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Congress Coverage: ASH 2021 – Focus on Leukemia and MDS

Full Report

December 15, 2021

Report Contents

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Meeting Snapshot

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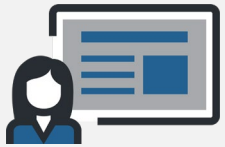
Virtual Closed-Door Roundtable

DATE:
December 15, 2021



DISEASE STATE AND DATA PRESENTATIONS by key experts

INSIGHTS REPORT including postmeeting analyses and actionable recommendations

PANEL: Key experts in leukemia

- 5 from US
- 4 from EU

LEUKEMIA-SPECIFIC DISCUSSIONS on therapeutic advances and their application in clinical decision-making

Panel Consisting of 5 US and 4 European Leukemia Experts

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Jae Park, MD
Memorial Sloan Kettering Cancer Center

Amir Fathi, MD
Massachusetts General Hospital

CHAIR:
Elias Jabbour, MD
MD Anderson Cancer Center

Naval Daver, MD
MD Anderson Cancer Center

Guillermo Garcia-Manero, MD
MD Anderson Cancer Center

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

CO-CHAIR:
Nicola Gökbuget, MD
Goethe University Hospital

Valeria Santini, MD
University of Florence

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

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Meeting Agenda

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Time (CST)	Topic	Speaker/Moderator
1.00 PM – 1.05 PM	**Welcome and Introductions**	Elias Jabbour, MD, and Nicola Gökbuget, MD
1.05 PM – 1.15 PM	**New Developments in MDS**	Guillermo Garcia-Manero, MD, and Valeria Santini, MD
1.15 PM – 1.45 PM	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
1.45 PM – 2.00 PM	**Advances in AML: Newly Diagnosed**	Amir Fathi, MD, and Charles Craddock, CBE, FRCP (UK), FRCPath, DPhil, FMedSci
2.00 PM – 2.25 PM	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
2.25 PM – 2.35 PM	**Advances in AML: Relapsed/Refractory**	Naval Daver, MD
2.35 PM – 3.00 PM	*Discussion and Key Takeaways*	*All* *Moderator: Elias Jabbour, MD*
3.00 PM – 3.05 PM	Break	
3.05 PM – 3.15 PM	**Advances in ALL: Newly Diagnosed**	Josep-Maria Ribera, MD, PhD
3.15 PM – 3.35 PM	*Discussion and Key Takeaways*	*All* *Moderator: Nicola Gökbuget, MD*
3.35 PM – 3.45 PM	**Advances in ALL: Relapsed/Refractory**	Jae Park, MD
3.45 PM – 4.10 PM	*Discussion and Key Takeaways*	*All* *Moderator: Nicola Gökbuget, MD*
4.10 PM – 4.15 PM	**Summary and Closing Remarks**	Elias Jabbour, MD, and Nicola Gökbuget, MD

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Congress Highlights

Updates on MDS

Initial Results of Phase I/II Study of Azacitidine in Combination with Quizartinib for Patients with Myelodysplastic Syndrome and Myelodysplastic/Myeloproliferative Neoplasm with *FLT3* or *CBL* Mutations

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Tareq Abuasab, et al, #1536

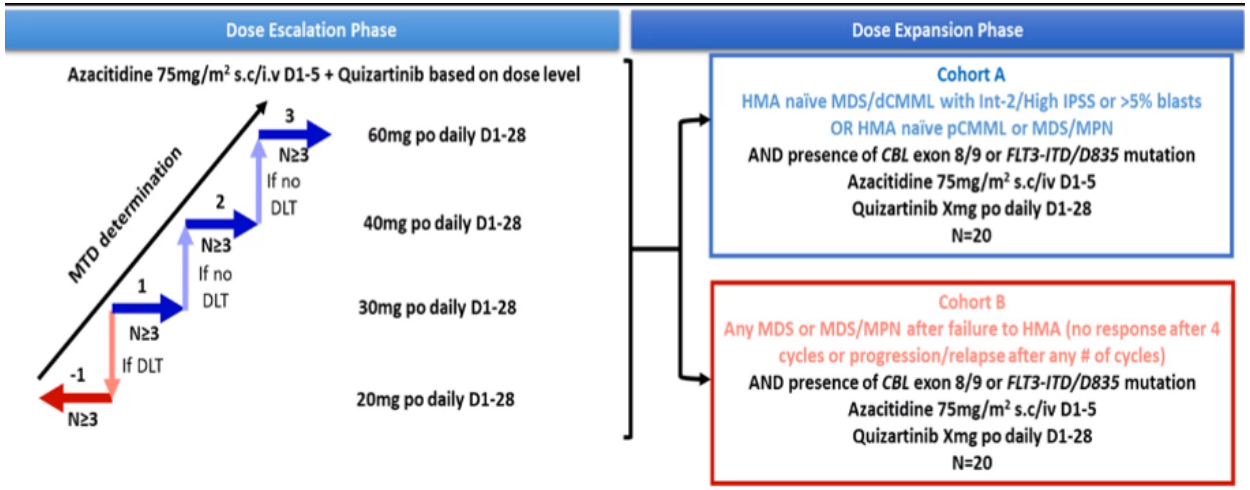
STUDY POPULATION

> Newly diagnosed patients with MDS and MDS/MPN with detectable *FLT3* mutation and/or *CBL* exon 8 or 9 deletions or point mutations
> Median age 73.5 yr (8 patients treated)
> High-risk MDS, MDS/MPN, and CMML

OUTCOME

> Marrow CR 86%, HI 29%, duration 6.8 mo
> Clearance or reduction of *FLT3* in all cases
> No reduction of *CBL*
> Acceptable toxicity, no early deaths

STUDY DESIGN



EXPERT CONCLUSIONS

> "*Only 1% of de novo MDS have FLT3 mutations; however, almost 20% do have these mutations after relapse, after failure of the HMAs, and therefore this is something that we should keep in mind to reevaluate molecularly our patients after HMA failure*"
> Further follow-up with a larger patient cohort is required to emphasize the safety and efficacy of this combination and evaluate depth and duration of response

Ivosidenib Monotherapy Is Effective in Patients With IDH1 Mutated Myelodysplastic Syndrome (MDS): The Idiome Phase II Study By the GFM Group

Marie Sebert, et al, #62

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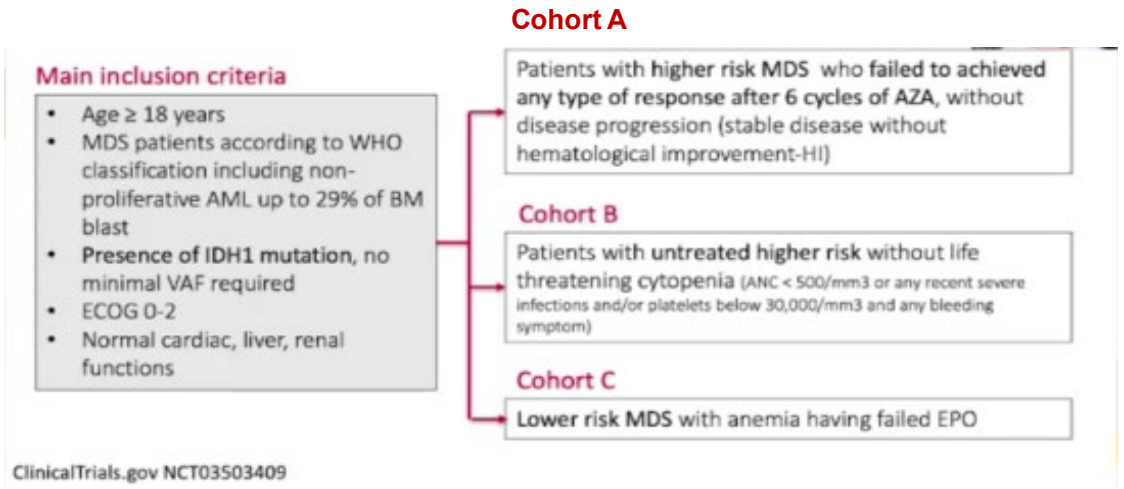
STUDY POPULATION

- Cohort A, n=29, higher-risk (HR) MDS for which azacitidine (aza) failed
- Cohort B, n=29, untreated HR MDS without life-threatening cytopenias or any recent severe infections and/or platelets below 30,000/mm^3 and any bleeding symptoms
- Cohort C, n=10, lower-risk (LR) MDS for which EPO failed
- Patients received continuous 28-day cycles of ivo – 500 mg orally QD
- Median age 76 and at data cutoff; 26 patients treated
- Median variant allele frequency (VAF) of *IDH1* mutation was 15% (HR 6%–18%, LR 44%)

OUTCOME

- ORR 69%; 54% in R/R MDS, 91% first line, 50% in LR MDS
- 46% CR
- Median OS 14 mo
- No concerning toxicity was reported

STUDY DESIGN



EXPERT CONCLUSIONS

- *"What is interesting is that there was no limitation for the variant allele frequency of IDH1 mutation"*
- Ivo was well tolerated in MDS patients, with significant responses in all cohorts. With a response rate of 91%, ivo was particularly effective in treating naive HR MDS patients with *IDH1* mutations
- These encouraging preliminary results must be confirmed in more patients

Enasidenib (ENA) Is Effective in Patients with IDH2 Mutated Myelodysplastic Syndrome (MDS): The Ideal Phase II Study By the GFM Group

Lionel Ades, et al, #63

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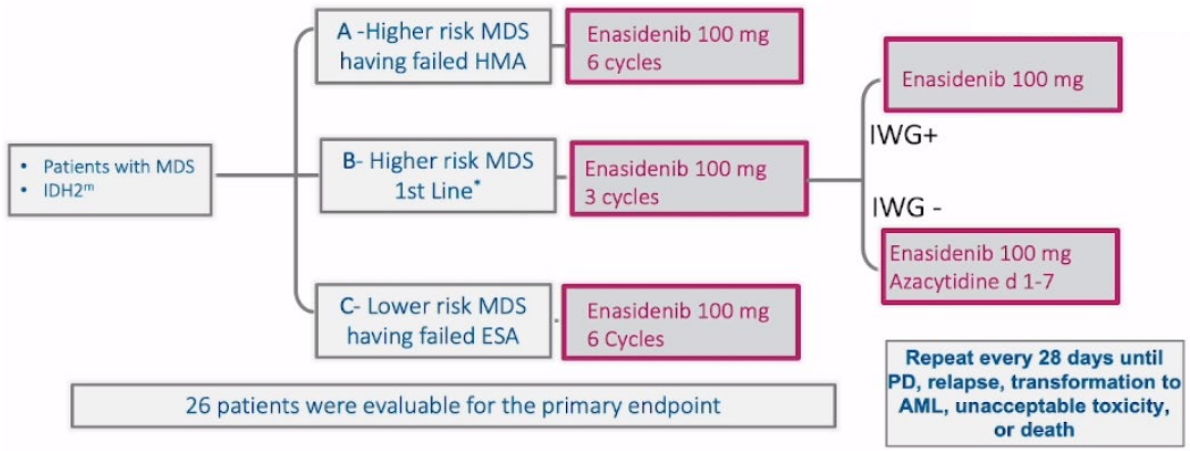
STUDY POPULATION

- Cohort A, n=29, HR MDS for which HMA failed
- Cohort B, n=29, untreated HR MDS without life-threatening cytopenias or any recent severe infections and/or platelets below 30,000/mm^3 and any bleeding symptoms
- Cohort C, n=10, LR MDS for which ESA failed
- Median age 75.5 yr
- Median VAF for *IDH2* mutation 36%
- Patients received continuous 28-day cycles of ena – 100 mg PO QD

STUDY DESIGN



OUTCOME

- ORR 42%; R/R HMA 27%, first line 56% (11% CR), LR MD 50%
- In cohort B, aza was added after 3 cycles in 3 out of 9 patients
- Median DOR was not reached with follow-up at 8.6 mo
- Median OS 17.4 mo, group C had a shorter OS

CONCLUSIONS

- Results from the first 26 patients show that ena has no limiting toxicity in patients with MDS, and it can provide responses in 42% of patients. These responses appear encouraging in first-line (low- and high-risk) patients

Long Term Follow-up and Combined Phase 2 Results of Eprenetapopt (APR-246) and Azacitidine (AZA) in Patients with *TP53* mutant Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia (AML)

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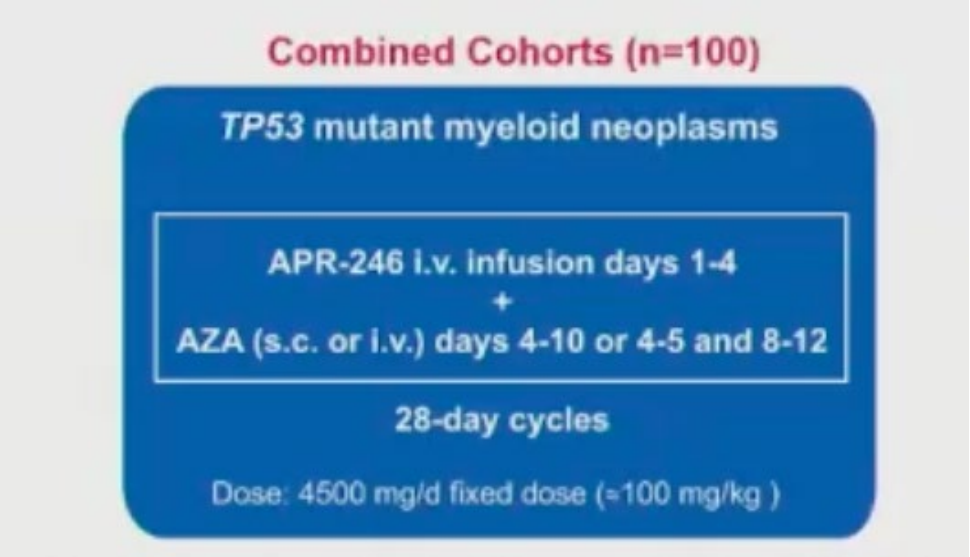
David A. Sallman, et al, #246

STUDY POPULATION

- HMA-naive *TP53* mutation HR MDS, MDS/MPN, and oligoblastic AML (≤30% blasts) patients
- Patients received APR-246 4500 mg IV (days 1–4) plus aza 75 mg/m^2 SC/IV × 7 days (days 4–10 or 4–5 and 8–12) in 28-day cycles
- Median age 68 yr, 100 patients treated (74 MDS, 22 AML, 4 MSD/MPN)
- Media VAF for *TP53* mutation 22%
- Eighty-eight percent of patients had biallelic and/or complex karyotype (very high risk)



OUTCOME

- ORR 69%, CR 43%
- Clearance of *TP53* mutation 40% (VAF <5%)
- Best responders were higher-risk patients with biallelic *TP53* mutation and complex karyotype; CR 49% vs 8%
- Patients with only *TP53* mutation did better than patients with additional mutations; CR 52% vs 30%
- With 28-mo follow up
  - Median OS 11.8 mo
  - Median OS in CR/PR 15.8 mo

EXPERT CONCLUSIONS

- *"The phase III did not show an advantage in CR for the patient treated with a combination vs azacitidine alone and this was probably due to the design of the study. . . . The co-mutations are different and therefore the analysis is somehow a little bit more difficult"*
- *"Also, choosing the endpoint is critical, because if you have too ambitious endpoints and you think you can really do much better than azacitidine alone, you may fail the role of the study"*

Molecular International Prognosis Scoring System for Myelodysplastic Syndromes

Elsa Bernard, et al, #61

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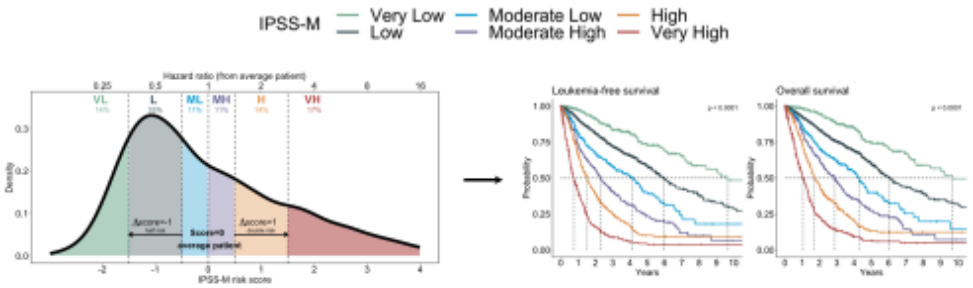
STUDY POPULATION

> Diagnostic MDS samples from 2,957 patients with <20% blasts and white blood cell count below 13×10⁹/L were profiled for mutations in 156 driver genes (discovery cohort)

> The IPSS-M risk score was built as a continuous index, defined as a weighted sum of prognostic variables. A six-risk category schema was defined on the basis of score cutoffs: Very Low (14%, n=387), Low (32%, n=876), Moderately Low (11%, n=299), Moderately High (11%, n=284), High (14%, n=382), and Very High (18%, n=473)

OUTCOME

IPSS-M patient-specific risk score & risk categories



Continuous risk score

Patient-specific score

Reproducible and Interpretable

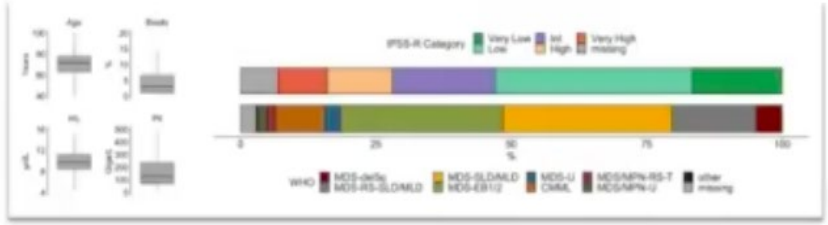
A six-category risk schema

Prognostic separation

Therapeutic decisions & clinical trial design

IWG-PM cohort clinical characteristics

Inclusion criteria: **diagnostic samples | blast percentages < 20% | white blood cell count < 13x10⁹/L**



- Median age of presentation 72 years (39-88, 95th range).
- Representative of all IPSS-R risk categories and WHO subtypes.
- 8% of patients had therapy-related MDS.
- 30% of patients treated with disease-modifying agents according to established guidelines.
- Median follow-up 3.8 years.

