POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

10° SESSIONE – LEUCEMIE ACUTE

Novità dal Meeting
della Società Americana
di Ematologia

Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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AMGEN			X				

ASH 2024 AML Highlights

HOT TOPICS

TRIPLETTE

MENINA INIBITORI

TARGET THERAPY

AGENDA

1)TERAPIA DI PRIMA LINEA-FIT (ABS 218, 57, 60, 55, 214, 215)

2)TERAPIA DI PRIMA LINEA-UNFIT (ABS 2896, 2883)

3)LAM RICADUTA/REFRATTARIA e NUOVI FARMACI (ABS 211, 213, 216, 223)

10-year follow up of C10603/RATIFY: midostaurin vs placebo plus intensive chemotherapy for newly diagnosed *FLT3*-mutant acute myeloid leukemia (AML) patients 18-59 years old

ABS N°218-ORAL

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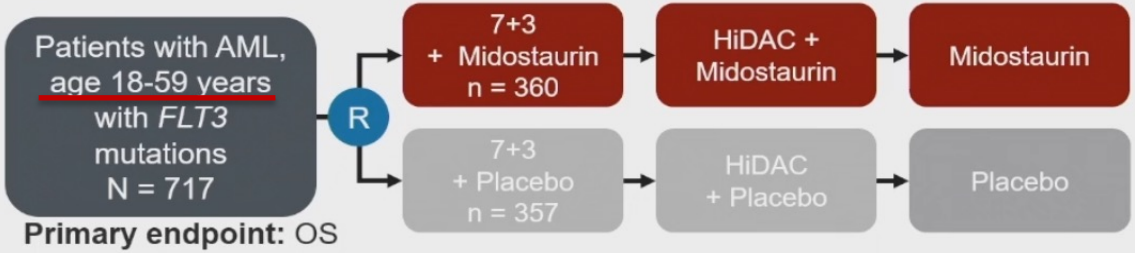
ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB10603 (RATIFY): Prospective Phase 3, Double-Blinded, Randomized Study of Induction and Consolidation +/- Midostaurin in Newly Diagnosed Patients < Age 60 With *FLT3*-Mutated AML

