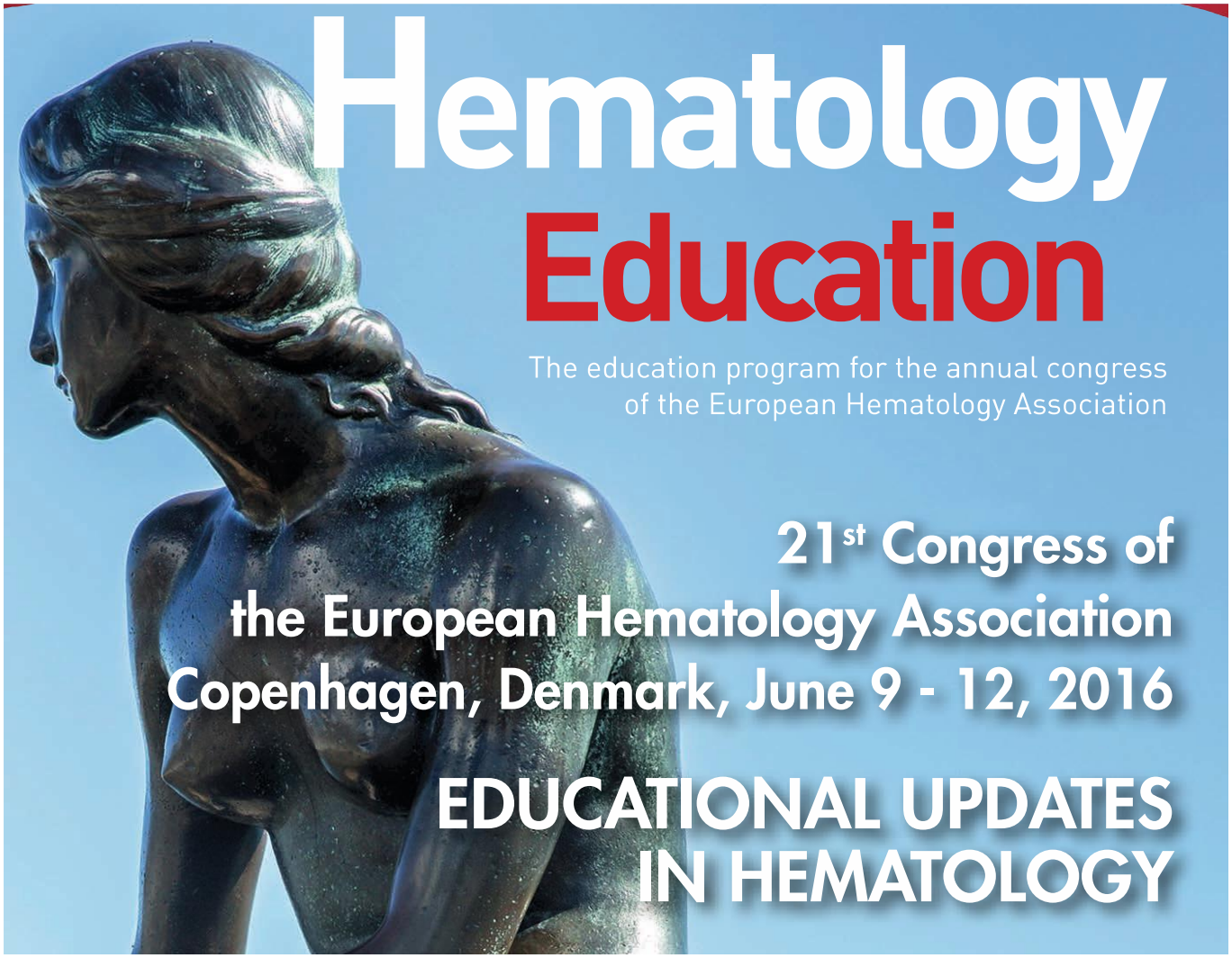
Key Points in AML

- ✓ Emerging Predictive and Prognostic Factors for AML
- ✓ Best Treatment Options for Patients with Newly Diagnosed AML
- ✓ Best Treatment Options for Patients with Relapsed/Refractory AML
- ✓ Novel Agents in Clinical Trials


Hematology
Education
The education program for the annual congress
of the European Hematology Association
21st Congress of
the European Hematology Association
Copenhagen, Denmark, June 9 - 12, 2016
EDUCATIONAL UPDATES
IN HEMATOLOGY

Acute myeloid leukemia

Stefan Fröhling (Coordinating Author)

National Center for Tumor Diseases, Heidelberg, Germany

Dissecting genetic and phenotypic heterogeneity to deliver personalized predictions in acute myeloid leukemia patients

Elli Papaemmanuil

Memorial Sloan Kettering Cancer Center, New York, USA

Targeting mutant isocitrate dehydrogenase

Eytan Stein

Memorial Sloan Kettering Cancer Center, New York, USA

Who should be transplanted in the molecular era?

