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Conference Coverage: EHA 2023 – Focus on Leukemia and MDS

Full Report

June 19, 2023

Report Contents

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Meeting Snapshot

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LIVE ROUNDTABLE MEETING

DATE:
June 19, 2023

DISEASE STATE AND DATA PRESENTATIONS by key experts

INSIGHTS REPORT including postmeeting analyses and actionable recommendations

PANEL: Key experts in leukemia and MDS

> 4 from the US
> 3 from the EU

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

Panel Consisting of 4 US and 3 EU Leukemia and MDS Experts

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Jae Park, MD
Memorial Sloan Kettering
Cancer Center

Gert Ossenkoppele, MD, PhD
VU University Medical Center
Amsterdam

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

Tapan Kadia, MD
University of Texas
MD Anderson Cancer Center

Valeria Santini, MD
University of Florence
Medical School

Josep-María Ribera, MD, PhD
Hospital Germans Trias i Pujol

Rami Komrokji, MD
Moffitt Cancer Center

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Meeting Agenda

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Time (CT/CEST)	Topic	Speaker/Moderator
8.30 AM/15.30	Welcome, Introductions, and Meeting Objectives	Elias Jabbour, MD
8.35 AM/15.35	**New Developments in First-Line Treatment of MDS**	Valeria Santini, MD
8.40 AM/15.40	Discussion	Elias Jabbour, MD
8.50 AM/15.50	**New Developments in Targeted Treatment of MDS and Treatment of R/R MDS**	Rami Komrokji, MD
8.55 AM/15.55	Discussion and Key Takeaways	Elias Jabbour, MD, Valeria Santini, MD, and Rami Komrokji, MD
9.10 AM/16.10	**Advances in AML: Newly Diagnosed**	Gert Ossenkoppele, MD, PhD
9.20 AM/16.20	Discussion and Key Takeaways	Elias Jabbour, MD, and Gert Ossenkoppele, MD, PhD
9.45 AM/16.45	**Advances in AML: Newly Diagnosed Elderly and/or Unfit and R/R Disease**	Tapan Kadia, MD
9.50 AM/16.50	Discussion and Key Takeaways	Elias Jabbour, MD, and Tapan Kadia, MD
10.15 AM/17.15	Break	
10.20 AM/17.20	**Advances in ALL: Newly Diagnosed**	Jae Park, MD
10.30 AM/17.30	Discussion and Key Takeaways	Elias Jabbour, MD, and Jae Park, MD
10.55 AM/17.55	**Advances in ALL: R/R Disease**	Josep-María Ribera, MD, PhD
11.00 AM/18.00	Discussion and Key Takeaways	Elias Jabbour, MD, and Josep-María Ribera, MD, PhD
11.25 AM/18.25	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 treated with KER-050 at the recommended phase-2 dose (RP2D; 3.75 mg/kg with titration to 5 mg/kg every 4 wk)
- Patients treated at RP2D (N = 59) included 31 (53%) high-transfusion-burden (HTB) pts and 42 (71%) RS-positive pts

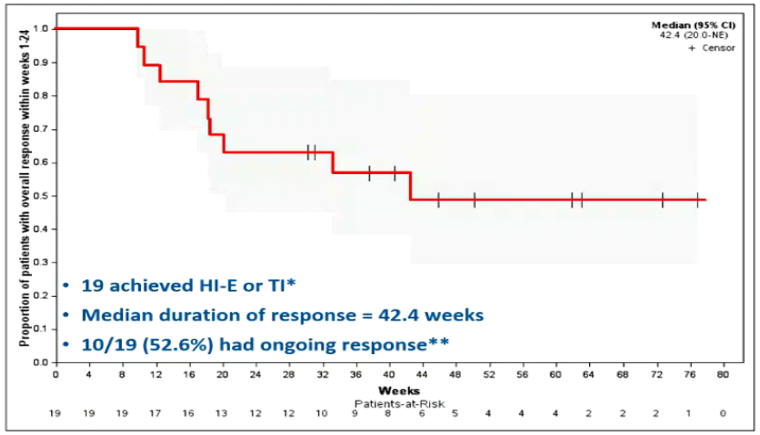
OUTCOME

- Mean treatment duration was 225 days; median doses received: 6 (1–22)
- The most frequent AEs regardless of causality were fatigue (22%), nausea, diarrhea (19% each), epistaxis (17%), COVID-19, and 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
- Responses to KER-050 were durable

Hematological response in low-risk 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 safety of the drug seems to be quite good because didn't have any treatment-related adverse event, only some nausea, some injection site reaction, but not such to stop treatment"*
- *"I think these data were quite exciting and challenging. We would see when the complete number of patients will be included, what is going to be maintained in terms of response"*

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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

Matteo Giovanni Della Porta, et al. S102

EPICS

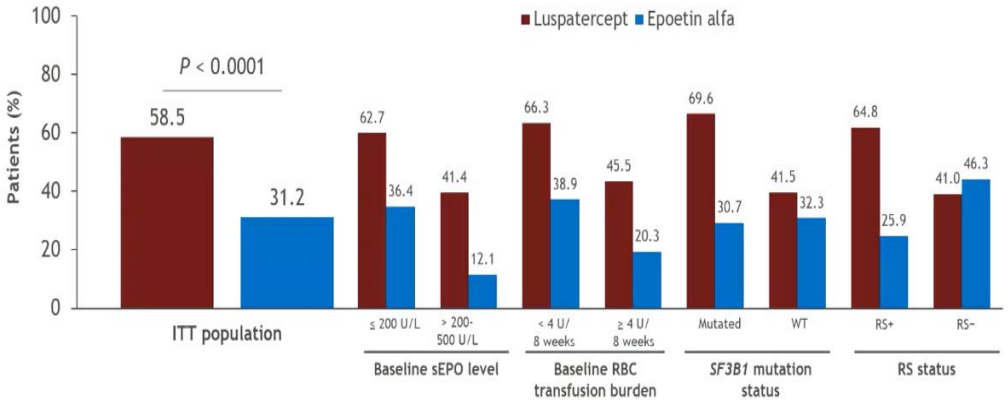
STUDY POPULATION

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

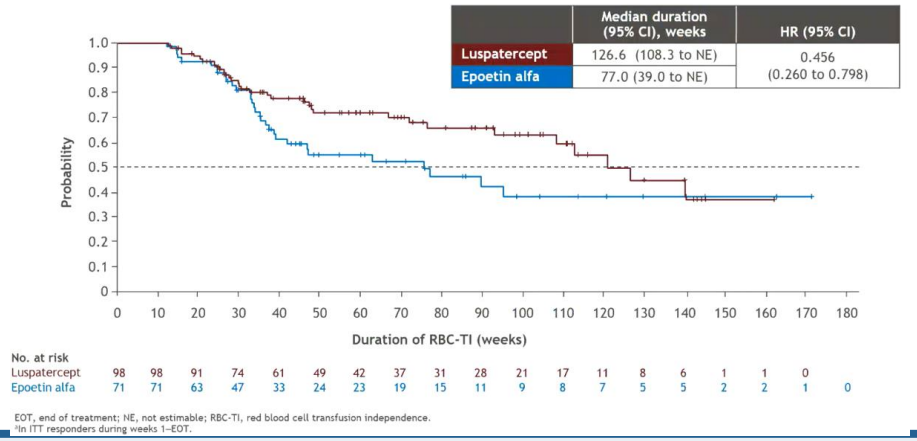
OUTCOME

- At data cutoff, 58.5% of pts receiving luspatercept and 31.2% epoetin alfa achieved the primary endpoint (*P* <.0001) (**Fig A**)
- Benefits in the primary endpoint were consistent across subgroups except for RS status; luspatercept and PBO appeared similar in RS-negative patients
- 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 wk 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

- *"The results were promising because again it seemed that luspatercept, it's more active in this setting with respect just to epo"*
- *"What is less favorable for luspatercept only is the absence of RS. The SF3B1 mutation favors significantly the luspatercept treatment"*
- *"The treatment with luspatercept is also really well tolerated"*

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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

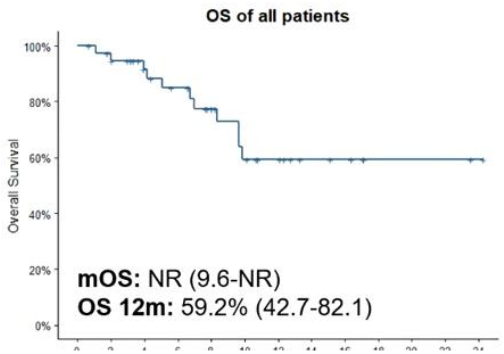
> Pts aged 27–94 yr with confirmed diagnosis of treatment-naive HR MDS or CMML (IPSS intermediate-2 or high) and bone marrow blasts >5%
> High frequency of *ASXL1* (48.7%) and *TP53* mutations (20.5%)

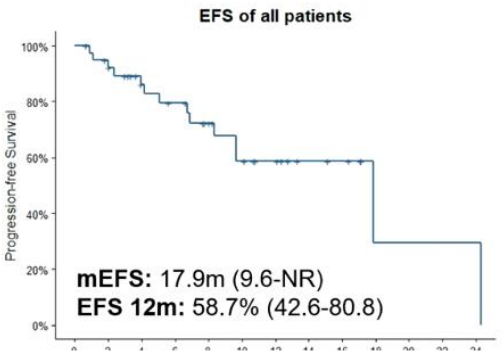
OUTCOME

> 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

> *"I think that's a feasible combination, and it's high time I think we go for total oral therapy in this kind of patient"*
> *"We have to see how many patients can in the future go for receiving more than 2 cycles and long treatment"*

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Discussion Summary

New Developments in First-Line Treatment of MDS

New Developments in First-Line Treatment of MDS (1/3)

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Lower-Risk (LR) MDS

KER-050

- When comparing the KER050-MD-201 phase II study with the established therapeutic profile of luspatercept, experts described the data showing a rebound of platelets as differentiating and promising for KER-050
- Experts found the responses in the high-transfusion-burden population to be the most impressive

> ***Dr Santini:***
> *I think these data were quite exciting and challenging. We will see when the complete number of patients are included, what is going to be maintained in terms of response*

New Developments in First-Line Treatment of MDS (2/3)

EPICS

Lower-Risk (LR) MDS

Luspatercept

- Although most experts do plan to move luspatercept into the front line in RS-positive LR MDS patients, many do not consider the COMMANDS ITT results "earth-shaking" and view the lack of response in RS-negative patients as a major shortcoming of the study
  - In contrast, Dr Santini found the increase in RBC transfusion independence of >12 wk in the COMMANDS ITT population (58.5% vs 31.2%) to be promising, especially considering that the response in the COMMANDS study not only includes transfusion independence, but also requires a concurrent mean hemoglobin increase of ≥1.5 g/dL
- Dr Santini and Dr Jabbour debated whether the demonstrated benefits outweigh the cost of luspatercept in practice for all comers
  - In addition to the cost, Dr Santini pointed out that EPO can be self-administered at home, whereas luspatercept currently requires a clinic visit. QOL associated with EPO vs luspatercept will also need to be considered
  - They believe that doctors will likely use EPO first in RS-negative patients and consider luspatercept next in patients who do not respond to EPO, citing the cost of luspatercept as a major reason for this approach

Unmet medical needs

- Dr Santini stated that patients with thrombocytopenia are the “Achilles’ heel” in the care of MDS because they have limited therapy options; another unmet need is RS-negative patients in whom EPO is not sufficient to maintain RBC count

> ***Dr Santini:***
> *What is less favorable for luspatercept only is the absence of ring sideroblasts. The SF3B1 mutation favors significantly the luspatercept treatment*

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

EPICS

Higher-Risk (HR) MDS

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

- The ORR of 94.5% in a “difficult” patient population with very-high IPSS-M is seen as a good achievement, making the total oral combination feasible
  - The experts support adoption of a total oral therapy in higher-risk MDS patients
  - Dr Santini found the response to venetoclax for patients with *TP53* mutations and complex karyotypes (patients typically not associated with good response to venetoclax) very interesting
- Experts agreed that a total oral therapy is attractive but indicated modifications to the 14-day venetoclax dosing schedule are required. They suggested that a 7-day dosing schedule would be better tolerated
  - Dr Santini said the myelosuppressive effects of this regimen were expected, but highlighted that some patients did not receive many cycles
  - Dr Santini suggested a larger study investigating how long patients can be treated on the same dosing scheme of venetoclax and oral decitabine-cedazuridine, as there could be cumulative toxicities
- Experts eagerly await the release of the VERONA trial data for additional results in HR-MDS
- The current trial and VERONA examine early treatment settings; one unmet need identified by experts is better therapies in the higher-risk R/R MDS setting
  - Dr Komrokji believes such trials should separate unique molecular categories; in particular, *TP53* mutations should not be lumped with other categories when looking at therapeutic options for patients with higher-risk MDS

> ***Dr Santini:***
> *This total oral therapy is something I really would support for this kind of patients*

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Conference Highlights

New Developments in Targeted Treatment of MDS and 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

EPICS

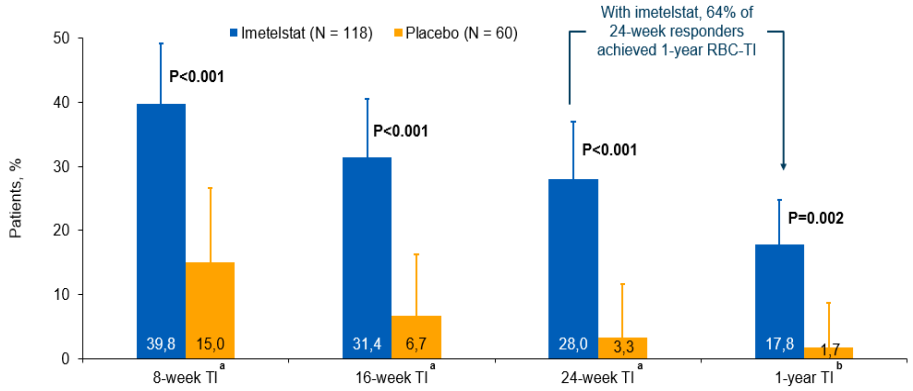
STUDY POPULATION

> Heavily 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

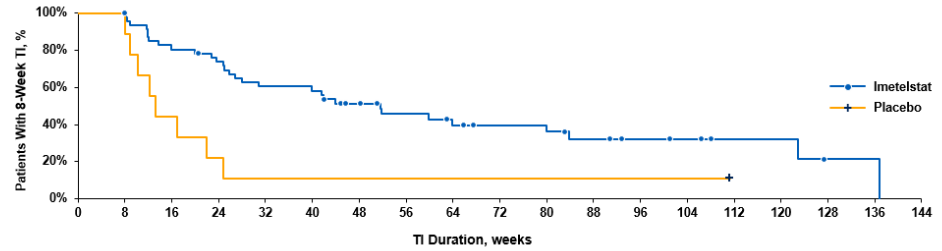
> Primary endpoint was met: 47 pts (39.8%) vs 9 pts (15.0%) receiving imetelstat vs PBO achieved 8-wk TI; *P* <.001 **(Fig A)**
> The rate of 8-wk TI was also significantly higher with imetelstat vs PBO across subgroups, including in RS-negative pts
> Median TI duration (95% CI) was 51.6 (26.9–83.9) 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