EXPERT CONCLUSIONS

> This risk score allows a more precise definition of the prognosis of the patient with respect to IPSS-R

> *"We need to understand how to validate and apply this system"*

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Evorpacept (ALX148), a CD47-Blocking Myeloid Checkpoint Inhibitor, in Combination with Azacitidine: A Phase 1 / 2 Study in Patients with Myelodysplastic Syndrome (ASPEN-02)

Guillermo Garcia-Manero, et al, #2601

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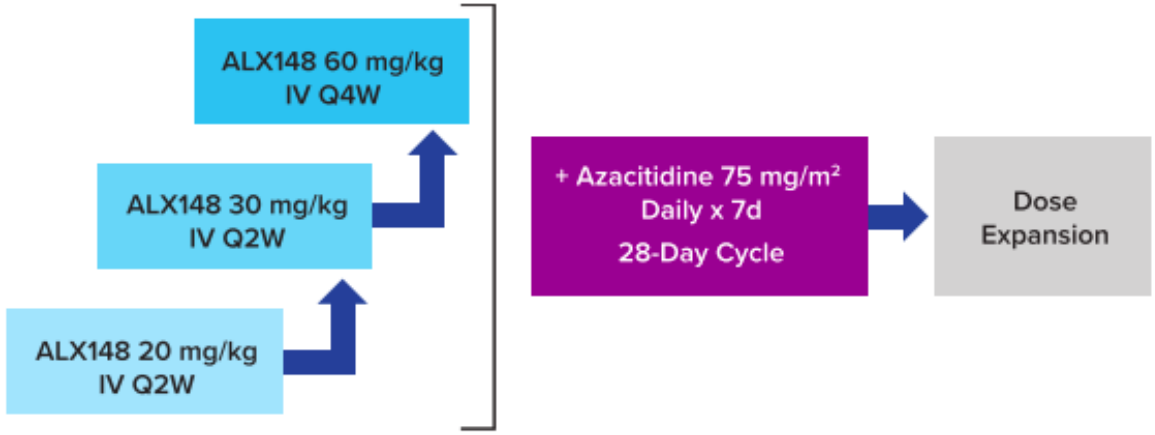
STUDY POPULATION

- Patients with newly diagnosed HR (IPSS-R >3.5) or R/R MDS
- 22 patients treated, 13 R/R MDS
- For first-line HR MDS, 78% patients had *TP53* mutation of complex karyotype
- Median age 70.5 yr

OUTCOME

- Short median follow-up of 3.4 mo
- ORR, first-line 50%, pts with *TP53* mutation 60%, R/R HR MDS 56%
- No severe adverse events
- Full CD47 occupancy in peripheral blood at all doses, 4 weeks after dosing

STUDY DESIGN



EXPERT CONCLUSIONS

- *"Short follow-up, but actually, not really severe adverse events"*
- *"Promising initial activity has been observed and eager to see the follow-up of the study"*

CPX 351 As First-Line Treatment in Higher-Risk MDS. A Phase II Trial By the GFM

Pierre Peterlin, et al, #243

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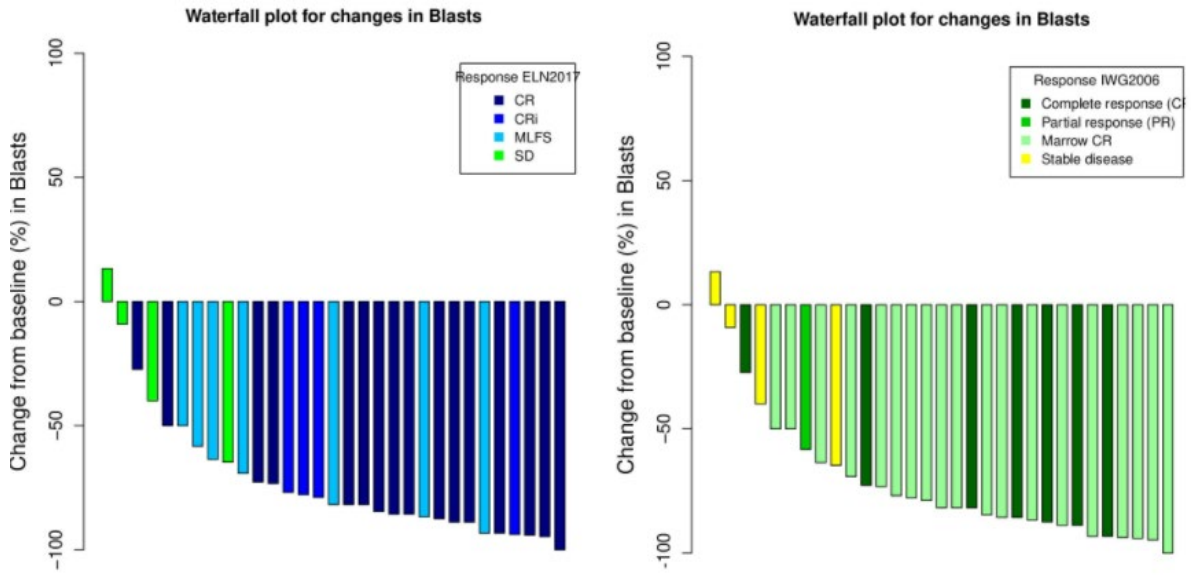
STUDY POPULATION

- Intermediate-2 or high IPSS MDS, previously untreated with HMA or chemotherapy, and aged <70 years
- Allo-SCT could follow after 1–4 consolidation cycles

OUTCOME

- Response rates, evaluated a median of 53 days (range 28–112) from onset of induction, were
  - With ELN 2017 criteria, CR 52%
  - With IWG 2006 criteria, CR 23%
- Twenty-four out of 27 patients with baseline marrow blasts >10%, reached <5% blasts after induction treatment
- One patient had grade ≥3 mucositis and 4 had grade ≥2 alopecia during induction treatment. No patient died during induction treatment or required management in the intensive care unit
- With a median follow-up of 201 days (range 102–350), 22 of the 30 patients initially considered for allo-SCT received transplant after no (10 patients), 1 (9 patients), 2 or 3 (3 patients) consolidation cycles, and 5 are planned for allo-SCT



EXPERT CONCLUSIONS

- The data show a very high rate of response with CPX-351
- "*I didn't see data on the presentation on the survival and the duration of these responses, so it seems to be very preliminary*"
- *"Some patients with this condition may benefit from a more traditional form of the chemotherapy"*

Pevonedistat (PEV) + Azacitidine (AZA) Versus Aza Alone As First-Line Treatment for Patients with Higher-Risk Myelodysplastic Syndromes (MDS)/Chronic Myelomonocytic Leukemia (CMML) or Acute Myeloid Leukemia (AML) with 20–30% Marrow Blasts: The Randomized Phase 3 PANTHER Trial (NCT03268954)

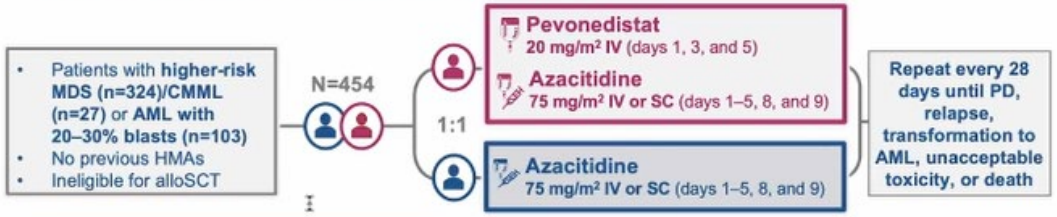
EPICS

Mikkael A. Sekeres, et al, #242

STUDY POPULATION

> Patients with HR MDS or HR CMML or AML with 20%–30% marrow blasts and who were chemotherapy/HMA naive and ineligible for upfront intensive chemotherapy and/or allogeneic stem cell transplantation
> Patients were stratified into 4 categories: very high-, high-, and intermediate-risk (per IPSS-R) MDS/CMML, and AML with 20%–30% marrow blasts

PANTHER (P-3001): global, open-label, multi-center, randomized phase 3 trial (NCT03268954)



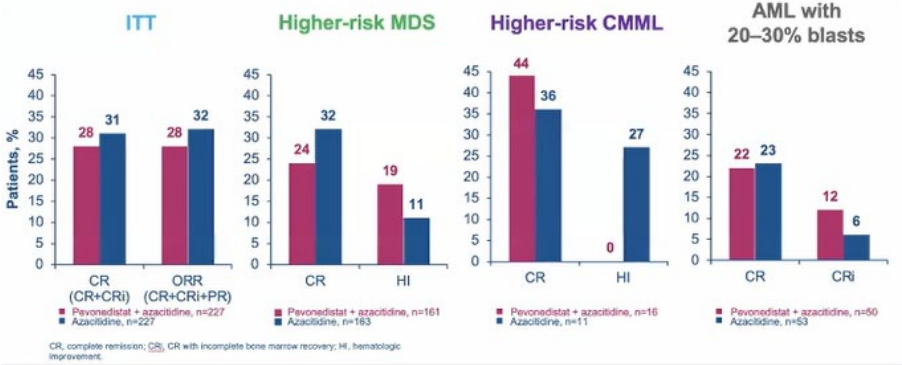
Stratification:
- IPSS-R risk category for higher-risk MDS or higher-risk CMML:
  - Intermediate
  - High
  - Very high
- AML with 20–30% blasts

Study endpoints:
- Primary endpoint: EFS in the ITT population and higher-risk MDS cohort (defined as time to death or transformation to AML in higher-risk MDS/CMML or time to death in AML with 20–30% blasts)
- Key secondary endpoint: OS

alloSCT, allogeneic stem cell transplant; IPSS-R, Revised International Prognostic Scoring System; ITT intent-to-treat; IV, intravenous; PD, progressive disease; SC, subcutaneous.

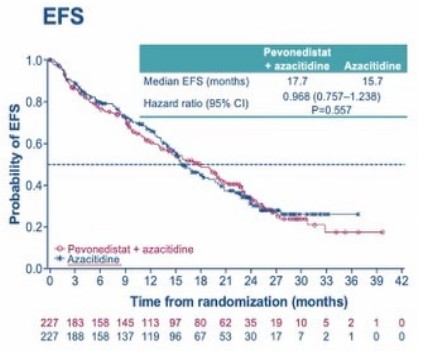
OUTCOME

Overall best response rate for complete ITT population and response rates in individual disease cohorts



CR, complete remission; CRi, CR with incomplete bone marrow recovery; HI, hematologic improvement.

EFS and OS for complete ITT



EXPERT CONCLUSIONS

> *"We are too enthusiastic and eager in some of these phase I trials that are not really close to reality"*
> *"We are not stratifying by molecular data in a prospective fashion, and this study actually shows that"*

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Discussion Summary

Updates on MDS

New Developments in MDS

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MDS with mutations

- Overall, new data indicate targeted agents are improving survival in patients with *FLT3* or *IDH* mutations; in particular, it appears promising after HMA failure
  - In a subset of patients with mutations, the goal can be to combine the targeted therapy with ven, to avoid HMA-ven
- Experience with different agents has shown that survival in patients with *TP53* mutation does not go beyond 12 months. This may be explained by a quick loss of response (can be 2 months) that is observed in this patient population
- In MDS, NGS for molecular profiling should be integrated at diagnosis and failure, as it will allow for a better choice of targeted therapy. It was noted that it is not available in all centers, although with time it will become more affordable and possible to integrate

High-risk MDS

- In the US at community hospitals, CPX-351 is being used more and more often as frontline treatment in patients with excess blasts, although more data are still needed to support its use
  - The challenge with the high-risk patients after treatment with CPX-351 is the prolonged time to count recovery, and it was pointed out that patients can only receive 1 or 2 cycles
- In frontline, expert preference is split between use of CPX-351 or HMA-ven, and in both instances treatment would be followed by transplant. Data show outcomes are similar with both induction treatment strategies
- It was noted that patients receiving CPX-351 should have normal karyotype (not complex)
- Promising data from investigational compounds in phase I trials do not always correlate with data from randomized phase III trials. This has happened with the randomized phase III PANTHER trial of pevonedistat plus azacitidine vs pevonedistat (Abstract 242), or with the phase II eprenetapopt (APR-246) study (Abstract 246). Important considerations for phase III trial design are
  - The disease is very heterogeneous and there is a need to apply molecular classification in MDS patients. Studies should be designed to stratify patients by molecular profiling
  - Endpoints based on the outcomes of phase I data may be overambitious. Phase I trials should be designed so they can be replicated in randomized phase III trials: "*We have to seriously think about how we do phase I/II data so that it is actually replicating*"
  - The selection of the control in randomized studies is very important
  - Patients with *TP53* mutation should be separated into different trials
  - Phase III failed studies should also be presented more widely: "*I think companies have a responsibility to really show that* [failed studies]"

Low-risk MDS

- Patients whose disease fails to respond to HMA therapy should be transplanted if they are transplant eligible

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Congress Highlights

Updates on Newly Diagnosed AML

Phase 3, Open-Label, Randomized Study of Gilteritinib and Azacitidine Vs Azacitidine for Newly Diagnosed *FLT3*-Mutated Acute Myeloid Leukemia in Patients Ineligible for Intensive Induction Chemotherapy

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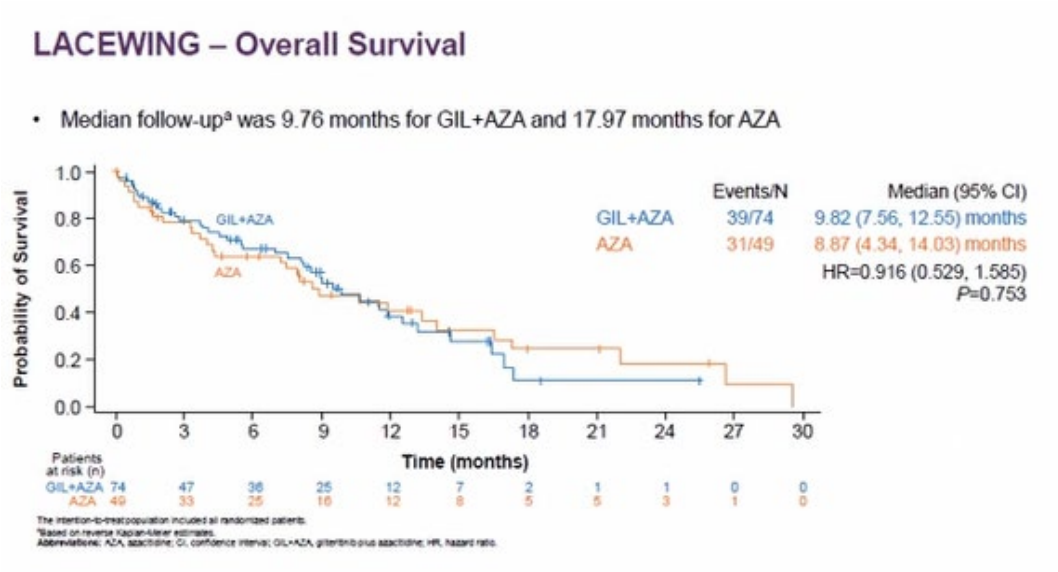
Eunice S. Wang, et al, #700

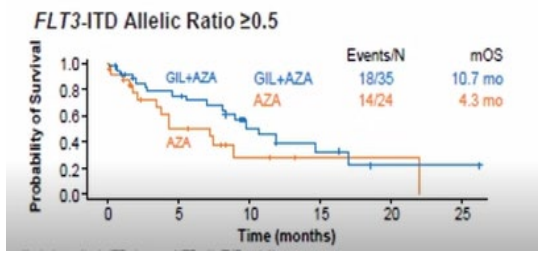
STUDY POPULATION

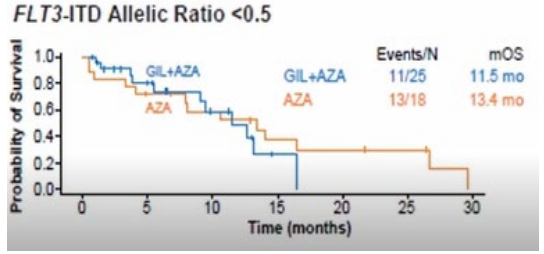
- Patients with newly diagnosed AML with *FLT3* mutations unable to receive intensive induction chemotherapy (IIC)
- Patients were then randomized (2:1) to gilt plus aza or aza alone
- Patient demographics: 47.3% for gilt plus aza arm vs 32.7% for aza arm of patients with ECOG ≥2
- A higher proportion of patients in the aza arm received subsequent FLT3 inhibitors therapy (4.1% in gilt plus aza vs 28.6% in aza)

OUTCOME

- Composite CR rates 58.1% gilt plus aza vs 26.5% aza
- Median OS was 9.82 mo for gilt plus aza and 8.87 mo for aza (hazard ratio 0.916 [95% CI 0.529, 1.585]; *P*=.753)







EXPERT CONCLUSIONS

- *"It is challenging in the current era when you have these targeted therapies available in second line, to design upfront therapies, because patients ultimately get those therapies anyway, so, overall survival ultimately gets impacted"*
- *"I can't still say whether azacitidine and gilteritinib is a combination that I should or should not use"*
- *"Trend for patients with high-allelic fraction to respond better vs low-allelic fraction. This makes sense if the disease is not driven by FLT3 mutations"*

Impact of *FLT3* Mutation Clearance After Front-Line Treatment with Gilteritinib Plus Azacitidine, or Gilteritinib or Azacitidine Alone in Patients with Newly Diagnosed AML: Results from the Phase 2 / 3 Lacewing Trial

Eunice S. Wang, et al, #3445

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STUDY POPULATION

- Adult patients with newly diagnosed *FLT3*+ AML ineligible for intensive induction chemotherapy
- The median age of patients enrolled in LACEWING was 77 years (range, 59–90), with 73% of patients aged >75 years
- Forty patients who achieved CRc and had sufficient DNA samples from bone marrow aspirates obtained at baseline and at least 1 additional postbaseline time point were included in the analysis

OUTCOME

- In patients who received gilt either alone or in combination with aza, *FLT3*-ITD mutation clearance was associated with an increase in median OS vs patients who did not achieve a mutation clearance

EXPERT CONCLUSIONS

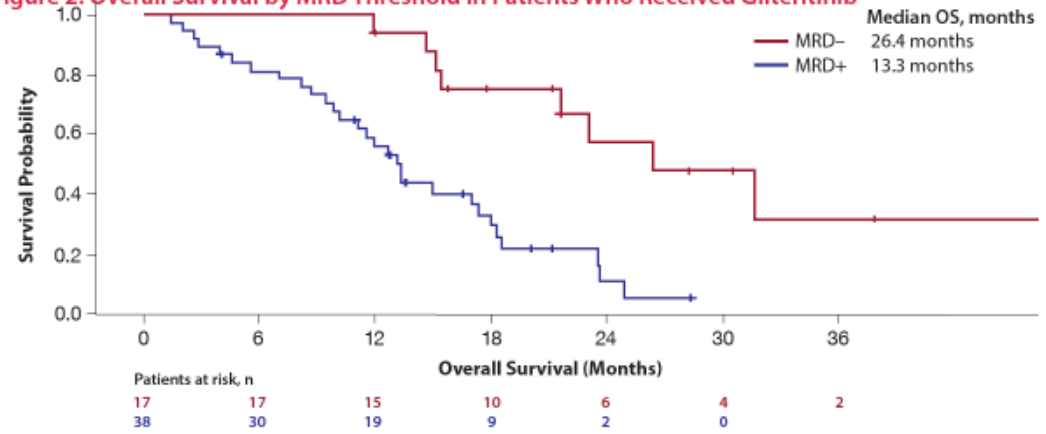
- "*Median OS for patients who achieved their MRD was twice that of those who did not, and although not surprising, these were still very interesting results*"

Table 2. Post-Treatment MRD Status by Cohort in Patients With Post-Baseline Samples Who Achieved CRc (N=66)

MRD Status[a]	Safety Cohort Gilteritinib 80/120 mg + AZA (n=8)	Arm AC Gilteritinib 120 mg + AZA (n=38)	Arm A Gilteritinib 120 mg (n=9)	Total Gilteritinib[b] (n=55)	Arm C AZA (n=11)
MRD–: $<10^{-4}$	4 (50)	10 (26)	3 (33)	17 (31)	4 (36)
MRD+: $\geq 10^{-4}$	4 (50)	28 (74)	6 (67)	38 (69)	7 (63)

[a]Percentages for MRD– and MRD+ may not add up to 100% because of rounding.
[b]Includes all patients who received gilteritinib in the Safety Cohort and in Arms A and AC.
Abbreviations: AZA, azacitidine; CRc, composite complete remission; MRD, measurable residual disease.

