## Target molecolari e metabolici per la terapia della AML

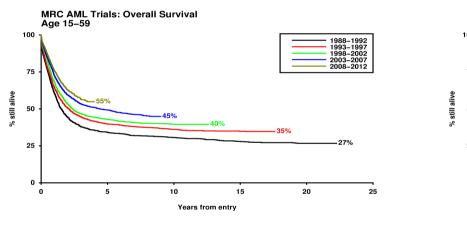
Sergio Amadori
Tor Vergata University Hospital
Roma

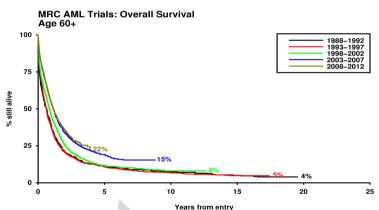


## Survival in AML by time period

#### **Younger patients**

#### **Older patients**





Drug resistance

Major obstacle to cure

## Prospects for improvement

Optimization of current therapy

 Induction, postremission, SCT Drug development

- New cytotoxics
- Targeted therapies

New prognostic factors

Risk-adapted therapy

## **Drug development**

### Protein kinase inhibitors

•FLT3, c-KIT

## Cycle/Signaling inhibitors

•MDM2, PLK, CDK, PI3K, mTOR, PIM

## **Epigenetic** modifiers

•AZA, DAC, SGI-110, HDAC, IDH1/2, BRD4, DOT1L

#### MoAb

•GO, SGN-CD33A, AMG-330, anti-CD123

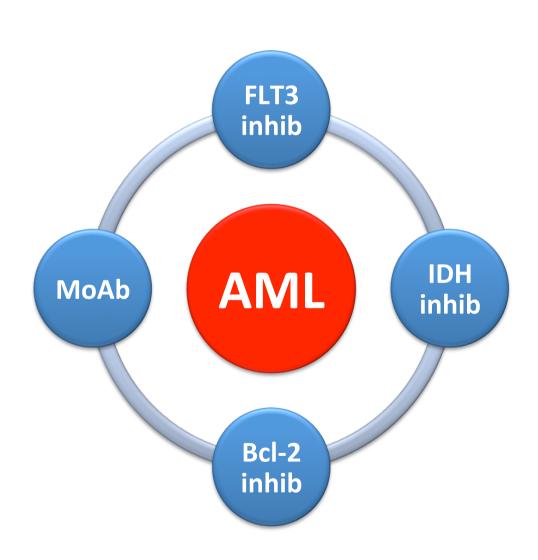
#### **Cytotoxic agents**

 Nucleosid analogs, Vosaroxin, CPX-351 AML

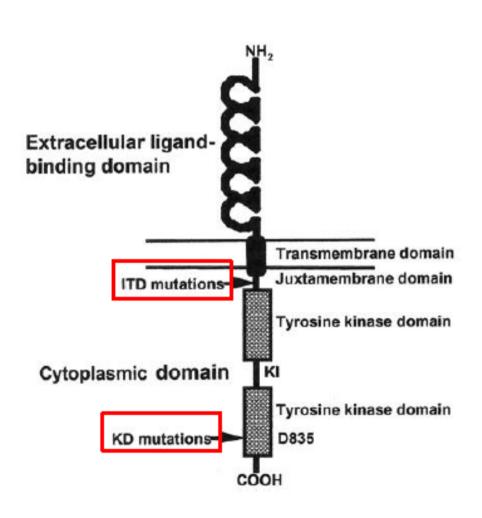
#### **Various**

•Tosedostat, LEN, Bcl-2, Plerixafor, SINEs

## Novel targeted therapies to watch....



## **Targeting FLT3**

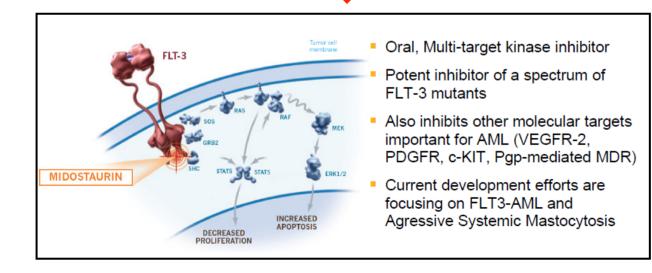


- Occur in 20% of all AML and 28-34% of normal karyotype AML
- Result in constitutive activation of FLT-3 kinase and growth-related signaling pathways
- Internal tandem duplications (ITD) in 25-30%
- Point mutations in the D835 activation loop of the kinase domain (TKD) in 7%