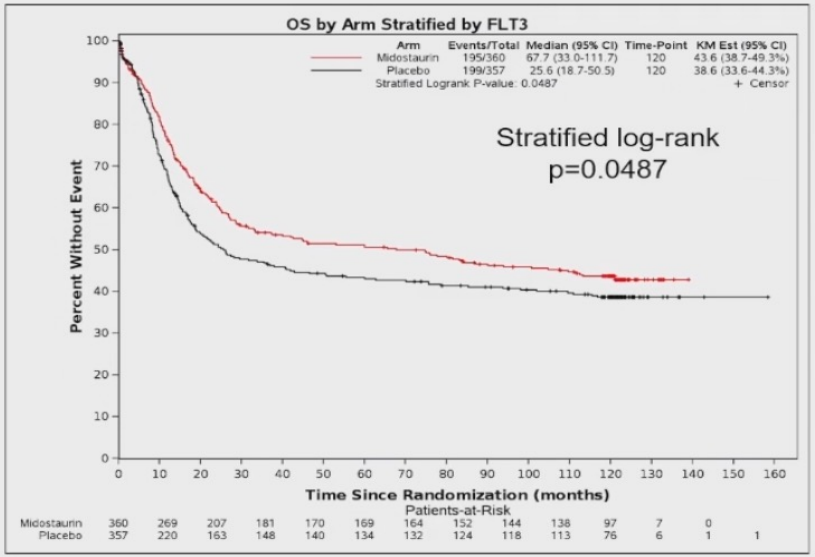


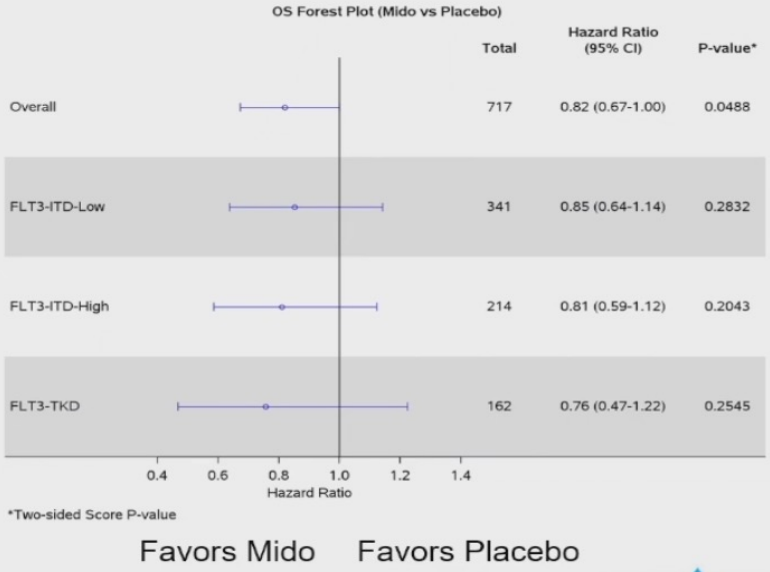
Primary endpoint: OS

Induction (Second cycle given based on day 21 marrow)	Daunorubicin	60 mg/m^2 IVP days 1-3
	Cytarabine	200 mg/m^2/day on days 1-7 via IVCI
	Midostaurin or placebo	50 mg orally twice daily on days 8-21
Consolidation (up to 4 cycles)	Cytarabine	3 gm/m^2 over 3 hours every 12 hours on days 1, 3, 5
	Midostaurin or placebo	50 mg orally twice daily on days 8-21
Maintenance	Midostaurin or placebo	50 mg orally twice daily days 1-28 x 12 cycles

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

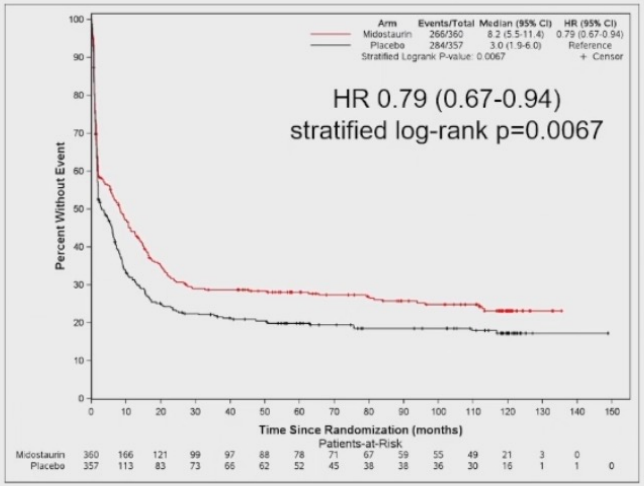
Overall survival by treatment arm- 10 y f/u

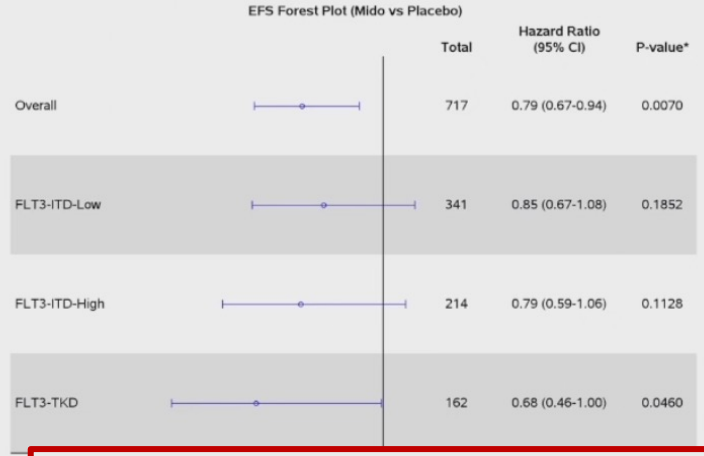




ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Event-free survival (10 y f/u)





EFS Event	Placebo (N=357)	Midostaurin (N=360)	Total (N=717)
Treatment Failure (No CR within 60 days)	159 (44.5%)	138 (38.3%)	297 (41.4%)
Death	35 (9.8%)	34 (9.4%)	69 (9.6%)
Relapse	90 (25.2%)	94 (26.1%)	184 (25.7%)
Censor	73 (20.4%)	94 (25.8%)	167 (23.3%)

Conclusions

- The EFS benefit of randomization to midostaurin vs placebo when added to chemotherapy was maintained over time, although the benefit for OS was diminished, likely due in part to aging process in both treatment arms.

Venetoclax Combined with "7+3" Induction Chemotherapy Induces High MRD-Negative Response Rates in Newly Diagnosed AML

Ioannis Mantzaris, Matan Uriel, Mendel Goldfinger, Aditi Shastri, Nishi Shah, Kira Gritsman, Noah S. Kornblum, Lauren Shapiro, R. Alejandro Sica, Anne Marie Munoz, Nicole Chambers, Aradhika Dhawan, Karen Fehn, Balda Tirone, Lamisha Shah, Shaunmonique Clark, Mimi Kim, Chenxin Zhang, Dennis L. Cooper, Amit K. Verma, Marina Konopleva, Eric J. Feldman

Part 1 - Dose escalation (3+3)
DCO Feb 15, 2024

Induction – 7+3+Ven

≤60 yrs	>60 yrs
Daunorubicin 60mg/m2* Days 2-4 Cytarabine 100mg/m2 Days 2-8	
D1: Ven 100mg D2: Ven 200mg **D3-8**: Ven 400mg	D1: Ven 100mg D2: Ven 200mg **D3-11**: Ven 400mg
	D1: Ven 100mg D2: Ven 200mg **D3-14**: Ven 400mg