> *"In general, the treatment is well tolerated"*
> *"Those are durable responses. And the median hemoglobin increase on the study was 3.6 g. This is really impressive in MDS"*
> *"What's unique about imetelstat, I think we see activity in the ring sideroblast negative that's almost similar to RS-positive"*

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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

EPICS

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

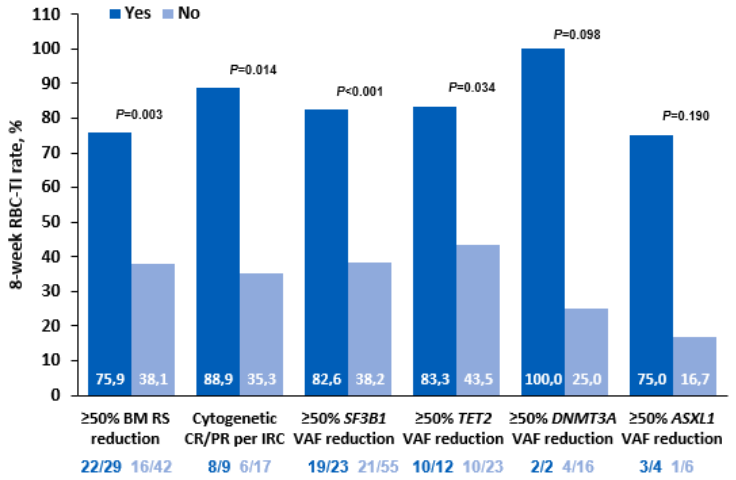
OUTCOME

> 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 and 40% with *ASXL1* mutation had ≥50% VAF reduction
> 8-wk and 24-wk RBC TI correlated with reductions in RS cells, cytogenetic responses, and VAF reduction in pts treated with imetelstat

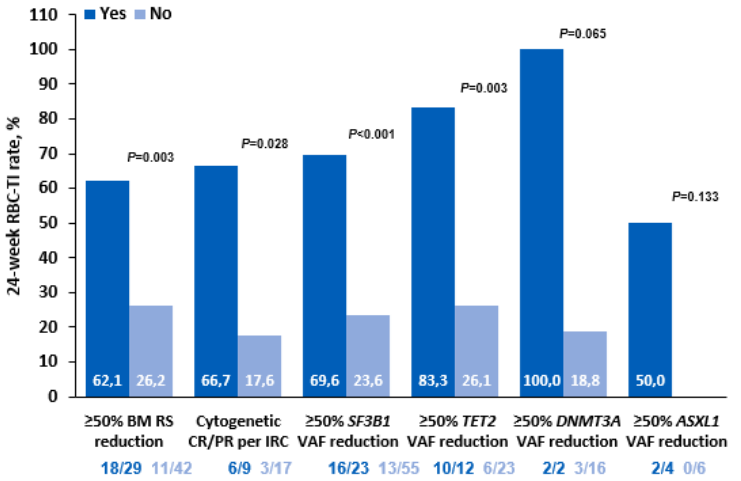
EXPERT CONCLUSIONS

> *"This is not seen in other medications. It suggests that it will be disease modifying, obviously, we need longer follow-up to see impact on survival"*

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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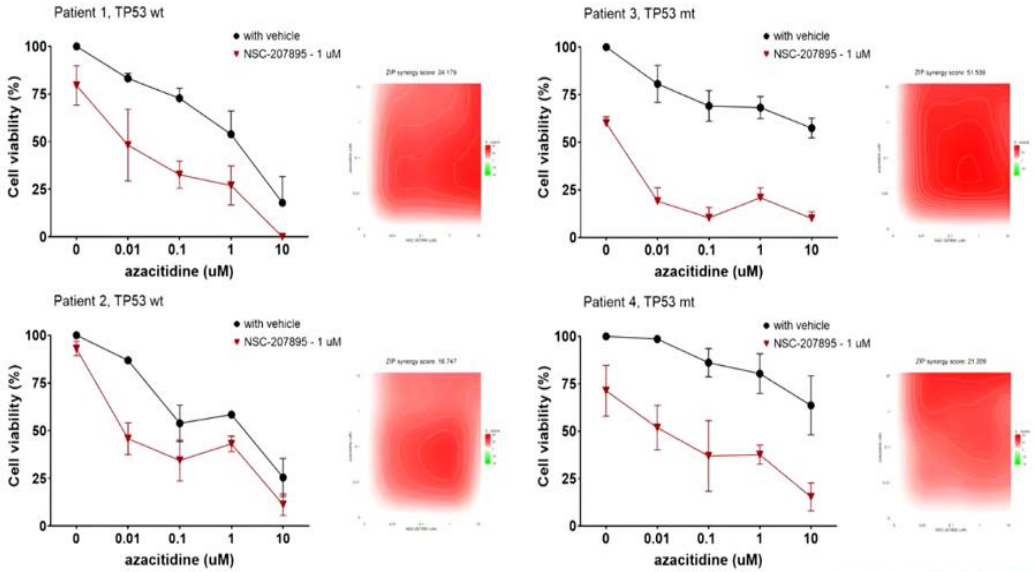
STUDY POPULATION

> 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



EXPERT CONCLUSIONS

> *"There is a concern about evolving TP53 mutation. I think we'll have to see a little bit more about this before getting excited in those combinations"*

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

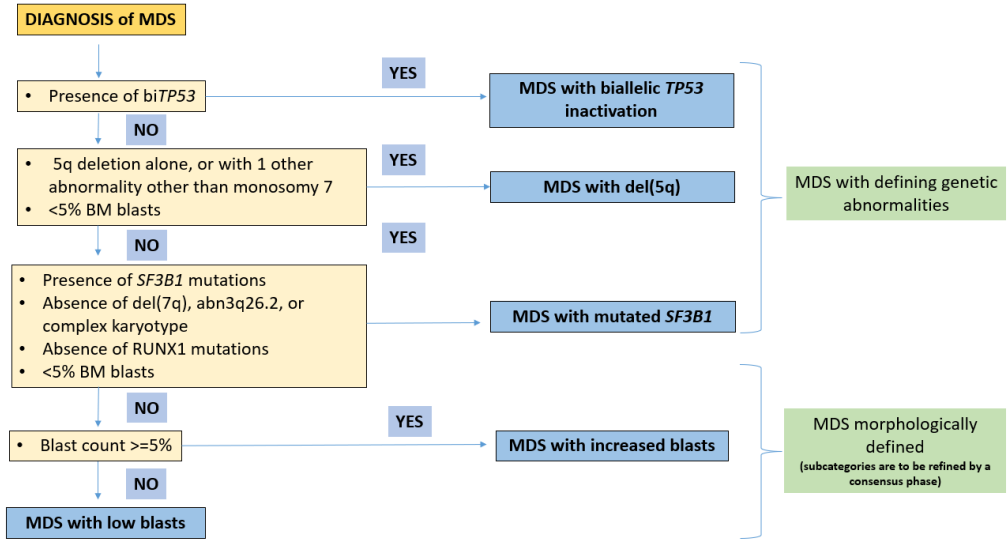
- In 2022, 2 new classifications for myeloid neoplasms were published: the World Health Organization (WHO) and International Consensus Classification (ICC)
- The aims were to validate and compare these 2 classifications in a large international cohort of MDS pts and to provide data-driven evidence for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

OUTCOME

- MDS-*SF3B1*m 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*m MDS pts had the shortest survival
- Pts with MDS-RS *SF3B1*wt had similar outcomes to MDS low blasts
- Increased myeloblasts are associated with worse outcome, but the exact cutoff is not clear

EXPERT CONCLUSIONS

- *"There are unique categories that we should not lump in clinical trials like SF3B1, deletion 5q, and biallelic P53. I think we should look at those in different trials, not lump them in trials in general"*



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 Targeted Treatment of MDS and Treatment of R/R MDS

New Developments in Targeted Treatment of MDS and Treatment of R/R MDS (1/2)

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LR-MDS R/R to ESA

Imetelstat in LR-MDS R/R to ESA

- Considering the presented data at EHA 2023, experts anticipate that imetelstat will be approved
- Experts were quite impressed by the median hemoglobin increase in IMerge, describing it as a “robust” restoration of erythropoiesis
- They appreciated the inclusion of patients with high transfusion burden in IMerge
  - The durable benefits of 16-wk TI of 31.4% vs 6.7% and the mDOR of 51.6 wk vs 13.3 wk (HR 0.23) were considered impressive
  - Experts see the responses in patients for whom EPO failed as better for imetelstat vs HMA; the only advantage recognized for HMA over imetelstat is that LR-MDS R/R patients can have concurrent neutropenia and thrombocytopenia that are unlikely to respond to imetelstat, whereas trilineage responses are possible with an HMA
- While the experts were impressed overall, they expect a label restriction for imetelstat in patients with concurrent neutropenia and thrombocytopenia
  - They sometimes have to hold the second cycle of imetelstat because of myelosuppression
- Experts plan to use imetelstat in the second-line treatment of LR MDS, with a preference to use luspatercept in the first-line treatment of RS-positive MDS and ESA for RS-negative MDS
  - However, they were encouraged by the responses seen for imetelstat in both populations
- Imetelstat disease-modification data, particularly the reduction of *SF3B1* VAF, are seen as very important and proof of concept that imetelstat not only reduces transfusion burden, but can also affect the disease course

> ***Dr Komrokji:***
> *In patients that will have good chance of response to luspatercept, it will be our first step, and this [imetelstat] is going to be second step. . . . In patients with RS negative, I think there is still going to be a role for ESA as first line and in second line; maybe imetelstat will become an option in the non-del(5q)*

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New Developments in Targeted Treatment of MDS and Treatment of R/R MDS (2/2)

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Higher-Risk (HR) R/R MDS

Higher *MDMX* expression is associated with HMA resistance

> Experts were unsure about MDMX inhibitors, stating their skepticism regarding the need to be *TP53*wt in order to have a good response; more data are needed

Unmet needs

> Better therapies in the higher-risk R/R MDS setting are needed

Dr Komrokji:
"I think higher-risk MDS after HMA failure is really an unmet area that we need to focus with new targeted agents"

WHO Classification From 2017–2022 and ICC 2022

MDS classification updates

> Experts' most important takeaway is that unique categories such as *SF3B1*, del(5q), and biallelic *TP53* that would benefit from mutation-specific separate clinical trials and should not be lumped together in clinical trials in the future

APTITUDE HEALTH®

EPICS

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, FLAG-IDA–GO had 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 PB PC2 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**)

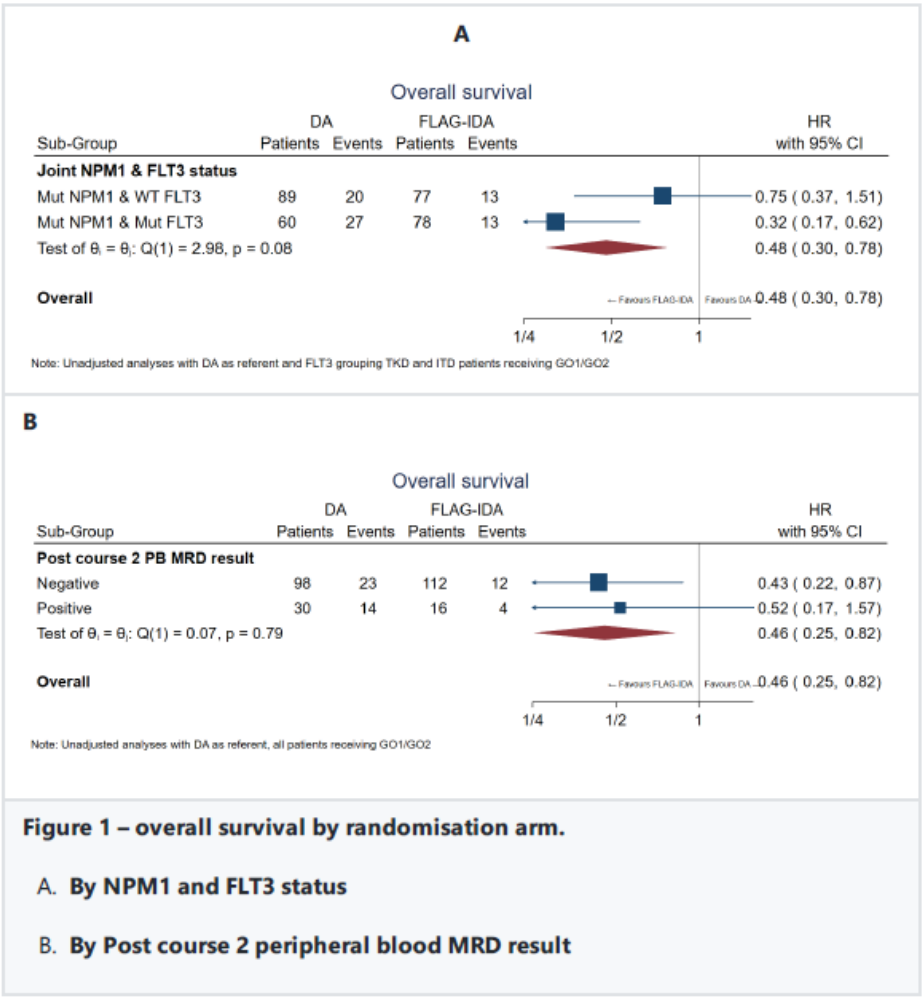

Figure 1 – overall survival by randomisation arm.