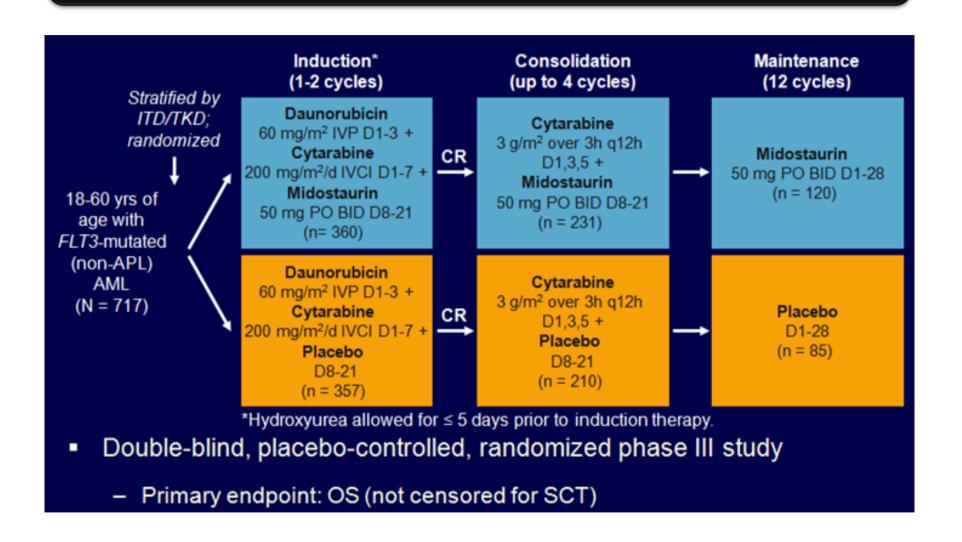
**Poor prognosis** 

## **FLT3** inhibitors

FLT3 inhibitors	Tandutinib	Lestaurtinib	Midostaurin	Sorafenib	Quizartinib	Crenolanib
FLT3 inhibition (IC50, nM)	220	3	<10	58	1.1	0.15
Structure	+ 6		OF STATE OF	orra;	Lycoppus	المرين الم



## **RATIFY: study design**



## Patients, CR rate, Safety

	MIDO (N=360)	PBO (N=357)	p value
Age (years), median (range)	47.1 (19.0-59.8)	48.6 (18.0-60.9)	0.27
Gender			0.045
Female	187 (51.9%)	212 (59.4%)	
Male	173 (48.1%)	145 (40.6%)	
FLT3 Stratification Groups			0.995
FLT3 TKD (No ITD)	81 (22.5%)	81 (22.7%)	
ITD Allelic ratio <0.7 (+/- FLT3 TKD)	171 (47.5%)	170 (47.6%)	
ITD Allelic ratio ≥0.7 (+/- FLT3 TKD)	108 (30.0%)	106 (29.7%)	

	MIDO (N=360)	PBO (N=357)	p *
CR by day 60	212	191	
Rate	59%	53%	0.15
Time to CR, median (range)	35 days (20-60)	35 days (20-60)	
CR in induction/consolidation**	239	211	
Rate	66%	59%	0.045
Time to CR, median (range)	37 days (20-99)	36 days (20-112)	

## Grade 3-4 Non-hematologic AEs, reported during treatment in ≥ 10% of patients

	MIDO	РВО	p *
	% (n= 360)	% (n=357)	
Febrile Neutropenia	81%	82%	0.92
Infection	40%	38%	0.49
Diarrhea	15%	16%	1.00
Hypokalemia	13%	17%	0.17
Pain	13%	13%	0.91
Infection - Other	12%	12%	1.00
ALT, SGPT	12%	9%	0.23
Rash/desquamation	13%	8%	0.02
Fatigue (asthenia, lethargy, malaise)	9%	11%	0.53

#### **Grade 5 AEs during treatment**

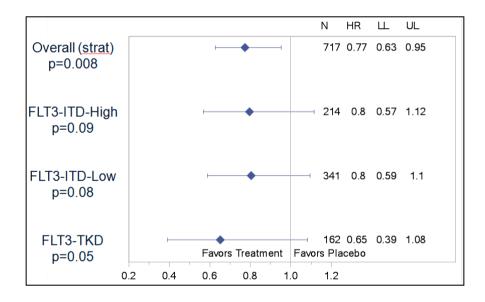
• Mido 5% vs PBO 5.3%

## **Overall Survival**

#### **OS (ITT analysis)**

#### 23% reduced risk of death in the Mido arm 100 4-year Survival 90 51.4% (95%CI: 46, 57) 80 44.2% (95%CI: 39, 50) 70 60 + Censor 40 30 Hazard Ratio\*: 0.77 1-sided log-rank p-value\*: 0.0074 72 time (months) Median OS: Mido 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

