts discussed the potential use of triplet therapy in patients with *IDH1/2* mutations
  - They agreed that the future with IDH inhibitors is unclear, unlike with *FLT3* inhibitors, where the physicians have experience
  - Experts concurred that a trial with triplet therapy HMA-VEN-olutasidenib for *IDH1* mutation-positive patients would be valuable

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Conference Highlights

Advances in AML: Relapsed/Refractory

VENETOCLAX (VEN) COMBINED WITH FLAG-IDA IS AN EFFECTIVE REGIMEN FOR PATIENTS (PTS) WITH NEWLY DIAGNOSED (ND) AND RELAPSED/REFRACTORY (R/R) ACUTE MYELOID LEUKEMIA (AML)

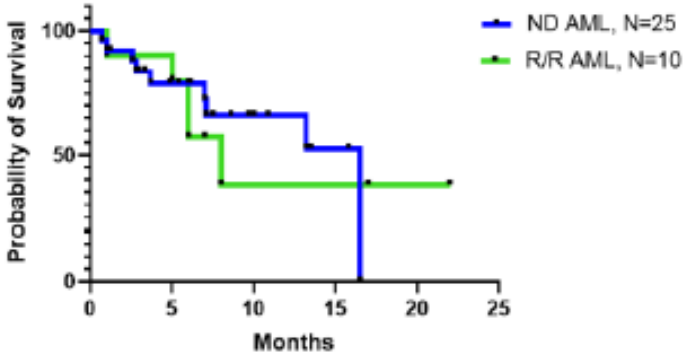
EPICS

Madelyn Burkart, et al. P545

STUDY POPULATION

> Single-center, retrospective study to assess the clinical activity of FLAG-IDA–VEN or cladribine-VEN in pts with AML (N=35; 25 ND and 10 R/R AML pts)
> VEN was administered for 7- or 14-days during induction and 7-days during consolidation with appropriate dose adjustment of VEN for azoles. Cladribine was used in consolidation due to shortages of fludarabine

Figure 1: Overall Survival of ND and R/R AML Patients Treated with FLAG-IDA+VEN



OUTCOME

> In pts with ND AML, 56% had adverse-risk disease. After median follow-up of 5.4 mo, 19 pts (76%) achieved CR/CRi. MRD status was available for 8 pts; 6 pts achieved MRD negativity using flow cytometry ($<10^{-3}$). Median OS: 16.5 mo
> In patients with R/R AML, 9 were in salvage 1 and 1 pt had received prior allo-SCT. All pts responded: 8 CR/CRi and 2 morphologic leukemia-free state (MLFS). Of the 8 pts who achieved CR/CRi, 6 were bridged to allo-SCT (2 of whom relapsed 2 mo after allo-SCT and died due to PD), 1 pt died in CR due to sepsis after 3 cycles of consolidation, and 1 remains alive in CR for 5+ mo. Median OS: 8 mo

EXPERT CONCLUSIONS

> Experts were intrigued by the activity of the VEN regimen in this study. However, the power of these data are limited by relatively few patients, the non-randomized and retrospective nature of the design, and the relatively short duration of follow-up

OLUTASIDENIB IN POST-VENETOCLAX PATIENTS WITH MUTANT IDH1 AML

Jorge Cortes, et al. P555

EPICS

STUDY POPULATION

> Olutasidenib is approved for R/R AML on the basis of the registrational cohort (n=153) of a phase II trial, with a CR/CRh of 35%, and DOR of 25.9 mo

> 17 pts from the phase II trial were previously treated with VEN combination regimens and are followed-up herein

