Acute Myeloid Leukemia

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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)

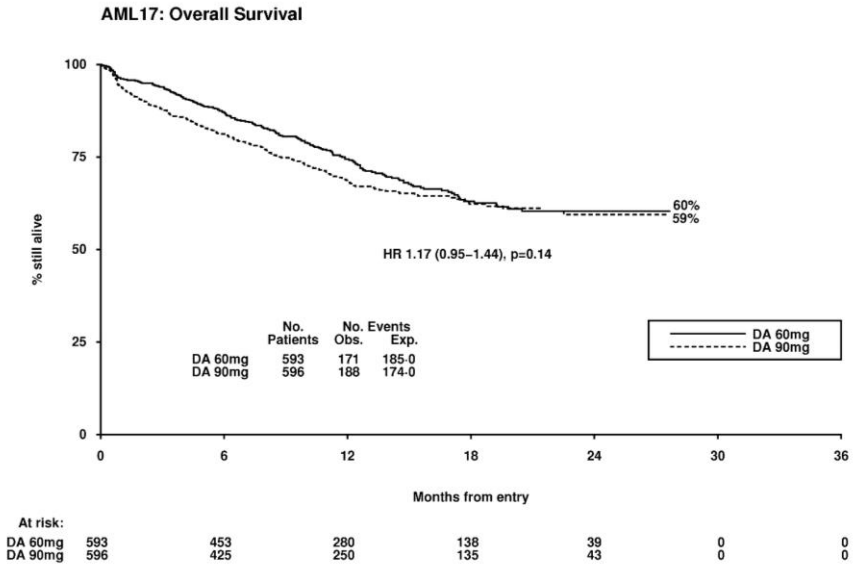
Novel targeted agents to watch….

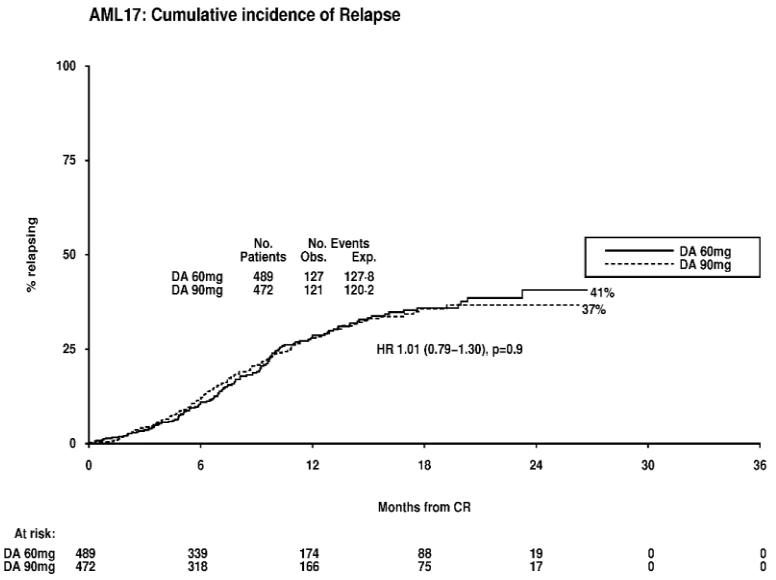
- SGN-CD33A in combination with HMA (phase 1/CD33+ AML)

Potential benefit of higher dose Daunorubicin in patients harbouring a FLT3-ITD mutation: updated results of the AML17 trial

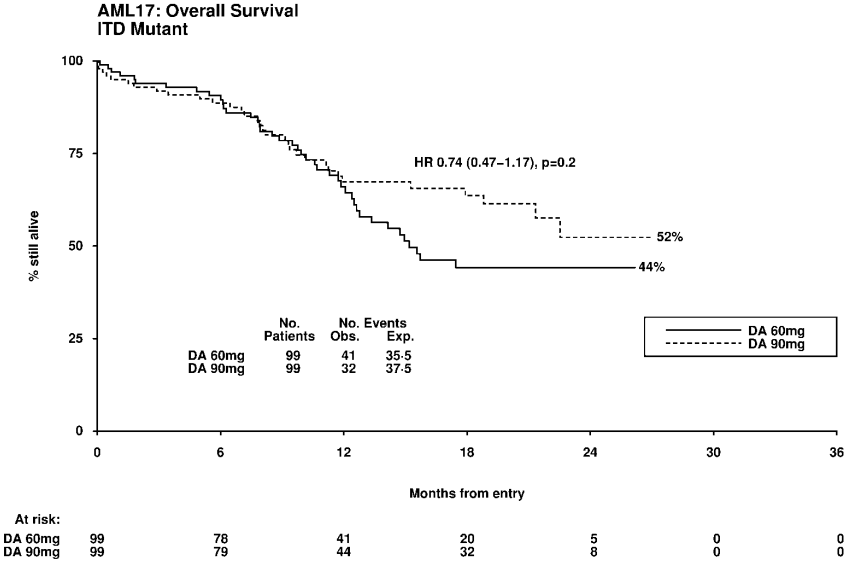
Burnett AK et al, on behalf of the United Kingdom National Cancer Research Institute (NCRI) AML Study Group

DNR 90 vs 60 mg (NCRI AML17)