Figure 2. Overall Survival by MRD Threshold in Patients Who Received Gilteritinib



Abbreviations: MRD, measurable residual disease; OS, overall survival.

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AGILE: A Global, Randomized, Double-Blind, Phase 3 Study of Ivosidenib + Azacitidine Versus Placebo + Azacitidine in Patients with Newly Diagnosed Acute Myeloid Leukemia with an *IDH1* Mutation

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Pau Montesinos, et al, #697

STUDY POPULATION

- Untreated AML patients, centrally confirmed *mIDH1* status, not eligible for intensive chemotherapy, ECOG 0–2
- Patients were stratified by region and de novo vs secondary AML
- As of the data cutoff date, 146 patients had been randomized (ivo plus aza, n=72; PBO plus aza, n=74)

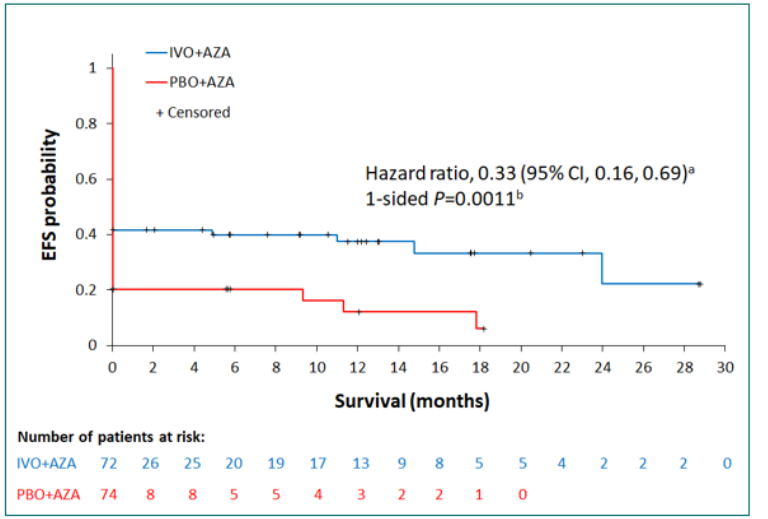
OUTCOME

- Ivo plus aza significantly improved EFS in *mIDH1* AML (HR = 0.33 [95% CI 0.16, 0.69]; *P*=.0011)
- Ivo plus aza significantly improved OS in *mIDH1* AML (median OS 24.0 mo vs 7.9 mo; hazard ratio 0.44 (95% CI, 0.27, 0.73) 1-sided *P*=.0005

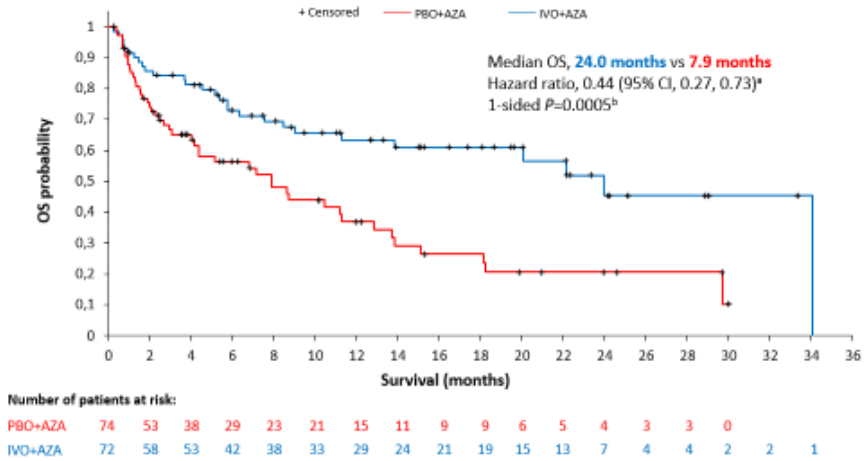
EXPERT CONCLUSIONS

- "[Median OS] . . . *24 months is probably the best we have seen in a combination HMA approach for older patients in the newly diagnosed setting*"
- " . . . *depending on the patient population, this [ivo plus aza] might be the right choice*"

EFS in the intent-to-treat population



Overall survival



APTITUDE HEALTH®

Phase I and Expansion Study of Eprenetapopt (APR-246) in Combination with Venetoclax (VEN) and Azacitidine (AZA) in *TP53*-Mutant Acute Myeloid Leukemia (AML)

EPICS

Guillermo Garcia-Manero, et al, #3409

STUDY POPULATION

- Forty-seven patients were enrolled with *TP53*-mutant AML
- Safety cohort 1 (SC1) received 1 prior line of HMA therapy for MDS, and safety cohort 2 (SC2) had no prior HMA. Expansion cohort 2 (eprenetapopt plus aza plus ven) enrolled patients with previously untreated AML without prior HMA

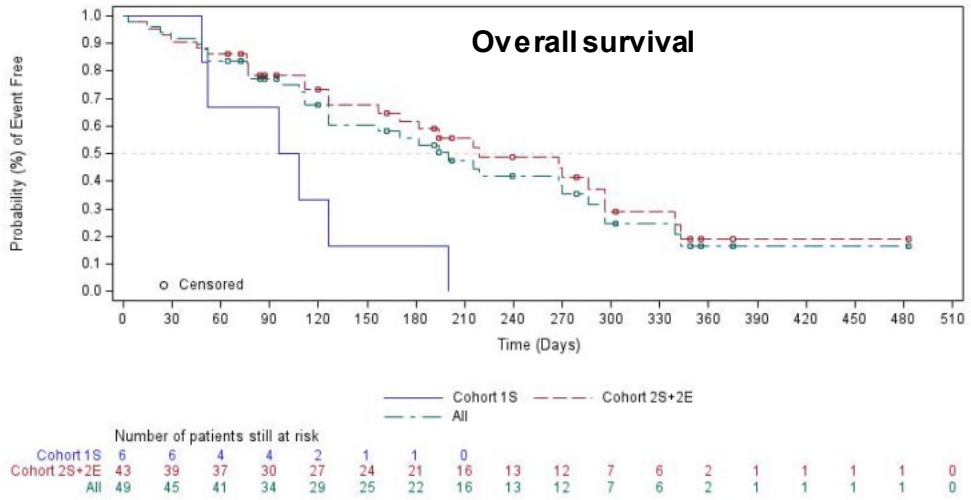
OUTCOME

- There were no DLTs observed in the 6 patients in SC1 and in the 6 patients in SC2. All-grade TEAEs in ≥30% included nausea (66%), febrile neutropenia (52%), diarrhea (50%), decreased appetite (41%), constipation and vomiting (39% each), hypokalemia (36%)
- First 30 efficacy-evaluable patients who received eprenetapopt plus ven plus aza: CR rate of 37% (11 patients)
- Median OS in patients receiving eprenetapopt plus ven plus aza: 7.3 mo

EXPERT CONCLUSIONS

- *"The overall response rate (64%) is encouraging, but the CR rate is modest (39%) . . . 7-month OS is slightly better than what you would expect with HMA-ven therapy. We will have to see, ultimately, where that goes"*

Endpoint	Triplet eprenetapopt plus ven plus aza N=39
ORR, n (%)	25 (64)
DOR (days), median (95%CI)	127 (82, 253)
CR, n (%)	**15 (39)**
DOCR (days), median (95%CI)	148 (60, NE)
CR+CRi, n (%)	22 (56)
CR+CRh, n (%)	22 (56)



APTITUDE HEALTH®

Updated Survival and Response Analyses from a Phase 1 Study of Ivosidenib or Enasidenib Combined with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed AML with an *IDH1* or *IDH2* Mutation

Eytan M. Stein, et al, #1276

EPICS

STUDY POPULATION

> Patients with newly diagnosed m*IDH1* or m*IDH2* AML were treated with induction therapy in combination with ivo (for m*IDH1*) or ena (for m*IDH2*). After induction, patients received up to 4 cycles of consolidation therapy while continuing the IDH inhibitor

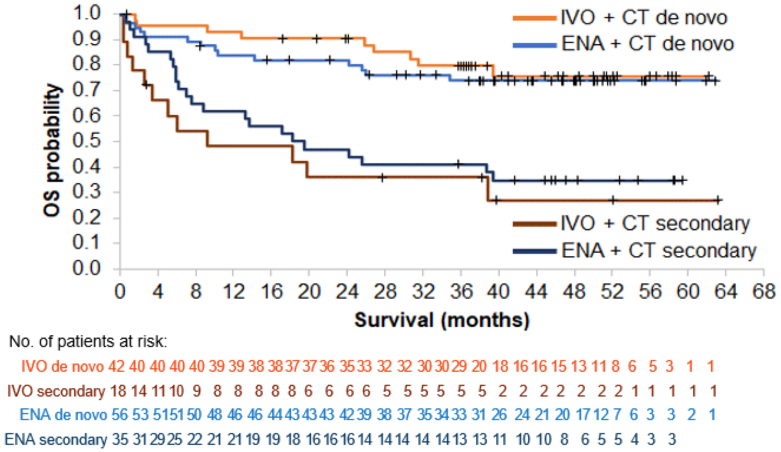
OUTCOME

> Response rates vary considerably in de novo vs secondary AML (88.1% vs 55.6%)

Table 4. Best overall response in the full analysis set[a]

Response,[b] n (%)	Ivosidenib + chemotherapy			Enasidenib + chemotherapy		
	De novo (n=42)	sAML (n=18)	All (n=60)	*De novo* (n=56)	sAML (n=35)	All (n=91)[c]
CR+CRi/CRp	37 (88.1)	10 (55.6)	47 (78.3)	45 (80.4)	22 (62.9)	67 (73.6)
CR	32 (76.2)	10 (55.6)	42 (70.0)	36 (64.3)	16 (45.7)	52 (57.1)
CRi/CRp	5 (11.9)	-	5 (8.3)	9 (16.1)	6 (17.1)	15 (16.5)
MLFS	3 (7.1)	1 (5.6)	4 (6.7)	5 (8.9)	5 (14.3)	10 (11.0)
PR	-	2 (11.1)	2 (3.3)	1 (1.8)	1 (2.9)	2 (2.2)
Treatment failure	2 (4.8)	5 (27.8)	7 (11.7)	5 (8.9)	7 (20.0)	12 (13.2)

Figure 5. Overall survival by AML type



- Median duration of follow-up for OS:
  - Ivosidenib 36.6 months
  - Enasidenib 36.9 months

EXPERT CONCLUSIONS

> "*We need actual randomized data to tell me it's better . . . but probably the combination in a subset of patients who do not have secondary AML makes more sense*"

Real-World Experience of CPX-351 As First-Line Treatment in 188 Patients with Acute Myeloid Leukemia

Christina Rautenberg, et al, #33

EPICS

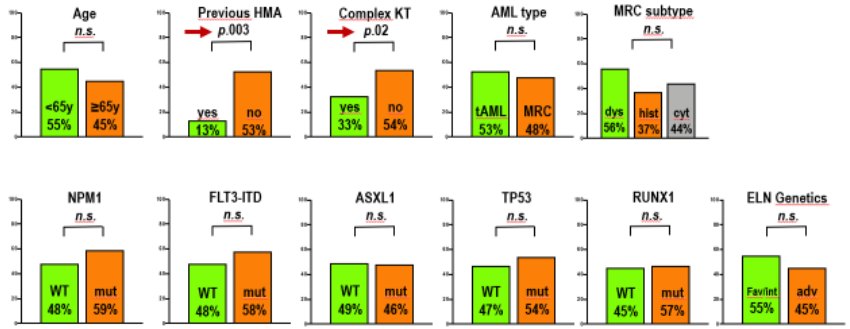
STUDY POPULATION

> Data were collected on baseline characteristics, treatment details, including allo-HCT and outcome from patients with newly diagnosed AML-MRC or t-AML who were treated with CPX-351 according to the EMA label between 2018 and 2020 in 25 German centers

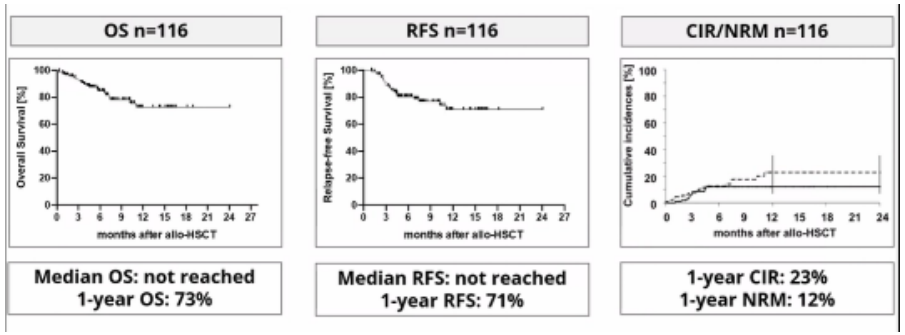
OUTCOME

> Patients with previous HMA or complex karyotype had lower CR rates. There was no significant difference between the *TP53* mutation or wild-type groups
> Median OS 21 mo, 1-year OS 64%. Prior HMA therapy and complex karyotype subgroups had worse outcomes
> Treatment is well tolerated regarding GI toxicities. However, there is prolonged myelosuppression and infectious complications
> Patients who underwent transplant after CPX-351 treatment had a good outcome (1-year OS 73%)

CR by Subgroup



Outcome Parameter	n (%) / median (range, days)
Frequency of blood count recovery, n (%)	
• ANC	79 (95%)
• PLC	76 (92%)
Time to blood count recovery, median (range)	
• ANC	33 days (6-99)
• PLC	30 days (7-77)
Grade III/IV non-hematologic toxicities	130 (69%)
• Infection	41 (22%)
• GI (mucositis, nausea, vomiting)	7 (4%)
• Bleeding	7 (4%)
• Renal failure	5 (3%)
• Febrile neutropenia	28 (15%)
• pneumonia	42 (22%)
Early death day 30	14 (8%)



CONCLUSIONS

> *"The 1-year OS of 64%, median OS of 21 months is quite remarkable . . . this treatment is, in my view, in the front end, very well tolerated, but the back end is challenging with prolonged marrow suppression and infectious complications"*

Long-Term Overall Survival (OS) with Oral Azacitidine (Oral-AZA) in Patients with Acute Myeloid Leukemia (AML) in First Remission after Intensive Chemotherapy (IC): Updated Results from the Phase 3 QUAZAR AML-001 Trial

Andrew H. Wei, et al, #871

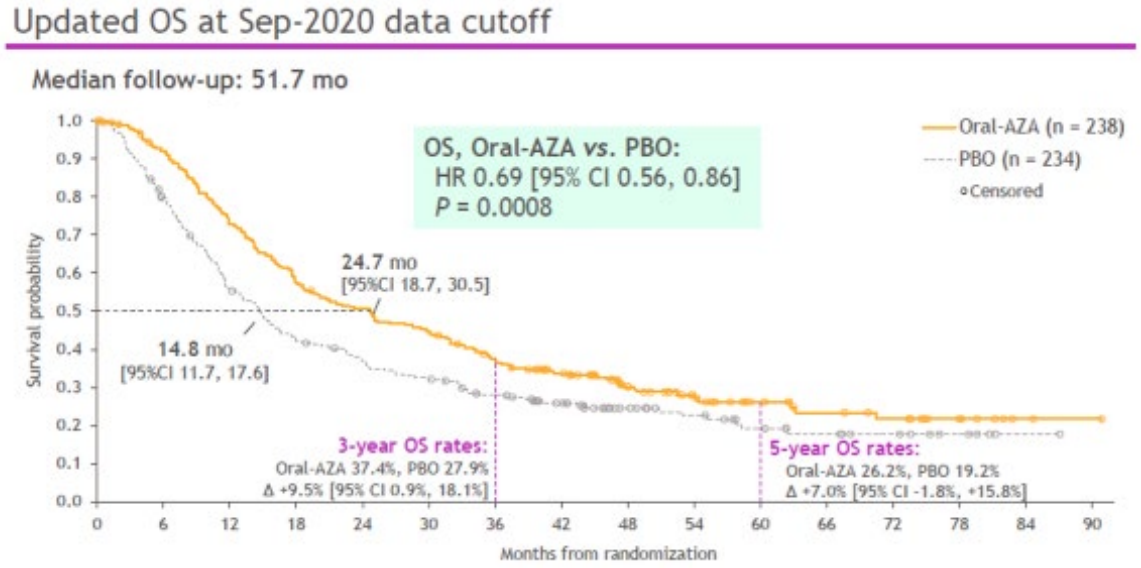
EPICS

STUDY POPULATION

- Eligible patients were aged ≥55 years with newly diagnosed AML, intermediate- or poor-risk cytogenetics at diagnosis, ECOG PS ≤3, and had achieved first CR or CRi after induction ± consolidation before screening
- Within 4 mo after CR/CRi, patients were randomized 1:1 to aza or PBO

OUTCOME

- At updated cutoff date (Sep 20, 2020) Median OS remained unchanged from the primary cutoff date (Jul 2019): 24.7 vs 14.8 mo with oral-aza vs PBO, respectively (*P*=.0008). However, the KM OS curves showed greater separation and did not touch or cross at any time
- Survivor group was more likely to have intermediate-risk cytogenetics (94% vs 81%) and an *NPM1* mutation (45% vs 19%) at diagnosis, and had become MRD– on study (76% vs 22%)



EXPERT CONCLUSIONS

- *"In the updated data, looking at the 3-year OS and the 5-year OS, you see those tails are not parallel to each other, and there is ongoing separation. So, there seems to be [an] ongoing advantage in terms of OS in patients who received oral azacitidine vs placebo"*

A Phase II Study of 5-Azacytidine (AZA) and Venetoclax As Maintenance Therapy in Patients with Acute Myeloid Leukemia (AML) in Remission

Alexandre Bazinet, et al, #2326

EPICS

STUDY POPULATION

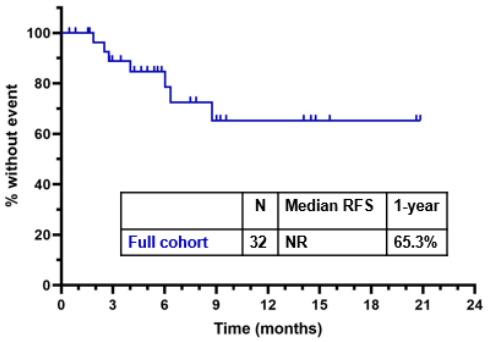
> Patients with AML were eligible for enrollment if they had achieved CR1 (CR/CRi), had ≥2 cycles of therapy prior to maintenance, and were not immediately eligible for aHSCT. Patients with detectable MRD in CR1 or beyond were also eligible

> Cohort 1 included patients treated with intensive chemo. Cohort 2 consisted of patients treated with low-intensity chemotherapy or HMA backbone who had received at least 2 cycles from time of CR/CRi to enrollment. Maintenance consisted of aza and ven