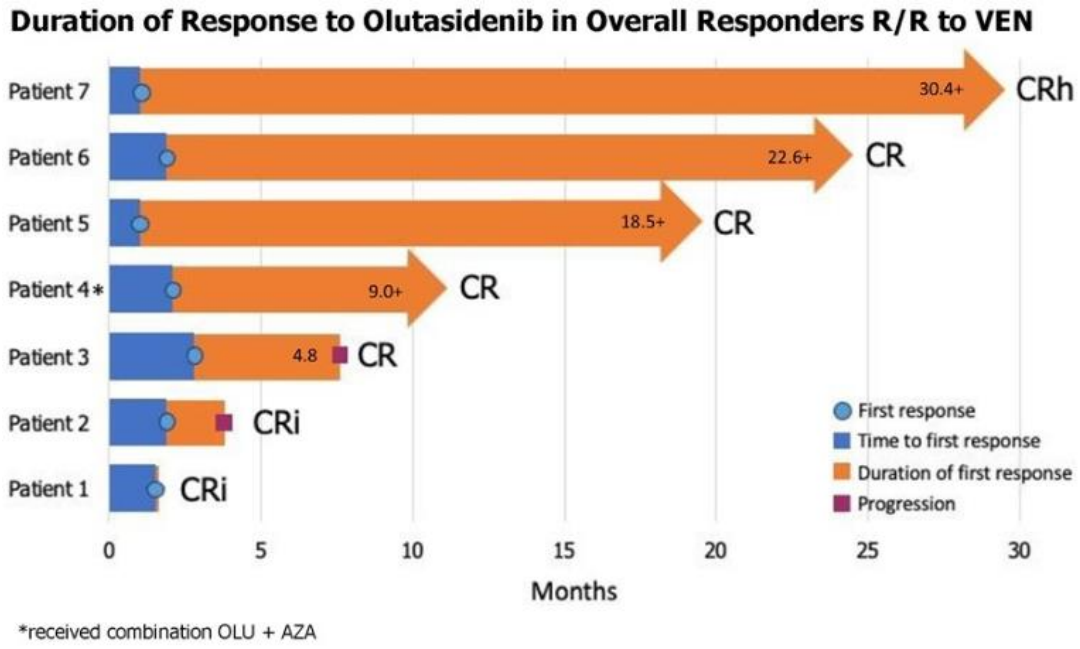
OUTCOME

> At the time of presentation, 5 are ongoing and 12 discontinued, due to: progressive disease (n=6), adverse events (n=4), or pt withdrawal (n=2)

> Best response to olutasidenib after prior VEN-containing regimen was CR/CRh: 29.4%, of which 4 (23.5%) were CR

> Median time to CR/CRh was 2.1 mo; median duration of CR/CRh was 18.5 mo and ongoing

> In 8 pts who received VEN-AZA, 3 (37.5%) pts achieved CR/CRh



EXPERT CONCLUSION

> *"…the message from the poster is, if you've used HMA-VEN and failed . . . go for olutasidenib"*

ACTIVITY, TOLERABILITY, AND RESISTANCE PROFILE OF THE MENIN INHIBITOR ZIFTOMENIB IN ADULTS WITH RELAPSED/REFRACTORY NPM1-MUTATED AML

Amir Fathi, et al. P504/LBA2713

EPICS

STUDY POPULATION

- Pts (median age: 70.5 yr [22–86 yr]) with R/R AML treated in the global, open-label phase I/II study of ziftomenib; 35% *FLT3,* 40% *IDH1/2*
- Median number of prior therapies was 3 with 65% prior VEN
- 20 pts treated at ziftomenib 600 mg PO daily

OUTCOME

- 85% had at least one G≥3 TEAE, with 30% of TEAEs potentially treatment related; G3 AEs were anemia, 25%; thrombocytopenia, 20%; 20%; 1 pt had G3 differentiation syndrome (DS)
- CR 35%, CRc 40%; median DOR 8.2 mo (still maturing); median time to CR 70 d
- Median OS 5.1 mo; at the cutoff, 57% of pts achieving CRc remained on treatment or in post-SCT follow-up
- Of 29 patients who received any dose level of ziftomenib, one patient who received a lower dose developed a resistance mutation (MEN1-M327I), which was detected at C4D28; pt had stable disease through cycle 7

Responses to treatment with ziftomenib

Best Overall Response	n (%)
Complete remission rate (CR)	**7 (35)**
CRc rate (CR+CRh+CRi)	8 (40)
Overall response rate (CR+CRh+CRi+MLFS)	9 (45)
CR	7 (35)
CRh	0
CRi	1 (5)
MLFS	1 (5)

33% CR co-*FLT3*m (N=6)
50% CR co-*IDH*m (N=8)

CONCLUSION

Ziftomenib continues to demonstrate significant clinical activity in heavily pretreated and co-mutated R/R *NPM1*-mutated AML pts where 35% of pts achieved CR. The safety profile remains consistent, and episodes of DS are clinically manageable. A single-arm registration-directed Phase II study is currently accruing to further evaluate ziftomenib monotherapy in R/R NPM1-mutated AML