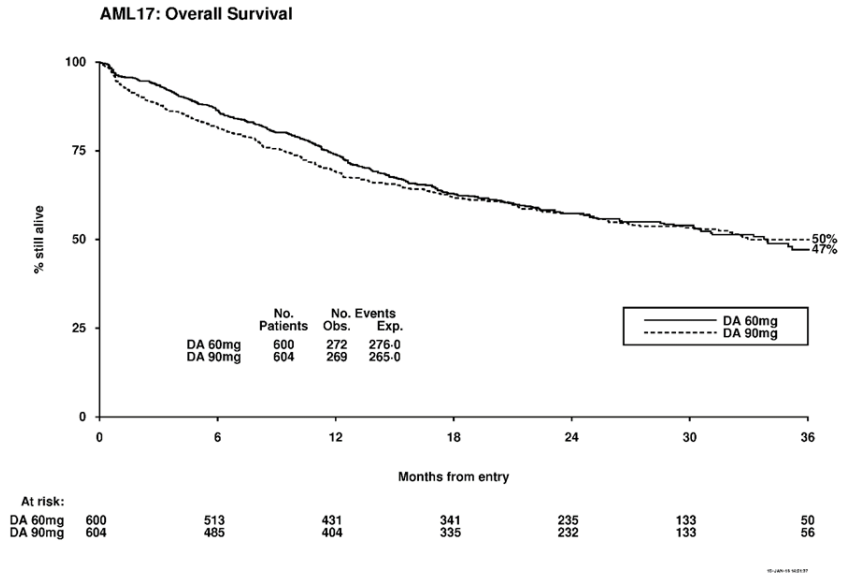
FLT3-ITD

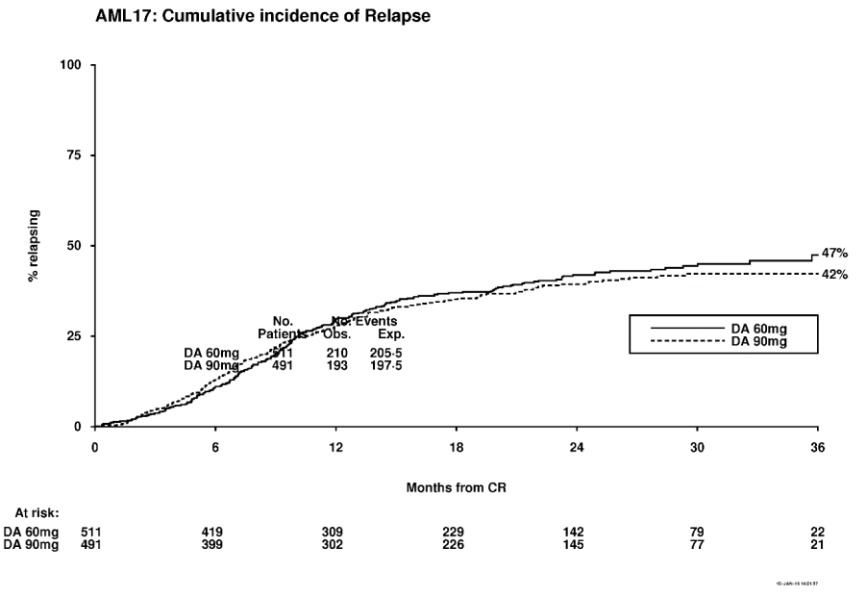


Burnett AK et al, Blood 2015

Updated Analysis

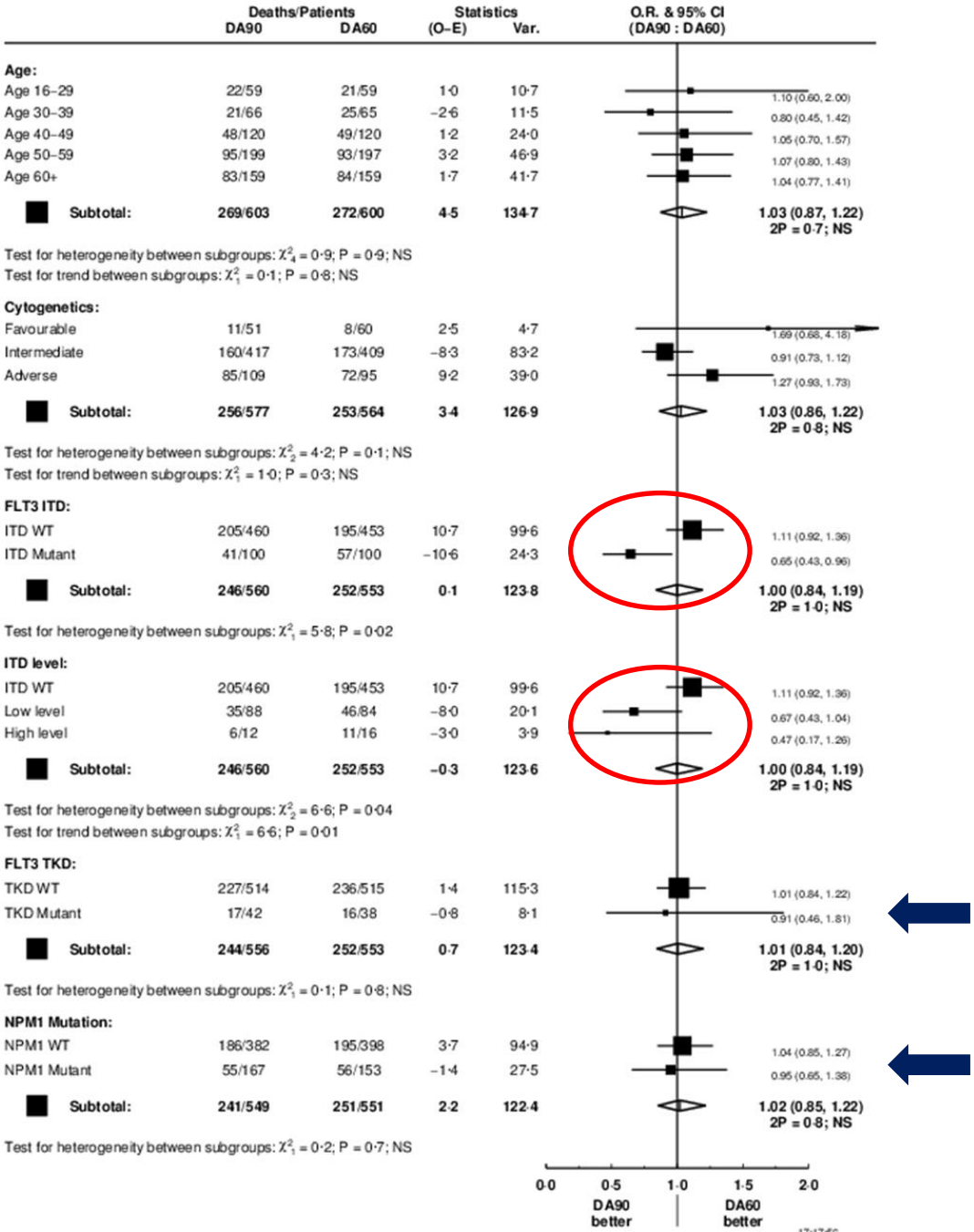
- **Follow-up extended to 1 March 2015.**
- **Median follow-up is now 28.0 mos extended from 14.8 mos**