OUTCOME

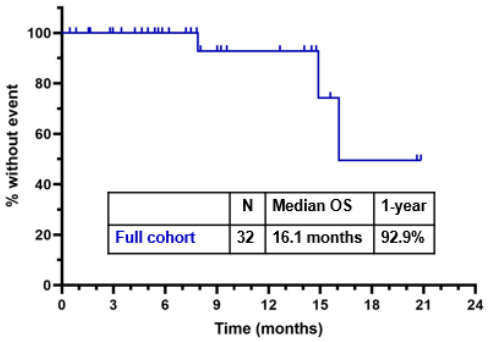
> EFS and OS at 6 mo were 87% and 100%, respectively, for the full cohort. With a median follow-up of 3.8 mo, the median OS was 16.1 mo and median RFS has not yet been reached. Median RFS for patients with or without prior ven was not reached and 10.1 mo, respectively

Relapse-free survival: Full cohort



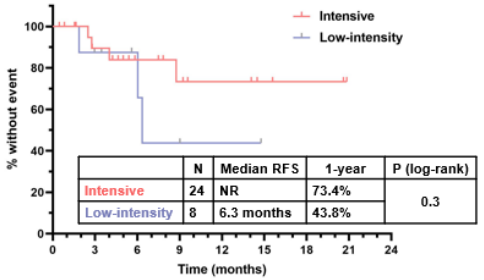
	N	Median RFS	1-year
Full cohort	32	NR	65.3%

Overall survival: Full cohort



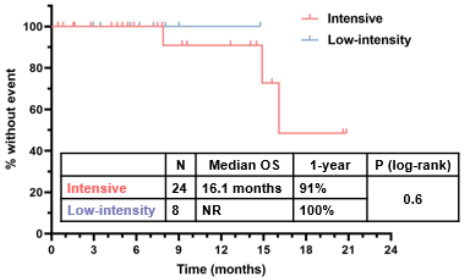
	N	Median OS	1-year
Full cohort	32	16.1 months	92.9%

RFS: Stratified by induction intensity



	N	Median RFS	1-year	P (log-rank)
Intensive	24	NR	73.4%	0.3
Low-intensity	8	6.3 months	43.8%	

OS: Stratified by induction intensity



	N	Median OS	1-year	P (log-rank)
Intensive	24	16.1 months	91%	0.6
Low-intensity	8	NR	100%	

CONCLUSIONS

> Maintenance therapy with aza-ven is a feasible and tolerable strategy in AML patients who have achieved CR following both high- and low-intensity induction regimens

> "*I think figuring out the timing of the schedule [7 days vs 14 days] is going to be very important for these patients. But the data are nevertheless interesting*"

Long-Term Survival after Intensive Chemotherapy or Hypomethylating Agents in AML Patients Aged 70 Years and Older: A Large Patient Data Set Study from Dataml, SAL and Pethema European Registries

Christian Recher, et al, #872

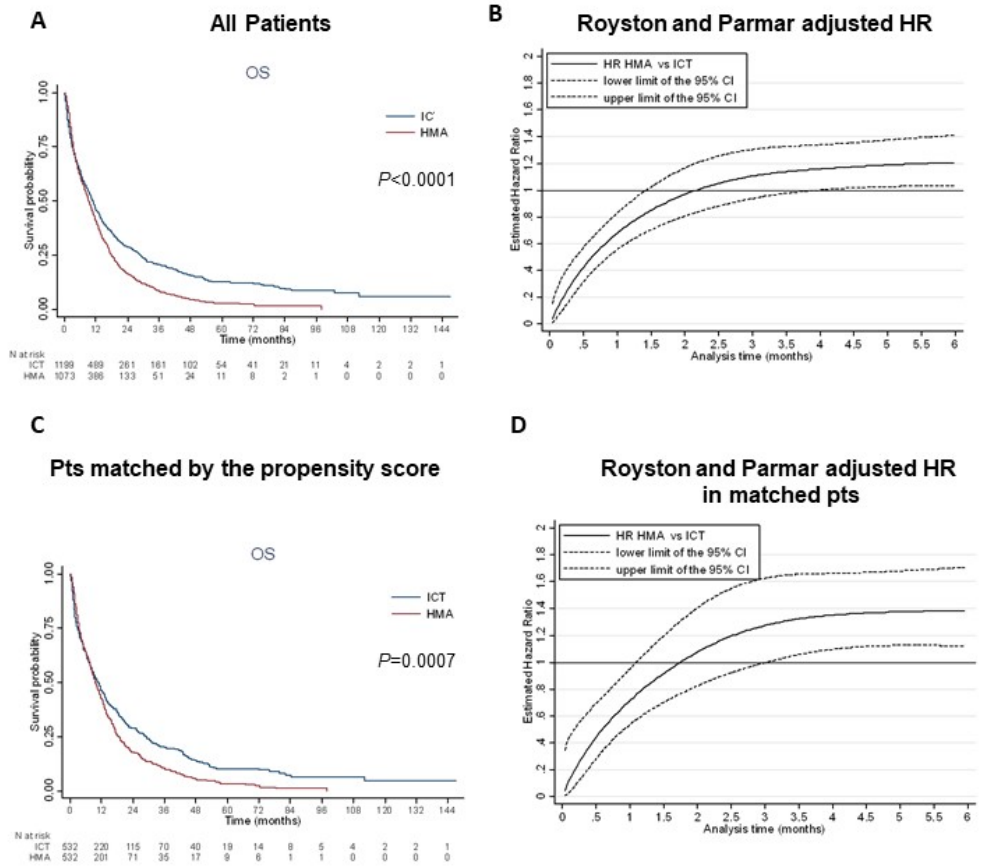
EPICS

STUDY POPULATION

> Retrospective registry analysis of outcomes in adults >70 years treated with either intensive chemotherapy (IC) or HMA
> 3,700 patients from DATAML, SAL, PETHEMA: 1,199 IC, 1073 HMA
> HMA patients: older, lower WBC and blast percentage, more ECOG >1, more secondary AML, and complex karyotype

OUTCOME

> CR: 56% IC group, 19.7% HMA group *P*=.0001
> Day 60 mortality: 20.6% IC group, 18% HMA group *P*=.129
> 1-yr, 3-yr, 5-yr OS in IC vs HMA: 46% vs 40%, 21% vs 8%, 12% vs 3%
> Treatment effect was time-dependent as determined by Royston and Parmar model; HMA patients had a significantly lower risk of death before 1.5 months of follow-up; there was no significant difference between both groups between 1.5 and 4.0 months, and OS was significantly better with IC from 4.0 months of follow-up



EXPERT CONCLUSIONS

> *"Challenges: A) retrospective analysis, B) outdated treatment option"*
> *"There are patients in this age population with intensive chemotherapy that have long-term survival, and this is particularly interesting, because the question is now emerging in patients treated with HMA-ven in this same age group as to when, if any, are cured"*

Phase I/II Study of Azacitidine (AZA) With Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML

Naval Daver, et al, #371

EPICS

STUDY POPULATION

- The phase II study enrolled patients in 3 arms: frontline, ven-naive R/R AML, and ven-exposed R/R AML
- Thirty-eight patients: 17 newly diagnosed (ND), 8 R/R ven-naive, 13 R/R ven failure

OUTCOME

- ND patients: CR/CRi rate 94%, CR rate 81%
- Seven of 7 *TP53*-mutation patients achieved CR
- MRD negativity by flow was achieved by 7/13 patients
- Ven-naive R/R patients: 5/8 achieved CR/CRi
- Ven-exposed patients: only 3/8
- Median time to ANC recovery 28 days (20–41)
- 8-week mortality 0%

Table 2. Response rates in evaluable patients with AML treated with azacytidine venetoclax and magrolimab.

Outcomes	Frontline AML (N=16)[1]	Relapsed / Refractory AML	
		Venetoclax-naïve (N=8)	Venetoclax failure (N=11)[2]
ORR	16 (100)	6 (75)	3 (27)
CR/CRi	15 (94)	5 (63)	3 (27)
CR	13 (81)	3 (38)	0 (0)
CRi	2 (13)	2 (25)	3 (27)
MLFS	1 (6)	1 (13)	0 (0)
No response	0 (0)	2 (25)	8 (62)
Time to first response	0.7 [0.6-1.5]	0.7 [0.6-4.1]	2.2 [1.8-2.6]
Time to best response (months)	1.1 [0.7-2.9]	1.5 [1.0-4.1]	2.3 [1.3-3.9]
Median time to ANC >0.5	28 [20 – 41]	-	-
Median time to platelet >50	24 [18 – 41]	-	-
4-week mortality	0 (0)	0 (0)	0 (0)
8-week mortality	0 (0)	1 (13)	3 (27)

All percentages are based on total number of patients in each cohort (N), unless specified. Results are reported as n (%) or median [range]. ORR = overall response rate = CR+CRi+MLFS, MLFS = morphologic leukemia-free state, 1. 1 pt from table 1 was too early to assess, 2. 2 pts from table 1 were too early to assess

EXPERT CONCLUSIONS

- *"Remarkable response rates and tolerability, especially in TP53-mutated AML"*
- *"Requires confirmation in randomized trials, but could be a game-changer, also in terms of how we think of intensive chemotherapy in this very-high-risk subgroup"*

Azacitidine, Venetoclax and Pevonedistat As Frontline Therapy for Patients with Secondary Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy: Results from a Phase I/II Study

Nicholas J. Short, et al, #2349

EPICS

STUDY POPULATION

> Adult patients with newly diagnosed s-AML, including patients with therapy-related AML (t-AML) or AML with MDS-related changes, who were unsuitable for intensive chemotherapy

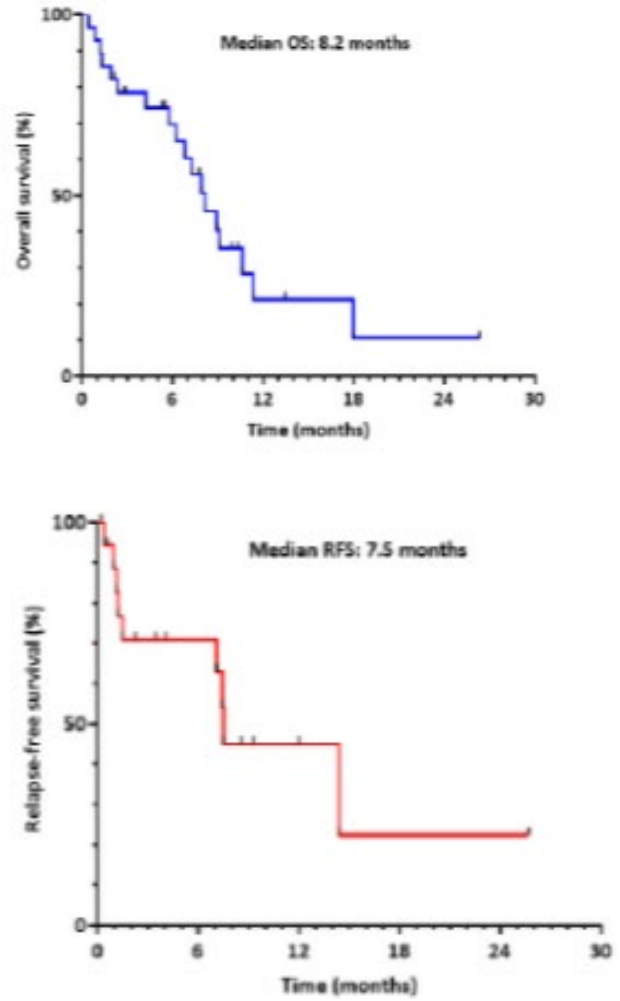
OUTCOME

> Overall response rate (CR/CRi/MLFS) 71%, CR/CRi 64%
> Safety: 4-week mortality 7%; 8-week mortality 14%
> Ongoing ven-aza vs ven-aza-pev trial (NCT04266795) is currently recruiting

EXPERT CONCLUSIONS

> "*Challenges: small number of patients, heterogeneous population, toxicity*"

Figure 1 – (A) Overall survival and (B) relapse-free survival for the entire cohort



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Iadademstat in Combination with Azacitidine Generates Robust and Long Lasting Responses in AML Patients (ALICE Trial)

Olga Salamero, et al, #3376

EPICS

STUDY POPULATION

> AML patients who have not received prior treatment other than hydroxyurea and are considered by the investigator as ineligible for intensive chemotherapy or have refused this treatment option

OUTCOME

> Twenty-two patients evaluable: 73% ORR; 5 CR, 6 CRi, 5 PR
> Well tolerated; number of AEs in line with the usual evolution of the disease and with other AML trials

EXPERT CONCLUSIONS

> *"Low response rate, no MRD data, slow trial recruitment, and there was really nothing in terms of translational biology to suggest that this may be a plausible pathway"*

Comparing Outcomes between Liposomal Daunorubicin/Cytarabine (CPX-351) and HMA + Venetoclax As Frontline Therapy in Acute Myeloid Leukemia

Justin Grenet, et al, #32

EPICS

STUDY POPULATION

> Retrospective study from 4 large US academic medical centers (Weill Cornell Medicine, Northwestern Medicine, Moffitt, Memorial Sloan Kettering Cancer Center) of patients who received either CPX-351 or HMA plus ven as frontline therapy for AML

> Two hundred eleven CPX-351 treated, 226 HMA-ven

OUTCOME

> Significant survival advantage for CPX-351 in *TP53* mutation. Greater transplant rate in CPX-351 population may underline the observed survival advantage

EXPERT CONCLUSIONS

> *"Limitations: retrospective study"*

> *"CPX-351 associated with improved OS but no difference in CR/CRi"*

> *"Allo-SCT is a central component of the treatment paradigm in older AML"*

> *" . . . we are needing to think about why are transplant outcomes so good after CPX"*

	CPX-351	HMA/VEN	
Median age	67 yrs	75 yrs	p<0.001
TP53	19%	27%	p<0.066
CR/CRi	57.8%	56.6%	
Median RFS (mos)	32.5	14.1	p=0.11
OS	17.3	11.1	p=0.007

Patient Subgroups	Vyxeos Frontline (N = X)	Venetoclax Frontline (N = X)	p-value
TP53 positive (n=95)			
CR + CRi, N (%)	11 (29.7)	28 (48.3)	0.073
RFS, Median Survival time, days (95% CI)	851 (164, 851)	204 (111, 310)	0.142
OS, Median Survival time, days (95% CI)	310 (232, 544)	191 (138, 275)	0.026
Prior myeloid malignancy (n=206)			
CR + CRi, N (%)	57 (50.0)	38 (41.3)	0.213
RFS, Median Survival time, days (95% CI)	774 (182, NA)	423 (245, NA)	0.625
OS, Median Survival time, days (95% CI)	416 (322, 522)	250 (176, 335)	0.026
Prior HMA therapy (n=65)			
CR + CRi, N (%)	18 (41.9)	9 (40.9)	0.941
RFS, Median Survival time, days (95% CI)	NA (156, NA)	168 (92, NA)	0.093
OS, Median Survival time, days (95% CI)	403 (232, 522)	178 (92, 304)	0.044
ELN – Adverse (n=291)			
CR + CRi, N (%)	65 (50.4)	85 (52.5)	0.724
RFS, Median Survival time, days (95% CI)	851 (223, NA)	330 (230, 728)	0.191
OS, Median Survival time, days (95% CI)	454 (323, 528)	291 (233, 369)	0.021

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EPICS

Discussion Summary

Updates on Newly Diagnosed AML

Advances in AML (1/2)

EPICS

Newly Diagnosed AML

FLT3 inhibitors

- Interpretation of survival data from the phase III LACEWING study of gilteritinib plus aza vs aza (Abstract 700) was questioned, as there was an imbalance regarding ECOG status in both arms, and many patients who were randomized to the aza arm upfront received gilteritinib in second line, thus impacting outcomes. The outcomes of the study were, therefore, deemed inconclusive
  - It was established that the trial should have been designed with a true placebo and the endpoint should have been EFS
- Currently preferred regimens are HMA-ven for patients with *FLT3* TKD mutation and for patients with *FLT3* ITD with a low-allelic fraction (<0.5). For patients who are *FLT3* ITD (high allelic ratio), the preferred regimen is HMA plus gilteritinib or HMA-ven, followed by addition of gilteritinib (if the *FLT3* levels by PCR increase at relapse)
- The ideal proposed randomized trial for *FLT3* ITD elderly patients included HMA-ven vs HMA-ven plus gilteritinib
  - With ven's myelosuppression, this combination needs to be administered in centers where patients can be closely monitored

IDH inhibitors

- The phase III AGILE trial data of ivosidenib plus aza are considered impressive (Abstract 697). This combination may be the right choice moving forward (vs HMA-ven) in patients with *IDH1* mutation (and *IDH2* mutation)
  - However, one challenge with the ivosidenib plus aza combination is that for a proliferative patient, it takes longer to work
- It was noted that ivo may be a more active drug than enasidenib, and there is an ongoing trial of ivo plus aza plus ven
- With regard to enasidenib plus aza vs HMA-ven, it remains unclear which of the 2 regimens performs better

Advances in AML (2/2)

EPICS

Newly Diagnosed AML (cont)

AML in older patients

- For older patients unfit for chemo, HMA-ven is regarded as standard of care
- Phase I data from the aza plus ven plus magrolimab in high-risk patients (Abstract 371) are regarded as potentially a "*game-changer*" if confirmed by randomized trials, and the importance of studying it in younger patients with the mutation (there is currently the ongoing randomized phase III study of aza plus magro [ENHANCE-2] vs physician's choice of ven plus azacitidine or intensive chem, which includes patients 18 years and older) was highlighted
- In patients 60–75 years old, achieving CR with an induction chemotherapy (HMA-ven or CPX-351) prior to transplant is considered a curative strategy. Important considerations to achieve this are
  - MRD status pre-transplant. This may differ depending on the agents used
  - Transplant-related mortality, which may differ depending on treatment and how CR is achieved, eg, transplant outcomes in patients who receive CPX-351 prior to transplant are very good
  - Choice of post-transplant maintenance therapies, in some instances with targeted agents
- Ongoing or proposed trials pre-transplant in patients 60–75 years old
  - A randomized study of CPX-351 vs CPX-351–ven should be explored to address the role of CPX-351 alone or in combination
  - There is currently an ongoing study in the UK of CPX-351 vs intermediate-dose Ara-C as bridging therapy
  - In the US, there is a multicenter study of HMA-ven vs conventional induction chemotherapy, including CPX-351 for all patients who are induction eligible, regardless of age
- Another important area of study for patients is maintenance post-transplant, as they may have a range of targeted therapies available to them

AML in young patients

- With the encouraging phase I data of magrolimab in older patients (Abstract 371), it was noted that a trial should also be conducted using younger patients with *TP53* mutation

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EPICS

Congress Highlights

Updates on Relapsed/Refractory AML

Venetoclax in Combination with Gilteritinib Demonstrates Molecular Clearance of *FLT3* mutation in Relapsed/Refractory *FLT3*-Mutated Acute Myeloid Leukemia

EPICS

Naval Daver, et al, #691

STUDY POPULATION

- Fifty-four patients were treated at the recommended phase II dose (RP2D) ven 400 mg plus gilt 120 mg
- Fifty-two patients (as assessed locally) had *FLT3*+ AML: 41 had *FLT3*-ITD only, 8 had tyrosine kinase domain only, 3 had both mutations, and 2 were *FLT3* wild-type
- Most patients (59%) had received ≥1 prior FLT3 TKI