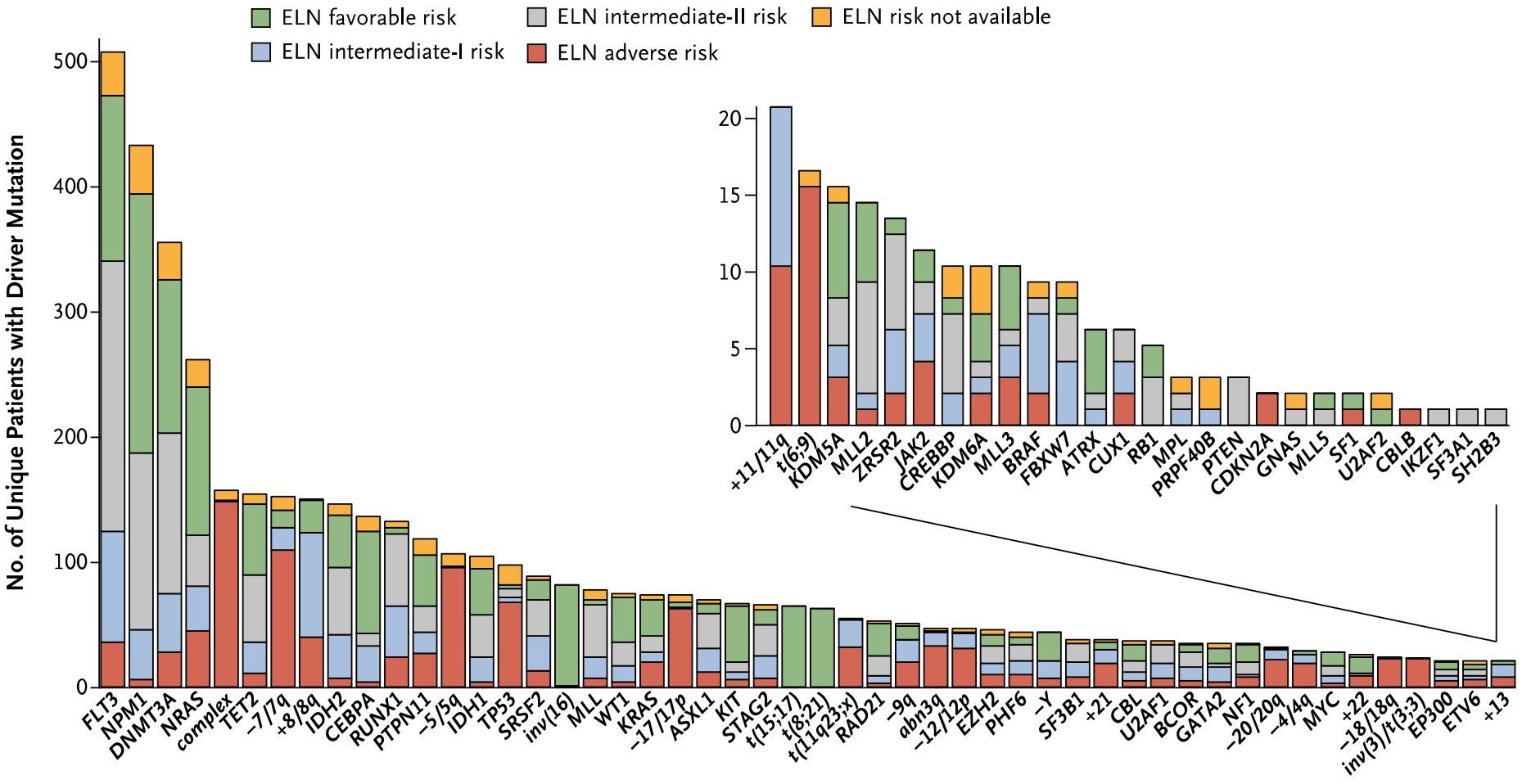
Richard Schlenk

University of Ulm, Germany

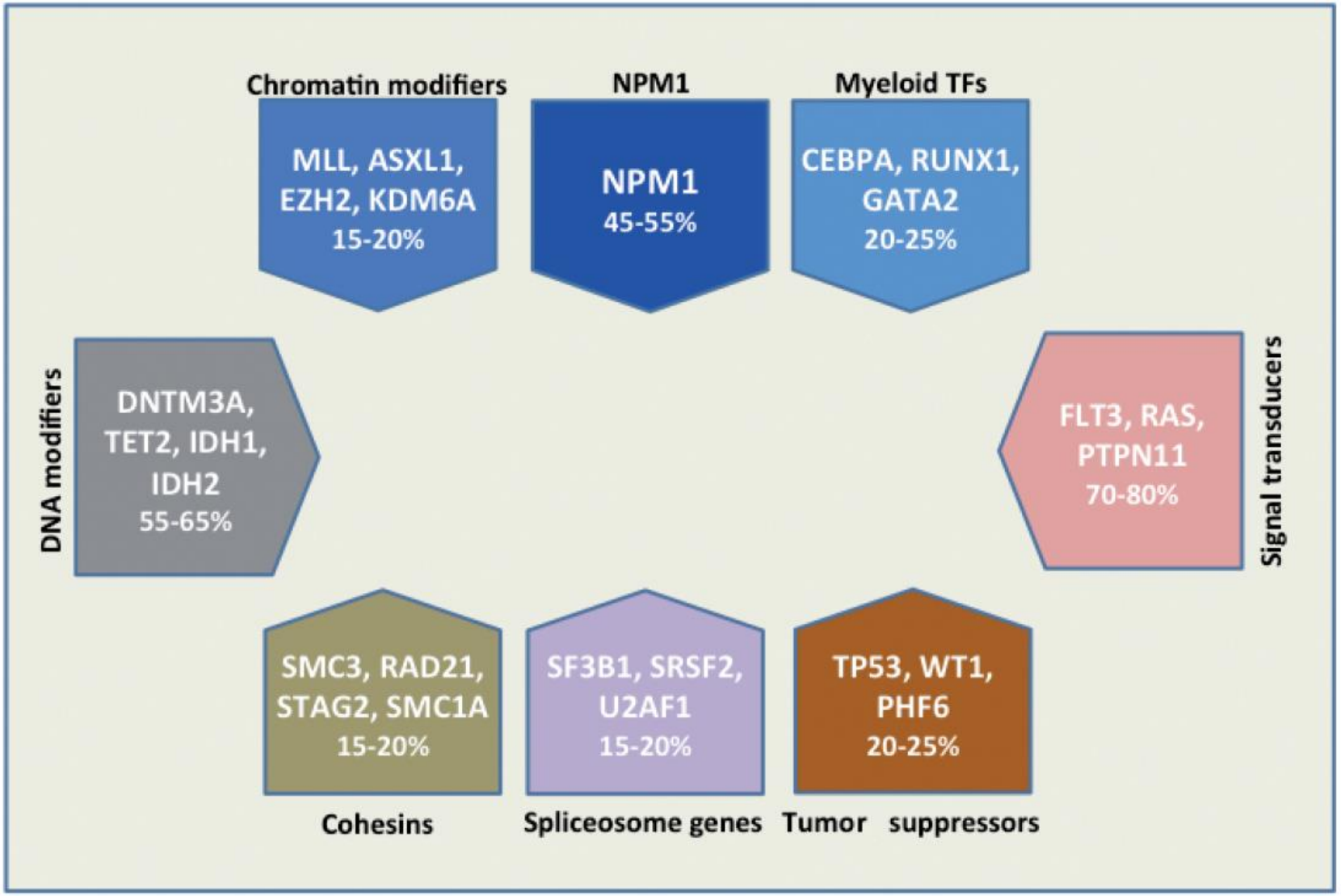
The NEW ENGLAND JOURNAL of MEDICINE JUNE 9, 2016 VOL. 374 NO. 23