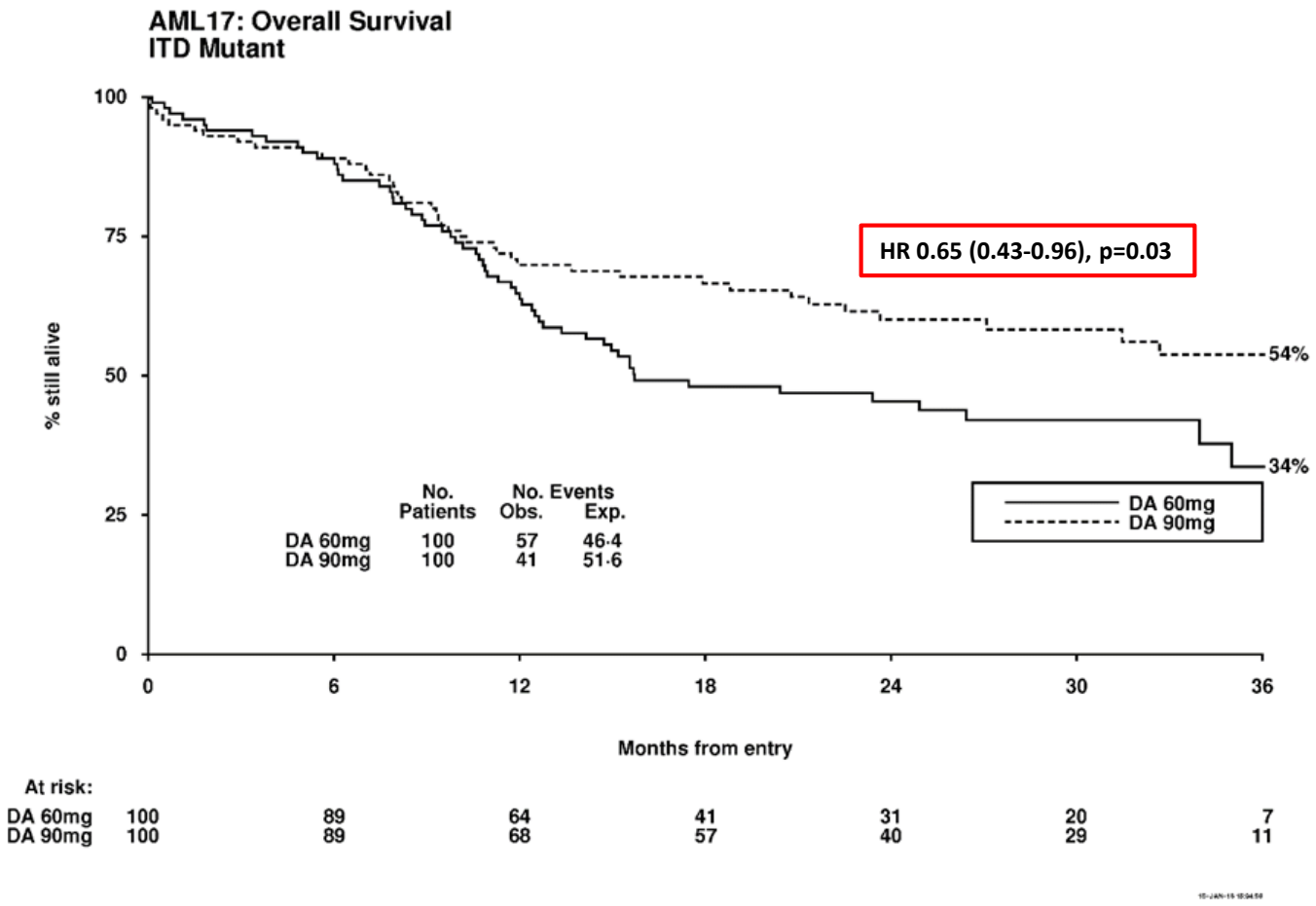


Burnett AK et al, EHA 2016

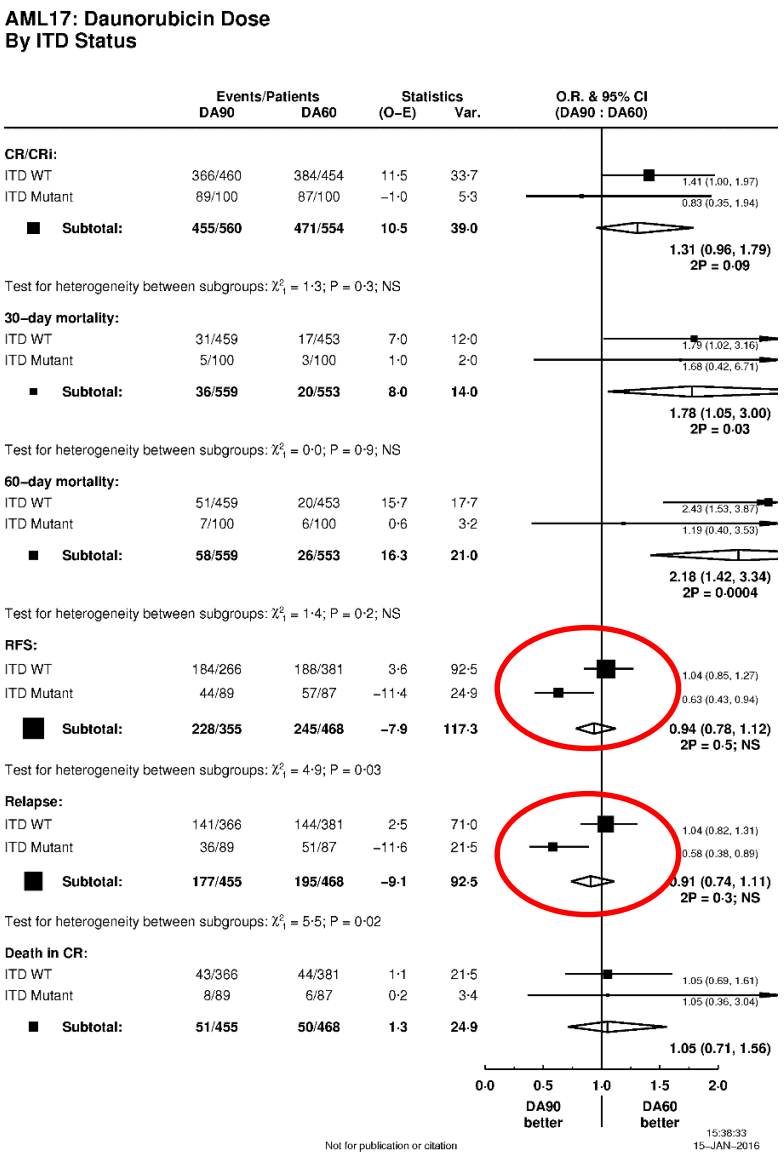
AML17: 90mg/m^2 vs 60mg/m^2: Stratified Analysis of survival



AML17: 90 vs 60mg/m^2: ITD mutant



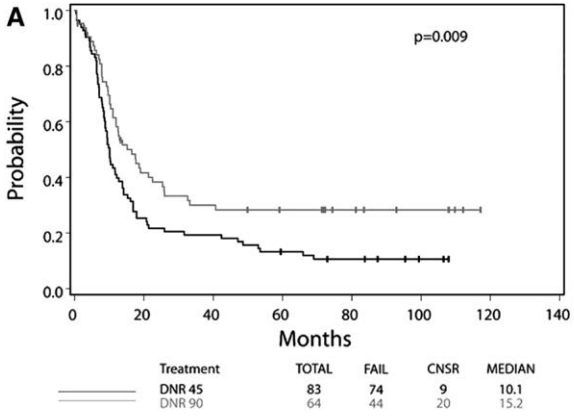
Analysis by ITD – other endpoints



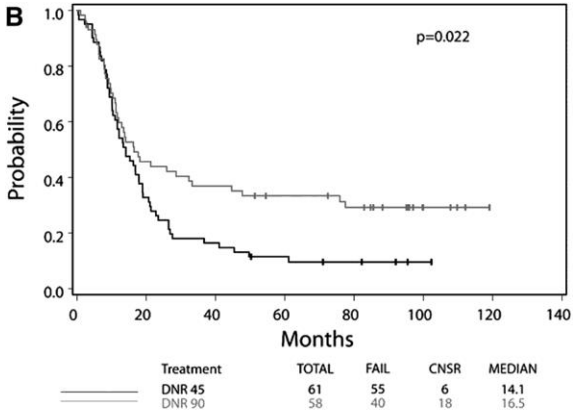
Update on ECOG 1900 trial (90 vs 45)