A. **By NPM1 and FLT3 status**

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

EXPERT CONCLUSIONS

- *"It seems that for those patients who are MRD negative after 2 cycles of FLAG-IDA–GO, it is really effective treatment, and no allogeneic stem cell transplantation is necessary"*

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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 was higher than in QuANTUM-First, at 60 mg/d × 14 d

OUTCOME

- At data cutoff, 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

Figure 1A: Event-free survival

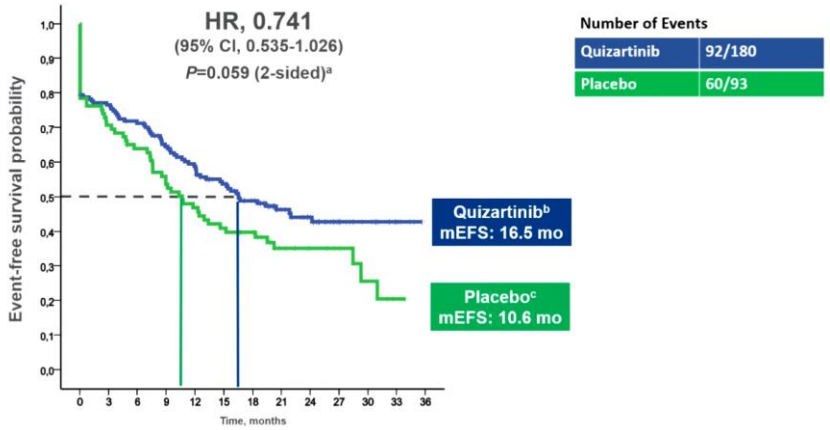
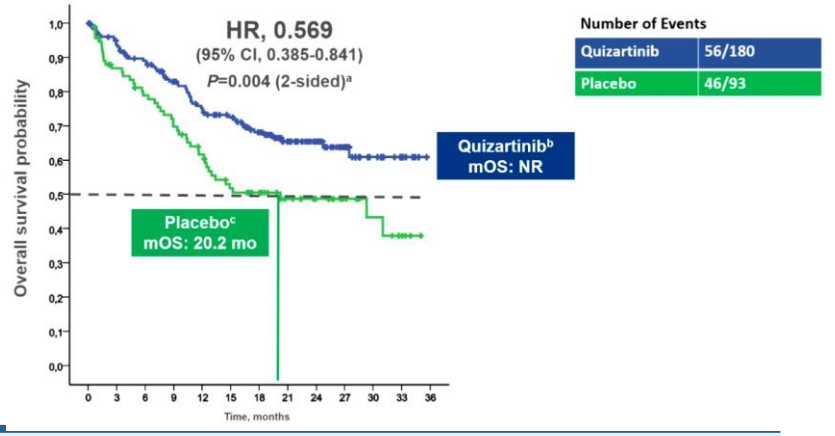


Figure 1B: Overall survival



EXPERT CONCLUSIONS

- *"The study suggests that quizartinib added to a classical intensive treatment scheme can prolong overall survival in newly diagnosed FLT3-ITD wildtype AML"*

APTITUDE HEALTH®

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 for *FLT3*-ITD AML

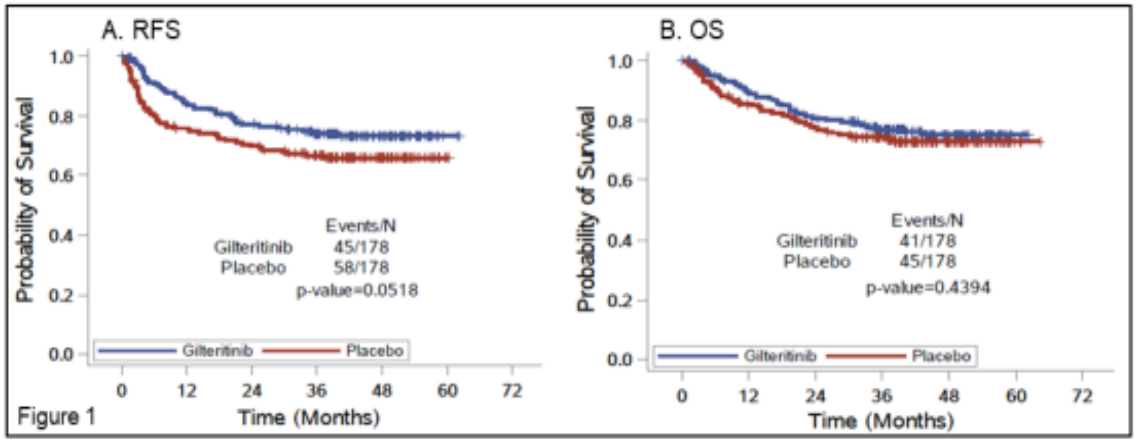


Figure 1

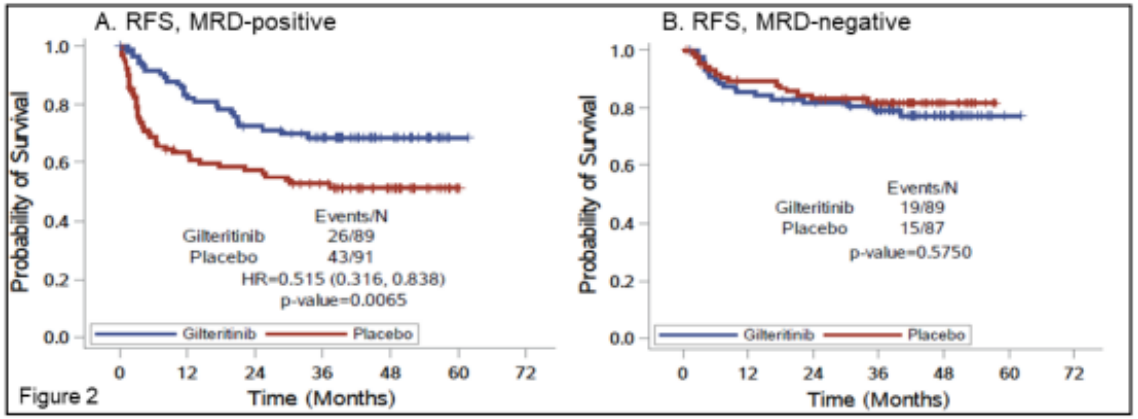


Figure 2

EXPERT CONCLUSIONS

- *"I think we all expected that it would be a positive study, but it was not and also the OS showed no difference between both arms"*
- *"I think one of the conclusions could be that gilteritinib appears to have a clear benefit in around 50% of patients who have detectable MRD pre or post-allo compared to those without detectable MRD"*

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 Schenk, et al. S137

EPICS

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

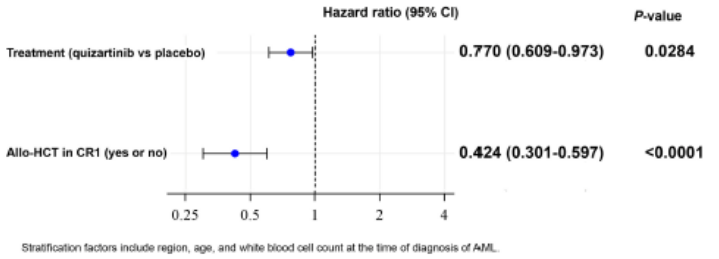
OUTCOME

- 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

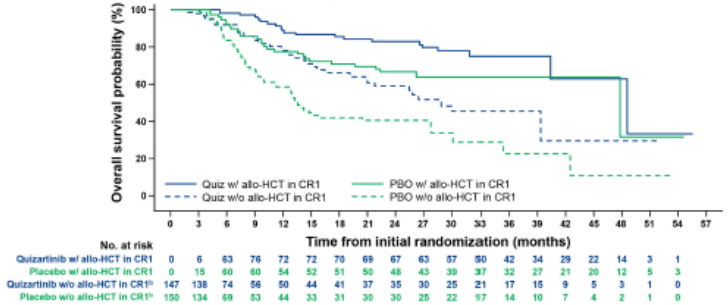
- *"Irrespective of pre-allo stem cell transplantation and MRD status, longer survival was observed in those treated with quizartinib vs placebo. I think it's most valuable in the MRD-positive population"*

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



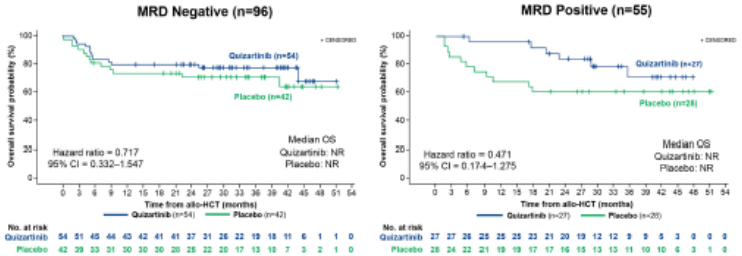
Stratification factors include region, age, and white blood cell count at the time of diagnosis of AML.

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.
[b]'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).

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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 age 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% overall (**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

EXPERT CONCLUSIONS

- *"Toxicity was no issue in this study"*
- *"This was comparable to the DAGO data alone that I presented in the first part of my presentation. But what was different is that and that is depicted here, that the level of MRD is much lower in those patients that received the combination of GO + midostaurin"*

Figure 1A: Overall survival

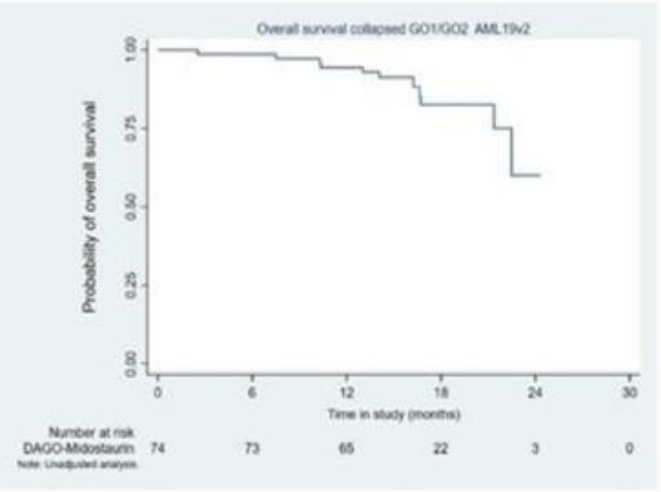
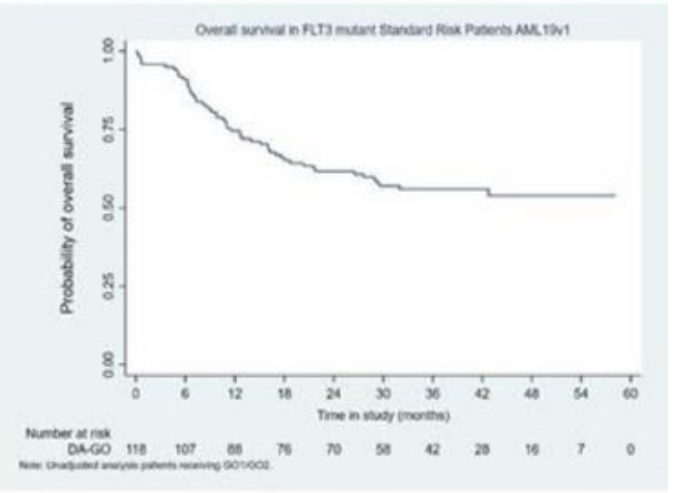


Figure 1B: Overall survival



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

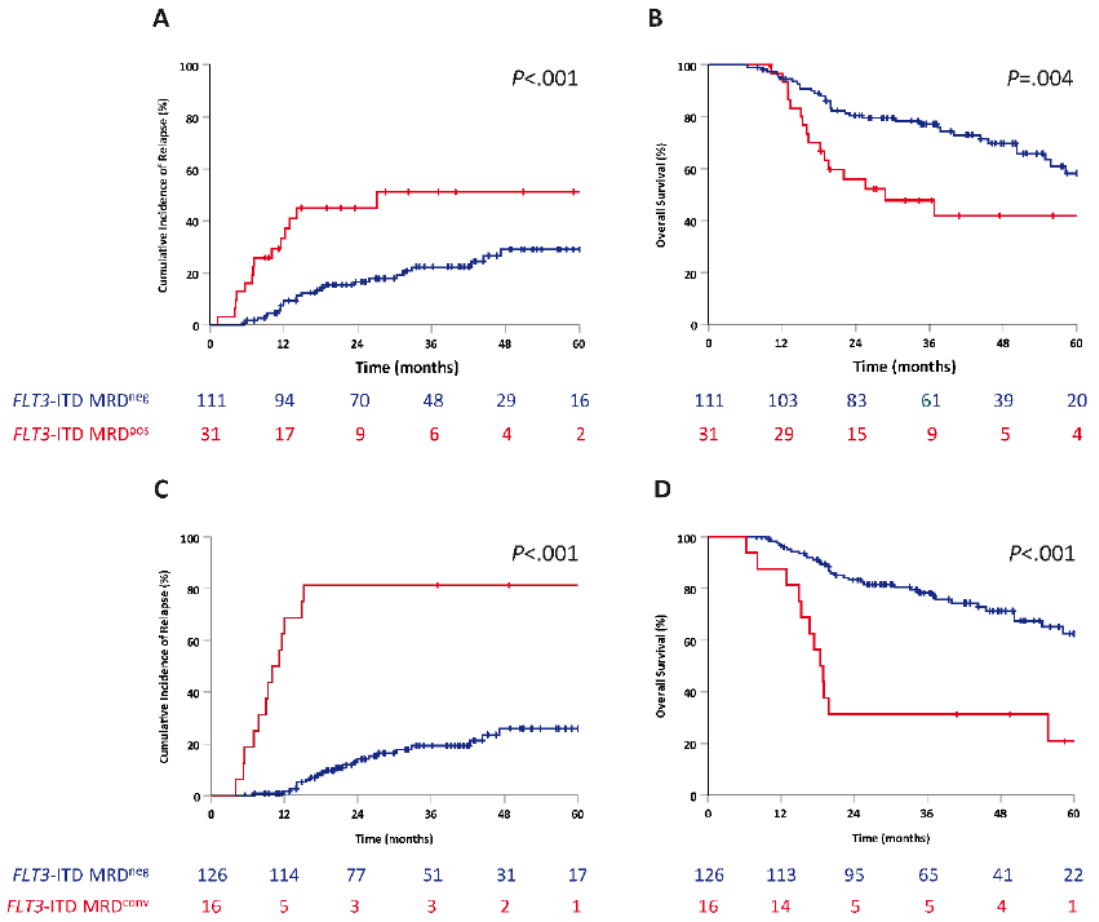
Frank G. Rücker, et al. S135

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 of these relapsed within a median time of 7 d (range, 0–197 d), translating into significantly worse relapse risk (2-yr CIR: 81% vs 14%; *P* <.001) and lower OS (2-yr OS, 31% vs 83%; *P* <.001) (**Fig 1C and D**)