	FLT3^{mut+} Patients With Prior TKI Exposure (n=32)	*FLT3*-ITD Patients (n=43)	All *FLT3*$^{mut+}$ Patients (n=51)
mCRc[a], n (%)	25 (78.1)	34 (79.1)	38 (74.5)
CR+CRp+CRi[*b]	10 (31.3)	17 (39.5)	19 (37.3)
MLFS	15 (46.9)	17 (39.5)	19 (37.3)

OUTCOME

- Among *FLT3*+ patients, mCRc was achieved by 74.5% (CR/CRp/CRi, 37.3% of patients), with a median follow-up time of 12 mo
- Molecular clearance of ven plus gilt was achieved (60.0% in *FLT3*-ITD patients achieving mCRc

FLT3-ITD burden, n (%)	<10^{-2} (1%)	<10^{-3}	<10^{-4}
Cycle 1 Day 28	9 (30.0)	3 (10)	0
Any time on therapy	18 (60.0)*	13 (43.3)	7 (23.3)

EXPERT CONCLUSIONS

- *"Response rates were encouraging . . . the key is that the people who had prior TKI were able to still get a similar response rate, which is kind of the people we are now seeing in our clinics"*
- *". . . looks like the combo is not only giving more marrow remission, but molecular clearance is better"*

Safety and Efficacy of Menin Inhibition in Patients (Pts) with MLL-Rearranged and NPM1 Mutant Acute Leukemia: A Phase (Ph) 1, First-in-Human Study of SNDX-5613 (AUGMENT 101)

Eytan Stein, et al, #699

EPICS

STUDY POPULATION

- The study included 2 parallel dose-escalation cohorts: patients not taking (Arm A) or taking (Arm B) strong CYP3A4 inhibitors
- Dose levels evaluated in Arm A were 113 (n=1), 226 (n=6), 276 (n=10), and 339 mg (n=8), and in Arm B 113 (n=16), 163 (n=6), and 226 mg (n=7)

OUTCOME

- Promising antileukemic activity in patients with heavily pretreated R/R *MLL*r and m*NPM1* acute leukemia

EXPERT CONCLUSIONS

- *"The overall response rate is pretty encouraging for a difficult patient population"*
- *"This has potential for eventual single-arm registration in the US . . . but we will have to wait and see the durability, survival"*
- *"The use of this drug, I think, will be best in combination upfront added to HMA-ven or added to intensive chemo"*

SNDX-5613 patients are heavily pretreated & have a poor prognosis

Baseline Characteristics	Safety Population n=59
Median age, years (range)	47 (1, 78)
Female, n (%)	37 (63)
ELN prognosis at study entry (n=36)	
Favorable	4 (7)
Intermediate	9 (15)
Adverse	23 (39)
Leukemia Type, n (%)	
AML	49 (83)
ALL	9 (15)
MPAL	1 (2)

Baseline Characteristics	Safety Population n=59
Genetics of enrolled pts, n (%)	
MLLr (translocations in ≥4 pts)	38 (64)
9;11	9 (15)
11;19	8 (14)
4;11	5 (8)
11;17	4 (7)
6;11	4 (7)
mNPM1	13 (22)
Non MLLr/Non mNPM1	8 (14)
Median prior therapies (range)	4 (1,12)
Stem cell transplant, n (%)	25 (42)
Venetoclax	35 (59)

Data cutoff: 18Oct2021

SNDX-5613 demonstrates promising antileukemic activity in relapsed/refractory MLLr and mNPM1 leukemias

	Best Response	Efficacy Population n = 51 (%)
Response	**Overall Response Rate[1]**	**28/51 (55%)**
	CR	8 (16%)
	CRh	4 (8%)
	CRp	7 (14%)
	MLFS	9 (18%)
MRD[neg]	**CRc MRD[neg] Rate[2]**	**16/51 (31%)**
	within CR/CRh MRD[neg]	11/12 (92%)
	within CR/CRh/CRp MRD[neg]	16/19 (84%)
MLLr	**Overall Response Rate[1]**	**23/38 (61%)**
	CR/CRh	9/38 (24%)
mNPM1	**Overall Response Rate[1]**	**5/13 (38%)**
	CR/CRh	3/13 (23%)

CR/CRh 12 (24%)

[1]Overall Response Rate = CR + CRh + CRp + MLFS; [2]CR + CRh + CRp; MRD status assessed locally by PCR or MCF

Data cutoff: 18Oct2021

Outcomes for Patients with Late-Stage Mutant-*IDH2* (m*IDH2*) Relapsed/Refractory Acute Myeloid Leukemia (R/R AML) Treated With Enasidenib Vs Other Lower-Intensity Therapies in the Randomized, Phase 3 IDHentify Trial

Courtney D. DiNardo, et al, #1243

EPICS

STUDY POPULATION

> Patients aged ≥60 yr with ECOG PS ≤2 and m*IDH2* AML R/R to 2–3 prior AML therapies
> Before randomization, patients were preselected to aza or IDAC or LDAC or BSC. Patients were then randomized 1:1 to receive ena (n=139) or conventional chemo regimen (CCR) (n=128)

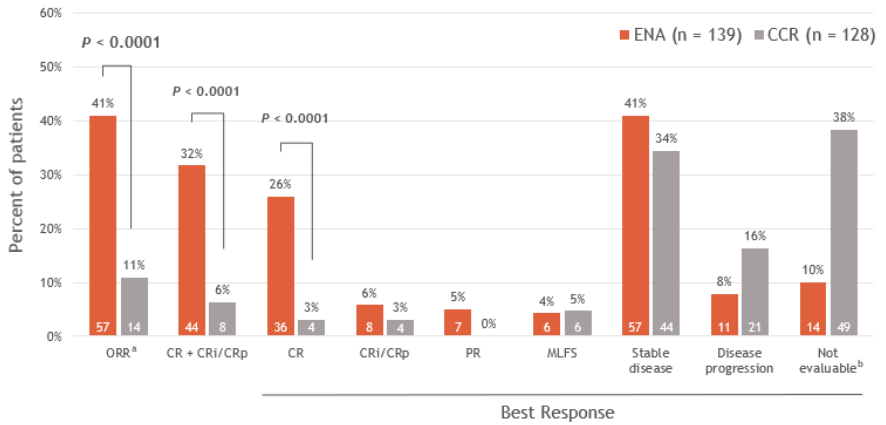
OUTCOME

> ORR was greater with ena vs CCR (41% vs 11%, respectively), and rates of CR (26% vs 3%) (*P* <.001, both comparisons)
> OS was prolonged with ena vs CCR (HR 0.74 [95% CI 0.56, 0.97]; *P*= .029), and 1-yr survival rates were 41% vs 26% (Δ15.0% [3.4%, 26.6%])

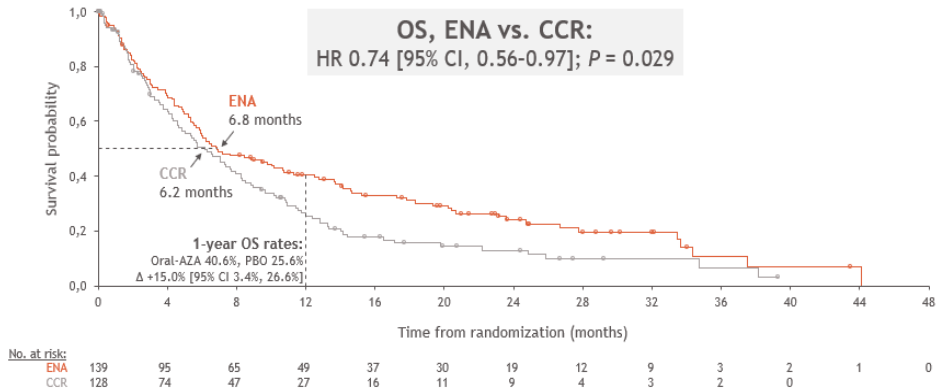
EXPERT CONCLUSIONS

> "*The trial was negative, but I really wonder if the patient selection in trial design had a big role to play in this, and I'm very happy that the frontline study of the aza-ivo is positive, so that ivo gets a global approval and IDH inhibitors can be used outside of the US now with that study*"

Morphologic response



Overall survival



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A Prospective Phase 2 Study of Venetoclax and Low Dose Ara-C (VALDAC) to Target Rising Molecular Measurable Residual Disease and Early Relapse in Acute Myeloid Leukemia

Ing S. Tiong, et al, #1261

EPICS

STUDY POPULATION

- Patients were in oligoblastic relapse (marrow blasts 5%–15%; Group A) or molecular MRD failure (Group B) as defined by the ELN recommendations (failure confirmed by 2 interval samples)
- Patients received ven plus LDAC

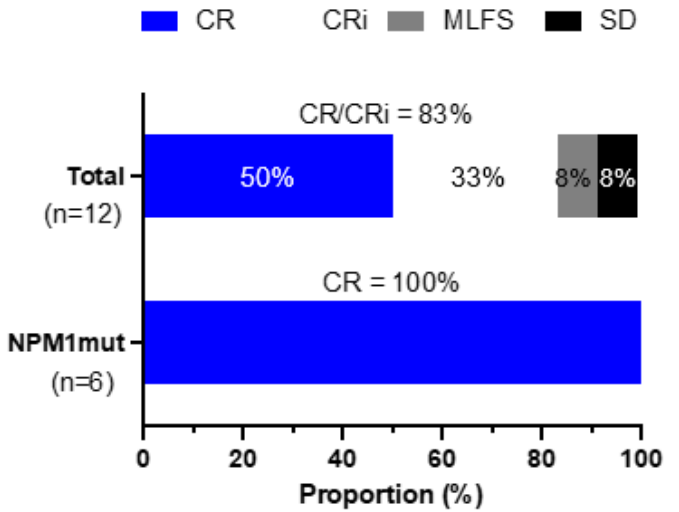
OUTCOME

- Overall, across both groups, median RFS and OS were not reached, estimated at 78% and 91% at 1 year, respectively
- Analysis of a subgroup of 6 patients from Group A with *NPM1*mt: a molecular response was achieved in all 6, with 100% complete response

EXPERT CONCLUSIONS

- "*Maybe ven plus LDAC is a good MRD-erase strategy for the NPM1 group, maybe for FLT3 we use ven-gilt, and for others we use such strategies, and trials are looking at that*"

Morphologic Response (Cohort A)



CR, complete response; CRi, CR with incomplete hematologic recovery; MLFS, morphological leukemia-free state; SD, stable disease

A Phase II Study of CPX-351 Plus Venetoclax in Patients with Relapsed/Refractory (R/R) or Newly Diagnosed Acute Myeloid Leukemia (AML)

Kunhwa Kim, et al, #1275

EPICS

STUDY POPULATION

- Ven plus CPX-351 in patients with newly diagnosed (frontline) and R/R AML who are considered fit for intensive chemotherapy
- The study was designed with a safety lead-in phase to establish the safe dose and schedule in R/R AML, followed by 2 expansion cohorts to explore efficacy in R/R AML (Cohort A) and frontline AML (Cohort B). Prior ven use was allowed for patients with R/R AML

OUTCOME

- Of 26 R/R AML patients, there was a 46% CR/CRi rate, including 15% CR and 31% CRi
- Rate of MRD negativity by flow cytometry was 78% in R/R AML
- Ten of 12 responding patients in the R/R cohort (83%) underwent SCT
- The median OS in frontline AML was not reached, compared with 7.1 months in R/R AML patients

Response	Frontline AML(n=5), n (%)	R/R AML (n=26), n (%)
ORR	4 (80)	12 (54)
CR/CRi	4 (80)	12 (54)
CR	1 (20)	4 (15)
CRi	3 (40)	8 (31)
MRD neg	3/4 (75)	7/9 (78)
4-week mortality	0 (0)	3 (12)
8-week mortality	0 (0)	5 (19)
Post-treatment SCT	4 (80)	11 (42)
Median no of cycles given (range)	2 (1-2)	1 (1-2)
Median no of cycles to response (range)	1 (1-2)	1 (0-2)

EXPERT CONCLUSIONS

- *"Encouraging that in salvage patients, CPX-ven was able to give a true CR/CRi rate of about 50%, and of those patients, a majority, could go to transplant. If they could get transplant, we were seeing an encouraging 2-year survival of up to 50%"*

Safety and Efficacy from a Phase 1b/2 Study of IMGN632 in Combination with Azacitidine and Venetoclax for Patients with CD123-Positive Acute Myeloid Leukemia

Naval Daver, et al, #372

EPICS

STUDY POPULATION

> Phase Ib/II study designed to determine the safety, tolerability, and preliminary antileukemic activity of IMGN632 combined with aza and ven in patients with CD123+ AML
> The triplet combination escalation consists of 5 cohorts of IMGN632 plus aza and ven

OUTCOME

> Efficacy was seen across all cohorts/doses and schedules (efficacy-evaluable population, n=29)
> ORR was 55% with a composite complete remission (CCR) rate of 31% (1 CR, 4 CRh, 2 CRp, 2 CRi)
> Higher-intensity cohorts (n=20) were associated with higher response rates: ORR 59%, CCR rate 38%. In these higher-intensity cohorts, in the ven-naive subset (n=15), ORR/CCR rates were 73%/53%, respectively. Significant activity was also seen in the *FLT3*-mutant subset (n=9), with ORR/CCR rates of 89%/78%

Antileukemic Activity Observed Across All Doses/Schedules

Place video here

Efficacy evaluable population# (All doses and schedules)	N	ORR N	CCR N	CR N (%)	CRh N (%)	CRp N (%)	CRi N (%)
	46	22 (48%)	14 (30%)	4 (9)	8 (17)	1 (2)	1 (2)
Higher intensity cohorts#	**N**	**ORR N**	**CCR N**	**CR N (%)**	**CRh N (%)**	**CRp N (%)**	**CRi N (%)**
	29	17 (59%)	11 (38%)	4 (14)	6 (21)	1 (3)	0

ORR (CR + CRh + CRp + CRi + MLFS)
CCR (CR + CRh + CRp + CRi)

Antileukemic Activity in Higher Intensity Cohorts: Subsets of Interest

Place video h

Previous Treatments	N	ORR	CCR
VEN naïve	15	73%	53%
Prior VEN	14	43%	21%
Prior HMA + VEN	12	42%	25%
Prior Stem Cell Transplant	7	71%	71%
High Risk Cytogenetics	**N**	**ORR**	**CCR**
ELN Adverse Risk	14	64%	36%
FLT-ITD	9	89%	78%

HMA = Hypomethylating agent, ITD = Internal tandem duplication

ORR (CR + CRh + CRp + CRi + MLFS)
CCR (CR + CRh + CRp + CRi)

EXPERT CONCLUSIONS

> *"I think of all the antibody-drug conjugates, this is the one kind of surviving most of the bites"*
> *"I think it has to go frontline, there is worry about the CD123 in the frontline because of the history of tagraxofusp and others, the CRS, capillary leak. . . . The nice thing is the safety profile has been pretty good"*

Additional ASH Abstracts*

EPICS

Olutasidenib (FT-2102) in Combination with Azacitidine Induces Durable Complete Remissions in Patients with mIDH1 Acute Myeloid Leukemia. Jorge E. Cortes, et al, #698

EXPERT CONCLUSIONS

> *"There has been some comment that the OS may be a little bit better. I find it personally challenging on how this will be developed when we're competing with venetoclax plus IDH or aza-ven-IDH"*
> *"I think that this particular drug is less likely to cause QT prolongation than ivosidenib; maybe that's a distinguishing factor. As a monotherapy it seems to have a slightly higher rate of CR and composite CR by about 5%–10%, but I don't know if that's enough to distinguish"*

Allogeneic Hematopoietic Cell Transplantation Outcomes of Patients with R/R AML or Higher-Risk MDS Treated with the TIM-3 Inhibitor MBG453 (Sabatolimab) and Hypomethylating Agents. Andrew M. Brunner, et al, #3677

EXPERT CONCLUSIONS

> *"The response rates for this combo have not been as what has been shown with aza-ven or APR-aza-magro, but the durability seems encouraging, and the tolerability. If it is positive, then it would be great to get immunotherapies out for MDS and AML"*

*These abstracts were not presented.

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Discussion Summary

Updates on Relapsed/Refractory AML

Advances in AML

EPICS

Relapsed/Refractory AML

- There is an ongoing study (*Blood.* 2021;138: 696) of aza plus ven plus gilteritinib in R/R *FLT3*-mutated AML (30 patients total, R/R n=16) that so far is showing very good remission rates (ORR 69%, CR/CRi, 32%). However, survival data need to mature to be able to tell if this regimen can move forward
- Combinations of FLT3 inhibitors (gilteritinib) or IDH inhibitors (ivosidenib or enasidenib) with ven will be the way forward. Ivosidenib and enasidenib do not appear to add myelosuppression, and these combinations will be "*easier* [regarding safety management]" to develop and implement
- It is encouraging that novel therapeutic strategies with immunotherapies (eg, magrolimab, sabatolimab) are moving into randomized phase III trials
  - The responses observed with magrolimab in the R/R AML *TP53* patient population were regarded as "*extraordinary*"

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Congress Highlights

Updates on Newly Diagnosed ALL

Ponatinib and Chemotherapy in Adults with *De Novo* Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Final Results of Ponalfil Clinical Trial

J.M. Ribera, et al, #1230

EPICS

STUDY POPULATION

> Adult patients with Ph+ ALL were treated with ponatinib and induction chemo, followed by consolidation and alloHSCT. Ponatinib was scheduled after alloHSCT only for patients with persistence/ reappearance of MRD

OUTCOME

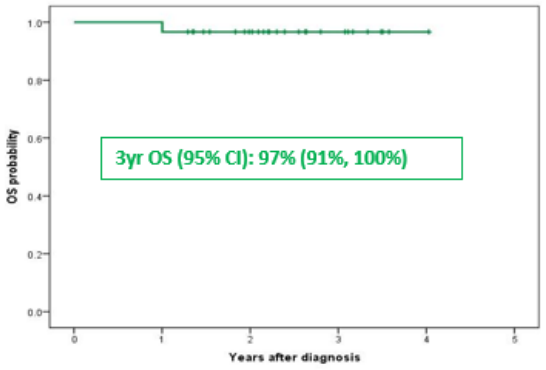
> CR was attained in 30/30 patients, CMR in 14/30 (47%), MMR in 5/30 (17%), and no molecular response in 11/30 (37%)
> Twenty-nine patients are alive (median follow-up 2.3 yr, range 1.3–4); 2-yr DFS and OS probabilities were 97% (91%–100%) and 97% (91%–100%)
> SAE (n=21) in 11 patients. Withdrawn from the trial (n=3) thrombosis of central retina artery, severe bowel infection, grade IV hepatic toxicity
> Cardiovascular events (n=2): angor pectoris; thrombosis retina