Genomic Classification and Prognosis in Acute Myeloid Leukemia

A



Mutation classes in AMLa with a normal karyotype and their frequencies.



Vassiliou et al, EHA 2015

Indagini molecolari ⟶ Prognosi

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	−5 or del(5q); −7; abnl(17p); complex karyotype‡

Risk	Index score in points	Survival probability, %	
		at 1 y	at 5 y
Favorable (9% of patients)	0-6	70	46
Intermediate (25% of patients)	7-9	49	18
Unfavorable (66% of patients)	10-14	16	4

The choice of Therapy…….

- ✓Biological Characteristics of Leukemic Clone (Cytogenetic molecular risk group)
- ✓Patient age
- ✓General Conditions – Comorbidities (Diabetes,Liver disease..)
- ✓Patient/Family Consensus

Clinical trials

- Benefit of HD-DAU in FLT3-ITD^{mut} AML (NCRI-AML17)
- Benefit of CPX-351 in FLT3^{mut} AML (update on phase 3/HR-AML)
- Volasertib+LDAC (phase 3/elderly AML)
- Vosaroxin+Decitabine (phase 1-2/elderly AML+HR-MDS)

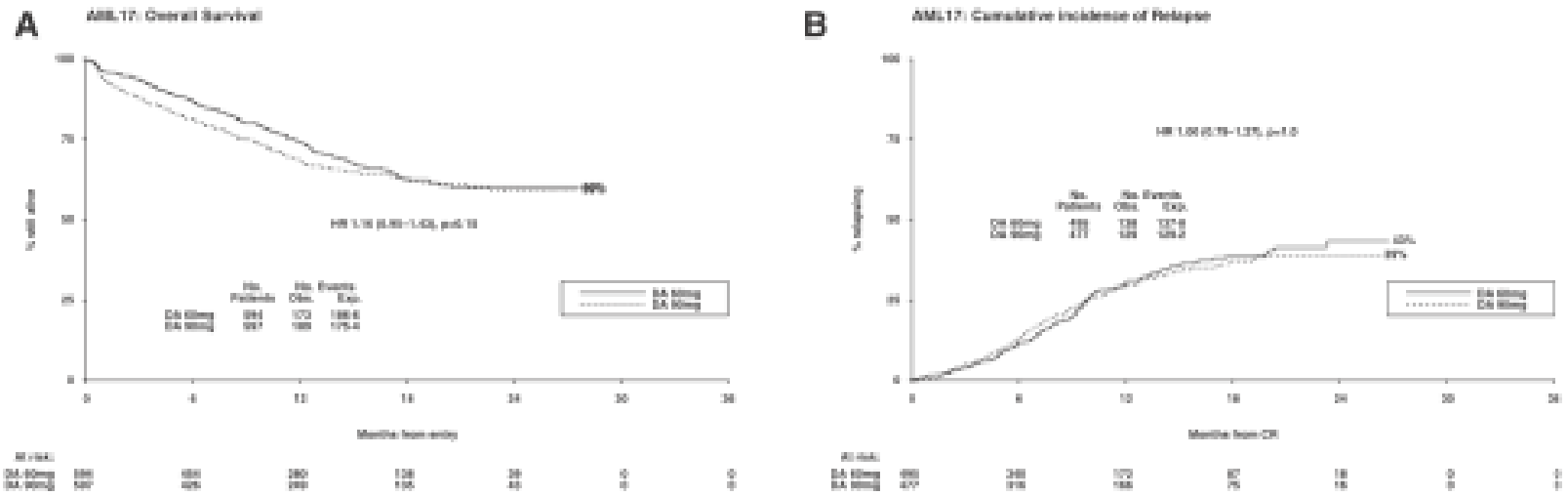
Novel targeted agents to watch....