Consolidation – IDAC+Ven

AraC 1500mg/m2 q12h Days 1,3,5

AraC 1000mg/m2 q12h Days 1,3,5

Ven 200mg Days 1-7

*One cohort of ptss 60yrs received Daunorubicin 90mg/m2 + AraC and Ven x8 days

Key Eligibility Criteria:

- Aged 18-75 years
- New diagnosis of non-APL AML or
- high-risk MDS (blasts>10% AND R-IPSS>3.5%)
- Fit for intensive chemotherapy
- WBC ≤ 25,000/uL (hydroxyurea and/or AraC cytoreduction allowed)
- Prior HMA +/- Ven therapy was allowed for prior MDS

Objectives/Endpoints:

Primary:

- Safety/tolerability
- Optimal Ven dose/duration RP2D

Secondary:

- CRc* (CR+CRh+CRp+CRi) rate
- **MRD(-) CRc rate* (MFC, LOD 0.02%)**
- DoR
- EFS
- OS

ABS N°57-Oral

Baseline characteristics for all treated patients

	All Cohorts (n=34)
Age, yrs median (range)	59 (27-71)
Sex, male n (%)	19 (56)
Race, n (%)	
white*	13 (38.2)
non-white*	21 (61.8)
WBC, x10³/uL median (range)	16.4 (1.2 - 343.6)
Secondary AML, n (%)	4 (11.7)
Cytogenetic risk, n (%)	
Favorable	5 (14.7)
Intermediate	20 (58.8)
Poor	9 (26.5)
ELN 2022 risk, n (%)	
Favorable	13 (38.2)
Intermediate	6 (17.7)
Poor	15 (44.1)

8dVEN=14; 11dVEN=9; 14dVEN=11

Induction Adverse Events

- No DLTs were observed at any Ven duration
- **The 30- and 60-day mortality rate was 0%**

Non-hematologic TEAEs	All Ven Cohorts (n=34)	
	Any Grade	Grade ≥3
	n (%)	
Febrile neutropenia	34 (100)	34 (100)
Sepsis/bacteremia/ Infection*	17 (50)	17 (50)
Mucositis, oral	6 (18)	3 (9)
Neutropenic enterocolitis	8 (24)	8 (24)
Nausea/vomiting	16 (47)	0^
Diarrhea	15 (44)	0^
AST/ALT increased	27 (79)	4 (12)
Bilirubin increased	26 (77)	2 (6)

- Median time to **ANC ≥500**/uL: **26** (21-44) days
- Median time to **ANC ≥1000**/uL: **27** (22-49) days
- Median time to **PLT ≥50**K/uL: **26** (21-62) days
- Median time to **PLT ≥100**K/uL: **28** (22-72) days

- Median time to hematologic recovery was similar (25-29d) across Ven dose cohorts and age groups (≤60 vs >60 yrs)

Treatment responses

	All Patients (n=34)	CBF (n=5)	NPM1 (n=13)	FLT3-ITD (n=7)	TP53 (n=5)
Response			n (%)		
No response	5 (15)	-	-	1 (14)	3 (60)
CR	**28 (82)**	5 (100)	13 (100)	6 (86)	2 (40)
CRh	**1 (3)**	-			
MFC-MRD-neg CR	**25/29 (86)**	5 (100)			
Mol-MRD-neg CR		5* (100)			

*3/5 of CBF and 1/9 NPM1c AML pts had with low-level MRD (<2%) after induction tha

Conclusions

- Ven in combination with "7+3" induction chemotherapy was tolerable in patients deemed fit for IC, up to the age of 75 years with 0% 30- and 60-day mortality
- MRD-negative responses were high across most AML genotypes

Secondary AML

#55 Saturday 9:30AM, Priyanka Mehta et al

Randomized Comparison of **CPX-351** and **FLAG-Ida** in Patients with High-Risk Acute Myeloid Leukemia (AML)/Myelodysplastic Syndrome (MDS) and MDS-Related Gene Mutations: A Subgroup Analysis of the **UK NCRI AML19 Trial**

#60 Saturday 10:45AM, Shai Shimony et al.