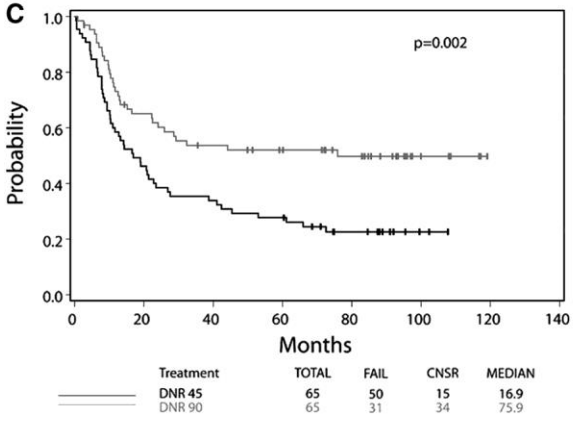
OS by treatment assignment

FLT3-ITD^{mut}



DNMT3A^{mut}





NPM1^{mut}

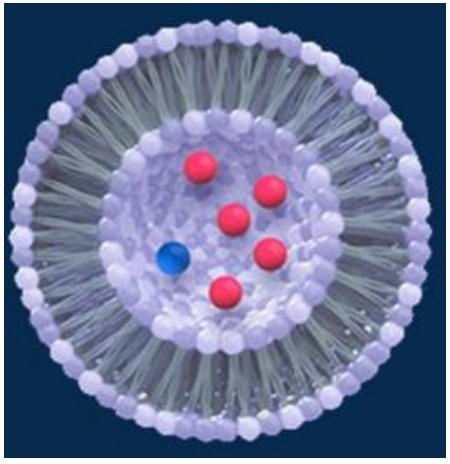
Luskin MR et al, Blood 2016

Conclusions

- **With longer follow up the AML17 trial shows a survival benefit for *FLT3 ITD* patients receiving DA90 over DA60 due to a reduction in relapse risk**
- **We could find no other groups that benefit including those with a *FLT3 TKD* or an *NPM1c* mutation (perhaps because of a high exposure to daunorubicin in the control arm)**
- **We cannot exclude benefit in other subgroups such as those with *DNMT3A* mutations**

CPX-351 treatment of previously untreated older patients with high-risk AML markedly increases the response rate over 7+3 in patients with FLT3 mutations

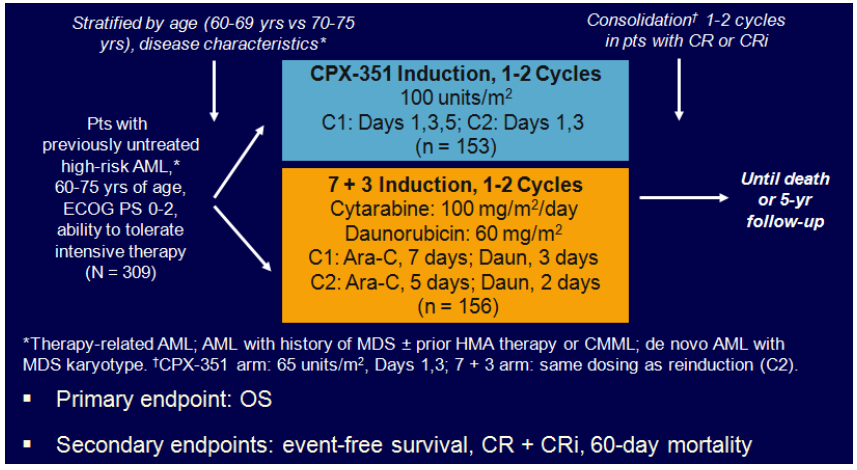
Lancet J et al



- 100 nm bilamellar liposomes
- 5:1 molar ratio of AC to DAU
- 1 U = 1 mg AC+0.44 mg DAU

Lancet J et al, EHA 2016

CPX-351 vs 3+7 phase 3 trial



EHA 2016 Update

CPX-351 significantly improves response rate over 3+7 in pts with FLT3^{mut} AML

- CPX-351 demonstrated superior efficacy vs standard 7+3 induction

Outcome	CPX-351 (n = 153)	7 + 3 (n = 156)	HR	Odds Ratio (95% CI)	*P* Value
Median OS, mos (95% CI)	9.56 (6.60-11.86)	5.95 (4.99-7.75)	0.69	NA	.005
Median EFS, mos (95% CI)	2.53 (2.07-4.99)	1.31 (1.08-1.64)	0.74	NA	.021
Response, %					
▪ CR	37.3	25.6	NA	1.69 (1.03-2.78)	.04
▪ CR + CRi	47.7	33.3	NA	1.77 (1.11-2.81)	.016

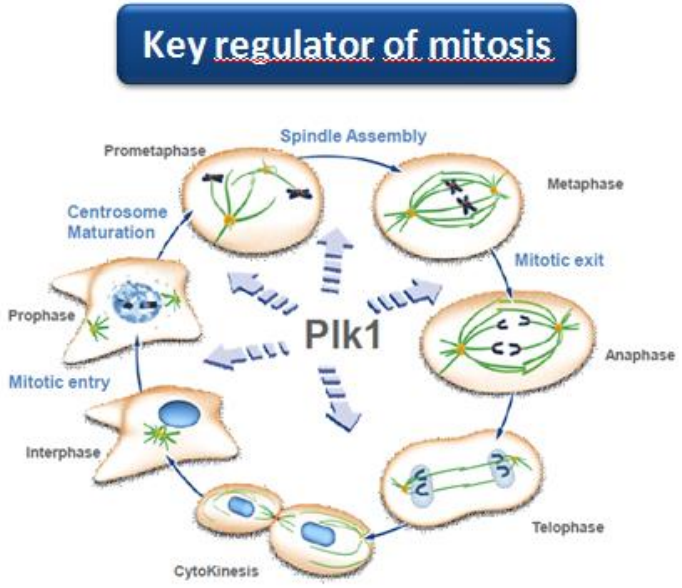
- In pts undergoing transplantation, OS higher with CPX-351 (n = 52) vs 7 + 3 (n = 39): NR vs 10.25 mos (HR: 0.46; 95% CI: 6.21-16.69; *P* = .0046)
- 30- and 60-day mortality rates lower with CPX-351 vs 7 + 3

Group	CR+CRi rate n(%)		P-value
	CPX arm	3+7 arm	
FLT3^{mut} (all)	**15/22 (68.2)**	**5/20 (25.0)**	**0.007**
FLT3 ITD+	12/19 (63.1)	3/13 (23.0)	
FLT3 TKD+	3/3 (100)	2/7 (28.6)	

Lancet J et al, ASCO 2016

Phase 3 randomized trial of VOL+LDAC versus Placebo+LDAC in patients aged ≥ 65 years with previously untreated AML, ineligible for intensive therapy