- SGN-CD33A in combination with HMA (phase 1/CD33+ AML)

2015 125: 3878-3885
doi:10.1182/blood-2015-01-623447 originally published online April 1, 2015

A randomized comparison of daunorubicin 90 mg/m^2 vs 60 mg/m^2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients

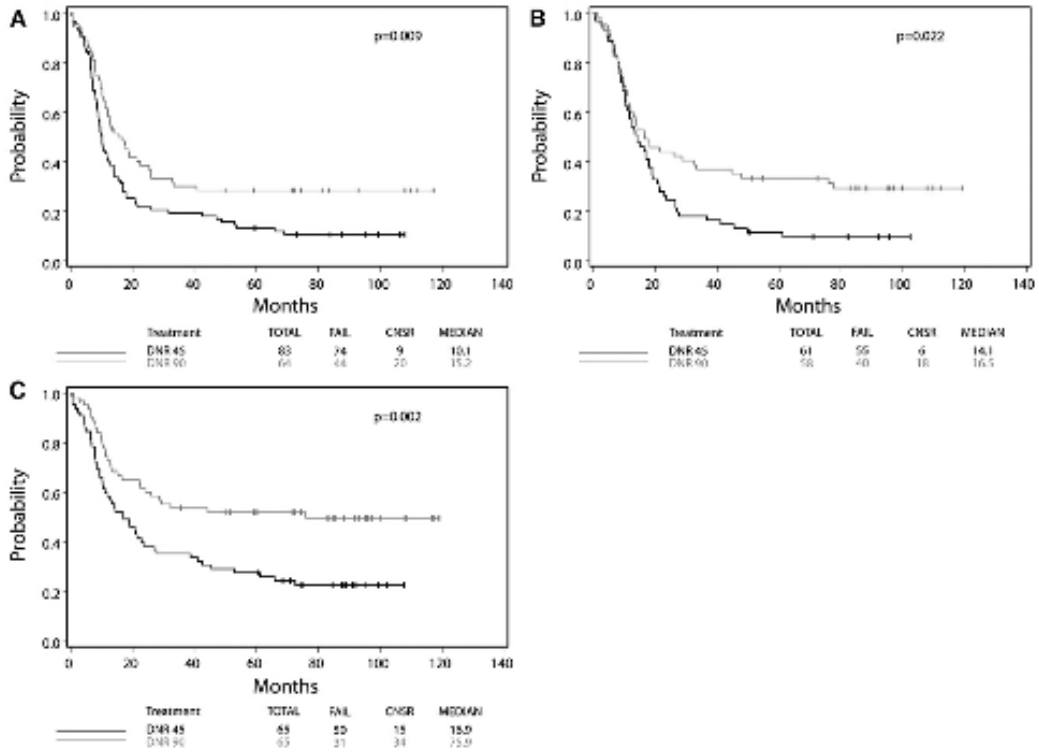
Alan K. Burnett, Nigel H. Russell, Robert K. Hills, Jonathan Kell, Jamie Cavenagh, Lars Kjeldsen, Mary-Frances McMullin, Paul Cahalin, Mike Dennis, Lone Friis, Ian F. Thomas, Don Milligan and Richard E. Clark

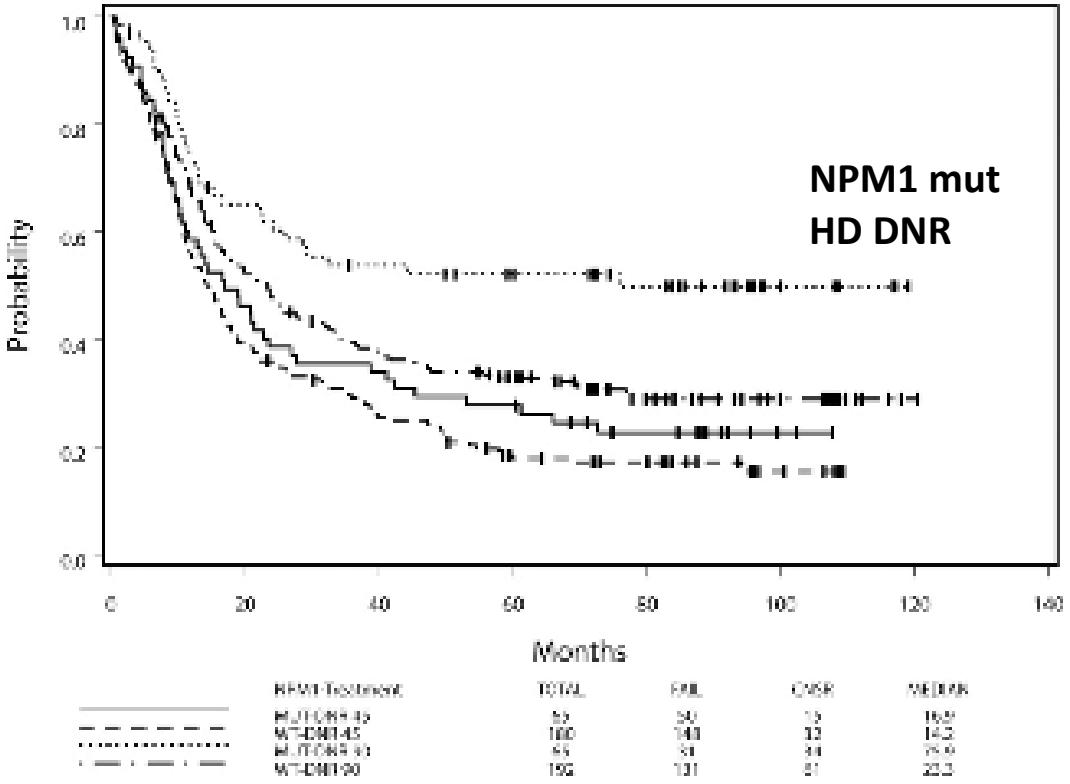


blood®
2016 127: 1551-1558
doi:10.1182/blood-2015-07-657403 originally published online January 11, 2016