View AML-MR Mutations Drive the Benefit of **CPX-351** over 7+3 in the Pivotal Phase 3 AML Trial

AML-MRC → AML-MR

The terminology of AML with myelodysplasia related changes (AML-MRC) is replaced by AML, myelodysplasia-related (AML-MR) in WHO-HAEM5, representing a single entity defined by the presence of at least one of the following: history of MDS or MDS/MPN, MR cytogenetic abnormalities and/ or MR gene mutations

alterazioni correlate a mielodisplasia (AML-MRC)

WHO 2016	WHO 2022	ICC 2022
AML-MRC	**AML-MR**	**AML with**
• complex karyotype • cytogenetic abnormalities: • unbalanced abnormalities • -7/del(7q) • del(5q)/t(5q) • i(17q)/t(17p) • -13/del(13q) • del(11q) • del(12p)/t(12p) • idic(X)(q13) • balanced abnormalities	**Defining cytogenetic abnormalities:** • complex karyotype • del5q or 5q loss • -7, del7q or 7q loss • del11q • del12p or 12p loss • -13 or del13q • del17p or 17p loss or i17q • idic(X)(q13) **Defining somatic mutations:** *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*	**MDS-related genetic abnormalities:** • complex karyotype • del(5q)/t(5q)/add(5q), • -7/del(7q), • +8 • del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p) • del(20q), • idic(X)(q13) **MDS-related gene mutations:** *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2, RUNX1*

ABS N°60-ORAL

AML-MR Drive the Benefit of CPX-351 over 7+3 in the Pivotal Phase 3 AML Trial

Shai Shimony*, H. Moses Murdock*, Julia Keating, Harrison K. Tsai, Christopher R. Reilly, Christopher J. Gibson, Stefan Faderl, Tony Wagner, Nalina Dronamraju, Tara L. Lin, Ellen K. Ritchie, Thomas Prebet, Jorge E. Cortes, Geoffrey L. Uy, Jeffery E. Lancet, Donna S. Neuberg, Richard M. Stone and R. Coleman Lindsley
*co-leading authors

OVER 60 yrs

12/07/2024

Dana-Farber
Cancer Institute

Unanswered question

What is the role of CPX-351 in the current diagnostic AML landscape?

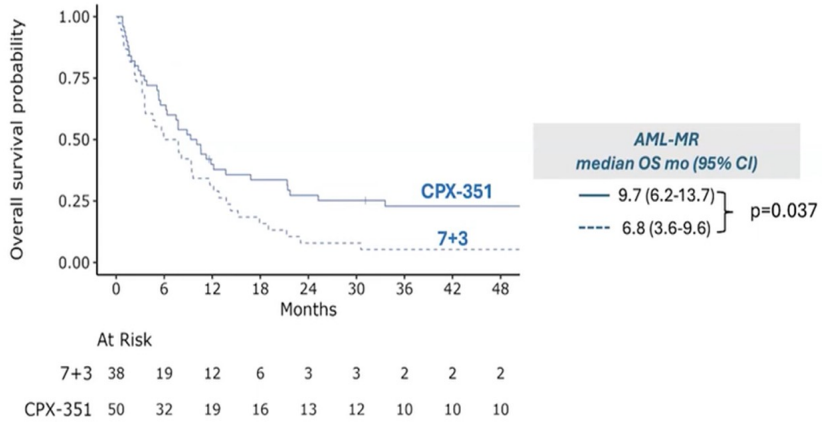
FDA-Label:

Therapy-related AML: biologically heterogenous

AML-MRC: no longer exists as a distinct diagnostic entity

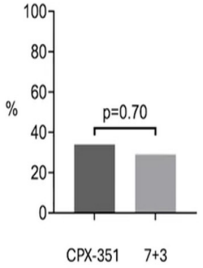
CPX-351 *vs.* 7+3

Superior survival with CPX-351 in AML-MR group

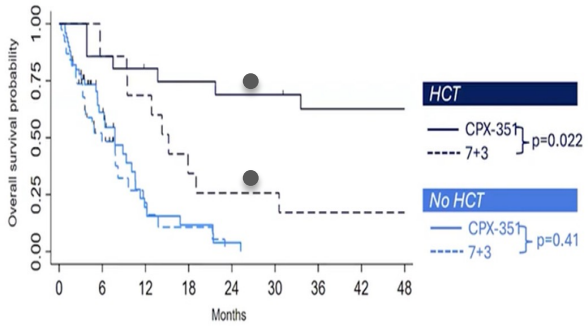


CPX-351 survival benefit in AML-MR is related to post-remission HCT

AML-MR HCT rates



OS by treatment and HCT (Simon-Makuch)



ABS N°55-ORAL

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

UNDER 60 yrs

A Randomized Comparison of CPX-351 and FLAG-Ida in Patients With High-Risk Acute Myeloid Leukemia (AML)/Myelodysplastic Syndrome (MDS) and MDS-Related Gene Mutations: A Subgroup Analysis of the UK NCRI AML19 Trial

Priyanka Mehta,[1] Roderick Murphy,[2] Saemi Park,[3] Nalina Dronamraju,[3] Tony Wagner,[4] Yana Lutska,[3] Stefan Faderl,[4] Ian Thomas,[5] Joanna Canham,[5] Alex Legg[2]

[1]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK;