Dohner H et al, on behalf of the POLO-AML-2 trial investigators



Volasertib

- Potent Plk1 inhibitor

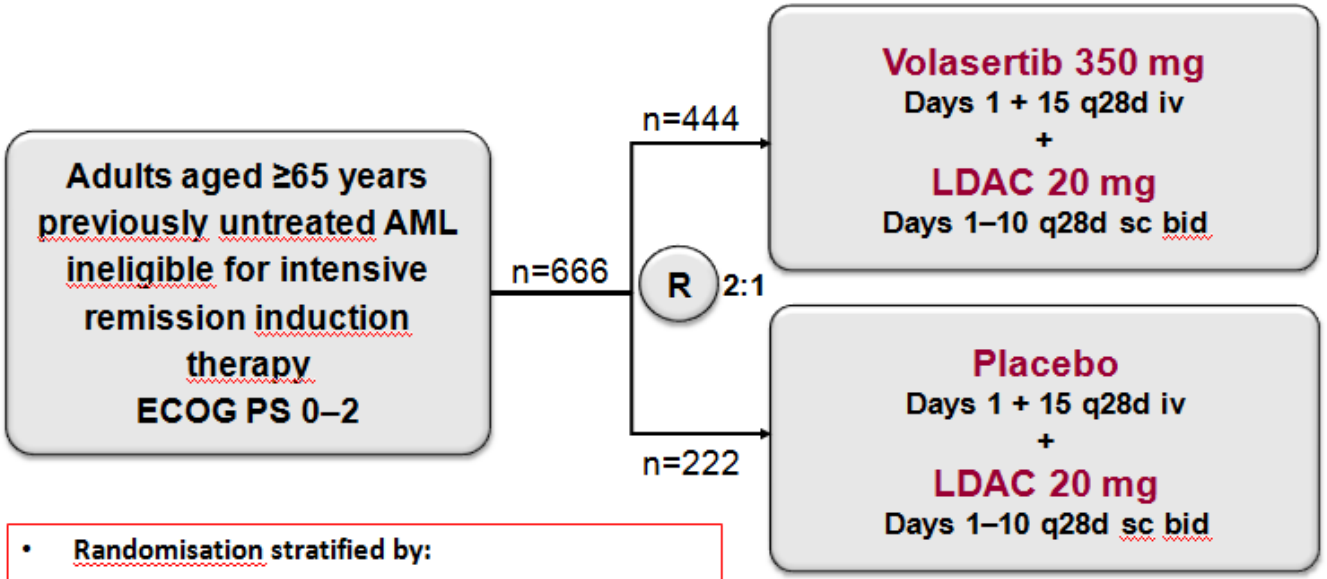
VOL+LDAC vs LDAC (R-phase 2)

- Improved remission rate (31% vs 13%)
- Improved EFS (HR: 0.57) and OS (HR: 0.63)

FDA Breakthrough Therapy 09/2013

- Phase 3 trial to confirm the phase 2 findings

VOL+LDAC (phase 3 trial)



- Randomisation stratified by:
  - Baseline ECOG PS (0/1 vs. 2)
  - Type of leukemia (*de novo* vs. secondary)
- Primary E-P: CR+CRi rate
- Secondary E-P: OS, EFS, RFS, Safety

Primary analysis set (N=371):
pts randomized ≥5 mos at clinical cut-off (08/2014)

Best overall response (N=371)

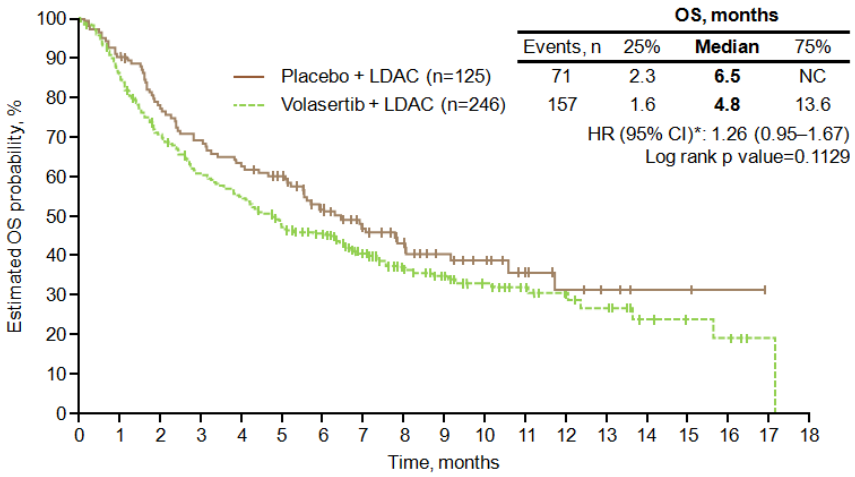
	Placebo + LDAC	Volasertib + LDAC
Patients randomised ≥5 months, n	125	246
Objective response (CR + CRi)	**21 (16.8)**	**62 (25.2)**
CR	12 (9.6)	23 (9.3)
CRi	9 (7.2)	39 (15.9)
OR estimate;* p value	1.659; p=0.071	
No assessment	14 (11.2)	91 (37.0)
Death ≤28 days post-randomisation	4 (3.2)	27 (11.0)
Death >28 days and ≤56 days post-randomisation	7 (5.6)	30 (12.2)
Death >56 days and ≤84 days post-randomisation	0 (0)	8 (3.3)

Grade ≥3 AEs

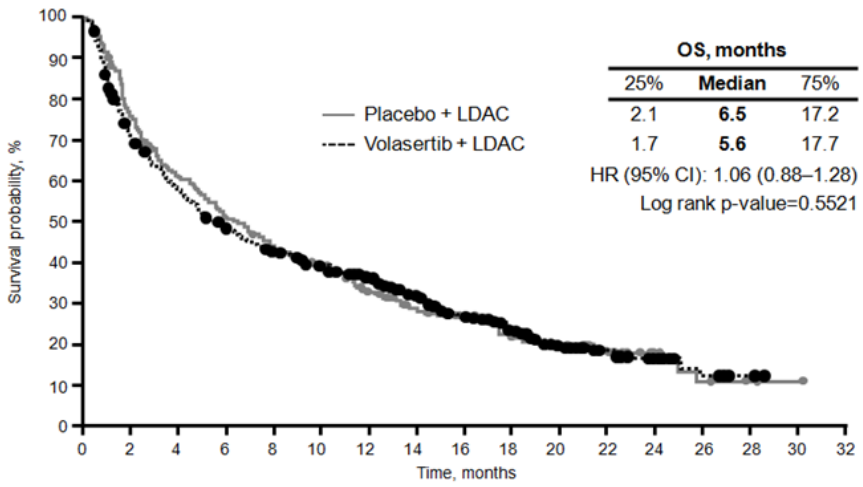
SOC, n (%)	Placebo + LDAC (n=178)				Volasertib + LDAC (n=355)			
	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
Total with AEs	174 (97.8)	54 (30.3)	64 (36.0)	27 (15.2)	344 (96.9)	65 (18.3)	160 (45.1)	99 (27.9)
Infections and infestations	106 (59.6)	41 (23.0)	16 (9.0)	9 (5.1)	273 (76.9)	104 (29.3)	31 (8.7)	59 (16.6)
Blood and lymphatic system disorders	105 (59.0)	42 (23.6)	55 (30.9)	1 (0.6)	268 (75.5)	86 (24.2)	175 (49.3)	2 (0.6)
Gastrointestinal disorders	121 (68.0)	17 (9.6)	3 (1.7)	–	252 (71.0)	45 (12.7)	3 (0.8)	–
General disorders and administration site conditions	124 (69.7)	22 (12.4)	2 (1.1)	–	228 (64.2)	43 (12.1)	14 (3.9)	6 (1.7)
Metabolism and nutrition disorders	74 (41.6)	14 (7.9)	5 (2.8)	–	174 (49.0)	56 (15.8)	14 (3.9)	–
Respiratory, thoracic and mediastinal disorders	76 (42.7)	14 (7.9)	4 (2.2)	4 (2.2)	169 (47.6)	28 (7.9)	13 (3.7)	5 (1.4)
Investigations	62 (34.8)	18 (10.1)	4 (2.2)	–	114 (32.1)	31 (8.7)	20 (5.6)	1 (0.3)