Benefit of high-dose daunorubicin in AML induction extends across cytogenetic and molecular groups

Marlise R. Luskin, Ju-Whei Lee, Hugo F. Fernandez, Omar Abdel-Wahab, John M. Bennett, Rhett P. Ketterling, Hillard M. Lazarus, Ross L. Levine, Mark R. Litzow, Elisabeth M. Paietta, Jay P. Patel, Janis Racevskis, Jacob M. Rowe, Martin S. Tallman, Zhuoxin Sun and Selina M. Luger




NPM1 mut
HD DNR
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
Months

blood®
2016 127: 71-78
doi:10.1182/blood-2015-07-604538 originally published online December 10, 2015

Emerging therapeutic drugs for AML

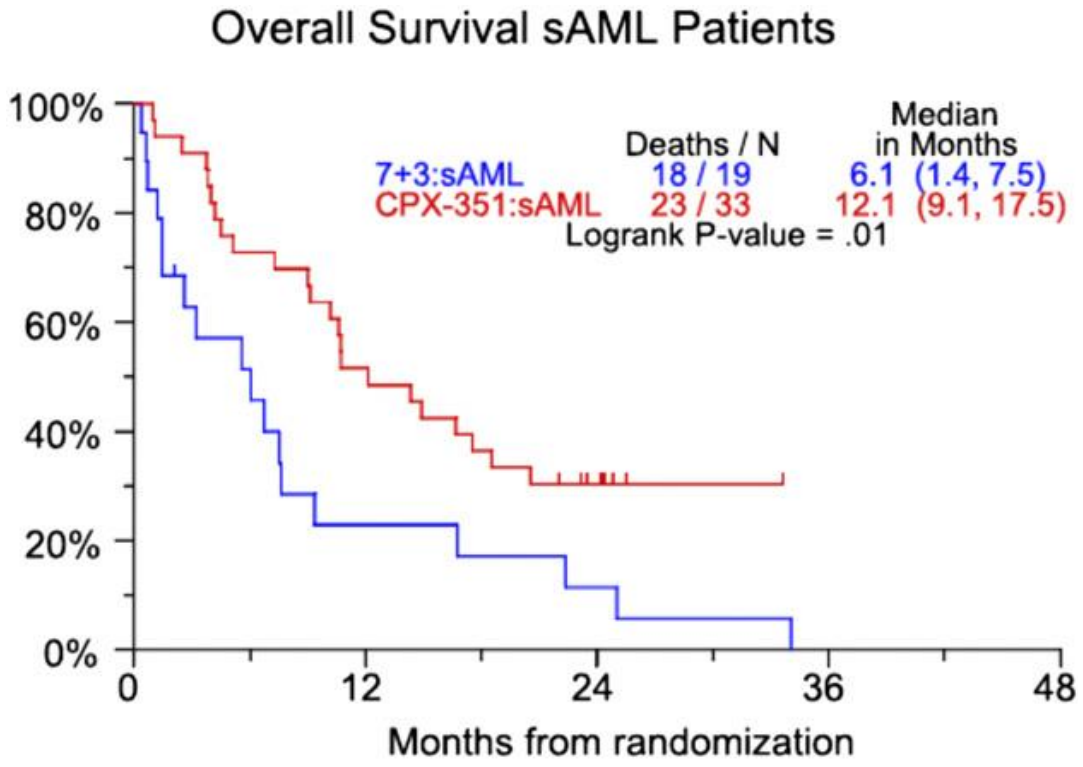
Eytan M. Stein and Martin S. Tallman

Agent	Mechanism of action	Suggested patient population	Notes
CPX-351	Liposomal formulation of 7+3 in 5:1 molar ratio	sAML fit for induction chemotherapy	Phase 2 study showed OS benefit in sAML Phase 3 study fully accrued and waiting for final analysis
Vosaroxin	Novel topoisomerase II inhibitor	Relapsed/refractory AML	OS benefit when censored for allogeneic transplant; mucositis notable as toxicity
Guadecitabine	Hypomethylating agent resistant to deamination	Unfit for intensive chemotherapy	May supplant LDC, decitabine, 5-azacitadine
SGN-CD33A	ADC against CD33 with stable linker	Being explored as a combination with hypomethylating and traditional induction	Next-generation ADC against CD33
Volasertib	Novel PLK1 inhibitor	Being explored as a combination with hypomethylating and traditional induction	OS benefit in small randomized phase 2 study when combined with LDC
Quizartinib	FLT3 inhibitor	FLT3 + AML	Impressive single-agent activity against FLT3-ITD; resistance emerges in most patients
Crenolanib	FLT3 inhibitor with activity against TKD-resistance mutation	FLT3-ITD or FLT3-TKD	Active against TKD mutations
ASP-2215	FLT3 inhibitor with activity against TKD-resistance mutation	FLT3-ITD or FLT3-TKD	Impressive single-agent activity with CRc rate of 43%
AG-221	IDH2 inhibitor	IDH2 mutated	Impressive single-agent activity (41% overall response rate) in relapsed or refractory AML
AG-120	IDH1 inhibitor	IDH1 mutated	Impressive single-agent activity in relapsed or refractory AML
EPZ-5676	DOT1L inhibitor	MLL rearranged	Combinations with standard of care should be explored
ABT-199	BCL2 inhibitor	Ongoing investigation	May have increased activity in patients with IDH mutations
OTX-015	BET inhibitor	Ongoing investigation	Combinations with standard of care should be explored
Pracinostat	HDAC inhibitor	Ongoing investigation	Impressive activity in combination with 5-azacitidine; awaiting survival data.