EXPERT CONCLUSIONS

> *"NGS-based FLT3-ITD MRD allows for the identification of patient with high risk of relapse"*
> *"Concurrent NPM1 and that was significant associated with deeper molecular responses in higher rates of MRD and I think the quality of PCR for NPM1 is more sensitive than the NGS that is currently used"*

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EPICS

Discussion Summary

Advances in AML: Newly Diagnosed

Advances in AML: Newly Diagnosed (1/3)

EPICS

*FLT3*wt AML

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

> Experts agreed these data indicate the addition of GO to induction chemotherapy should be considered the standard of care in *NPM1*m AML
> Prof Ossenkoppele stated that the results indicate FLAG-IDA–GO is very effective in *NPM1*m AML regardless of *FLT3* mutational status, particularly for patients who are MRD negative after 2 cycles
  – The use of FLAG-IDA–GO in this patient population is sufficient; experts agreed the study provides convincing evidence that allogeneic SCT is not necessary with the regimen in this setting

Standard chemotherapy + quizartinib in patients with *FLT3*-ITDwt AML

> Although the primary endpoints have not been met, the experts noted clear separation of the curves can been seen in both mEFS and mOS, favoring the quizartinib arm, and they look forward to the expansion of this study
  – Prof Ossenkoppele found the mOS endpoint more important in these patients
> Though the data are impressive and provocative, the experts would like to see more data before considering standard chemotherapy + quizartinib the new standard of care in *FLT3*-ITDwt AML
  – Dr Kadia stated the findings of this study mirrored those of the SORMAIN study investigating the addition of sorafenib
> Experts agreed the use of FLT inhibitors in *FLT3*wt AML patients must be explored in a randomized trial to confirm the findings of the QUIWI trial

> ***Prof Ossenkoppele:***
> *It seems that for those patients who are MRD-negative after 2 cycles of FLAG-IDA–GO, it is a really effective treatment, and no allogeneic stem cell transplantation is necessary. . . . [In NPM1 mutated, adding GO to induction regimen should be considered standard of care?] I think GO in NPM1-mutated AML, You are absolutely right*

Advances in AML: Newly Diagnosed (2/3)

EPICS

*FLT3*m AML

Gilteritinib as posttransplant maintenance for *FLT3*-ITDm AML

> Experts were surprised that the primary objective was not met, the OS endpoint was not met, and that MORPHO was negative

> The difference in RFS by region was discussed; Dr Kadia indicated the dissimilarity in pre-HCT use of FLT3 inhibitor could explain the variations seen

> Prof Ossenkoppele concluded that the jury is still out on whether *FLT3*m patients need a TKI posttransplant if they receive a TKI pretransplant

GO-based induction chemotherapy with midostaurin for *FLT3*m AML

> In the "MIDOTARG" pilot trial, DAGO + mido seemed to have no additional toxicity concerns while demonstrating a much higher level of MRD negativity among patients with *NPM1*m vs DAGO alone. Prof Ossenkoppele noted this study has confirmed that induction chemotherapy with DAGO *can* be combined with midostaurin in ND *FLT3*m AML, a previously unanswered question

> The experts discussed the use of midostaurin when quizartinib and gilteritinib have been shown to be superior. However, this is a British study, and NICE has only approved midostaurin for reimbursement

"***Prof Ossenkoppele:***
I think the reason is that NICE has only approved midostaurin for reimbursement. I think that is one of the many reasons that they use midostaurin. But I agree with you that there are better choices"

Advances in AML: Newly Diagnosed (3/3)

EPICS

*FLT3*m AML

Impact of allo-HCT in first CR with quizartinib in *FLT3*-ITD AML

- The subanalysis of QuANTUM-First indicated an OS benefit for patients who received quizartinib vs placebo in addition to high-dose cytarabine, and experts agreed it is most valuable in patients who were MRD positive pre–allo-HCT
  - Experts agreed the better outcomes with the addition of quizartinib vs placebo to high-dose cytarabine in patients who were MRD positive pre–allo-HCT, while expected, were good to see in a randomized study

NGS-based MRD monitoring in AML with *FLT3*-ITD treated with intensive chemotherapy + midostaurin

- NGS assessment of MRD status is considered very important and should now be standardized
- Experts found the cumulative incidence of relapse in *FLT3*-ITD MRD-negative vs *FLT3*-ITD MRD-positive disease to be highly significant and striking

> ***Prof Ossenkoppele:***
> *NGS-based FLT3-ITD MRD allows for the identification of patients with high risk of relapse. It's combining midostaurin and this intensive chemotherapy, resulting in high proportion of patients becoming MRD negative after cycle 2 and also after end of treatment, and was the strongest independent favorable prognostic factor for relapse and overall survival*

APTITUDE HEALTH®

EPICS

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

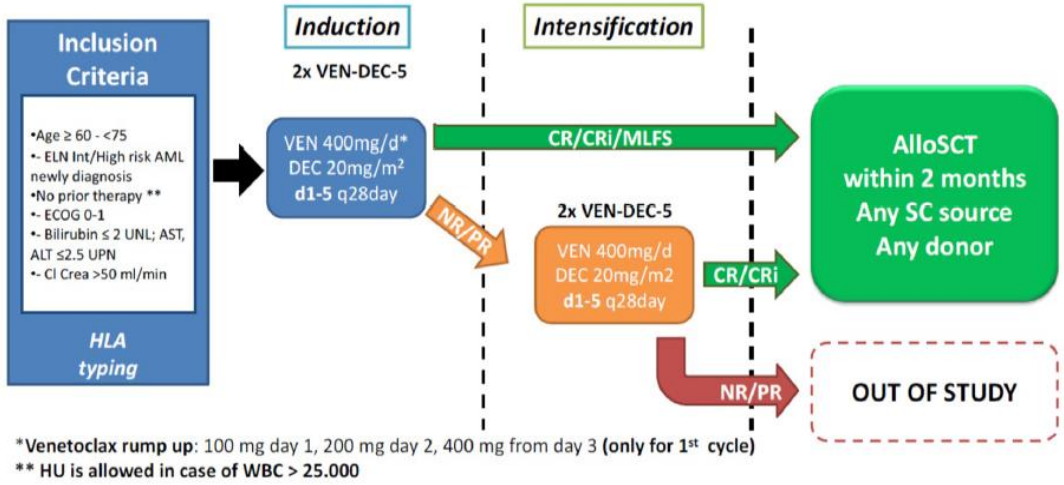
Domenico Russo, et al. P502

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 cycles (C) and were evaluable for response
> CR in 49 pts after 2 C (65.3%); of the remaining pts, 4 (15%) achieved CR after 2 additional C
> 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 CONCLUSIONS

> *“Forty-four percent in this study is actually quite good. And certainly, we could continue to improve on this. I think that this is an important study showing the importance of low intensity toward transplantation.”*

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

Juan Miguel Bergua Burgues, et al. S132

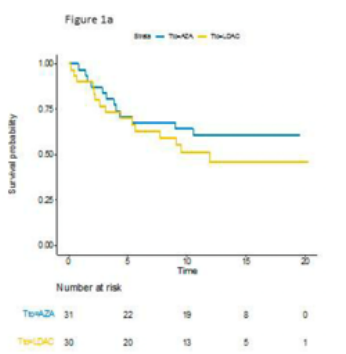
EPICS

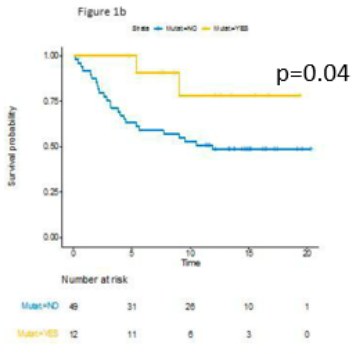
STUDY POPULATION

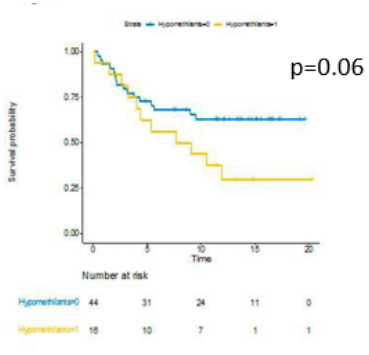
- Newly diagnosed AML pts >70 yr or unfit pts >65 yr
- Pts with previous antecedents of myeloproliferative disease, MDS; prior treatment with HMA allowed
- Randomization 1:1 QUIZ + either VEN-AZA or VEN-LDAC
- *FLT3*-ITD–positive pts included (n=12)

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 triplets could be feasible. But as you can see here, this is not really a low-intensity chemotherapy regimen"*
- *"It needs to be used with caution, but also maybe considering some dose modifications, such as an early bone marrow on day 14 to assess whether or not the quizartinib and the venetoclax can be held in the absence of bone marrow blasts"*

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

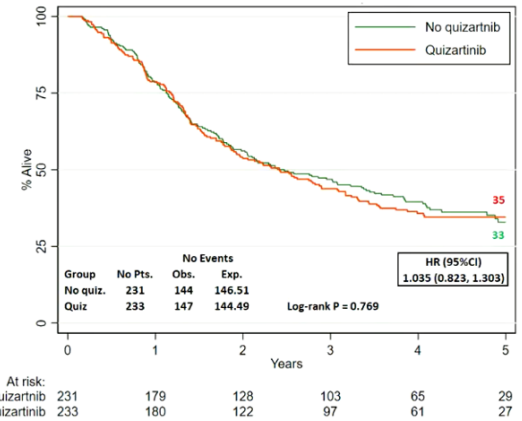
- Pts from NCRI AML18: ≥60 yr fit for intensive therapy (N=464), received a course of IDA ± GO and were then randomized to have QUIZ 14 mg/d × 14 d or no QUIZ added in the second course of induction (DA or FLAG-IDA) and a single course of consolidation (DA, mini–FLAG-IDA, or IDAC) in older AML, regardless of *FLT3*-ITD status
- There was a second randomization to a shorter vs longer QUIZ (short-QUIZ = 40 mg/d for 14 d after chemotherapy C 2 and 3 and for an additional 28 d following recovery from final course; long-QUIZ = short QUIZ but with an additional 12 × 28-d maintenance cycles)

OUTCOME

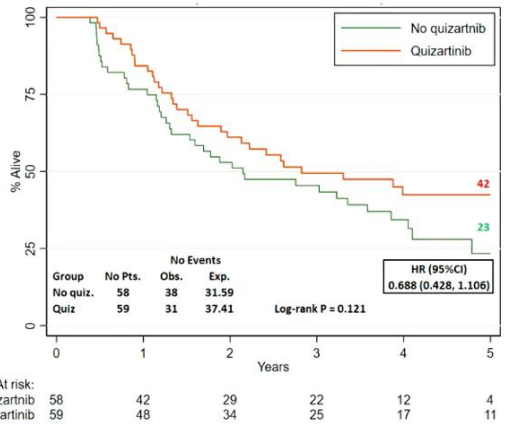
- Remission status at time of QUIZ randomization: CR 68%, CRi (9%), flow MRD positive: 43%, MRD negative 57%
- 96 pts (22%) were *FLT3*-ITD positive and 23 *FLT3*-TKD positive; 2 (<1%) had both mutations
- Addition of QUIZ and duration of maintenance QUIZ (when adjusted for HSCT) had no effects on OS 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*m pts showed a trend toward OS benefit, consistent with data from QuANTUM-First trial
  - Benefit with QUIZ in *FLT3*m pts 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 CONCLUSIONS

- *“This is different than what we saw in the QUIWI study in younger patients, where there was a difference in the randomized phase II interim analysis. And so, this is very interesting and obviously provocative – which is the right answer? Is it just that older patients don’t benefit?”*

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Discussion Summary

Advances in AML: Newly Diagnosed Elderly and/or Unfit

Advances in AML: Newly Diagnosed Elderly and/or Unfit (1/2)

EPICS

AML in Older and/or Unfit Patients

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

- The mOS of 14.47 months for the quizartinib + VEN + AZA arm of the phase II VEN-A-QUI trial is seen as promising, and this triplet was described as “very active” in this patient population
- The toxicity of venetoclax + azacitidine + quizartinib is considered daunting; the 22% death rate in induction is hard to justify. Dr Jabbour and Dr Kadia believe this is likely due to the 28-day and 21-day dosing of venetoclax and quizartinib, respectively
  - Dr Kadia mentioned that although the dosing of venetoclax and quizartinib is staggered, the length of dosing likely contributes to the myelosuppression and risk of early mortality seen in the phase II portion of the study
    - Dr Kadia suggested venetoclax dose modifications similar to gilteritinib studies (14-day venetoclax and 14-day gilteritinib during induction) would likely improve the toxicity of the regimen
    - Dr Kadia also recommended performing a bone marrow assessment at day 14; if ablation is observed, then treatment should be held to allow counts to recover
  - Dr Kadia would be comfortable giving a 67-year-old patient the triplet regimen, but believes an alternative strategy to modify the dosing schedule would especially be needed
- Experts noted that to get this combination approved, a study randomizing HMA + venetoclax vs HMA + venetoclax + FLT3 inhibitor is needed

“***Dr Kadia:***
I would not give the 28 days of venetoclax or 3 or 4 weeks of the FLT3 inhibitor in each case. I think that the strategy of giving 14 days of both drugs, getting a bone marrow at day 14. And if we do note that there is bone marrow ablation, we hold both drugs and allow count recovery during that first cycle and assess MRD”

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

EPICS

AML in Older and/or Unfit Patients

VEN-decitabine: GITMO study – midterm update

> Experts agreed that the use of low-intensity therapies to "bridge to transplant," such as HMA + venetoclax, is important, and more studies are needed in this setting
  - Experts highlighted the importance of considering toxicities in patients who are going to allo-SCT, stating that a low-intensity therapy + venetoclax, such as decitabine, is a great option for elderly patients aged 60–70 years who are allo-SCT eligible
> That 44% of patients went to allo-SCT is considered fairly favorable, considering the elderly study population, which typically has a transplant rate of ~18%