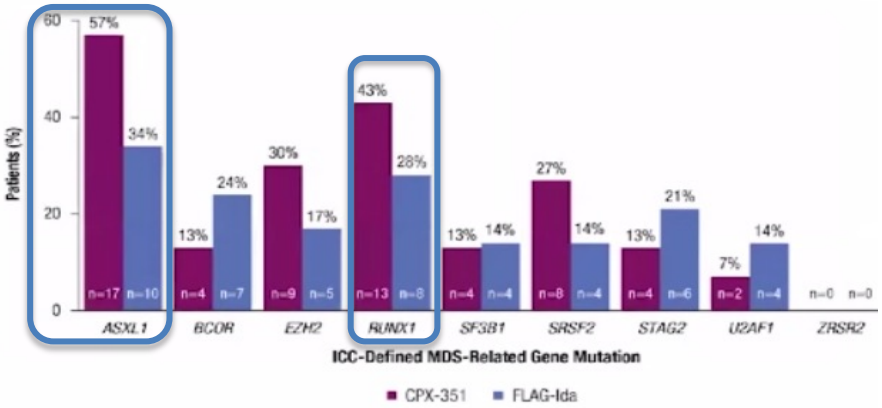
[5]Centre for Trials Research, Cardiff University, Cardiff, UK

Poster presented at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, and online.

Baseline Characteristics

	CPX-351 (n=30)	FLAG-Ida (n=29)
Male, n (%)	19 (63)	17 (59)
Female, n (%)	11 (37)	12 (41)
Age, median (min, max), years	57.5 (40, 68)	58.0 (20, 67)
AML subtype, n (%)		
De novo	15 (50)	14 (48)
Secondary	4 (13)	7 (24)
High-risk MDS	11 (37)	8 (28)
WHO performance status, n (%)		
0 (normal activity)	16 (53)	20 (69)
1 (restricted activity)	12 (40)	8 (28)
2 (in bed <50% waking hours)	2 (7)	1 (3)
Cytogenetic risk group by Grimwade 2010 criteria, n (%)		
Normal	0	3 (10)
Intermediate	6 (20)	3 (10)
Adverse	23 (77)	22 (76)
Missing/not conducted	1 (3)	1 (3)

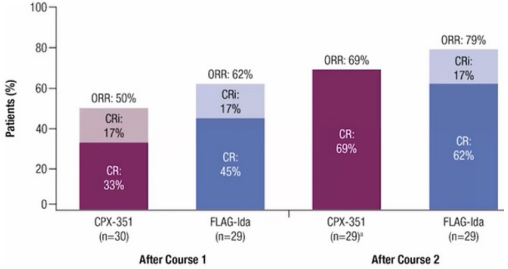
Proportion of Patients With ICC-Defined MDS-Related Gene Mutations (AML-MR)



AML, acute myeloid leukemia; FLAG-Ida, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; ICC, international consensus classification; MDS, myelodysplastic syndrome; WHO, World Health Organization.

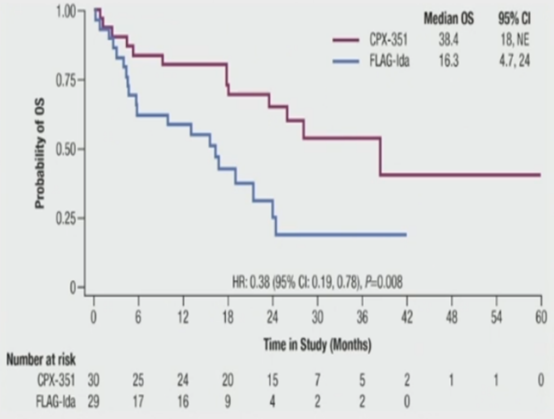
Exploratory sub-group analysis of AML19 to further characterize the efficacy and safety outcomes with CPX-351 vs FLAG-Ida in patients with high-risk AML and MDS-related gene mutations (*ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*, excluding *TP53*) as per International Consensus Classification criteria 2022