Agent	Mechanism of action	Suggested patient population	Notes
CPX-351	Liposomal formulation of 7+3 in 5:1 molar ratio	sAML fit for induction chemotherapy	Phase 2 study showed OS benefit in sAML Phase 3 study fully accrued and waiting for final analysis
Vosaroxin	Novel topoisomerase II inhibitor	Relapsed/refractory AML	OS benefit when censored for allogeneic transplant; mucositis notable as toxicity
Guadecitabine	Hypomethylating agent resistant to deamination	Unfit for intensive chemotherapy	May supplant LDC, decitabine, 5-azacitadine
SGN-CD33A	ADC against CD33 with stable linker	Being explored as a combination with hypomethylating and traditional induction	Next-generation ADC against CD33
Volasertib	Novel PLK1 inhibitor	Being explored as a combination with hypomethylating and traditional induction	OS benefit in small randomized phase 2 study when combined with LDC
Quizartinib	FLT3 inhibitor	FLT3 + AML	Impressive single-agent activity against FLT3-ITD; resistance emerges in most patients
Crenolanib	FLT3 inhibitor with activity against TKD-resistance mutation	FLT3-ITD or FLT3-TKD	Active against TKD mutations
ASP-2215	FLT3 inhibitor with activity against TKD-resistance mutation	FLT3-ITD or FLT3-TKD	Impressive single-agent activity with CRc rate of 43%
AG-221	IDH2 inhibitor	IDH2 mutated	Impressive single-agent activity (41% overall response rate) in relapsed or refractory AML
AG-120	IDH1 inhibitor	IDH1 mutated	Impressive single-agent activity in relapsed or refractory AML
EPZ-5676	DOT1L inhibitor	MLL rearranged	Combinations with standard of care should be explored
ABT-199	BCL2 inhibitor	Ongoing investigation	May have increased activity in patients with IDH mutations
OTX-015	BET inhibitor	Ongoing investigation	Combinations with standard of care should be explored
Pracinostat	HDAC inhibitor	Ongoing investigation	Impressive activity in combination with 5-azacitidine; awaiting survival data.

Novel formulation of Cytotoxic Chemotherapy

- CPX-351 is a liposomal formulation of Arac and DNR (5:1 molar)