Addition of quizartinib to intensive chemotherapy in elderly patients with AML: NCRI AML18 trial

> The addition of quizartinib to intensive chemotherapy in this elderly population did not make a difference in OS, in contrast with the positive results seen for a younger patient population in the QUIWI study
> Dr Kadia discussed the need to further investigate the difference in responses seen between the elderly and younger patients receiving quizartinib + IC

"***Dr Kadia:***
Certainly, we could continue to improve on this. I think that this is an important study showing the importance of low intensity toward transplantation"

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Conference Highlights

Advances in AML: Relapsed/Refractory Disease

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)

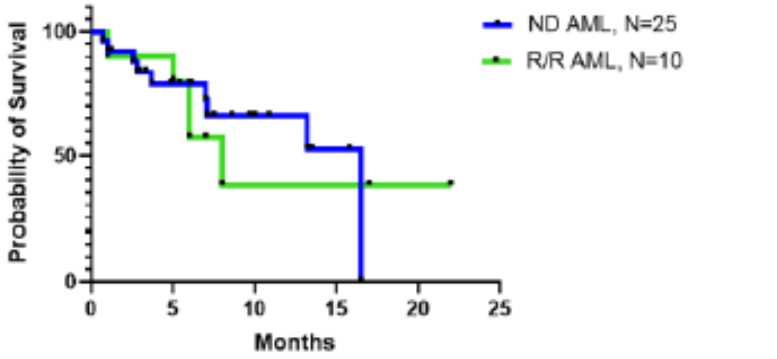
EPICS

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 d during induction and 7 d 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 (75%) 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. 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

- *"I think another example of intensive chemo and ven being incorporated and potentially changing our landscape"*

OLUTASIDENIB IN POST-VENETOCLAX PATIENTS WITH MUTANT IDH1 AML

Jorge Cortes, et al. P555

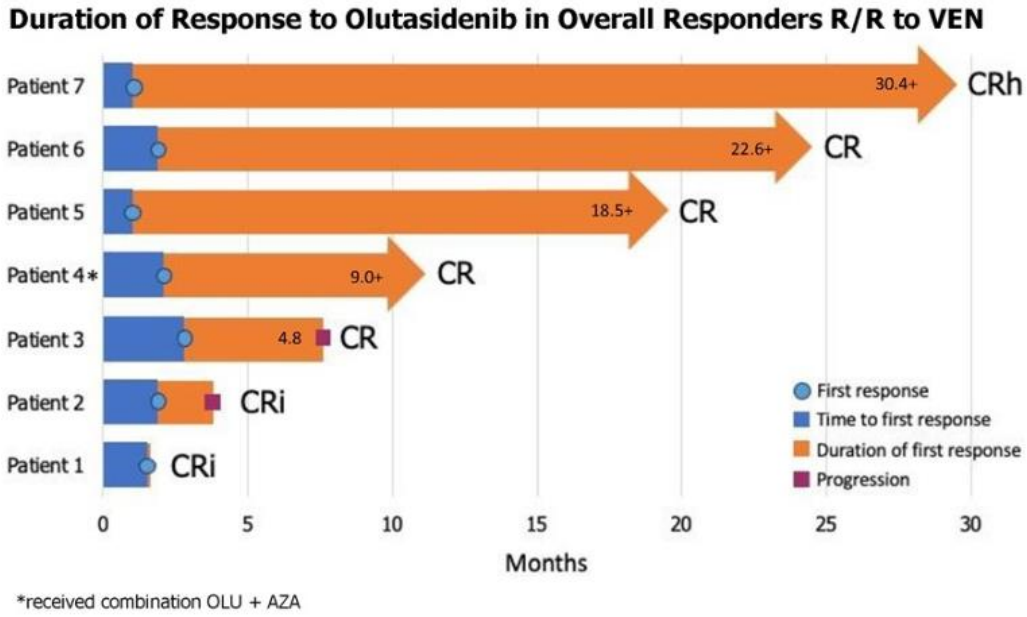
EPICS

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 their follow-up was reviewed

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 1 (5.9%) in CRh and 4 (23.5%) in 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 CONCLUSIONS

- *"Forty-one percent [CR/CRi post-venetoclax failure] is taken with a grain of salt, but certainly impressive responses as a monotherapy"*

UPDATED DATA FOR ZIFTOMENIB IN PATIENTS WITH *NPM1*-MUTATED RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

Amir Fathi, et al. P504

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%; 1 pt had G3 differentiation syndrome
- 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 pts who received any dose level of ziftomenib, 1 pt 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)

EXPERT CONCLUSIONS

- *"I think definitely a strong signal response. Clearly something that urges us to consider studying this in earlier lines of therapy, potentially for salvage or even front line in combination with chemotherapy after the phase I dose is discovered"*
- *"The single-arm registration study is clearly accruing for monitoring a ziftomenib monotherapy in single-agent relapsed/refractory, mutated NPM1 AML"*

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Discussion Summary

Advances in AML: Relapsed/Refractory Disease

Advances in AML: R/R Disease (1/2)

EPICS

R/R AML

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

- The CRc of 80% and the duration of response for R/R AML are considered quite impressive
- Experts stated the addition of venetoclax to intensive chemotherapy in this setting could potentially change the treatment landscape
- However, venetoclax + FLAG-IDA in ND and R/R disease must be further studied in a randomized trial before experts would adopt this regimen widely in clinical practice
  - Experts agreed this is not a regimen for elderly patients; the regimen is rather toxic in that patient population
  - A comparator study is needed investigating the standard of care vs venetoclax + FLAG-IDA in this patient population
- Experts believe it is important in the younger patient population to use intensive chemotherapy-based regimens to bridge patients to SCT, citing the need to achieve a CR and MRD negativity

Dr Kadia:
I think this is another example of intensive chemo and ven being incorporated and potentially changing our landscape

Prof Ossenkoppele:
You need a randomized study and also in the elderly population, because it will be rather toxic, and we already have some data that it's really toxic for elderly people or at least for intensive chemotherapy

Advances in AML: R/R Disease (2/2)

EPICS

R/R AML

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

> Experts noted that despite the small numbers of patients, the responses to olutasidenib (CR 24%, CR + CRh 29%, and CR + CRh + CRi 41%) are impressive
  - Dr Kadia stated that although there are no direct comparisons, the data seem a little better for olutasidenib than ivosidenib
> Experts believe these data could lead to some changes in the standard of care for AML with *IDH1* mutations post-HMA + venetoclax failure, which is an area of interest in their practice
  - Experts discussed the efficacy of venetoclax post-IDH1 failure, stating the results seem better compared with the efficacy of IDH1 inhibitors post-venetoclax failure

Menin inhibitor ziftomenib in patients with *NPM1*m R/R AML

> The mDOR of 8.2 months in the ziftomenib phase I/II study is considered quite impressive
  - Nonetheless, experts noted that earlier data in R/R *KMT2a*-positive AML for another Menin inhibitor, SNDX-5613, appear more promising than these recent ziftomenib data
> Experts believe the strong responses seen for single-agent ziftomenib in a heavily pretreated population suggest the agent might be successful in earlier lines of therapy in combination with chemotherapy, although the dose and schedule would need to be optimized
> Dr Kadia believes Menin inhibitors will revolutionize the treatment of certain subsets of AML patients
> Experts look forward to studies on Menin inhibitors in ND AML patients

> ***Dr Kadia:***
> *This is clearly an area of interest to research because we are seeing a lot of HMA + ven failures. And coming up with a regimen that is active in IDH1-mutated AML post-HMA + ven failure and demonstrating this with a larger number of patients could potentially lead to some change in the standard of care*

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EPICS

Conference Highlights

Advances in ALL: Newly Diagnosed

A Chemotherapy-Free Combination of Ponatinib and Blinatumomab for Patients With Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Subgroup Analysis From a Phase II Study

Nicholas Short, et al. S118

EPICS

STUDY POPULATION

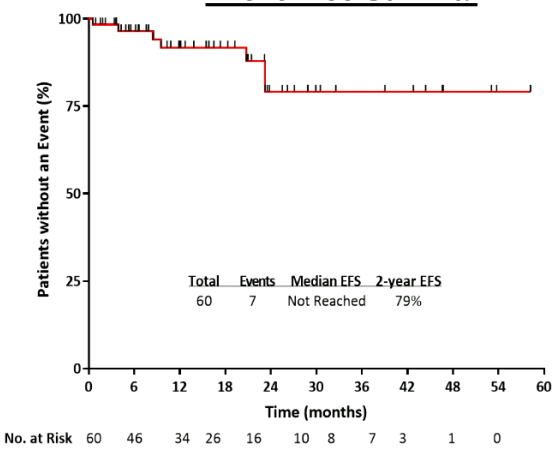
> Phase II study to evaluate a chemotherapy-free approach of ponatinib and blinatumomab in pts with ND Ph-positive ALL
> N= 54 pts aged ≥18 yr with ND Ph-positive ALL. Pts who received 1–2 previous cycles of chemotherapy ± a BCR::ABL TKI could still be enrolled

Characteristic	Category	N (%) / median [range]
Age (years)		55 [20-83]
	≥ 60	23 (38)
Performance status	0-1	50 (83)
	2	10 (17)
CV risk factors	Hypertension	27 (45)
	Hyperlipidemia	19 (32)
	Diabetes	13 (22)
	Coronary artery disease	1 (2)
≥1 CV risk factor		34 (57)
WBC ($x10^9$/L) at start		4.7 [0.4-23.7]
CNS involvement		3 (5)
CD19 expression		99.8 [74.9-100]
BCR::ABL1 transcript	p190	46/59 (78)
	p210	13/59 (22)

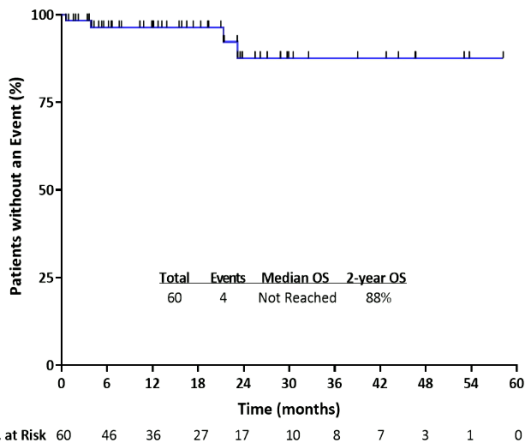
OUTCOME

> In 35 pts evaluable for hematologic response, 97% achieved a CR or CRi
> Among 48 pts evaluable for CMR, 71% achieved CMR after 1 cycle, and 90% achieved CMR at any time
> 89% of tested pts became MRD negative by NGS
> The 2-year EFS is 79% and 2-year OS is 88%
> Most toxicities were G1–2 and consistent with known toxicities associated with the 2 agents; 2 pts discontinued ponatinib due to related AEs, and 2 deaths in CR occurred

Event Free Survival



Overall Survival



EXPERT CONCLUSIONS

> *"Very good survival data . . . without any chemotherapy exposure, so just in ponatinib + blinatumomab alone and the ponatinib maintenance"*

Consolidation With Blinatumomab Improves Overall and Relapse-Free Survival in Patients With Newly Diagnosed B-Cell Acute Lymphoblastic Leukemia: Impact of Age and MRD Level in ECOG-ACRIN E1910

Ryan Mattison, et al. S115

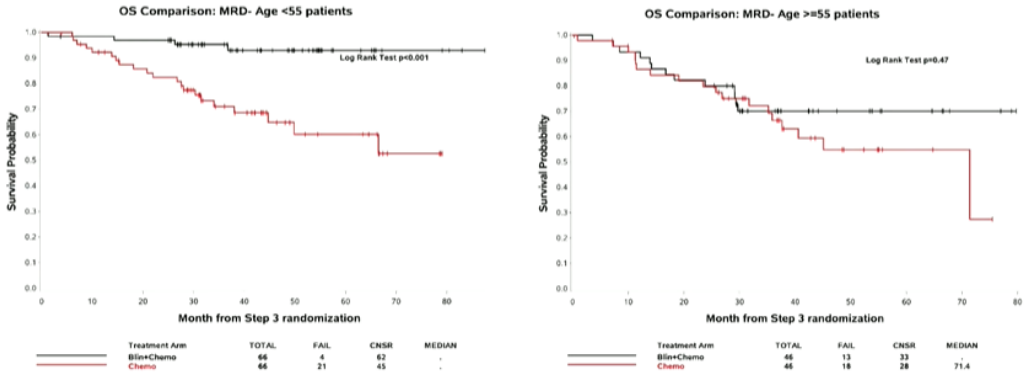
EPICS

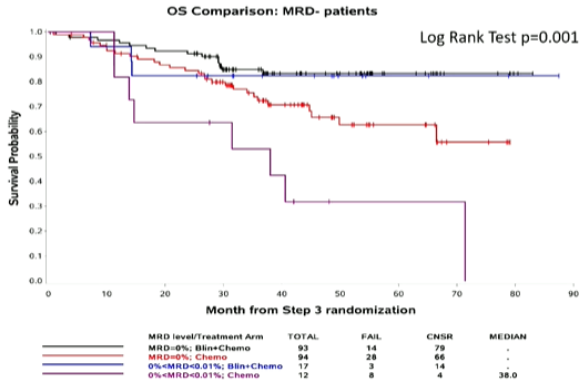
STUDY POPULATION

- Subgroup analysis of ECOG-ACRIN E1910 outcomes based on age <55 or ≥55 yr
- Phase III trial included 488 pts enrolled with 224 MRD-negative pts randomized (112 in each arm)

OUTCOME

- By age
  - In 132 pts <55 yr, OS favored the blinatumomab arm (mOS NR in either arm; HR 0.18)
  - In 92 pts ≥55 yr, mOS NR for blinatumomab vs 71.4 mo for control arm
- By MRD level
  - In 187 pts with undetectable MRD, OS favored the blinatumomab arm (mOS NR in either arm; HR 0.51)
  - 37 pts with MRD between undetectable and 0.01%, OS NR for blinatumomab vs 38.0 mo for control (HR 0.35)





EXPERT CONCLUSIONS

- *"I think it's very intriguing. The data seems to be so pronounced; it's a striking difference in overall survival"*
- *"I think this data was interesting, that MRD lowered the disease burden; undetectable MRD is better. Younger patients did better, and why that's the case?"*