Overall survival – Primary analysis

- Patients randomised ≥5 months at the time of clinical cut-off



OS – Updated analysis



1 year after primary analysis and trial unblinding (all R-pts, 11/2015)

Conclusions

- **Primary endpoint (CR+CRi rate) was not met**
- **Unfavorable OS trend for VOL+LDAC vs PBO+LDAC at the primary analysis**
  - **Updated OS data (1-year after unblinding): no advantage for VOL+LDAC**
- **Final OS analysis pending**
- **VOL is being further investigated in AML/MDS (using alternative dosing schedules)**

Phase 1/2 study of Vosaroxin and Decitabine in newly diagnosed older patients with AML and HR-MDS

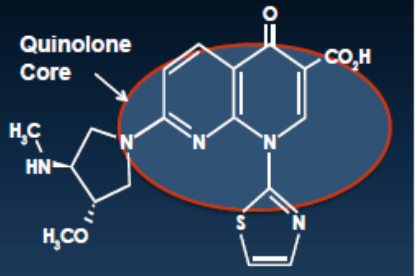
Daver N et al

Vosaroxin+DAC in Newly Dx Older AML-MDS: Background

Key Characteristics

- Targeted topoisomerase II inhibitor
- Active in anthracycline-resistant settings
- Evades common drug resistance pathways (P-gp)
- Lower potential for off-target damage (cardiotoxicity)

Vosaroxin



Vosaroxin intercalates DNA and inhibits topoisomerase II, causing replication-dependent, site-selective DNA breaks, G2 arrest and cell death by apoptosis.

Evanchi. *Drug Metab Disp* 2009; Hoch. *Cancer Chemother Pharmacol* 2009; Scaten. ibid 2010; Advani *Clin Cancer Res* 2010; Hawtin. *PLoS One* 2010; Hawtin. *Oncotarget* 2010; *Haematologica* 2011; Lancet *Leukemia* 2011.

Vosaroxin+DAC in Newly Dx Older AML-MDS: Background

- Vosaroxin in newly dx pts with AML ≥ 60 yr (REVEAL-1): CR/CRp = 32%, Med survival = 7.0 mos, 30-day mortality = 12%
- Vosaroxin Plus Cytarabine Vs Placebo Plus Cytarabine in first relapse AML (VALOR, n=711)

	IDAC	IDAC+V	P-value
CR	16%	30%	<0.0001
Med OS	6.1 m	7.5 m	P=0.06 Stratified P=0.02
OS ≥ 60 yr	5.0 m	7.1 m	P=0.003
OS censoring for SCT	5.3 m	6.7 m	P=0.02
60-day Mortality	19.4%	19.7%	NS

Stuart RK, et al. Br J Haematol. 2014
Ravandi F, et al. Lancet Oncology 2015

Vosaroxin+DAC in Newly Dx Older AML-MDS: Design

- Vosaroxin 70 – 90 mg/m² on Day 1 and 4
- Decitabine 20 mg/m² IV daily x 5 days
- Max up to 7 cycles on protocol
- Cycles repeated every 4-6 weeks depending on count recovery and toxicity

Vosaroxin+DAC in Newly Dx Older AML-MDS: Inclusion Criteria

- Untreated AML (≥ 20% blasts)
- HR-MDS or HR-CMML (≥ 10% blasts)
- Therapy for prior MDS before progression to AML acceptable
- Age ≥ 60 years and unsuitable for standard induction*
- Adequate hepatic and renal function
- No uncontrolled infection

Phase I

- 6 pts received vosaroxin 90 mg/m² D1 and 4
- No dose-limiting toxicities

Phase II

- 16 pts received vosaroxin 90 mg/m² D1 and 4
  - Grade 3 mucositis in 4 pts
- Subsequent 41 pts received vosaroxin 70 mg/m² D1 and 4

Vosaroxin+DAC in Newly Dx Older AML-MDS: Response (N=63)

Response / Outcome	N (%)
Evaluable	63
CR	31 (49)
CRp	11 (17)
CRi	5 (8)
ORR (CR + CRp + CRi)	47 (75)
No Response	10 (16)
Early Death ≤ 4 wks	0 (0)
Early Death ≤ 8 wks	7 (11)
MRD (-) by multi-parameter flow	22/34 (65)

Vosaroxin+DAC in Newly Dx Older AML-MDS: Response (N=63)

Parameter	Category	Overall Response; N (%)
Age	60-69	30/38 (79)
	≥70	17/25 (68)
Cytogenetics	Diploid	19/24 (79)
	Miscellaneous	11/14 (79)
	-5/-7/Complex	15/22 (68)
Mutation status	*IDH2*	10/11 (91)
	TET2	9/10 (90)
	TP53	10/13 (77)
	RAS	6/11 (55)
	IDH1	3/9 (33)

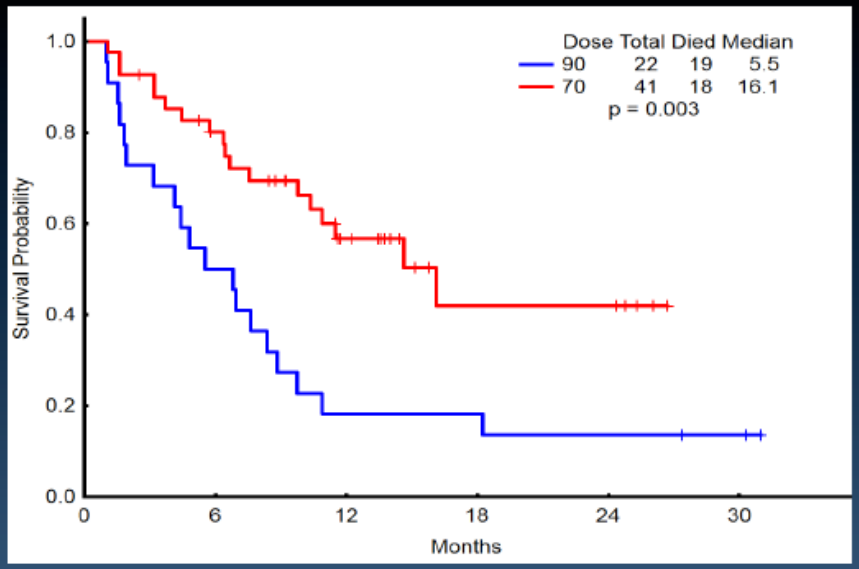
Vosaroxin+DAC in Newly Dx Older AML-MDS: Response by Induction Dose (N=63)

Induction dose	Pts (N)	Deaths ≤ 8 wks	Responders	Need > 1 course to response
90 mg/m^2	22	6 (27%)	16 (73%)	3/16 (19%)
70 mg/m^2	41	2 (5%)	31 (76%)	13/31 (42%)