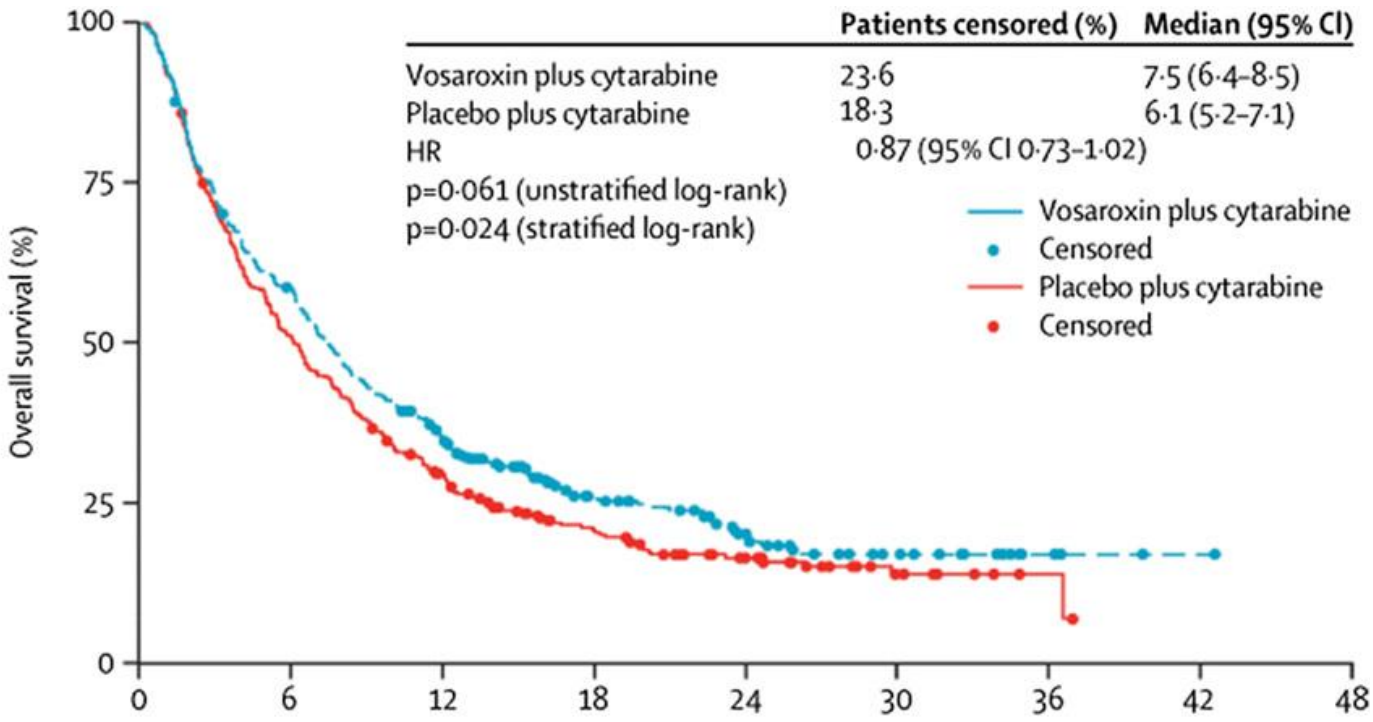


P=.07

Phase 3 Study in sAML, age 60-75

VOSAROXIN is a quinolone derivative that inhibits Topoisomerase II without the production of Oxigen free radicals that lead to the cardiac toxicity observed with other Topo II Inhib.

In phase 3 study 711 pts primary refractory AML or Relapse



Guadecitabina is a dinucleotide of Decitabine and Deoxyguanosine that increases the in vivo exposure of Decitabine by protecting it from deamination.

- Phase 3 trial comparing Guad. Vs Decit. 51 Pts no differences in CR (true CR) but

  OS 10.5 m vs 18.2

- Phase 3 trial comparing Guad.,Decit.,Aza. has been initiated……..

  Aza. and Decit. are now generic !!!

Antibody Drug Conjugated

- **SGN-CD33A** is a novel ADC….that crosslink DNA leading to cell death

There is ongoing study of SGN-CD33A alone and in combination with hypomethylating agents.

All antiCD33 ADCs induce myelosuppression…..

- **SGN-CD33A** has the antileukemic activity of GO without liver toxicity.

Molecularly Targeted Agents

- **FLT3 inhibitors:**

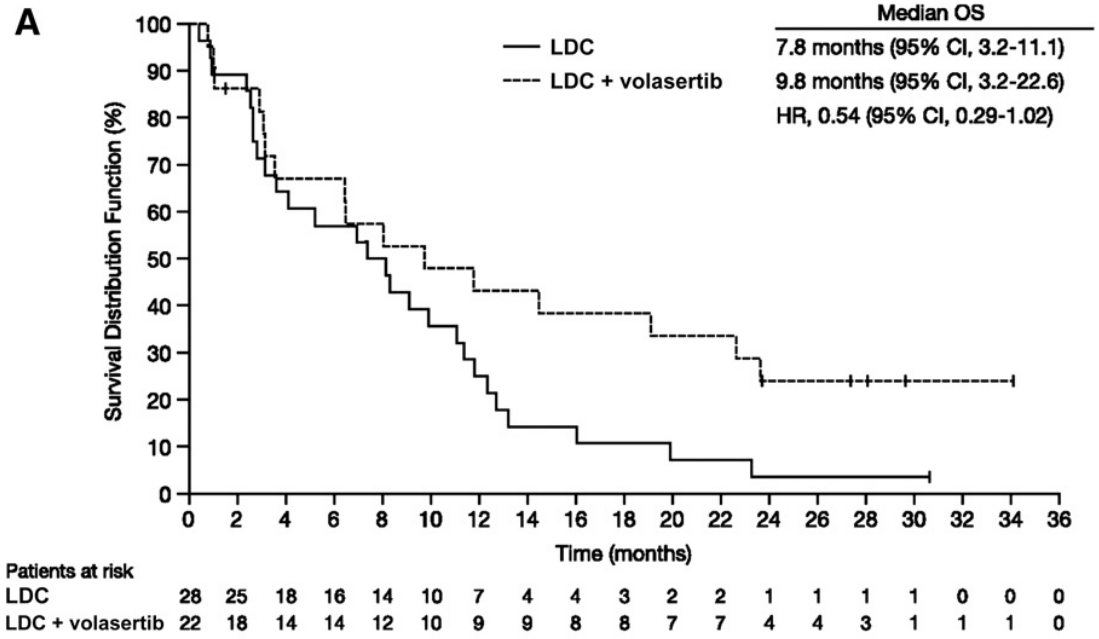
Midostaurin is an inhibitor of FLT3,cKIT,PDGFRB,VEGFR-2 and protein kinase C

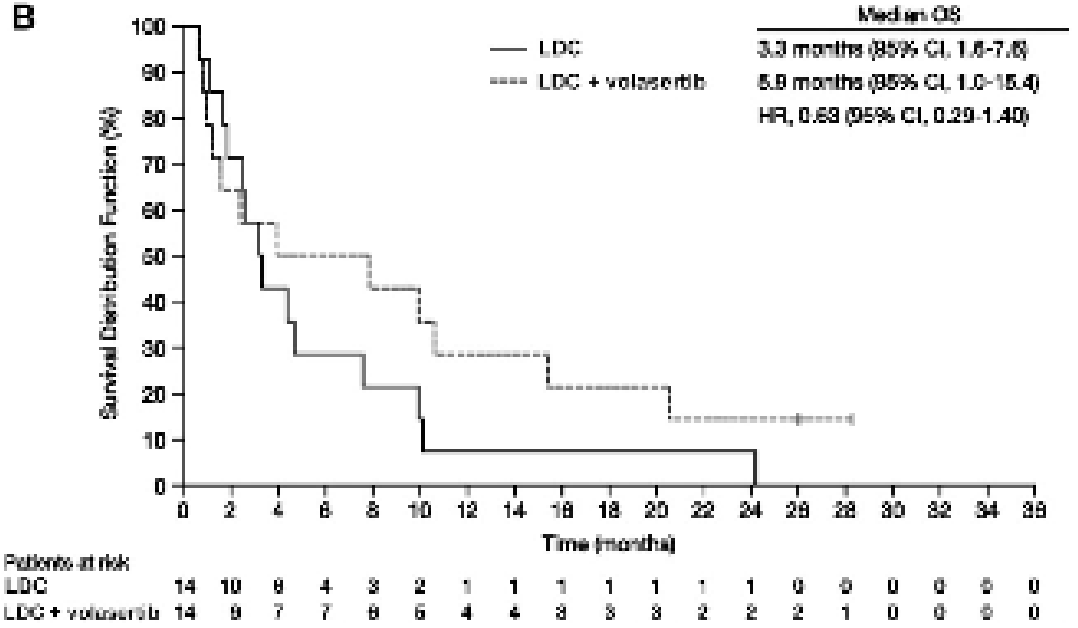
Phase 3 Trial **RATIFY** explored the activity of PKC412+DNR+ARAC vs Placebo +DNR+ARAC