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Discussion Summary

Advances in AML: Relapsed/Refractory

Advances in AML: Relapsed/Refractory (1/2)

EPICS

Latest Updates

Venetoclax + FLAG-IDA in newly diagnosed and R/R AML

- Recent results from a phase Ib/II trial from MD Anderson were considered for the combination FLAG-IDA–VEN in newly diagnosed and R/R AML
  - The experts agreed that the additional data from a second center *(Northwestern Memorial Hospital, Chicago, US)* further support these findings; however, the follow-up is short, and there are still no randomized data
  - Dr Altman commented, *"There is increasing experience with FLAG-IDA–VEN and an increasing ability to handle the regimen safely at experienced institutions"*

Olutasidenib in post-VEN patients with *IDH1*-mutated R/R AML

- Experts agreed that the data showing olutasidenib induced durable remissions in patients with *IDH1*-mutated R/R AML, including those for whom prior treatment with a VEN-based regimen failed, support using olutasidenib in patients post–HMA-VEN. Dr Altman noted, "*Importantly, I would consider olutasidenib in VEN-exposed patients, in IDH1-mutated patients*"
- While most of the experts would add olutasidenib to HMA, they acknowledged that the label will most likely be as a single agent
- Experts concurred that this could be practice changing, if confirmed in more patients (~40)
- Experts also agreed that additional data to support triplet therapy with an IDH1 inhibitor would be valuable
- The experts discussed the future use of ivosidenib vs olutasidenib in the community, given the label differences (ivosidenib label is broader, in front line and R/R, whereas olutasidenib will only be in R/R). Dr Altman noted that the data presented are critical, given there are no favorable data for ivosidenib post–AZA-VEN. The experts agreed that this could be an important differentiator for olutasidenib
- Dr Altman commented that it would be good to have data on the use of olutasidenib as up-front therapy

Advances in AML: Relapsed/Refractory (2/2)

EPICS

Latest Updates

Ziftomenib in patients with *NPM1*-mutated R/R AML

- The experts are encouraged by the data with ziftomenib but agreed that longer follow-up is needed. Dr Altman noted, *"My takeaway is that we need to continue to follow these patients, so longer follow-up and optimizing of use, by which I mean with upcoming combinatorial studies"*
- Regarding the safety profile of ziftomenib, Dr Altman (a co-author on abstract P504) confirmed that there were no reports of QT prolongation, which is in line with her clinical experience. Dr Daver commented that there are differences between the Menin inhibitors; however, he is encouraged that the incidence of DS was not severe or fatal with ziftomenib
- In general, the experts agreed that there is excitement about Menin inhibitors in R/R AML, but it is unclear which one will be the front-runner, and in which population

Conference Coverage: EHA 2023 – Focus on AML and MDS

EPICS

Overall Conclusions: Dr Jabbour

MDS

- *"I am excited about the COMMANDS trial and luspatercept as a 'newborn' in the frontline"*
- *"HMA-VEN is promising in MDS… but I think 14 days is a lot, it should be 7 days"*
- *"I've heard about the classification without prognostic implication and all in blood, which is fine"*
- *Imetelstat is disease modifying, and I think the future is to move it to higher risk in combination with HMA"*

AML

- "*What I retain as practice changing is quizartinib plus intensive chemotherapy in wild type, GO in NPM1 mutated group and FLT3 positive"*
- *"MORPHO and other studies showing MRD are critical to decide what to do post transplant"*
- *"I am happy with the olutasidenib data, which is really good data. We need larger set of patients but it's a good option in post HMA-VEN and I don't think that the ivosidenib label should influence the way we treat in second line"*
- *"We need more data on FLAG-IDA-VEN to confirm the experience in MD Anderson with zero percent early mortality"*

APTITUDE HEALTH®

US 5901-C Peachtree Dunwoody Road NE
Suite 200, Atlanta, GA 30328, US

EU Wilhelmina van Pruisenweg 104
2595 AN The Hague, the Netherlands

UK 6th Floor, 2 Kingdom Street
London, W2 6BD, United Kingdom

aptitudehealth.com