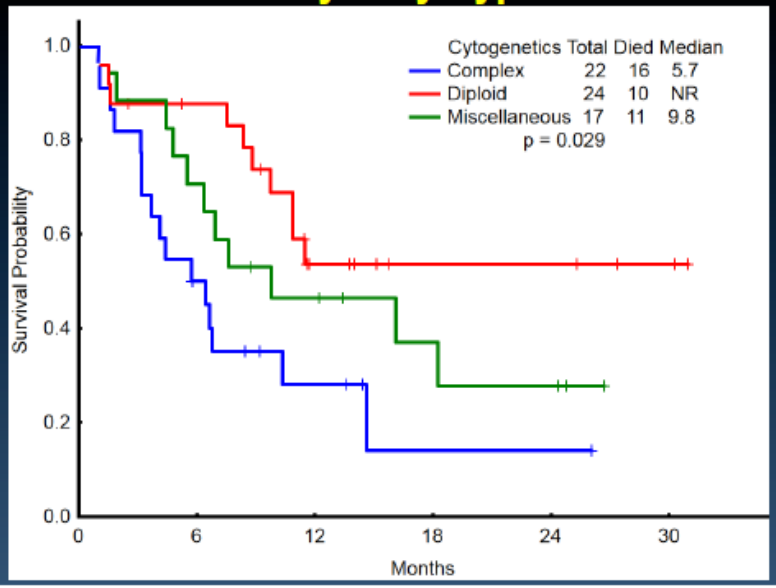
Vosaroxin+DAC in Newly Dx Older AML-MDS: Related Toxicities (N=63)

Toxicities	G1/2	G3/4	Total (%)
Bilirubin	33	8	41 (67)
Diarrhea	2	0	2 (3)
Mucositis	39	11	50 (82)
Nausea/Vomiting	9	1	10 (16)
Fungal infections	0	2	2 (3)
Major infections (pneumonia, sepsis)	0	34	34 (56)
Other infections	0	6	6 (10)

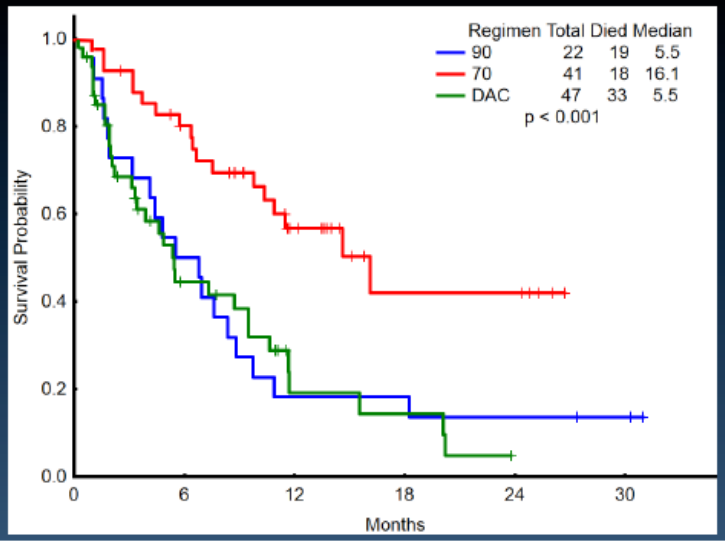
Vosaroxin+DAC in Newly Dx Older AML-MDS



Vosaroxin+DAC in Newly Dx Older AML-MDS: OS by Karyotype



Vosaroxin+DAC in Newly Dx Older AML-MDS: Vosaroxin + Decitabine vs Decitabine alone



Conclusions

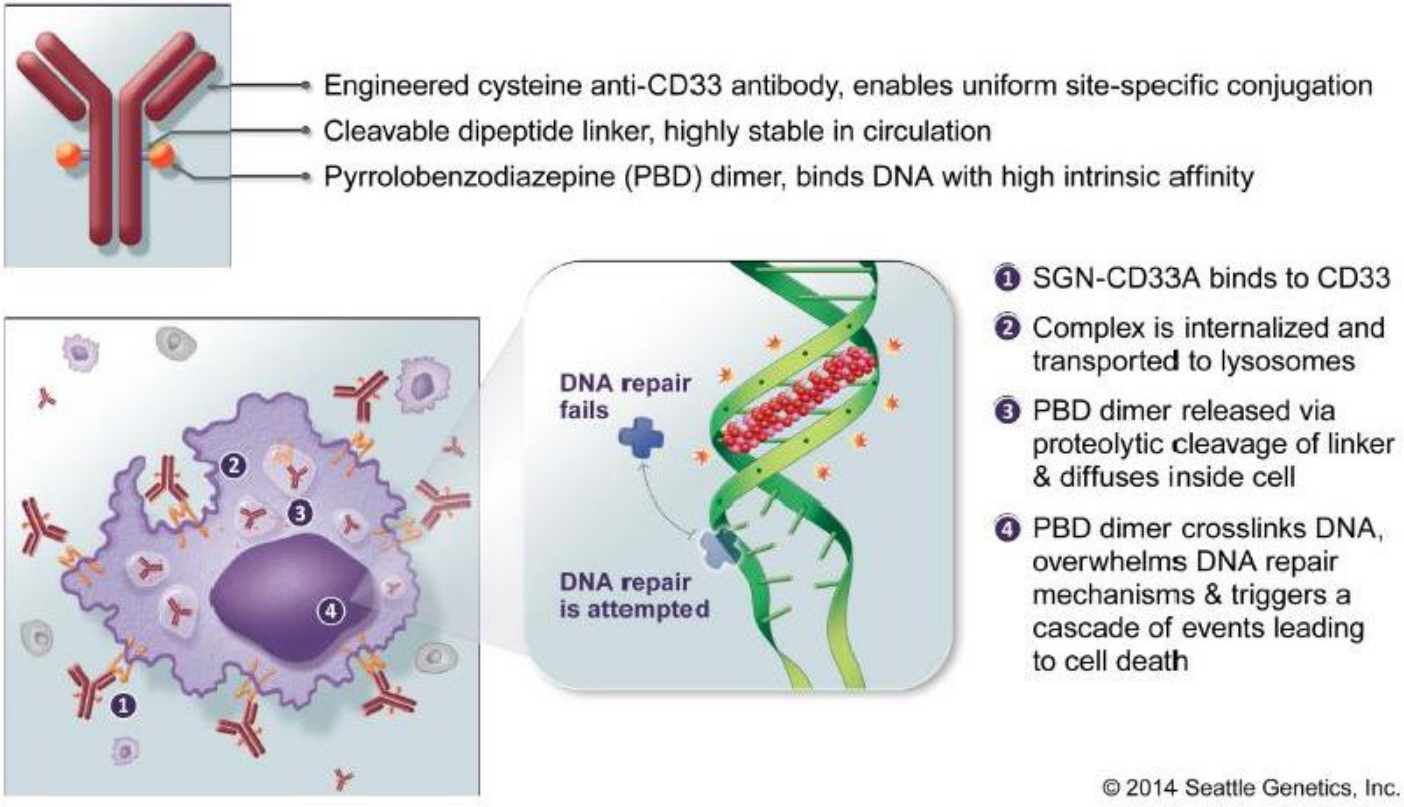
Vosaroxin+DAC in Newly Dx Older AML-MDS: Conclusions

- Vosaroxin plus decitabine CR/CRi = 75%, ≤ 8 wk mortality = 11%.
- 70 mg/m^2 well tolerated; median OS 16.1 mo; 8 wk mortality 5%.
- 42% need more than 1 cycle to response at 70 mg/m^2
- Future Plan:

  Multicenter study of Vosaroxin+DAC vs. Vosaroxin+AraC vs. 3+7 in AML ≥ 60 yrs.