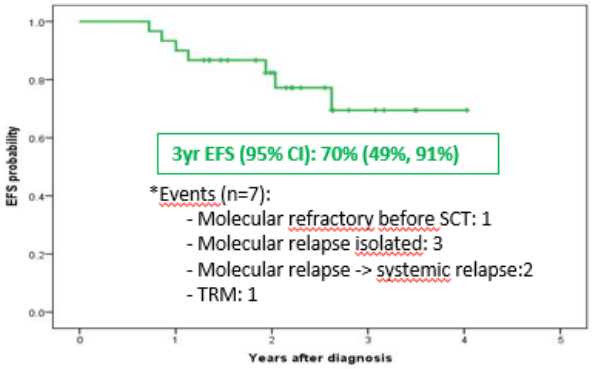
EXPERT CONCLUSIONS

> *"Ponatinib in first-line therapy followed by allo-SCT has high antileukemic efficacy and safe profiling, and compares favorably with the same approach with imatinib"*

	Post-induction (n=30)	Post-consol/ Pre-HSCT (n=28*)	Post-HSCT (n=26)
CMR (<0.01%)	14/30 (47%)	20/28 (71%)	26/26 (100%)
MMR (<0.1%)	5/30 (17%)	7/28 (25%)	-
No-response (>0.1%)	11/30 (36%)	1/28 (4%)	-

OS and EFS (median f-u: 2.5 yr)





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Updated Results of a Phase II Study of Ponatinib and Blinatumomab for Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

N.J. Short, et al, #2298

EPICS

STUDY POPULATION

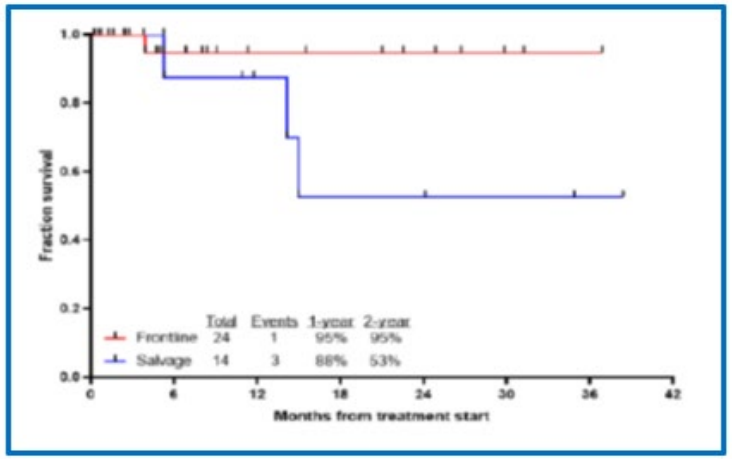
> Adults with newly diagnosed (ND) Ph+ ALL, R/R Ph+ ALL, or chronic myeloid leukemia in lymphoid blast phase (CML-LBP) were eligible
> Patients received up to 5 cycles of blinatumomab as a continuous infusion at standard doses. Ponatinib 30 mg daily was given during cycle 1. Ponatinib was decreased to 15 mg daily once a complete molecular response (CMR) was achieved. After completion of blinatumomab, ponatinib was continued for at least 5 years in responding patients

OUTCOME

> Among 32 patients evaluable, all but 1 patient (97%) responded. The CR/CRi rate was 100% for ND patients, 91% for R/R patients, and 100% for CML-LBP patients
> Eighty-four percent of responding patients achieved CMR (91% in the ND cohort, 91% in the R/R cohort, and 40% in the CML-LBP cohort)
> Estimated 2-year EFS and OS for the ND cohort is 95%

	ND	R/R	CML-BP
CR/CRi (%)	100	91	100
CMR after 1 cycle	64	82	20
CMR	91	91	40
OS/EFS (%)	95*	39/53	

*No allo HSCT



EXPERT CONCLUSIONS

> *"Particularly favorable outcomes of ND Ph+ ALL who were not transplanted in CR1"*
> *"This chemo-free regimen may serve as an effective transplant-sparing regimen in this population"*

APTITUDE HEALTH®

Updated Results from a Phase II Study of Mini-Hyper-CVD Plus Inotuzumab Ozogamicin, with or without Blinatumomab, in Older Adults With Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia

N.J. Short, et al, #3400

EPICS

STUDY POPULATION

> Patients (range 60–87 years) with newly diagnosed Ph– pre–B-cell ALL received mini–hyper-CVD plus ino. Rituximab (if CD20+) and prophylactic IT chemotherapy were given for the first 4 cycles

Response (N = 69)	N (%)
ORR	68 (99)
CR /CRp /CRi	61 (86) / 6 (10)/ 1 (2)
60-day mortality	3%
Flow MRD response d21	57/71 (0%)
Flow MRD resp overall	71/74 (96%)

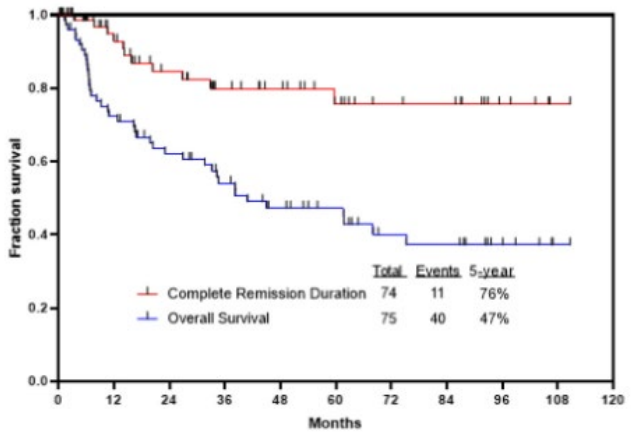
Outcome	N
Relapse	11 (15%)
Death in remission	28 (38%)
MDS/AML	9 (12%)
VOD/SOS	6/75 (8%)
On Tx/end Tx	32 (43%)

OUTCOME

> Among 69 patients evaluable for morphologic response, 99% responded (CR, n=61; CRp, n=6; CRi, n=1). MRD negativity by flow cytometry was achieved in 80% after 1 cycle and 96% overall. The 30-day and 60-day mortality rates were 0% and 3%, respectively

> With a median follow-up of 56 months (range, 1–111 months), the 5-year continuous remission and OS rates were 76% and 47%, respectively

Figure 1. (A) Continuous remission duration (CRD) and overall survival (OS) for the whole cohort; (B) overall survival stratified by age and cytogenetic risk



EXPERT CONCLUSIONS

> *"It's especially of note that this trial works very well for less-elderly people, people around 60 years old"*

Fractionated Inotuzumab Ozogamicin Combined with Low-Intensity Chemotherapy Provides Very Good Outcome in Older Patients with Newly Diagnosed CD22+ Philadelphia Chromosome-Negative B-Cell Precursor Acute Lymphoblastic Leukemia: First Results from the EWALL-INO Study

EPICS

P. Chevalier, et al, #511

STUDY POPULATION

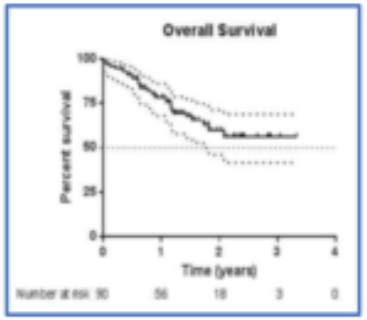
> Patients (≥55 years) with newly diagnosed CD22+ (20% or more of positive blast cells) Ph– BCP-ALL
> Patients received attenuated doses of ino during in induction 1 and induction 2, and then the patients proceeded to typical consolidation and maintenance therapy

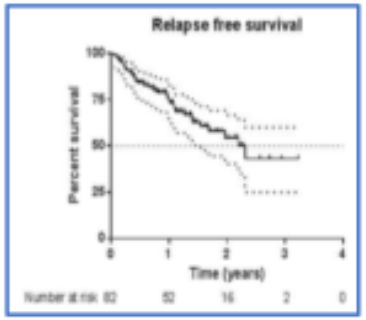
OUTCOME

> ORR was 87.7%; CR/CRp rate was 79% (71/90, 8 CRp) after induction 1
> One-year OS was estimated to be 78.5% (95% CI 68, 85.9) and median OS was not reached. One-year relapse-free survival was 74.5% (95% CI 63.5, 82.6)

Response (N = 90)	N (%)
ORR	79 (87.7)
CR /CRp	71 (79) / 8 (9)
TRM	2/90 (2.2)
1-yr OS	78.5% (95%CI 68-85.9)
1-yr RFS	74.5% (95CI 63.5-82.6)

Outcome	N
Relapse	16 (18%)
Death in remission	13 (14%)
G III-IV liver toxicity	8 (9%)
VOD/SOS	3 (3%)





EXPERT CONCLUSIONS

> *"Fractionated inotuzumab ozogamicin at reduced doses (0.8/0.5/0.5/0.5 mg/m²) combined with low-intensity chemotherapy is a very active and well-tolerated frontline therapy for older patients with CD22+, Ph– BCP-ALL"*

Final Induction Therapy Results of an Open Label Phase II Study Using Inotuzumab Ozogamicin for Induction Therapy, Followed By a Conventional Chemotherapy Based Consolidation and Maintenance Therapy in Patients Aged 56 Years and Older With Acute B-Lymphoblastic Leukemia (INITIAL-1 trial)

EPICS

M. Stelljes, et al, #2300

STUDY POPULATION

> Patients (≥56 years) with newly diagnosed Ph/BCR-ABL– acute B-precursor ALL were eligible. Leukemic blasts had CD22 surface expression of at least 20%. The 3 induction cycles included ino

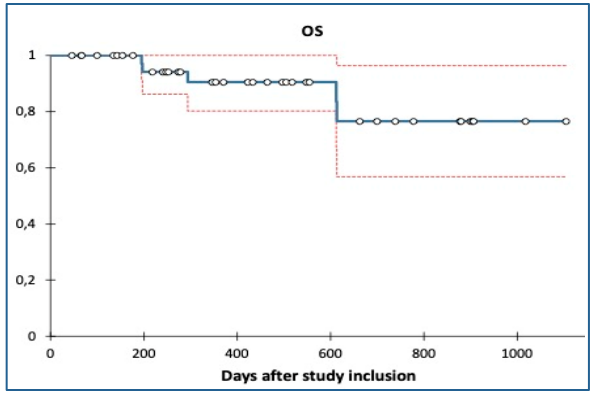
OUTCOME

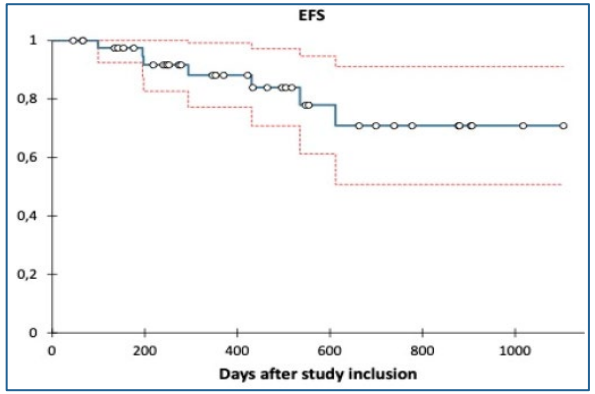
> Due to suspected therapy-related liver toxicities, a single patient received only 2 induction cycles (CR after first induction). All other patients completed 3 cycles of induction therapy and achieved CR/CRi, mainly after the first induction

> Twenty-three of 43 (53%) and 31/42 (74%) patients were MRD negative after second and third induction therapy, respectively

Patients	N
N	45
Evaluable	43
Age (median)	64 (56-80)
CD22 expression	69% (21-99%)
CR/CRi	100%
MRD neg (qPCR)	23/43 (53%) I2 31/42 (74%) I3
Events (n=7)	Death in CR: 4 Relapse: 3
OS 1y 2y	91% (80-100%) 77% (57-96%)

Grade ≥3 AE I-1 to I-3	
Leukocytopenia	60%, 12%, 3%
Thrombocytopenia	35%, 7%, 3%
↑ liver enzymes	14%, 5%, 0%
VOD/SOS	1 pt (I-2)





EXPERT CONCLUSIONS

> *"It will be very important to have longer follow-up for this trial because the results are promising. . . . The number of patients with VOD is really very low, and the tolerability was good, so it's another good trial including inotuzumab in first-line therapy"*

> *"Very high remission rates, MRD response in up to 90% (MRD negativity or MRD levels <10^{-4}) and promising EFS and survival rates"*

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Frontline Consolidation with Blinatumomab for High-Risk Philadelphia-Negative Acute Lymphoblastic Adult Patients. Early Results from the Graall-2014-QUEST Phase 2

N. Boissel, et al, #1232

EPICS

STUDY POPULATION

- Patients with high-risk Ph– BCP-ALL in continuous CR after induction and consolidation 1 were prospectively included to start blinatumomab at week 12
- Patients were spilt as very high risk (received allo-SCT) or high risk (received additional cycles of blina at consolidation and maintenance)

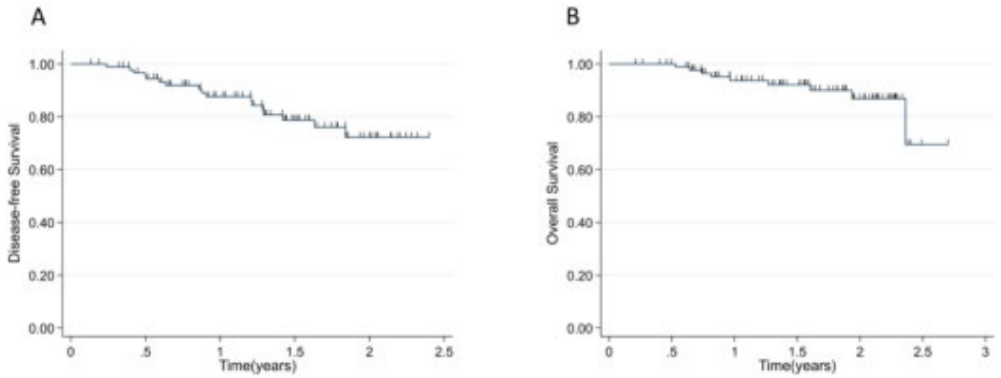
OUTCOME

- Last pre-blinatumomab MRD was <0.01% in 49/88 (56%) evaluable patients. After blinatumomab, a complete MRD response (with at least 0.01% sensitivity) was achieved in 61/82 (74%) evaluable patients and in evaluable patients with pre-blinatumomab detectable MRD
- With a median follow-up of 20 months, 18-month DFS and OS was 78.8% and 92.1%, respectively
- A total of 40 patients (42%) received an allo-SCT

Patients (N=94)	
HR /VHR	45 / 49 pts
Pre-Blin MRD<0.01%	49/88 (56%)
Post Blin MRD<0.01%	61/82 (74%)
AlloHSCT	40
18-month DFS	78.8% (66.9-86.8)
18-month OS	92.1% (83.2-96.4)
Better DFS	-HR (vs. VHR) -DUX4/ERGdel -Low pre-blin MRD -Complete MRD resp after blin

SAE	N
CRS	1 (grade 2)
Neurotoxicity	8 (G2[1],G3[3],G4[3], G5[1]
Infections	19
Other	11

Figure 1. Disease-Free Survival (A) and Overall Survival (B) of high-risk Ph-negative ALL patients consolidated with blinatumomab.



EXPERT CONCLUSIONS

> *"In patients with high-risk BCP-ALL, blinatumomab added to consolidation is safe and gives promising results. A longer follow-up is needed"*

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Dose Reduced Chemotherapy in Sequence with Blinatumomab for Newly Diagnosed Older Patients With B-Precursor Adult Lymphoblastic Leukemia (ALL): Results of the Ongoing GMALL Bold Trial

N. Gökbuget, et al, #3399

EPICS

STUDY POPULATION

> Older patients (56–76 yr) with CD19+, Ph– B-precursor ALL were treated with 1 dose-reduced chemotherapy induction cycle (IP1). Patients with CR, CRu, or PR received blina 1. Patients with failure to IP1 were treated with IP2 followed by blina 1

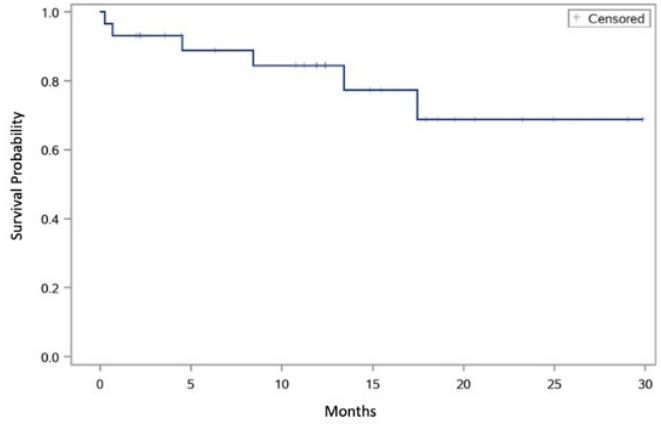
OUTCOME

> 33 patients were evaluable for IP1: 76% achieved CR/CRu. 29% (N=9) had a molecular response (17% MolCR)
> 1/3 patients with failure after IP1 had a CR after IP2. 29 patients were evaluable for the primary endpoint after blina 1. Twenty-four were in hematologic CR (83%), 82% of the CR patients (N=19) had a molecular response (69% MolCR)
> Survival probability for the efficacy population (N=29) after 1 year was 84%. The 1-yr OS was 89% for c/pre-B-ALL and 75% for pro-B-ALL

Table 1: Results of Remission Induction

	Induction I	Blina I
Evaluable for Hematologic Response (N)[1]	33	29
Hematologic CR	25 (76%)	24 (83%)
Early death	2 (6%)	2 (7%)[3]
Failure/PR/Relapse	6 (18%)	3 (10%)
Evaluable for Molecular Response (N) [2]	24	23
Molecular CR	4 (17%)	16 (69%)
Molecular Low positive	3 (12%)	3 (13%)
Molecular Failure	14 (58%)	2 (9%)
Molecular not evaluable	3 (12%)	2 (9%)

Figure 1: Overall Survival Efficacy Population (N=29)



EXPERT CONCLUSIONS

> *"Overall tolerability and efficacy of the regimen was promising with a high cytologic and molecular response rate and low mortality for this age group"*

Updated Results from a Phase II Study of Hyper-CVAD with Sequential Blinatumomab in Adults with Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia

EPICS

N.J. Short, et al, #1233

STUDY POPULATION

> Patients aged 14–59, newly diagnosed Ph– pre–B-cell ALL, including patients who had received no more than 1 prior cycle of chemotherapy, were eligible. Patients received hyper-CVAD followed by 4 cycles of blinatumomab at standard doses

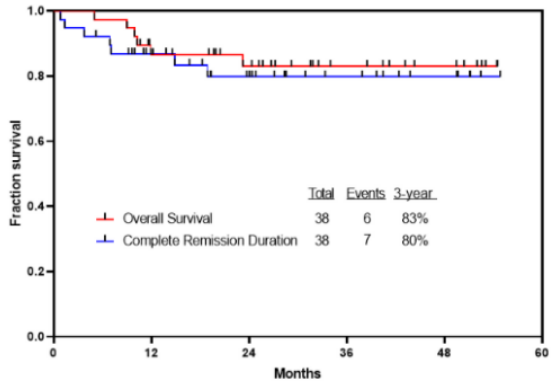
OUTCOME

> Among 32 patients with active disease at study entry, 100% achieved CR, with 81% achieving CR after the first cycle. MRD negativity by flow cytometry was achieved in 22/26 responding patients (85%) after 1 cycle and 37/38 patients (97%) overall
> The 60-day mortality rate was 0%. With a median follow-up of 27 months, the 3-year continuous remission and OS rates were 80% and 83%, respectively
> Three patients (34%) underwent allo-SCT in first remission (including 2 additional patients who relapsed post-SCT)
> Treatment was well tolerated overall