Chemotherapy-Free Treatment With Inotuzumab Ozogamicin and Blinatumomab for Older Adults With Newly-Diagnosed, Ph-Negative, CD22-Positive, B-Cell Acute Lymphoblastic Leukemia: ALLIANCE A041703

Matthew Wieduwilt, et al. S117

EPICS

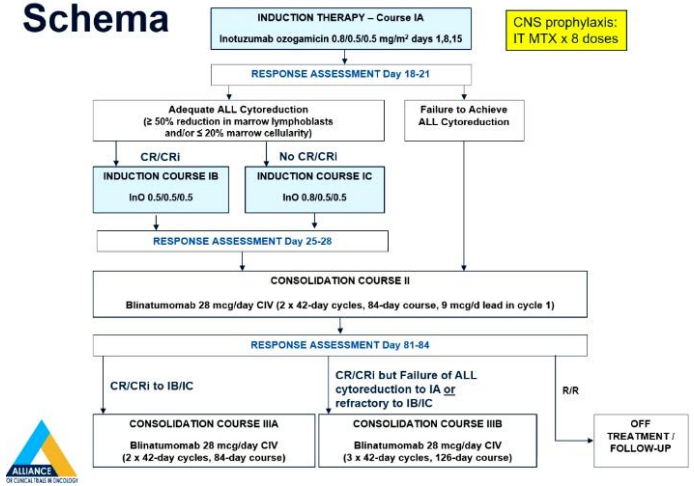
STUDY POPULATION

> Phase II trial investigating the efficacy of InO-based induction followed by blinatumomab consolidation in older adult Ph-negative CD22-positive B-ALL pts
> Eligible pts were ≥60 yr (median 71 yr, range 60–84 yr) with ND, Ph-negative, CD22-positive B-lineage ALL with no plan to proceed for allo-HCT

OUTCOME

> Of 33 eligible pts, 85% achieved a composite CR following induction with InO, and 97% achieved composite CR following blinatumomab
> With a median follow-up of 22 mo, 1-yr EFS was 75% and 1-yr OS was 84%
> 9 relapses, 2 deaths in remission occurred (1 during blinatumomab and 1 after allo-HCT), and 1 death without remission occurred
> Common G≥3 AEs: neutropenia (88%), thrombocytopenia (73%), anemia (42%), leukopenia (39%), lymphopenia (27%), febrile neutropenia (21%), and encephalopathy (12%)

Schema



N=33	Induction InO I A/B/C	Blinatumomab Course II
Composite CR*	28 (**85%**)	32 (**97%**)
CR	15 (45%)	19 (58%)
CRh	11 (33%)	12 (36%)
CRi	2 (6%)	1 (3%)
Refractory	3 (9%)•	-
Survival		
1-yr EFS	75% (95% CI 61-92%)	
1-yr OS	84% (95% CI 72-92%)	

*CR+CRh+CRi

• 1 completed IA only, 2 proceeded to course II

EXPERT CONCLUSIONS

> *"This does suggest InO induction followed by blinatumomab consolidation is highly active and tolerable therapy for older patients with newly diagnosed [Ph-negative AML]"*
> *"Skipping of the maintenance therapy, which is provocative and interesting – we'll want to see whether the responses that we achieve for these patients will be durable"*

Updates From a Phase II Trial of Mini-Hyper-CVD Inotuzumab With or Without Blinatumomab in Older Patients With Newly Diagnosed Philadelphia Chromosome (Ph)-Negative Acute Lymphoblastic Leukemia

Fadi Haddad, et al. P373

EPICS

STUDY POPULATION

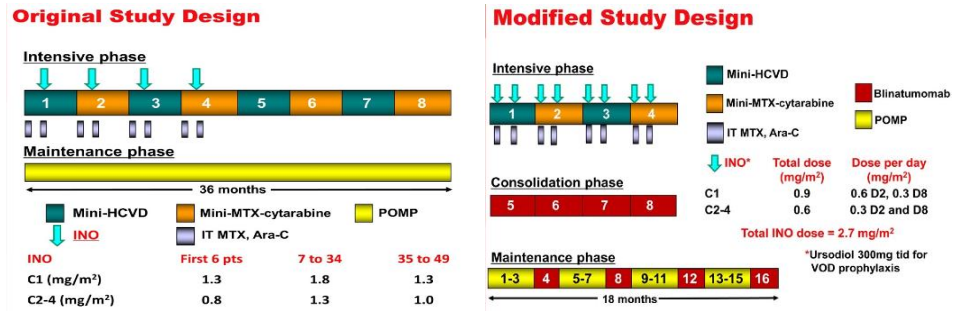
> Phase II trial investigating the addition of blinatumomab to mini–hyper-CVD–inotuzumab in older ND Ph-negative ALL pts
> 83 pts were enrolled (median age 68 yr, range 60–87 yr)

OUTCOME

> Among 77 evaluable pts (6 of 83 pts were in CR at baseline), 99% responded, with 90% achieving a CR. Among those who responded, 94% overall achieved MRD negativity by flow cytometry, 79% following first cycle
> After a median follow-up of 65 mo, the 5-yr continuous remission duration was 78% and the OS rate was 48%
> The 5-yr OS for 40 pts aged 60–69 yr without adverse cytogenetics, 15 pts aged 60–69 with adverse cytogenetics, 24 pts aged ≥70 yr without adverse cytogenetics, and 4 pts aged ≥70 yr with adverse cytogenetics was 72%, 27%, 38%, and 0%, respectively

EXPERT CONCLUSIONS

> *"And I think this is interesting. . . . This does kind of suggest that the mini-CVD + InO + blin is safe and effective in older patients"*

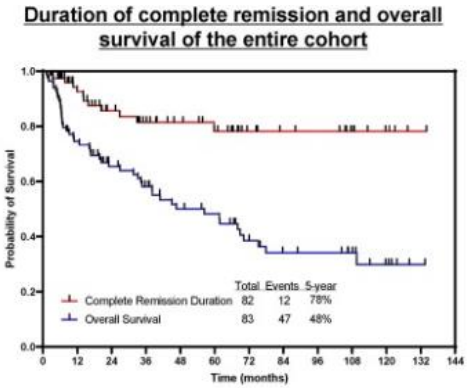


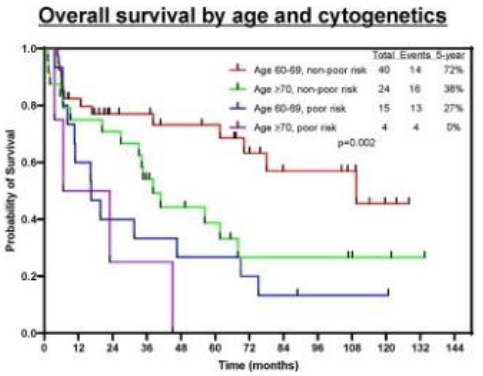
Results

Response (N = 77*)	n (%)
ORR	76 (99)
CR	69 (90)
CRp	6 (8)
CRi	1 (1)
No response	1 (1)
Early death	0

* 6 patients were enrolled in CR

MRD negativity rate	n (%)
By flow cytometry, on Cycle 1, Day 21	59/75 (79)
By flow cytometry, overall	72/77 (94)
By next-generation sequencing, overall	12/13 (92)





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Interim Analysis of a Registration Enabling Study of Pivekimab Sunirine (PVEK, IMGN632) a CD123-Targeting Antibody-Drug Conjugate, in Patients With Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

Naveen Pemmaraju, et al. S139

EPICS

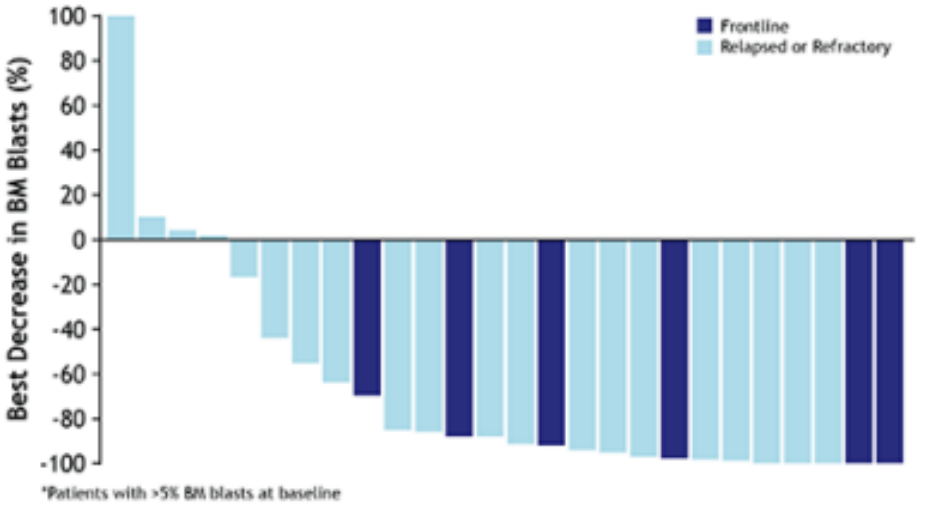
STUDY POPULATION

- Phase Ib/II study investigating the safety and efficacy of PVEK in frontline and R/R BPDCN pts
- 16 frontline pts (median age 74 yr, range 60–80 yr) and 42 R/R pts (median age 69 yr, range 19–83 yr)
  - 50% of frontline pts had prior/concomitant heme malignancies
  - 33% of the R/R pts had prior SCT and 45% had prior TAG

OUTCOME

- Among the 16 frontline pts, 81% achieved an ORR, 75% achieved a CCR
- In the front line, median time to response was 1.5 mo with median DOR of 10.7 mo
- Among the 42 R/R pts, 31% achieved an ORR and 19% achieved a CCR with median DOR of 3.1 mo
- No treatment-related deaths occurred, 1 treatment-related AE led to dose reduction, and 2 pts discontinued PVEK due to a TRAE

Figure 1. Best Decrease in BM Blast (%) for Patients with Frontline and R/R BPDCN treated with PVEK*



R/R patients (N=49)		
	ORR	Composite CR
All R/R patients	**33% (16/49)**	**20% (10/49)**
Patients who received prior tagraxofusp (n=21)	**33% (7/21)**	**19% (4/21)**
Patients who had prior SCT (n=16)	**50% (8/16)**	**31% (5/16)**
Time to first response in all R/R patients		
Median (range), months	1.3 (0.6-3.7)	1.4 (0.7-1.9)

EXPERT CONCLUSIONS

- *"This may kind of suggest another very effective CD123-targeted therapy in BPDCN patients. . . . Easier to give compared to what we have seen [with previous CD123-targeted therapies]"*

PhALLCON: A Phase 3 Study Comparing Ponatinib Versus Imatinib in Newly Diagnosed Ph+ ALL

Elias Jabbour, et al. S110

EPICS

STUDY POPULATION

- Phase III study comparing imatinib vs ponatinib in combination with reduced-intensity chemotherapy (randomized 2:1 ponatinib:imatinib)
- A total of 245 pts were randomized to ponatinib or imatinib. At data cutoff, 78 pts were on treatment

OUTCOME

- MRD-negative CR rate at end of induction was 38% for ponatinib compared with 12% for imatinib
- Median duration of MRD negativity was NR for ponatinib and 20.9 mo for imatinib
- While not mature, mEFS was reached for imatinib but not for ponatinib (HR 0.65)
- Treatment-emergent AEs were similar among the imatinib and ponatinib arms

EXPERT CONCLUSIONS

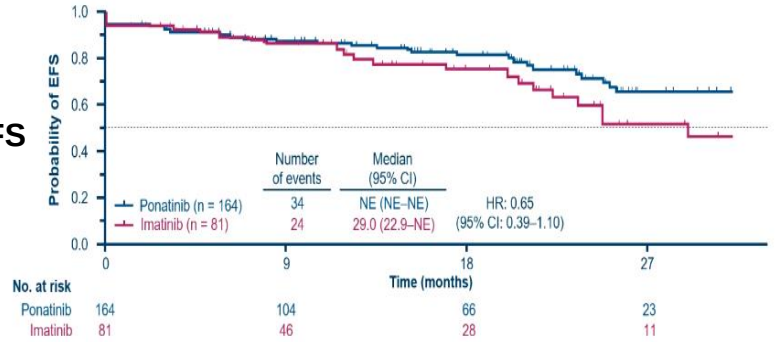
- *"This, again, suggests that ponatinib is superior to imatinib, which we might have expected, but the study does definitively kind of produce that with the earlier MRD-negativity and CR rate"*
- *"Obviously, we'll need to see the survival data, but I think this, again, kind of argues for moving more-potent-generation TKIs to the frontline regimen as opposed to the imatinib"*

Table

	Ponatinib	Imatinib
Responses at EOI, n (%)*	**(N=154)**	**(N=78)**
MRD-neg (*BCR::ABL1* ≤0.01%) CR	53 (34)	13 (17)
P value	0.0021	
MR 4 (*BCR::ABL1* ≤0.01%)	64 (42)	16 (21)
MR 4.5 (*BCR::ABL1* ≤0.0032%)	39 (25)	10 (13)
AEs, n (%)	**(N=163)**	**(N=81)**
Grade 5 TEAEs/TRAEs	8 (5)/0	4 (5)/1 (1)
Grade 3–4 TEAEs	139 (85)	71 (88)
TE AOE (any grade)	4 (2)	1 (1)

*Efficacy evaluable.
AE, adverse event; AOE, arterial occlusive event; CR, complete remission; EOI, end of induction; MR, molecular response; MRD-neg, minimal residual disease negativity; TE, treatment-emergent; TR, treatment-related.