Induction Response by Treatment Arm

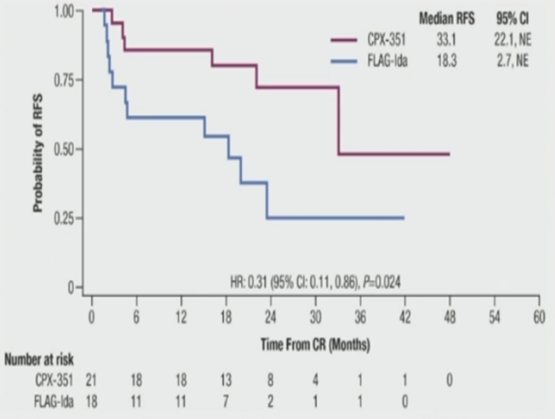


AML19 cohort (N=187)→ 59 patients (32%) had MDS-related gene mutations

OS

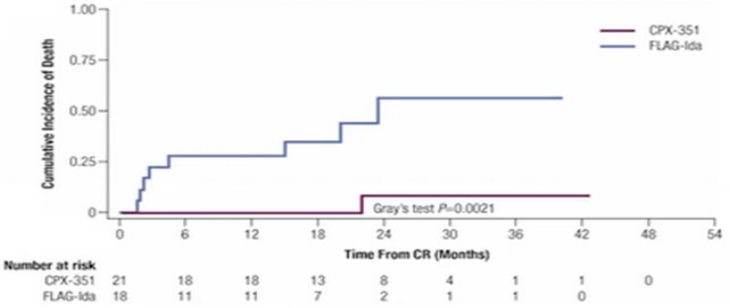


RFS in Patients Who Achieved CR



Safety

Cumulative Incidence of Death in Patients Who Achieved CR



Summary of AEs by Treatment Arm

	CPX-351 (n=30)	FLAG-Ida (n=29)
AE (any grade)	29 (97)	29 (100)
AE (grade ≥3)	21 (70)	26 (90)
SAE	3 (10)	22 (76)
Most common serious AEs[a]		
Infection	2 (7)	10 (34)
Neutropenia	0	7 (24)
Thrombocytopenia	0	3 (10)
Hypokalemia	0	2 (7)
Neutropenic sepsis	0	2 (7)
AEs leading to death	2 (7)[b]	4 (14)[c]

Rates of serious AEs were considerably lower with CPX-351 vs FLAG-Ida due to fewer infections, neutropenia, and thrombocytopenia

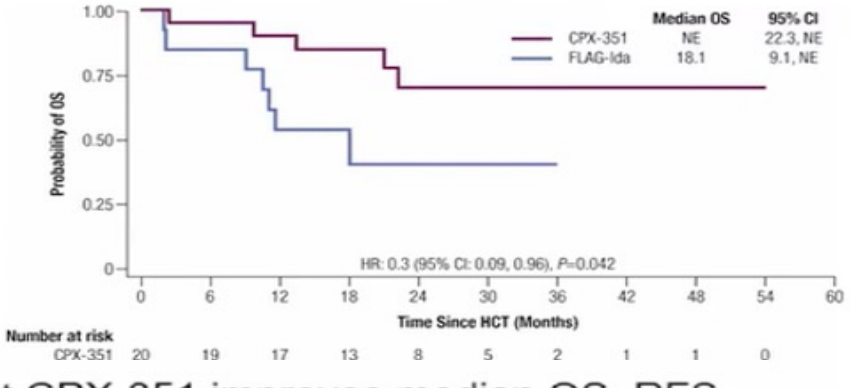
Data are n (%).
[a]Occurring in ≥5% of patients in either treatment arm.
[b]AEs leading to death were hypoxia/pulmonary oedema and lung infection in course 1 (n=1 for each).
[c]AEs leading to death were cerebral hemorrhage in course 1 and neutropenic sepsis, encephalitis infection, and acute subdural and subarachnoid hemorrhage with midline shift in course 2 (n=1 for each).
AE, adverse event; CI, confidence interval; CR, complete remission; FLAG-Ida, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; SAE, serious AE.

HCT Rates and Survival Outcomes Post-HCT

HCT Rates

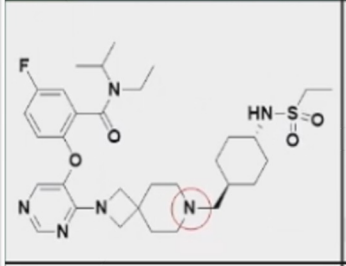
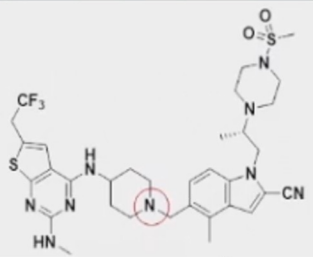
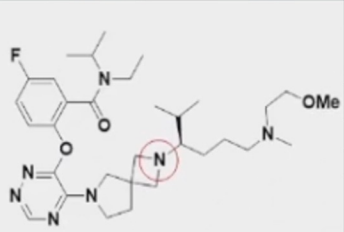
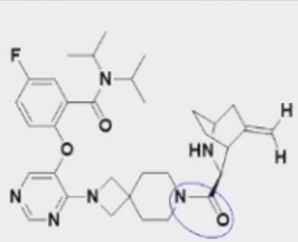
Allogeneic Transplant	CPX-351 (n=30)	FLAG-Ida (n=29)	*P* value
Transplant at any time, n (%)	20 (67)	14 (48)	0.15
Transplant in first response, n (%)	15 (75)	11 (48)	0.07