Results in ASH 2015….

- **Volasertib** inhibits polo-like kinase 1(PLK1, which is over-expressed in human AML cells

In a phase 2 study, 89 patients were randomly assigned 1:1 to volasertib with LDAC or LDAC alone.[27] The dose of volasertib was 350 mg on days 1 and 15 of a 28-day cycle. CRc was 31% in the combination arm compared with 13.3% with LDAC monotherapy with a strong trend toward statistical significance ($P = .052$). Both EFS and OS were significantly longer in the combination arm; median OS was 8.0 months with volasertib with LDAC and 5.2 months with volasertib alone (Figure 3). Clinical trials of volasertib in combination with induction chemotherapy (NCT02198482) and decitabine (NCT02003573) are ongoing.


A
Median OS
LDC
LDC + volasertib
7.8 months (95% CI, 3.2-11.1)
9.8 months (95% CI, 3.2-22.6)
HR, 0.54 (95% CI, 0.29-1.02)
Survival Distribution Function (%)
Time (months)
Patients at risk
LDC 28 25 18 16 14 10 7 4 4 3 2 2 1 1 1 1 0 0 0
LDC + volasertib 22 18 14 14 12 10 9 9 8 8 7 7 4 4 3 1 1 1 0


B
Median OS
LDC
LDC + volasertib
3.3 months (95% CI, 1.6-7.6)
5.9 months (95% CI, 1.0-15.4)
HR, 0.63 (95% CI, 0.29-1.40)
Survival Distribution Function (%)
Time (months)
Patients at risk
LDC 14 10 8 4 3 2 1 1 1 1 1 1 1 0 0 0 0 0 0
LDC + volasertib 14 9 7 7 6 5 4 4 3 3 3 2 2 2 1 0 0 0 0

Molecularly Targeted Agents

- **FLT3 inhibitors:**

Quizartinib(AC220) is a selective inhibitor of FLT3,

Despite the promising single-agent activity of quizartinib, 50% of patients relapsed within 3 months. Further studies suggest that the mechanism of resistance to quizartinib is acquired mutations in the tyrosine kinase domain of the *FLT3* gene, including mutations in D835 and F691 Because of this, agents that overcome this resistance and lead to a longer duration of response are seen as crucial to the development of targeted inhibitors of mutant *FLT3*. Crenolanib is such an agent.

Crenolanib as a pan selective FLT3 inhibitor overcomes Quizartinib resistance

Crenolanib is now being investigated in combination with induction chemotherapy in patients with newly diagnosed AML with an *FLT3*-ITD or *FLT3*-TKD mutation (NCT02283177).

Gliterinib(ASP-2215) is a potent inhibitor of both FLT3-ITD and TKD mutations

The new generation of *FLT3* inhibitors are remarkably active in patients with relapsed/refractory *FLT3*-positive AML. These inhibitors are able to clear blasts from the bone marrow, but they are less effective at restoring normal hematopoiesis.

FLT3 inhibitors with other novel agents, induction chemotherapy, or hypomethylating agents may lead to improved CR and OS.

IDH1 and IDH2 inhibitors

Inhibitors of mutant *IDH1* in clinical development include AG-120 (Agios) and IDH305 (Novartis). Early results for AG-120 in patients with relapsed AML have shown evidence of efficacy similar to that of the *IDH2* inhibitor, with an overall response rate of 31% and a true CR rate of 15%. An additional 27 patients had stable disease. Dose escalation continues, and expansion cohorts in patients with relapsed/refractory AML have been initiated.

blood®
2016 128: 971-981
doi:10.1182/blood-2015-11-684225 originally published online June 22, 2016

DOT1L as a therapeutic target for the treatment of *DNMT3A*-mutant acute myeloid leukemia

Rachel E. Rau, Benjamin A. Rodriguez, Min Luo, Mira Jeong, Allison Rosen, Jason H. Rogers, Carly T. Campbell, Scott R. Daigle, Lishing Deng, Yongcheng Song, Steve Sweet, Timothy Chevassut, Michael Andreeff, Steven M. Kornblau, Wei Li and Margaret A. Goodell

- Data from *Dnmt3a*$^{-/-}$ mice implicate Dot1l as a critical mediator of the malignant gene expression program of *Dnmt3a*-mediated leukemia.
- Pharmacologic inhibition of DOT1L exerts potent antileukemic activity in *DNMT3A*-mutant human acute myeloid leukemia in vitro and in vivo.