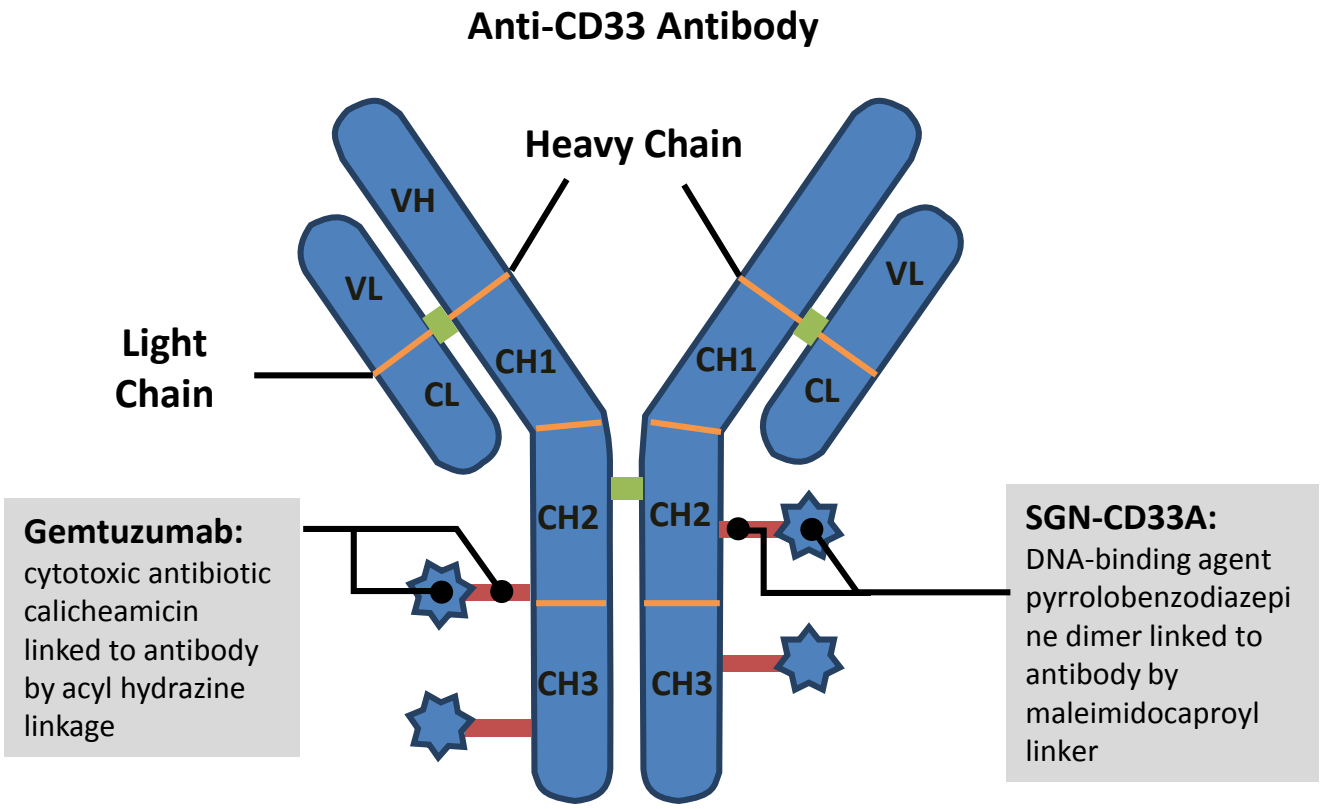
SGN-CD33A in combination with hypomethylating agents: a novel, well-tolerated regimen with high remission rate in older patients with AML

Fathi A et al



Fathi A et al, EHA 2016

SGN-CD33A vs GO: Key differences



SGN-CD33A has more reliable loading of the cytotoxic agent:
~ 2 pyrrolobenzodiazepine dimers per antibody whereas only ~ 50% of the antibodies in clinical-grade gemtuzumab are conjugated to calicheamicin

SGN-CD33A + HMAs: phase 1

Key eligibility criteria

- Untreated CD33+ AML
- Declined IC

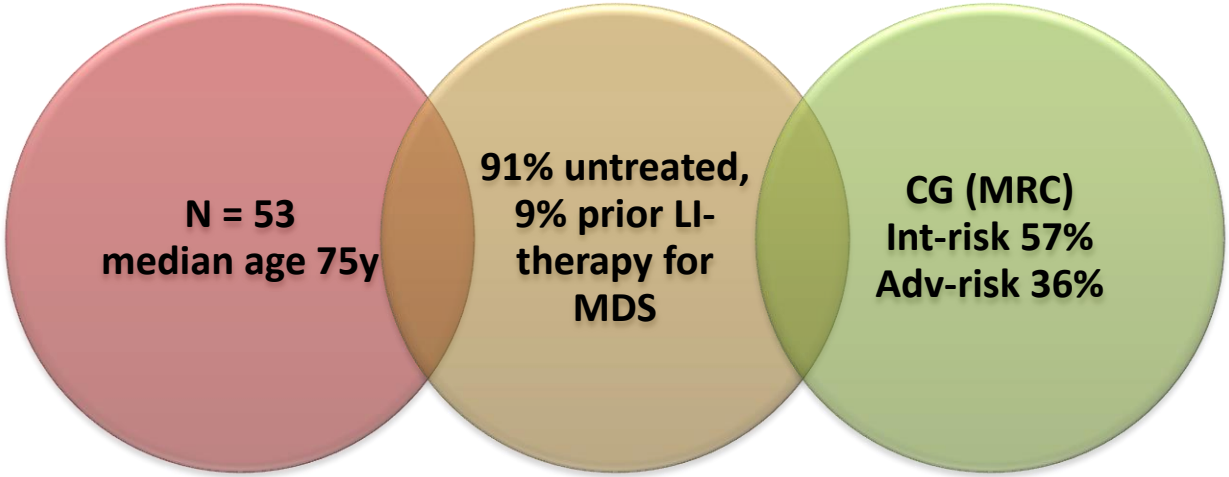
HMA

- AZA (75 x 7) or DAC (20 x 5)

SGN-CD33A

- 10 µg/Kg iv, q 4wks on the last day of HMA

Responders may continue until relapse or toxicity



Fathi A et al, EHA 2016

SGN-CD33A + HMAs: phase 1

Best clinical response per investigator (N=49)

CR+CRi rate	• 71% (AZA 71%, DAC 72%) • Median time to response: 2 cycles (1-4)
Response in HR patients	• Prior MDS: 73% • Adverse CG: 83%
30/60-day mortality	• 2%/8%
MRD by flow	• 42% CR pts, 33% CRi pts
Interim survival data	• Median RFS 7.7 mos (51% alive) • Median OS 12.8 mos (first 25 pts enrolled)
Grade 3-4 TR-AEs	• Febrile neutropenia, thrombocytopenia, anemia, fatigue

New approaches starting to bear fruit…