EFS



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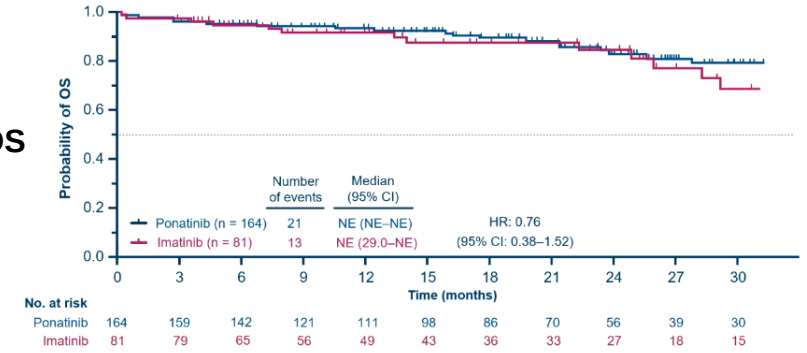

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A Phase II Study of Flumatinib With Chemotherapy for Newly Diagnosed Ph/BCR-ABL1-Positive Acute Lymphoblastic Leukemia in Adults: Updated Results From RJ-ALL2020.2A Trial

Weiyang Liu, et al. P363

EPICS

STUDY POPULATION

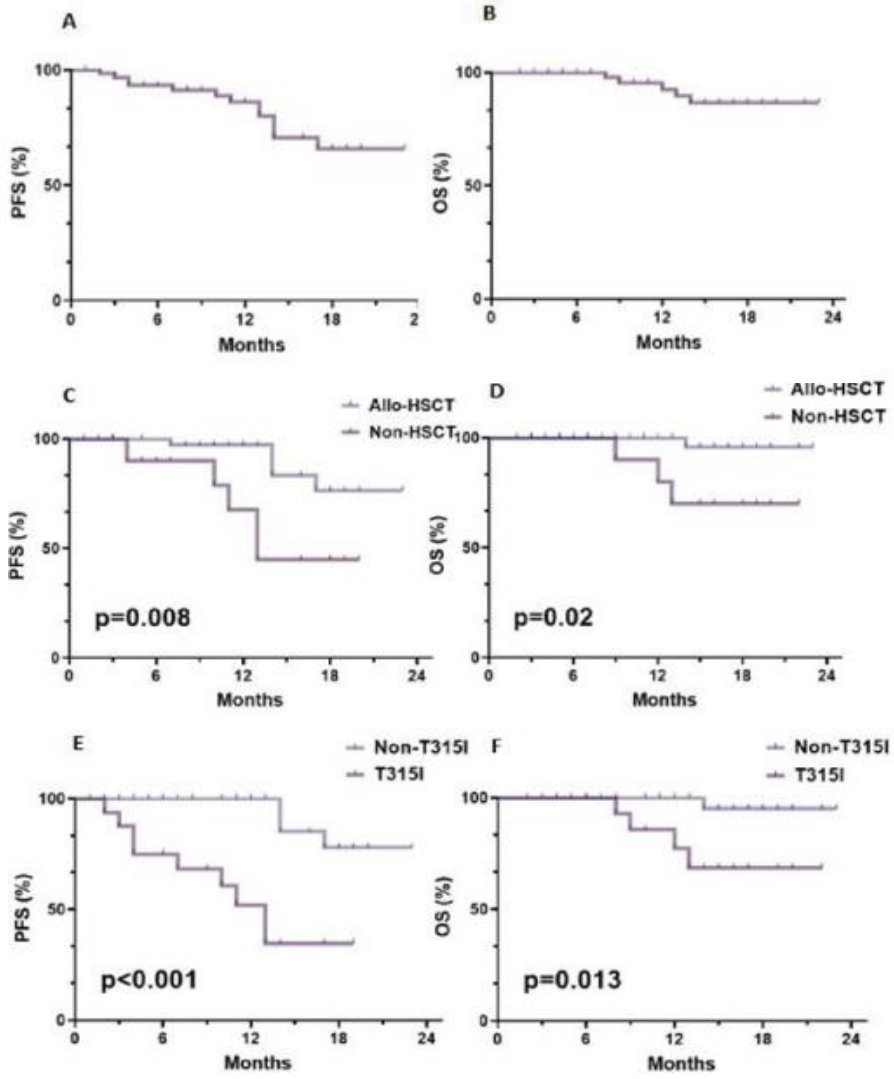
- Phase II study investigating the safety and efficacy of flumatinib in ND Ph-positive B-ALL adult pts
- 63 enrolled pts aged 18–65 yr (median 43 yr, range 19–63 yr)

OUTCOME

- 95.2% of pts achieved a CR at end of induction, with a CMR rate of 28.1% at end of induction and 51.9% at 3 mo
- MRD negativity (by MFC) at end of induction was 66.1% and was 80% at 3 mo
- With median follow-up of 14 mo, the 1-yr PFS was 86.1% and the 1-yr OS was 92.5%
- 37 pts went to allo-SCT with a median time of 6 mo from diagnosis
- No pts discontinued flumatinib due to toxicity
- Most non-heme AEs were G1–2 and most G3–4 AEs were hematologic

EXPERT CONCLUSIONS

- *"There's, again, in the Chinese population with the second-generation TKI, this may present a good alternative"*
- *"Not actually quite sure kind of what TKI is available in China, but it appears to be better than first-generation data with the imatinib"*



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EPICS

Discussion Summary

Advances in ALL: Newly Diagnosed

Advances in ALL: Newly Diagnosed (1/5)

EPICS

Monoclonal and Bispecific Antibodies

Consolidation with blinatumomab in patients with ND B-cell ALL

- This subgroup analysis of the E1910 phase III trial examined OS outcomes on the basis of age <55 years or ≥55 years in patients who were MRD negative following chemotherapy ± blinatumomab
- The significant OS benefit in patients with undetectable MRD after induction (HR 0.51), especially for those <55 years old (HR 0.18), is striking. Further studies were suggested to understand why the responses were seen in these patient populations, but no significant benefit was detected in *older* patients who were MRD negative after induction (eg, use of PEG-asparaginase only in the <55-year-old patients)
  - Experts speculated why the response in MRD-negative, ≥55-year-old patients was not as striking, noting this could be due to the continuation of chemotherapy in the blinatumomab arm resulting in more complications in older patients
- The number of blinatumomab cycles received while on study is unclear, and experts would like additional information
- Dr Park indicated the key question and challenge is how to incorporate these data for practicing physicians not using the E1910 induction backbone
- While experts agreed the OS survival data indicate blinatumomab up front should be the new standard of care, Dr Park currently prefers the CALGB regimen, and has not yet incorporated blinatumomab outside of clinical trials

> ***Dr Park:***
> *I think I would argue that it [blinatumomab] should be the standard of care. Based on the clear overall survival benefit, that's the trouble that I'm having, and it will be interesting to hear what others' perspective is, that even though it's a standard of care that we have not incorporated [blinatumomab] into our frontline regimen yet*

Advances in ALL: Newly Diagnosed (2/5)

EPICS

Monoclonal and Bispecific Antibodies (cont.)

Ponatinib + blinatumomab for patients with ND Ph-positive ALL

- The OS and EFS seen in the study are very impressive and comparable with previous studies for dasatinib + blinatumomab
  - Overall, this combination is a very potent and effective regimen with favorable toxicities. Experts believe these data suggest the ability to eliminate chemotherapy in Ph-positive ALL patients, although longer follow-up studies are needed
  - Experts agreed this combination offers high and durable remission rates, but indicated uncertainty regarding the need for maintenance therapy in this setting
- While experts see blinatumomab + ponatinib as the new standard of care in ND Ph-positive ALL patients, they emphasized the need for phase III randomized trials
  - Dr Park believes the current data are compelling, and has personally adopted TKI + blinatumomab as a frontline regimen in ND Ph-positive ALL patients
- Experts believe less chemotherapy, even in younger patients, appears to be better, citing long follow-up data for blinatumomab-based combinations with ponatinib or dasatinib
- Experts no longer automatically send to transplant patients who are MRD negative and achieve CMR in CR1

> ***Dr Park:***
> *The data looks excellent and suggests that we may be able to eliminate chemotherapy altogether in the Ph-positive ALL patients*

Advances in ALL: Newly Diagnosed (3/5)

EPICS

Monoclonal and Bispecific Antibodies (cont.)

Inotuzumab and blinatumomab in older adults with ND B-cell ALL

> Inotuzumab induction followed by blinatumomab consolidation appears to be effective in older Ph-negative B-ALL patients. However, experts noted that further follow-up regarding the durability of response and efficacy of skipping maintenance therapy in this setting is needed before this approach should be used outside the clinical trial setting

> Experts agreed these data suggest a chemotherapy-free approach is possible and effective for older ND B-cell ALL patients

Mini–hyper-CVD + inotuzumab ± blinatumomab in older patients with ND Ph-negative ALL

> Mini–hyper-CVD + InO ± blinatumomab is seen as safe and effective in older patients; indeed, patients 60–69 years old without poor-risk cytogenetics had the best outcomes
  - Dr Park believes this study highlights the need for better approaches for patients with poor-risk cytogenetics

> Experts stated that the ability to reduce the amount of chemotherapy in older Ph-negative ALL patients will be important, due to the increased risk of chemotherapy-related toxicities associated with this patient population

> However, experts still have concerns with the increased veno-occlusive disease risk when using inotuzumab in older patients

> ***Dr Park:***
> *This does suggest InO induction followed by blinatumomab consolidation is highly active and tolerable therapy for older newly diagnosed patients. I think . . . for me, we need longer follow-up with the skipping of the maintenance therapy, which is provocative and interesting. We'll want to see whether the responses that we achieve for these patients will be durable*

Advances in ALL: Newly Diagnosed (4/5)

EPICS

TKIs

Ponatinib vs imatinib in ND Ph-positive ALL

- Ponatinib demonstrated superiority to imatinib in terms of CR rate and early achievement of MRD negativity
  - Experts would like to see OS data, but the study sets up a strong case for moving more-potent TKIs, including ponatinib, to frontline regimens
- Though the primary endpoint, CR MRD negativity, was met, no difference was seen for OS; experts believe this can largely be attributed to the short follow-up and the SOC arm outperforming expectations, based on historical data

Flumatinib with chemotherapy for ND Ph-positive ALL

- This TKI, which is approved in China for use in CML, has now also demonstrated activity in a Chinese ALL population
- Responses are considered similar to those previously reported for other newer-generation TKIs (ie, more active than first-generation TKIs)

> ***Dr Park:***
> *This suggests that ponatinib is superior to imatinib, which we might have expected, but the study does definitively kind of produce that with the earlier MRD-negativity and CR rate*

Advances in ALL: Newly Diagnosed (5/5)

EPICS

CD123 Antibody-Drug Conjugate

Pivekimab sunirine (PVEK) in patients with BPDCN

> The high efficacy rates, ORR of 81%, and CCR of 75% in ND patients are seen as very promising data

> Experts also found the lower incidence of CLS/CRS for PVEK impressive, leading them to speculate that this therapy will likely have a robust benefit:risk ratio

Dr Park:

This may suggest another very effective CD123-targeted therapy in BPDCN patients, and easier to give compared to what we have seen so far

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EPICS

Conference Highlights

Advances in ALL: R/R Disease

Combination of Mini-Hyper-CVD and Inotuzumab (InO) Followed by Blinatumomab (blina) Consolidation in Patients With Relapsed/Refractory (R/R) Acute Lymphoblastic Leukemia (All): A Phase II Trial

Nicholas Short, et al. S119

EPICS

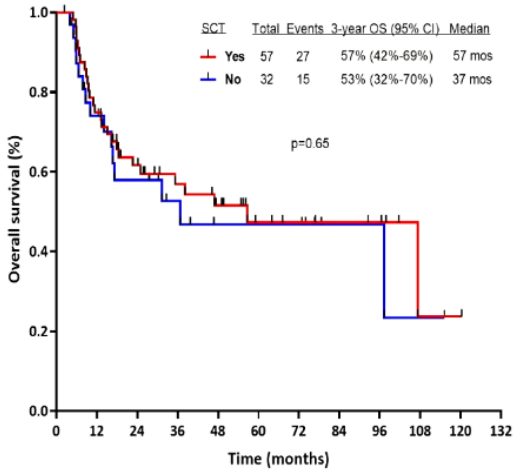
STUDY POPULATION

> Phase II trial assessing the safety and efficacy of mini-HCVD in combination with InO ± blinatumomab, in R/R ALL. Included sequential dose-modification treatment cohorts
  - Original (pts 1–67) mini–hyper-CVD + InO (on d 4 for first 4 courses, 1.3 mg/m^2 for C 1 and 1.0 mg/m^2 C 2–4) and POMP (maint). Note that there was no blina incorporation in the original regimen
  - Modification 1: (pts 68–110) Reduction of InO (4 C, total dose 2.7 mg/m^2) + blina × 4 (consol + maint. Total: 8)
  - Modification 2: (pts 111–125+): Same total InO dose + blina × 6 (InO + Consol) + blina × 4 (maint). Total: 10

OUTCOME

> ORR of 95% in salvage 1, ORR of 59% in salvage 2, and ORR of 57% in salvage 3+ for the overall population
> After median follow-up of 48 mo, mOS was 17 mo (4-yr OS 36%) and mRFS was 13 mo (4-yr RFS 37%)
  - Salvage 1 4-year OS: 43% vs 18% in salvage 2+
  - Salvage 1 4-year RFS: 38% vs 27% in salvage 2+
> No clear benefit for ASCT (4-yr OS of 49% vs 48% for pts who did and did not undergo ASCT in the overall population (see figure)

Response	N (%)			
	Overall (n = 125)	Before Blinatumomab (n = 67)	After Blinatumomab (n = 43)	Dose Dense (n = 15)
ORR	91 (83)	51 (76)	40 (93)	15 (100)
CR	69 (63)	40 (60)	29 (67)	13 (87)
CRp	19 (17)	10 (15)	9 (21)	2 (13)
MLFS	3 (3)	1 (1)	2 (5)	0
No response	12 (11)	9 (13)	3 (7)	0
Early death	7 (6)	7 (10)	0	0



EXPERT CONCLUSIONS

> *"I think that this approach for R/R patients, it's a promising approach, especially if blina is included early in the course of the treatment"*

Safety and Efficacy of Obecabtagene Autoleucel (Obe-Cel), a Fast-Off Rate CD19 CAR in Relapsed/Refractory Adult B-Cell Acute Lymphoblastic Leukaemia: Top Line Results of the Pivotal FELIX Study