OS landmarked at HCT



Conclusions

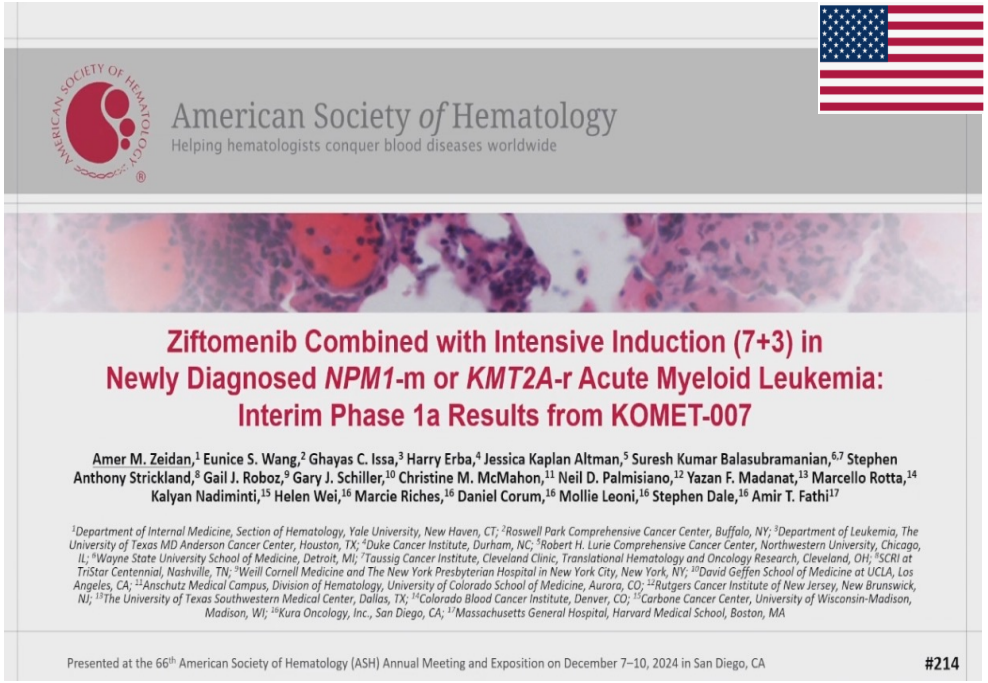
- This exploratory AML19 analysis suggests that CPX-351 improves median OS, RFS, and post-HCT OS, and reduces the number of deaths in remission vs FLAG-Ida in younger adults with high-risk AML/MDS and MDS-related mutations
- These data provided evidence for treating patients in alignment with the recently revised AML classification systems **(AML-MR)**

Revumenib	Ziftomenib	Bleximenib	Enzomenib
			
Tertiary amine bond	Tertiary amine bond	Tertiary amine bond	**Amide bond**

Biotechnology Information (2024). PubChem Compound Summary for CID 132212657, 138497449, 156498110, 146430058

- **Menin inhibitors are an exciting new class of targeted therapies for *NPM1*-mutated and *KMT2Ar* AML**
  - Revumenib first menin inhibitor FDA-approved for treatment of R/R acute leukemia patients with *KMT2Ar*
- **Frontline treatment approaches and combination studies with menin inhibitors ongoing**

ZIFTOMENIB + 3/7



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Ziftomenib Combined with Intensive Induction (7+3) in Newly Diagnosed *NPM1*-m or *KMT2A*-r Acute Myeloid Leukemia: Interim Phase 1a Results from KOMET-007

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Presented at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition on December 7–10, 2024 in San Diego, CA #214

ABS N°214-Oral

N° CASES: 51 (Adverse Risk)
27 KMT2A, 24 NPM1

RESPONSE:
- CR RATE 92% (in both groups)
- MRD Neg 76%

SAFETY:
- 7/3 + ZIFTO = 7/3 ALONE
- NO TRM

Brief Follow-up (31 w)
- Median OS: NR
- Median duration CR: NR

BLEXIMENIB + 3/7

Phase 1b Study of Menin-KMT2A Inhibitor Bleximenib in Combination with Intensive Chemotherapy in Newly Diagnosed Acute Myeloid Leukemia with *KMT2Ar* or *NPM1* Alterations

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https://www.congresshub.com/ASH2024/Oncology/EarlyAssets/Recher

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Presented by C Recher at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

ABS N°215-Oral

N° CASES: 28 (13 KMT2A, 15 NPM1)

RESPONSE:

- **CR RATE 86% (in both groups)**
- **ORR 95% (in both groups)**

SAFETY:

- **7/3 + BLEXI = 7/3 ALONE**
- **NO TRM**

Brief Follow-up

AGENDA

1)TERAPIA DI PRIMA LINEA-FIT

2)TERAPIA DI PRIMA LINEA-UNFIT (ABS 2896, 2883)

3)LAM RICADUTA/REFRATTARIA e NUOVI FARMACI

TOT THERAPY

All oral AML therapy 

Newly diagnosed AML	Regimen	N	Outcome	OS	Ref
Non-targeted	DEC-C VEN	60	ORR 67% (CR 40%)	mOS 10.2m	ASH 2024 #2896 (Bazinet)
IDH1/2	DEC-C VEN IDHi	50	ORR 92%	2-year OS 82%	ASH 2024 #2883 (Marvin-Peek)