Table 1. Patient characteristics and responses

Characteristic	N (%) / median [range]
Age (years)	37 [17-59]
ECOG performance status ≥2	8 (21)
WBC (x10^9/L)	3.1 [0.5-360.9]
Karyotype	
Diploid	11 (29)
High hyperdiploidy	3 (8)
Low hypodiploidy / near triploidy	6 (16)
KMT2A rearranged	3 (8)
Complex	3 (8)
Others	12 (32)
CD19 expression	99.8 [41.9-100]
CD20 expression ≥20%	17/33 (52)
CRLF2+	6/32 (19)
TP53 mutation	10/37 (27)
Response	
CR after induction	26/32 (81)
CR at any time	32/32 (100)
MRD negativity after induction	22/26 (85)
MRD negativity at any time	37/38 (97)

Figure 1. Continuous remission duration (CRD) and overall survival (OS) for patients treated with hyper-CVAD plus blinatumomab



SAE	N
CRS	4 (G2) [3], G3 [1])
Neurotoxicity	16 (42%,any grade) 4 (grade3)
Discontin. to Blin AE	1

EXPERT CONCLUSIONS

> *"This study shows the potential benefit of incorporating frontline blinatumomab into the treatment of younger adults with ALL and also shows that reduction of chemotherapy in this context is feasible"*

First Results of the Risk-Adapted, MRD-Stratified GMALL Trial 08/2013 in 705 Adults with Newly Diagnosed Acute Lymphoblastic Leukemia/Lymphoma (ALL/LBL)

N. Gökbuget, et al, #362

EPICS

STUDY POPULATION

> Patients aged 18–55 years with newly diagnosed ALL/LBL had a 2-phase induction: a reinduction phase, and conventional maintenance up to 2.5 yr
> Six hundred thirty-eight had ALL (B, Ph–: 55%; Ph+: 20%; T: 25%), and 67 patients LBL (B: 12%; T: 88%)

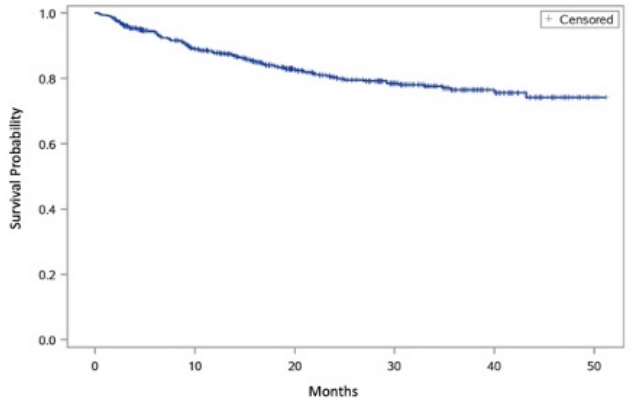
OUTCOME

> For ALL the hematologic (Hem) CR rate after C1 was 93% and the MolCR rate 61% (75% mol response)
> At a median follow-up of 23 mo, OS for all patients (N=705) was 88% and 76% at 1 and 3 yr, respectively
> Seventy-nine percent of patients with an indication for SCT were transplanted. The OS of SCT patients after SCT was 75% at 3 yr
> Sixty-three patients with MolFail became candidates for a targeted therapy. The molecular response was evaluable in 51 patients and reached 55% (N=40) and 18% (N=11) after 1 cycle of blina or nelarabine, respectively. Patients with MolFail (N=63) achieved an OS of 84% at 1 yr and 72% at 3 yr, respectively (71% for Ph– and 76% for Ph+)

Table 1: Total Outcome and Subgroups for ALL

	Total	B-ALL/Ph-	B-ALL/PH+	T-ALL	B/T SR[4]	B/T HR[4]
Evaluable for Hematologic Response (N) [1]	599	326	122	151	261	217
Hematologic CR	93%	94%	95%	89%	96%	88%
Early death	4%	5%	3%	5%	3%	7%
Failure/PR[2]	3%	1%	2%	7%	1%	4%
Evaluable for Molecular Response (N) [3]	542	306	116	120	248	178
Molecular CR	61%	65%	41%	67%	74%	54%
Molecular Failure	19%	18%	28%	11%	10%	25%
Molecular Low positive	14%	11%	17%	20%	12%	16%
Molecular not evaluable	6%	6%	13%	3%	4%	5%
N Overall Survival	638	350	128	160	276	234
Overall Survival 1y	88%	88%	85%	88%	94%	81%
Overall Survival 3y	76%	77%	74%	74%	85%	65%

Figure 1: Overall Survival for ALL and LBL - GMALL Study 08 (N=705)



EXPERT CONCLUSIONS

> *"These results are really promising, and we will expect with interest the conclusion of this study and to have longer follow-up"*

Genomic Data Improves Prognostic Stratification in Adult T-Cell Acute Lymphoblastic Leukemia Patients Enrolled in Measurable Residual Disease-Oriented Trials

C. Gonzalez-Gil, et al, #3486

EPICS

STUDY POPULATION

> Targeted deep sequencing was used to analyze the genetic profile of 125 T-ALL patients enrolled in 3 consecutive MRD-oriented trials from the Spanish PETHEMA group

> Genomic information was analyzed together with the main clinical and biologic data in a subset of 111 patients with detailed clinical and outcome data to determine the prognostic significance for OS and cumulative incidence of relapse (CIR)

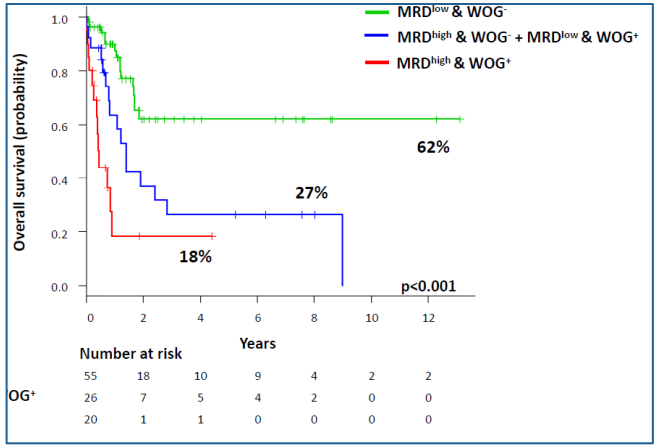
OUTCOME

> Mutations in the NOTCH1 and FBXW7 pathways were found in 88/125 (70%) patients

> Patients with mutations in *JAK3, DNMT3A, N/KRAS, IL7R, MSH2,* or *U2AF1* were associated with lower OS (vs unmutated patients). They were grouped as a cluster defined as WOG

> OS according to WOG and MRD allowed risk-stratification of T-ALL into low-, intermediate-, and high-risk (HR) patients with significantly different outcomes (*P*<.001)

	% OS (95% CI)		
Gene	Mutated patients	Non-mutated patients	p
JAK3	11% (0%-31%)	46% (34%-58%)	0.033
DNMT3A	13% (0%-27%)	43% (31%-55%)	<0.0001
N/KRAS	24% (0%-52%)	42% (30%-54%)	0.007
IL7R	30% (0%-62%)	41% (29%-53%)	0.041
MSH2	20% (0%-55%)	41% (29%-53%)	0.026
*U2AF1**	25% (0%-68%)	50% (39%-61%)	0.021



EXPERT CONCLUSIONS

> *"Genetic signature with independent prognostic significance of MRD could help to improve risk-stratification of adult T-ALL"*

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EPICS

Discussion Summary

Updates on Newly Diagnosed ALL

Advances in ALL: Newly Diagnosed

EPICS

Ph+ ALL – TKIs

- Ponatinib trial data alone or in combination are very promising. However, long-term data from randomized trials are needed to establish its effectiveness. Currently, the trial with the longest follow-up is with ponatinib and hyper-CVAD, and has shown a 70% OS at 5 years of follow-up. There is an ongoing phase III trial that is still recruiting (PhALLCON) of ponatinib vs imatinib with reduced-intensity chemo. It will also assess the activity of ponatinib in newly diagnosed Ph+ ALL
- Although longer follow-up is needed, early data suggest immunotherapies may play a role in frontline treatment of Ph+ ALL patients (where they could increase survival by 20%)
- Which Ph+ patients should be transplanted, even when they have a good molecular remission after frontline treatment, remains an open question
  - The phase II D-ALBA study of dasatinib and blina at induction and consolidation, respectively, led to 24 (of 63 patients) receiving transplant, but it is unclear how those patients were selected, despite achieving a hematologic complete response after treatment
  - The phase II study of ponatinib plus blina (Abstract 2298) will shed some light on the outcome of patients who undergo transplant or do not
- It was noted that to facilitate comparison among TKIs, the methodology to determine molecular response rate should be comparable among the different trials, particularly where MRD is now an endpoint in trials

Ph− ALL – Monoclonal and bispecific antibodies

- Data demonstrate that low-intensity chemo works as a backbone. In the US, older patients are treated with mini-hyperCVD plus ino
- Some of the discrepancies seen in toxicity profiles across trials may be explained by patient population: 55- to 65-year-old patients who qualify as "older patients" are not the same as 75- to 85-year-old patients
  - One plausible explanation for observed differences is that older ALL patients appear to develop emerging new clones of MDS/AML, and this is now being investigated at the single-cell level
- It is noted that older patients who receive immunotherapies (ino or blina) and have a good MRD– response do not need transplant
- For younger patients, the question of low-intensity chemo was discussed, although data still need to mature. On one hand, standard chemo is very effective (it can achieve 90% CR) and therefore, the place for low-intensity chemo plus immunotherapies may be after induction. On the other hand, asparaginase is fairly toxic in B-ALL patients, and chemo treatment requires a long consolidation to keep the remission; therefore, a less-intensive regimen is worth exploring at consolidation and maintenance
  - The concept advocated is to use low-intensity chemo plus immunotherapies (ino or blina) frontline to monitor for MRD response and deepen MRD negativity, in order to de-escalate therapy in favorable-risk patients

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Congress Highlights

Updates on Relapsed/Refractory ALL

Long-Term Follow-up of the Combination of Low-Intensity Chemotherapy Plus Inotuzumab with or without Blinatumomab in Patients with Relapsed-Refractory Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia

EPICS

F. Haddad et al, #3363

STUDY POPULATION

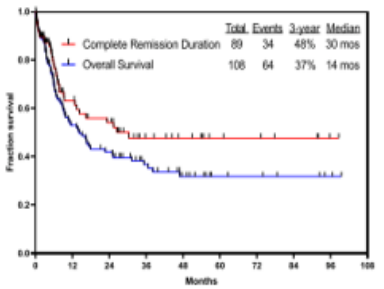
- Patients with Ph– B-cell ALL were treated with ino plus low-intensity chemotherapy (mini-HCVD) with or without blina in R/R ALL
- One hundred eight patients were enrolled and treated, including 41 patients with mini-HCVD plus ino plus blina

OUTCOME

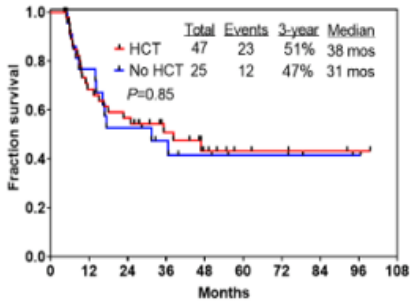
- Eighty-nine patients responded, for ORR of 83%
- Among 87 responding patients who were evaluable for MRD, 71 (82%) achieved MRD negativity. Forty-seven (44%) proceeded to HCT, overall
- Three-year CR duration and OS rates were 48% and 37%, respectively. Patients who achieved MRD negativity had higher 3-year OS rate of 58% compared with 8% who were MRD+ at best response (*P*=.0003)
- The combination of mini-HCVD plus ino ± blina resulted in a significantly longer median OS compared with ino monotherapy (14 mo vs 6 mo; *P*<.0001)
- Three-year OS rates were similar between patients who underwent subsequent HCT and those who did not (51% vs 47%, respectively; *P*=.85)

Response, No. (%)	
Salvage 1	71/77 (93)
S1, primary refractory	14 (100)
S1, CRD1 <12 months	21 (84)
S1, CRD1 ≥12 months	36 (95)
Salvage 2	10 (59)
≥Salvage 3	8 (57)
Overall	89 (83)
MRD negativity	71/87 (82)
Salvage 1	59/69 (86)
≥Salvage 2	12/18 (67)
Early death	7 (6)*
Veno-occlusive disease	10 (9)Δ

Overall survival of the entire cohort and complete remission duration among responders



Overall survival by transplant status



EXPERT CONCLUSIONS

- *"Ino and blina in the relapse setting, when combined together, a subset of these patients can get a durable remission with acceptable toxicity"*

Outcome after Inotuzumab Ozogamicin for Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia and Extramedullary Disease

S. Kayser, et al, #3404

EPICS

STUDY POPULATION

> Thirty-one patients CD22+ at relapse/progressive disease and extramedullary B-cell ALL (EM-ALL) received ino monotherapy

OUTCOME

> CR after the first ino cycle was achieved in 10 of 24 assessed patients (42%). After 2 ino cycles, CR was achieved in 17 of 31 patients (55%)
> Median follow-up was 29 months and median OS 12.8 months. One-year and 2-years OS rates were 53% and 18%, respectively
> Twelve patients went on to allo-SCT (CR, n=6)
> In patients achieving a CR after ino treatment (n=16), median OS was 10 months with no difference (*P*=.80) in RFS if an allo-SCT was performed (n=6) or not (n=10)

EXPERT CONCLUSIONS

> *"You may need a better, more effective consolidated strategy even after receiving inotuzumab, and a traditional allogeneic transplant may not be the best, although that's the best of what we have now, and we have to see whether the CAR T cells will be better than transplant, although we have less data there"*

Response after the first InO cycle (n=24)

	Number	%
CR:	10	42
PR:	9	37.5
Stable disease:	2	8
Resistant disease:	3	12.5

No response assessment after the 1st cycle: n=7 (23%)
Including n=1 early death at day 11 due to cerebral hemorrhage

Response after two InO cycles (n=31)

	Number	%
CR:	17	55
PR:	9	29
Early death:	1	3
No further treatment:	4	13

	Number
• Allo-SCT after InO treatment:	12
• Disease status prior to allo-SCT:	
CR:	6
PR:	3
PD:	3
• Applied InO cycles prior to allo-SCT:	
≤2 cycles	8
≤4 cycles	4

Disease status of CR/PR patients at last follow-up (n=26):

• Relapse/progressive disease:	10
• Molecular relapse*:	1
• Death in remission:	2
• Ongoing PR	1
• Ongoing CR	9

*successfully treated with InO re-exposure

Blinatumomab and Inotuzumab for Treatment of Multiply Relapsed Acute Lymphoblastic Leukemia: A Real-Life Campus ALL Study

M. Sciumè, et al, #3408

EPICS

STUDY POPULATION

> Describes the clinical characteristics and outcome of 71 patients with R/R B-ALL treated with both blina and ino in any sequence (blina-ino or ino-blina) at different disease recurrences

> Blina was the first salvage treatment (blina-ino sequence) in 57 patients (80%) and ino (ino-blina sequence) in 14 (20%). Twenty-seven patients (38%) underwent a previous allogeneic HSCT

Blina/InO population	No. 57	InO/Blina population	No. 14
Previous treatment - median (range)	1,5 (1-8)	**Previous treatment** - median (range)	3 (1-9)
Previous HSCT - no. (%)	24 (42)	**Previous HSCT** - no. (%)	3 (21)
WBC (x10e9/L)- median (range)	4,8 (0,7-98)	**WBC** (x10e9/L)- median (range)	6,275 (1-101,4)
Bone marrow blast count (%) - median (range)	17 (0-100)	**Bone marrow blast count** (%) - median (range)	64 (2-90)
Ph+ - no. (%)	10 (17)	**Ph+** - no. (%)	6 (43)
Organomegaly - no. (%)	7 (12)	**Organomegaly** - no. (%)	4 (29)
Extramedullary involvement - no. (%)	5 (42)	**Extramedullary involvement** - no. (%)	1 (7)
Number of Blina cycles - median (range)	2 (1-9)	**Number of InO cycles** - median (range)	2 (1-4)
Toxicity G3/4 - no. (%)	15 (26)	**Toxicity G3/4** - no. (%)	3 (21)
Hematological	3 (5)	Hematological	1 (7)
Extrahematological	12 (21)	Extrahematological	2 (14)
Infectious complications - no. (%)	17 (30)	**Infectious complications** - no. (%)	4 (29)
Response - no. (%)		**Response** - no. (%)	
Complete remission	31 (54)	Complete remission	13 (93)
Complete molecular remission	24 (42)	Complete molecular remission	5 (36)
HSCT post-Blina	24 (42)	**HSCT post-InO**	2 (14)
DLI after HSCT post-Blina	6 (10)	**DLI after HSCT post-InO**	2 (14)
Alive in CR	14 (24)	**Alive in CR**	3 (21)

OUTCOME

> In the ino-blina group, a CR was reached in 13 cases (93%) with 5 patients (36%) achieving CMR

> In the blina-ino group, a CR was reached in 31 cases (54%), with 24 (42%) being achieving CMR

> In the ino-blina group, median OS was 9.4 months and DFS was 6.6 months

> In the blina-ino group, median OS was 19 months and DFS was 13 months

EXPERT CONCLUSIONS

> *"I don't think we can make much out of this study where we could say that they should receive blinatumomab first. This [trial] again wasn't designed to answer that question, but I think what we can get away though, is that after blina failure, ino works; after ino failure, blinatumomab can rescue some of these patients"*

Blina/Ino Group:
Median DFS/OS: 13 and 19 months
Ino/Blina Group:
Median DFS/OS: 6.6 and 9.4 months

The Efficacy and Safety of Low-Dose Inotuzumab Ozogamicin in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia: Interim Results of a Phase 4 Study

M. Özcan, et al, #1208

EPICS

STUDY POPULATION

> Twenty-two (of planned 102) patients with R/R ALL who are eligible for HCT and who have a higher risk of post-HCT sinusoidal obstruction syndrome (SOS) received low-dose ino (1.2 mg/m^2/cycle)

OUTCOME

> In stage 1 of the run-in phase, 3/7 patients achieved CR/CRi and the trial proceeded to stage 2. By the end of stage 2, half of patients achieved CR/CRi, with 73% of these patients being MRD–
> Almost a third of patients proceeded to HCT (31.8%)
> Of patients who proceeded to HCT, 28.5% (2/7) had post-HCT SOS: one was grade 5 (a patient with ongoing or prior hepatic disease) and the other was grade 2 (a patient in salvage ≥2 with prior HCT)

Table 3: TEAEs occurring in ≥10% of patients and AEs of special interest with InO at a starting dose of 1.2 mg/m^2/cycle