Claire Roddie, et al. S262

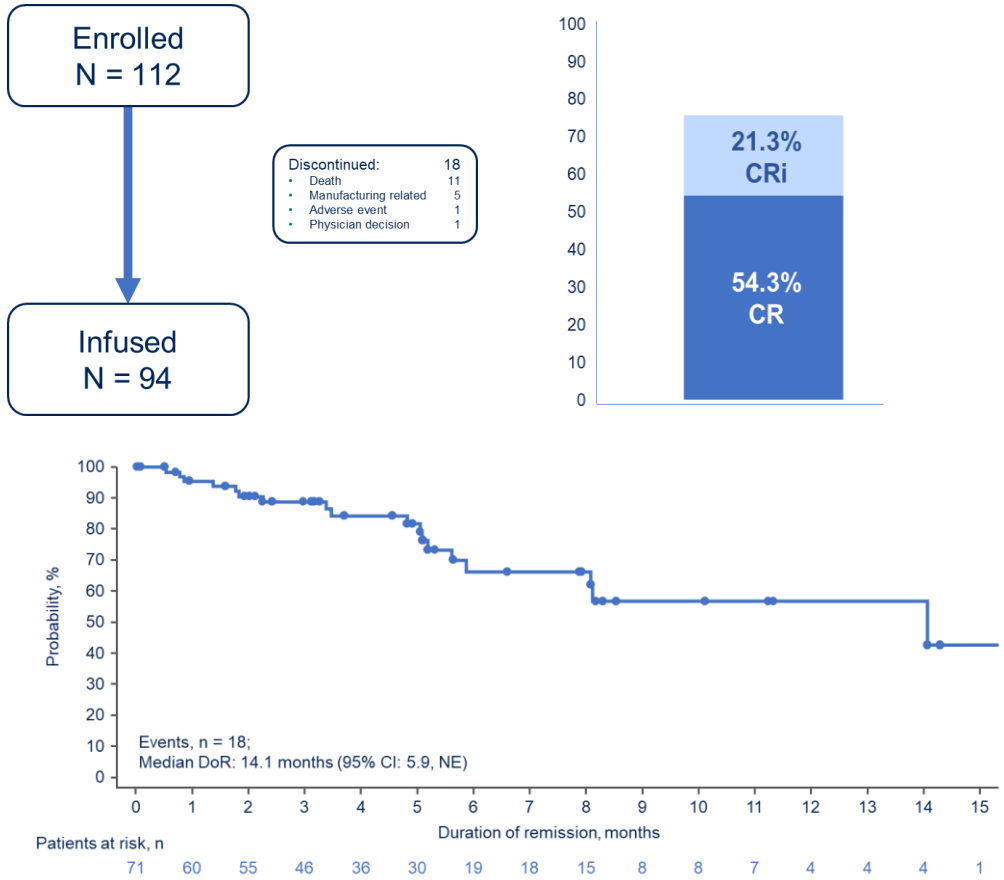
EPICS

STUDY POPULATION

> Open-label, multicenter, global, single-arm phase Ib/II study investigating safety and efficacy of obe-cel in adults with R/R B-ALL
> 112 pts were enrolled; 92 pts (median age 50 yr, range 20–81 yr) were evaluable after receiving obe-cel at data cutoff

OUTCOME

> 84% of the enrolled pts received obe-cel with a median vein-to-delivery time of 21 d
> An ORR of 76% was achieved with a CRi in 21.3% and a CR in 54.3%
> 61% of responders achieved durable remissions without new anticancer therapies (13% of responders proceeded to SCT while in remission)
> Median duration of response was 14.1 mo
> Low rates of CRS and ICANS were observed: G≥3 CRS occurred in 3.2% and G≥3 ICANS occurred in 7.4%



EXPERT CONCLUSIONS

> *"I think it's one of the safer constructs and the efficacy similar to the other constructs approved for adults with relapsed/refractory ALL. I think that the strength of these CAR T is the safety"*

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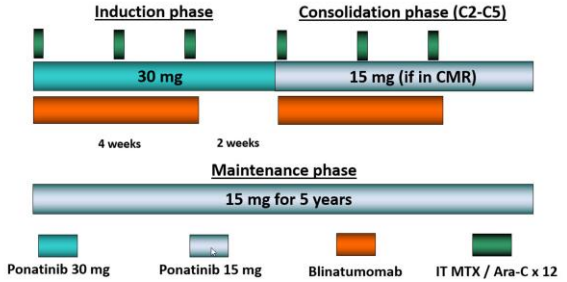
Ponatinib and Blinatumomab in Relapsed/Refractory Philadelphia-Positive Acute Lymphoblastic Leukemia or Chronic Myeloid Leukemia in Lymphoid Blast Phase: Subgroup Analysis From a Phase II Trial

Fadi Haddad, et al. P379

EPICS

STUDY POPULATION

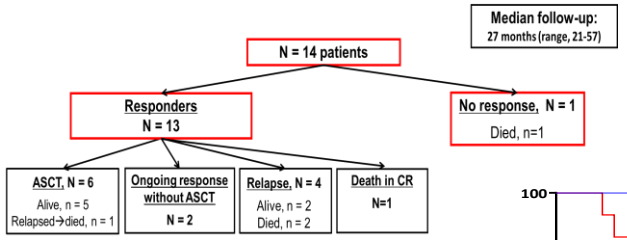
> Phase II trial assessed efficacy and safety of blinatumomab and ponatinib in pts with R/R Ph-positive ALL or CML-LMP (CML-LMP not included in presentation)
> 14 patients with R/R Ph-positive ALL were enrolled between 2/2018 and 7/2022 (median age 38 yr, range 24–61 yr)

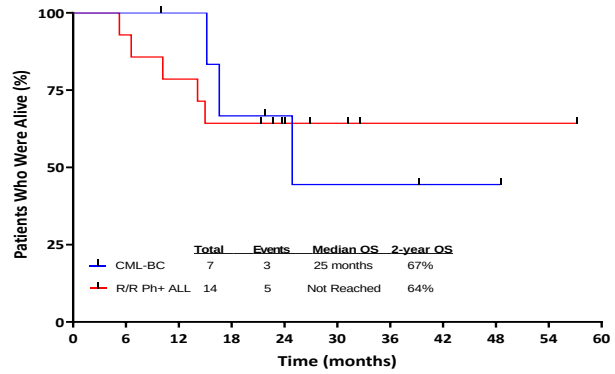


Characteristics N (%) / Median [range]	R/R Ph+ ALL N = 14
Age (years)	38 [24-61]
WBC (x10^9/L) at start	4.7 [2.1-10.4]
P190	13 (93)
p210	1 (7)
CR	11/13 (85)
CR/CRi	12/13 (92)
CMR after 1 cycle	10/14 (71)
CMR overall	11/14 (79)

OUTCOME

> The rate of CR/CRi among the 14 pts with R/R Ph-positive ALL was 92% with a CR occurring in 85% (the 1 nonresponder had prior ponatinib exposure)
> MMR was achieved in 86% and CMR was achieved in 79%
> With a median follow-up of 24 mo: 1 pt did not respond, 6 proceeded to allo-SCT, 4 pts did not undergo ASCT (relapsed after median 6.4 mo), 1 pt died in CR, and 2 pts are ongoing without ASCT (median CR duration 34 mo)
> One pt discontinued ponatinib due to TRAE and 1 pt discontinued blinatumomab due to TRAE; no G4–5 events were observed





EXPERT CONCLUSIONS

> *"But really, ponatinib + blina in relapsed and refractory provides not-bad outcome, although the number of patients is still limited"*

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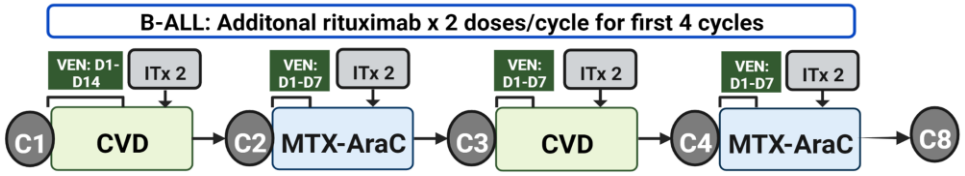
A Phase II Trial of Mini-Hyper-CVD With Venetoclax for Patients With Relapsed/Refractory (R/R) Philadelphia Chromosome (Ph)-Negative Acute Lymphoblastic Leukemia (ALL)

Fadi Haddad, et al. P377

EPICS

STUDY POPULATION

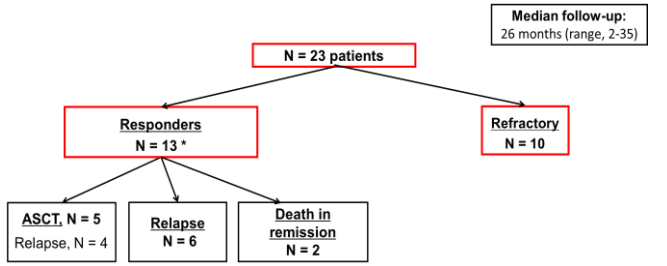
- Evaluate the tolerability and efficacy or venetoclax added to mini–hyper-CVD in pts aged ≥18 yr with R/R Ph-negative ALL
- 23 pts were treated (median age 45 yr, range 20–70 yr; 78% B-ALL and 22% T-ALL)
- Median number of prior therapies 2; 13 pts had prior ASCT

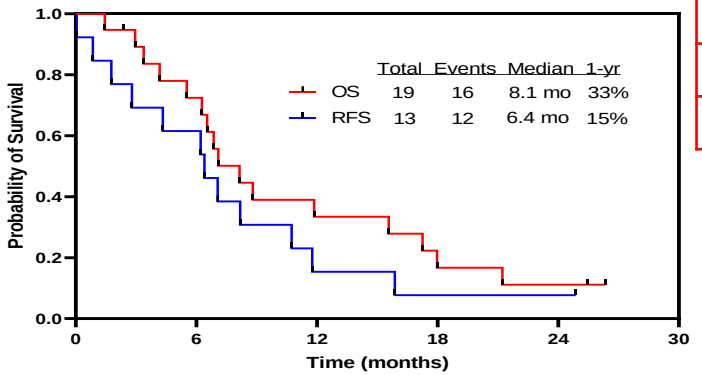


T-ALL: Nelarabine × 2 after C4 (D1-D5 w/o VEN + PEG-ASP (D5)

OUTCOME

- Median duration of follow-up was 26 mo
- 55% of pts had an ORR; 41% achieved a CR
- Among the 13 total responders: 6 pts relapsed, 5 pts underwent ASCT, and 2 pts died in remission
- Median RFS was 6.4 mo (1-yr RFS 15%) and median OS was 8.1 mo (1-yr OS 37%)
  - Worse OS occurred in pts with adverse cytogenetics (1-yr OS 17%)





Characteristics (N = 23)	N (%) / Median [range]
Age (years)	45 [20-70]
B-cell ALL T-cell ALL	18 (78) 5 (22)
Salvage 1 *Salvage 2+*	10 (43) 13(57)
Prior therapies	2 (1-6)
Prior allo-HSCR	13 (57)

EXPERT CONCLUSIONS

- *"Practically no survival [adverse-cytogenetics patients] . . . but the other patients with no complex cytogenetics can show a median survival, promising, and this is quite a good schedule, mini–hyper-CVD + blinatumomab, in order of clinical efficacy, and in order to safety profile"*

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EPICS

Discussion Summary

Advances in ALL: R/R Disease

Advances in ALL: R/R Disease (1/2)

EPICS

Reduced-Intensity Chemotherapy Combinations, TKIs, and CAR T-Cell Therapy

Obecabtagene autoleucel (obe-cel) safety and efficacy in adult patients with R/R B-cell ALL

- Efficacy outcomes are seen as impressive, but experts consider the most important differentiator between obe-cel and brexucabtagene autoleucel to be obe-cel's low toxicity rates (grade ≥3 CRS: 3.2%; grade ≥3 ICANS: 7.4%)
  - Further follow-up is needed to determine if the durability of the response can match that seen in ZUMA-3
- Experts see CAR T-cell therapy having a role in the treatment of patients with complex genetic disease where immunotherapy + TKI is not sufficient
- Dr Ribera believes if blina is moved to the front line, CAR T-cell therapy will become the new go-to therapy in second line
- Experts expressed concerns regarding cytopenias and B-cell aplasia if InO is used in combination with chemotherapy, stating less InO may be better when planning for CAR T-cell therapy at relapse
- Experts are not convinced that blinatumomab should be avoided prior to CD19-directed CAR T-cell therapy
- Experts discussed the anticipated impact of bispecific CAR T cells on the R/R AML landscape
  - While the response rates are "good," experts are not impressed by the relapse rates and do not see this as the best approach in the R/R setting
    - Dr Park wondered whether the higher-than-expected relapse rates could be attributed to the uneven targeting of antigens by the cellular therapy

"***Dr Park:***
I think that the data looks very good. I mean, efficacy-wise, it's comparable to ZUMA-3. . . . But as Dr Ribera also mentioned, I think the key distinguishing feature here is the toxicity"

Advances in ALL: R/R Disease (2/2)

EPICS

Reduced-Intensity Chemotherapy Combinations, TKIs, and CAR T-Cell Therapy

Mini–hyper-CVD + inotuzumab followed by blinatumomab consolidation

> The ORR of 95% at salvage 1 is seen as excellent, indicating the addition of blinatumomab consolidation in this setting has promise

> Overall, the experts see little to no role for allo-SCT in this setting and view the effect of blinatumomab addition to mini–hyper-CVD and InO as additive, clearly improving the outcomes in patients

Ponatinib + blinatumomab in patients with R/R Ph-positive ALL

> The efficacy of ponatinib and blinatumomab is seen as promising in the R/R Ph-positive ALL setting, especially the CR of 85% and the median OS, with the caveat that this was a small study population

Mini–hyper-CVD with venetoclax for patients with R/R Ph-negative ALL

> Experts described the ORR of 55% and CR of 41% as “not bad,” but believe the OS in patients with adverse cytogenetics is not impressive (1-year OS rate: 17%)
  - The data in patients without high-risk cytogenetics are seen as promising for this disease
  - Dr Ribera stated his interest in studying the addition of immunotherapy to mini–hyper-CVD with venetoclax in this setting

“***Dr Ribera:***
Patients with no complex cytogenetics show a median survival that is promising, and this is quite a good schedule, mini–hyper-CVD + venetoclax, in order of clinical efficacy, and in order to safety profile. Really, one thing, why not to combine my mini–hyper-CVD, immunotherapy, and venetoclax?”

Conference Coverage: EHA 2023 – Focus on AML and MDS

EPICS

Overall Conclusions: Dr Jabbour

MDS

> *"Two randomized trials, both very positive – the COMMANDS and IMerge"*

AML

> *"GO is new standard of care in NPM1-mutated AML"*
> *"The question of intensive chemotherapy vs low-intensity chemotherapy needs to be addressed when going to transplant"*

ALL

> *"Chemotherapy-free approaches in both Ph-positive or Ph-negative ALL"*
> *" New CAR T-cell therapy raises questions on how to sequence therapies"*

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