Abstract #2883

Clinical Outcomes Using Frontline "Triplet" Regimens for Newly Diagnosed *IDH*-Mutated Acute Myeloid Leukemia (AML): A Pooled Analysis of Two Phase Ib/2 Clinical Trials

Authors: *Jennifer Marvin-Peek, MD, Himachandana Atluri, MD, Nicholas J. Short, MD, et al.*

This analysis included **50 patients** treated with either azacitidine (AZA) + VEN + ivosidenib (IVO) or oral decitabine/cedazuridine (ASTX727) + VEN + IVO/enasidenib (ENA). The median patient age was **71 years**. **Adverse-risk disease accounted for 72%, and 24% had secondary AML (tsAML).**

	All Frontline[1] (n=50)	*IDH1*-mutated	*IDH2*-mutated
2-year OS	82%	83%	78%
2-year EFS	63%	67%	62%
2-year DOR	58%	61%	58%
CRc[3]	92%	87%	96%
ORR	96%	93%	100%
MRD negativity[4]	78% (36/46)	80% (20/25)	95% (19/20)

Early Mortality:
30-day: 0% (0/50)
60-day: 2% (2/50)

AGENDA

1)TERAPIA DI PRIMA LINEA-FIT

2)TERAPIA DI PRIMA LINEA-UNFIT

3)LAM RICADUTA/REFRATTARIA e NUOVI FARMACI

(ABS 211, 213, 216, 223)

Menin Inhibition Abstracts at ASH

#211, Saturday 2:00PM, Ibrahim Aldoss et al.

Updated Results and Longer Follow-up from the AUGMENT-101 Phase 2 Study of **Revumenib** in All Patients with Relapsed or Refractory (R/R) KMT2Ar Acute Leukemia

#212, Saturday 2:15PM, Emma Searle et al.

Bleximenib Dose Optimization and Determination of RP2D from a Phase 1 Study in Relapsed/Refractory Acute Leukemia Patients with KMT2A and NPM1 Alterations

#213, Saturday 2:30PM, Joshua F. Zeidner et al.

Phase 1 Results: First-in-Human Phase 1/2 Study of the Menin-MLL Inhibitor **Enzomenib (DSP-5336)** in Patients with Relapsed or Refractory Acute Leukemia

#214, Saturday 2:45PM, Amer M. Zeidan et al.

Ziftomenib Combined with Intensive Induction (7+3) in Newly Diagnosed NPM1-m or KMT2A-r Acute Myeloid Leukemia: Interim Phase 1a Results from KOMET-007

#215, Saturday 3:00PM, Christian Recher et al

Phase 1b Study of Menin-KMT2A Inhibitor **Bleximenib** in Combination with Intensive Chemotherapy in Newly Diagnosed Acute Myeloid Leukemia with KMT2Ar or NPM1 Alterations

#216, Saturday 3:15PM, Ghayas C. Issa et al

View Phase I/II Study of the All-Oral Combination of **Revumenib (SNDX-5613)** with **Decitabine/Cedazuridine (ASTX727)** and **Venetoclax (SAVE)** in R/R AML

AML REFRACTORY/RELAPSE

STUDY	DRUG	POPULATION	ORR	CRR	Notes
SAVE Study **ABS 216-Oral, Issa et al.**	**REVUMENIB+ DEC-C+VEN**	• 33 pts • AML R/R • KMT2A or NPM1 • Median age 35 (12-81)	**82%**	60%	

ASH 2024 AML Highlights

HOT TOPICS

TRIPLETTE

MENINA INIBITORI

TARGET THERAPY

POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

10° SESSIONE – LEUCEMIE ACUTE

Leucemie Acute Mieloidi

Anna Candoni

Università degli Studi di Modena e Reggio Emilia-UNIMORE

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Phase I/II Study of the All-Oral Combination of Revumenib (SNDX-5613) with Decitabine/Cedazuridine (ASTX727) and Venetoclax in R/R AML (SAVE)

Ghayas C. Issa[1], Branko Cuglievan[2], Naval Daver[1], Courtney D. DiNardo[1], Aziz Farhat[1], Nicholas J. Short[1], David McCall[2], Allison Pike[1], Sheila Tan[1], Brianna Kammerer[2], Aimee Marshal[1], Musa Yilmaz[1], Tapan M. Kadia[1], Naveen Pemmaraju[1], Maro Ohanian[1], Hussein A. Abbas[1], Abhishek Maiti[1], Alexandre Bazinet[1], Elias Jabbour[1], Koji Sasaki[1], Gautam Borthakur[1], Guillermo Montalban-Bravo[1], Nitin Jain[1], Yesid Alvarado[1], Farhad Ravandi[1], Guillermo Garcia-Manero[1], Michael Andreeff[1], and Hagop M. Kantarjian[1]

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