	InO (N=22)	
n (%)	Grade ≥3	All grades
Hematologic disorders[a]	7 (31.8)	9 (40.9)
Infections[b]	8 (36.4)	11 (50.0)
Febrile neutropenia	4 (18.2)	4 (18.2)
Neutropenia[c]	3 (13.6)	4 (18.2)
Disease progression	3 (13.6)	3 (13.6)
Thrombocytopenia	2 (9.1)	5 (22.7)
Neutrophil count decreased[c]	2 (9.1)	4 (18.2)
Pneumonia	2 (9.1)	3 (13.6)
Pyrexia	1 (4.5)	5 (22.7)
ALT increased	1 (4.5)	5 (22.7)
Hepatic SOS	1 (4.5)	2 (9.1)
AST increased	1 (4.5)	4 (18.2)
Epistaxis	0	3 (13.6)

Table 2: Efficacy of InO at a starting dose of 1.2 mg/m^2/cycle

n (%)[a]	InO (N=22)
CR/CRi	11 (50.0)
CR	5 (22.7)
CRi	6 (27.3)
MRD negativity[b]	8 (72.7)
OS, median (95% CI), mo	4.5 (3.2–8.6)
6-mo OS probability (95% CI), %	40.6 (19.7–60.7)
PFS, median (95% CI), mo	2.8 (1.7–4.5)
6-mo PFS probability (95% CI), %	26.0 (9.6–46.1)
Time to remission, median (range), mo[c]	0.76 (0.6–0.9)
Duration of remission, median (95% CI), mo[c]	4.5 (1.9–NR)
Proceeded to HCT	10 (45.5)

[a] Unless otherwise noted. [b] Minimum MRD <0.01%; percentage based on number of patients achieving CR/CRi (N=11); assessed using flow cytometry at Navigate, Carlsbad, CA, USA. [c] Among patients who achieved CR/CRi (N=11). CR=complete remission; CRi=complete remission with incomplete hematologic recovery; HCT=hematopoietic cell transplantation; InO=inotuzumab ozogamicin; MRD=minimal residual disease; NR=not reached; OS=overall survival; PFS=progression-free survival

EXPERT CONCLUSIONS

> *"They will proceed to the randomized phase of looking at the approved dosing, which is 1.8 vs this reduced dose, to see whether they could be equally beneficial, hopefully with lowered SOS"*

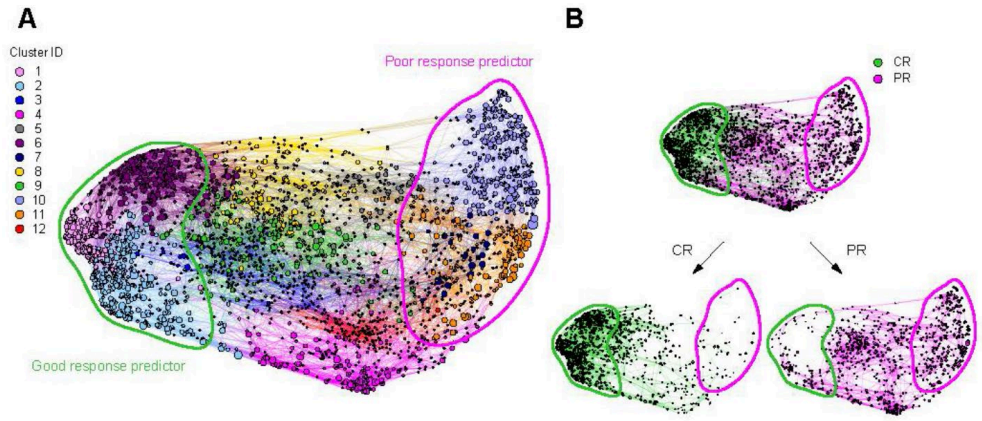
CD22^{low}/Bcl-2^{high} Expression Identifies Poor Response to Inotuzumab in Relapsed/Refractory Acute Lymphoblastic Leukemia

E. Diaz-Flores, et al, #614

EPICS

STUDY POPULATION

- Sixty-eight samples were analyzed from 28 patients with multiple R/R ALL enrolled in Children's Oncology Group trial AALL1621 (NCT02981628)
- Samples were collected before and after treatment with ino. B-ALL–centric protein profiling was performed using a custom CyTOF panel, encompassing 35 rationally selected proteins (antigens) as potential predictors of ino treatment



OUTCOME

- Analyses identified the presence of CD22^{high} cells and CD22^{low}/Bcl-2^{high} cells as predictors of good and poor response, respectively
- Furthermore, analysis of residual leukemia cells at the end of cycle 1 or 2 showed persistent high expression of Bcl-2 family members

EXPERT CONCLUSIONS

- *"This suggests that perhaps a Bcl-2–targeted agent such as venetoclax may rescue or have a synergistic or additive effect to inotuzumab-resistant patients at CD22^{low} or Bcl-2^{high} cells. . . . I think it's kind of the beginning of the work to shed some light on some resistance to the CD22-targeted immunotherapy ADCs like inotuzumab"*

Impact of Allogeneic Hematopoietic Cell Transplantation (HCT) As Consolidation Following CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy for Treatment of Relapsed Acute Lymphoblastic Leukemia (ALL)

J.H. Park, et al, #3880

EPICS

STUDY POPULATION

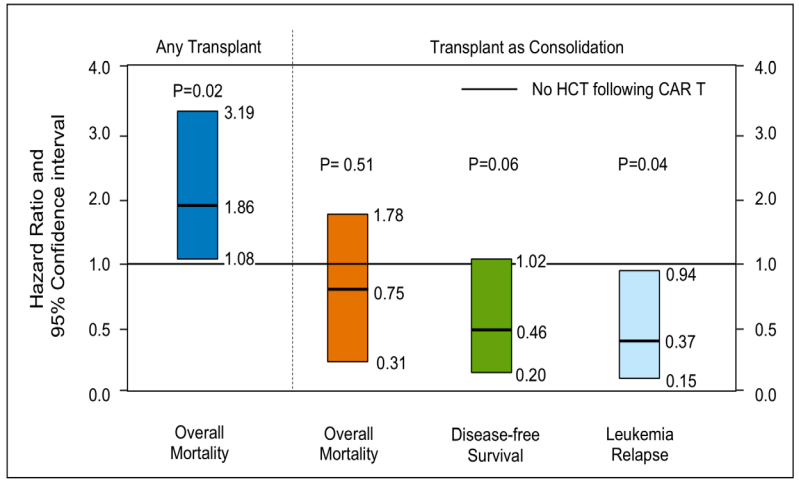
- Patients up to 26 years treated with CD19 CAR T cells from 2014 to 2019 in the United States were included; 347 patients were identified
- Objectives were to examine the impact of post-CAR HCT on mortality, DFS, leukemia relapse, GVHD, and transplant-related mortality among HCT recipients. The intent of HCT was analyzed as consolidation when there was no evidence of post-CAR T-cell relapse prior to HCT

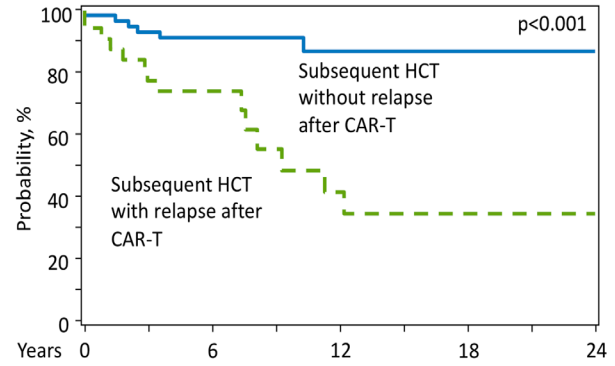
OUTCOME

- With a median follow-up of 12.7 months, DFS at 3, 6, and 12 months, following CAR T-cell infusion was 80.9%, 71.2%, and 57.6%, respectively. OS at 3, 6, and 12 months was 93.6%, 89.8%, and 79.4%, respectively
- Incidences of relapse without censoring at subsequent HCT at month 3, 6, and 12 were 18.5%, 28.2%, and 40.6%, respectively
- "*There was no overall survival benefit with a transplant or not, but the leukemia relapse rate was low with a consolidative transplant*"
- "*The outcome is better if you received transplant after CAR T first remission vs CAR T relapse*"

EXPERT CONCLUSIONS

- "*. . . it tells us that in some of those patients who were transplant naive that we are struggling to send or not [to transplant], perhaps we should be considering consolidative transplant earlier than later*"





# at Risk					
Subsequent HCT without relapse after CAR-T	59	40	15	8	2
Subsequent HCT with relapse after CAR-T	28	15	6	3	1

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High Effectiveness and Safety of Anti-CD7 CAR T-Cell Therapy in Treating Relapsed or Refractory T-Cell Acute Lymphoblastic Leukemia (T-ALL)

J. Yang, et al, #473

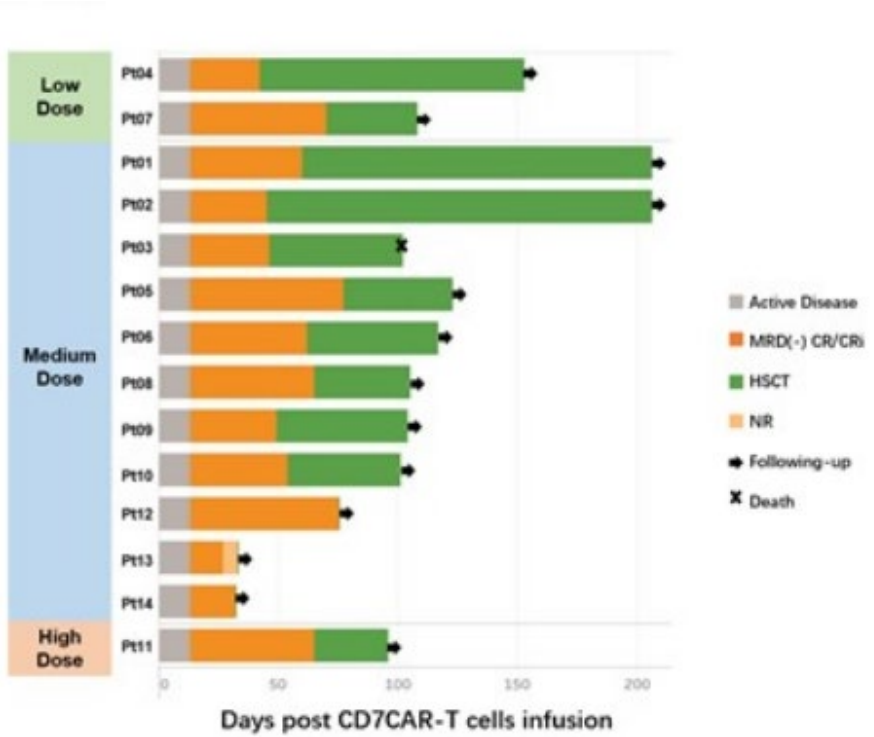
EPICS

STUDY POPULATION

- Seventeen R/R T-ALL patients were enrolled; median age 17 years, and treated with CD7 CAR T cells
- Patients were heavily pretreated, with a median 5 prior lines of therapy (range: 3–8 lines) and 3 relapsed from prior allo-HSCT

OUTCOME

- By the data cutoff date (July 12, 2021), median follow-up time was 105 days
- By day 28 post-infusion, 92.9% (13/14) of patients achieved CR (N=4) or CRi (N=9), with all 13 patients achieving MRD– CR/CRi
- A total of 11/14 patients were bridged to consolidation allo-HSCT at a median 57 days post-CD7CAR infusion, of whom 9 patients have remained in MRD– CR/CRi
- Thirteen of 14 patients experienced mild CRS (grade ≤2); one patient had grade 3 CRS



EXPERT CONCLUSIONS

- *"The data does look very promising, and this is kind of the huge unmet need"*

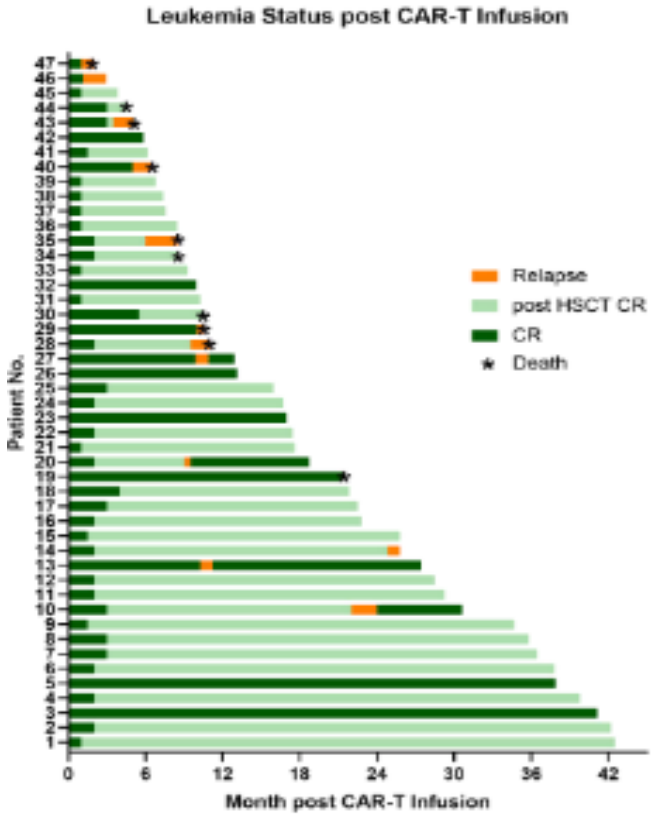
Tandem CD19/CD22 Dual Targets CAR T-Cells Bridging Hematopoietic Stem Cells Transplantation Acquires Robust Remission for Relapsed and Refractory B Acute Lymphoblastic Leukemia Patients

W. Cui, et al, #1753

EPICS

STUDY POPULATION

- Forty-seven R/R B-ALL patients were enrolled, and treated with CD19/CD22 CAR T cells
- Twenty-seven patients (57.4%) had high disease burden, with 20% or more blasts in BM
- Thirty-four of 47 patients (72.34%) proceeded to a bridging allo-HSCT



OUTCOME

- At day 28 assessment, 47 patients (100%) achieved hematologic CR, and 40 of 47 patients (85.1%) achieved MRD-CR
- Cox regression analyses showed better long-term survival in patients with MRD-CR status, as well as bridging allo-HSCT
- The toxicities of CD19/CD22 CAR T-cell therapy were reversible and clinically manageable. Cytokine release syndrome of any grade occurred in 41 of 47 patients (87.23%) and was severe (grade >2) in 8 (17.02%)

EXPERT CONCLUSIONS

- *" . . . The response rates are quite good . . . but one of the challenges in the interpretation of bispecific CAR at this point is that we still don't know whether this is better than CD19 CAR in comparison. It makes it even harder for a study like this, because a majority of the patients do go to transplant, so durability of the remission will be the key endpoint for this type of study to see whether individual targeting works better"*

Outcomes after Reinfusion of CD19-Specific Chimeric Antigen Receptor (CAR)-Modified T Cells in Children and Young Adults with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

R.M. Myers, et al, #474

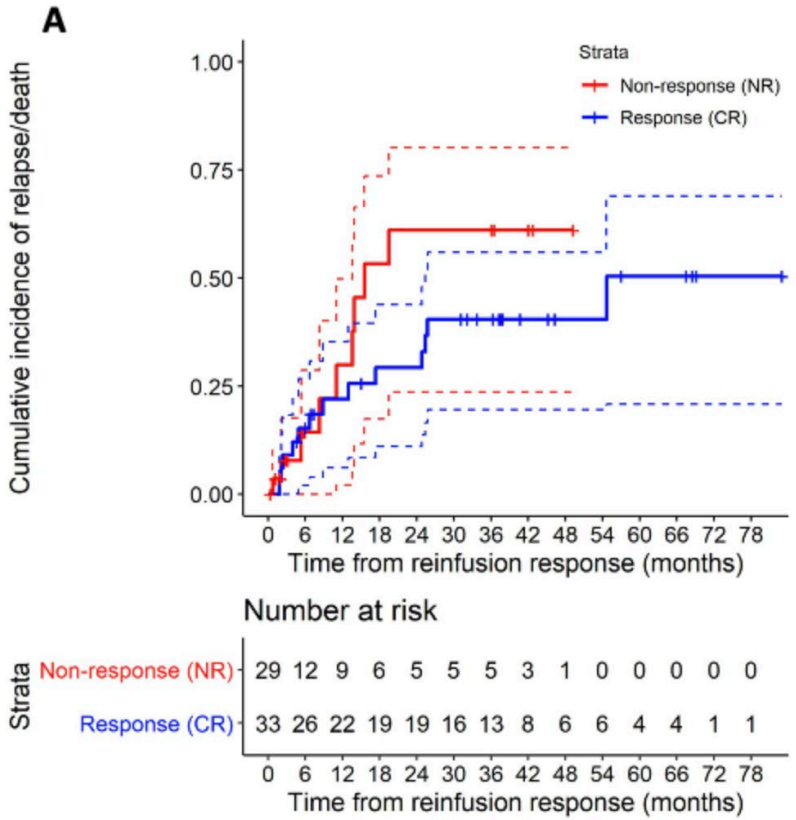
EPICS

STUDY POPULATION

- Patients <30 years
- Two hundred and twenty-nine patients were CAR naive and 33 were CAR exposed. They were treated with CD19 CAR between 2012–2020
- Eighty-one patients received ≥1 reinfusions

OUTCOME

- Among the 63 patients reinfused for relapse prevention, 33 (52%) had a CR at day 28. With median duration of follow-up of 38 mo, 13 experienced a subsequent relapse, 4 received alternative therapy or HSCT in remission, and 16 remain in remission without further therapy at a median 39 mo after first reinfusion
- Of the 10 patients reinfused for relapse, 5 (50%) had a CR, 2 subsequently experienced a CD19+ relapse, 2 received an HSCT in remission, and 1 remains in remission without further therapy at 18 mo after reinfusion
- CRS grade ≥2 occurred in 19 patients (grade 2, n=13; grade 3, n=4; grade 4, n=2). Grade 3–4 events only occurred in patients with active disease at time of reinfusion



EXPERT CONCLUSIONS

- *"CD19 CAR infusion works better when you receive them as B-cell recovery, so almost as a preventive strategy. So, CD19 CAR reinfusion for morphologic relapse didn't really work very well with a very short remission duration"*

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EPICS

Discussion Summary

Updates on Relapsed/Refractory ALL

Advances in ALL: Relapsed/Refractory

EPICS

- For first salvage therapy, disease burden and kinetics of the disease are important in determining therapy choice. For high-burden disease, the choice is ino, and for low-burden disease (<50% blasts), blina is an option
  - If there is an early relapse after ino or blina, CAR T therapy is a consideration
  - At MD Anderson Cancer Center, the preferred strategy is cytoreduction with chemo plus low-dose ino, followed by consolidation with blina
- Ino and blina can work after each other's failure, and also after CAR T failure, although durable remissions remain challenging
  - Current opinion is that use of immunotherapy is not an impediment for CAR T therapy afterward. However, CAR T will not be used as bridging therapy to transplant
- The question of transplant post-CAR T remains open. Data favor this strategy in adult fit patients or younger patients who are transplant naive
- Preliminary data on infusion of 2 different CARs (eg, CD19 and CD22) show that one CAR may take over the other CAR, expand, and persist