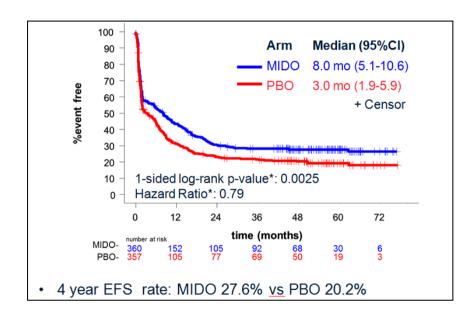
#### OS by FLT3 status

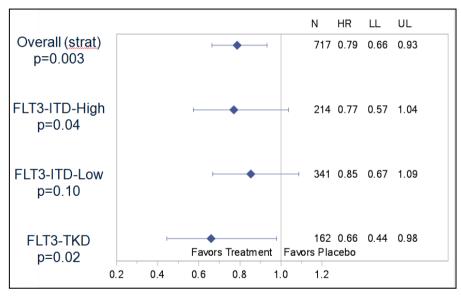


## **Event-free Survival**

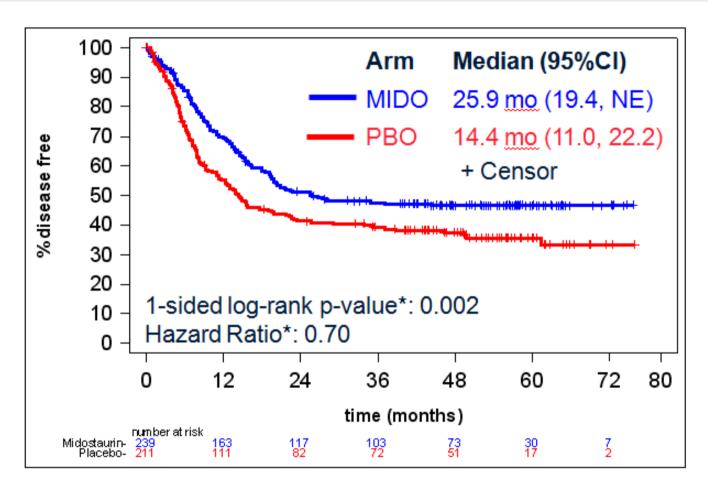
**EFS** 

#### **EFS by FLT3 status**





## **Disease-free Survival**



4 year DFS rate: MIDO 46.4% vs. PBO 37.4%

## **Targeting IDH mutations**

Isocitrate dehydrogenase (IDH)

Critical metabolic enzyme in the citric acid cycle

IDH mutations in AML/MDS

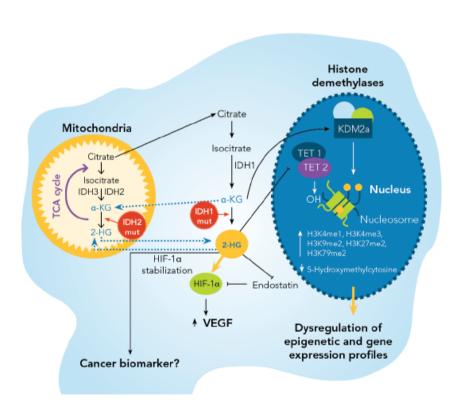
- IDH1m 7.5% AML, 5% MDS
- IDH2m 15% AML, 5% MDS

IDH mutations produce 2-HG

- Increased H+DNA methylation
- Impaired cellular differentiation

**IDHm** inhibitors

- AG-120 (IDH1m)
- AG-221 (IDH2m)



## AG-221: phase 1/2 study

#### **Dose Escalation**

Completed

- Advanced heme malignancies with IDH2 mutation
- Continuous 28 day cycles
- Cumulative daily doses of 50-650 mg

#### **Expansion Phase I**

completed (n=25 pts per arm)

RR-AML age ≥60, or any age if relapsed post-BMT

RR-AML age <60, excluding pts relapsed post-BMT

Untreated AML pts age ≥60 who decline standard of care

Any hematologic malignancy ineligible for other arms

Phase 2
Ongoing

AG-221 100 mg PO QD

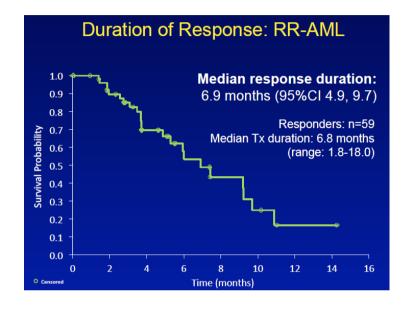
RR-AML (N ≈ 125)

#### **Key Endpoints:**

- Safety, tolerability, MTD, DLTs
- Response rates as assessed by local investigator per IWG criteria
- Assessment of clinical activity

## **Outcomes**

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall Response (CR, CRp, CRi, mCR, PR)	59 (37%)	10 (42%)	7 (50%)	79 (38%)
CR	29 (18%)	4 (17%)	3 (21%)	37 (18%)
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)



Overall response by IDH mutation type: R140Q 36% / R172K 42%

#### **Dose-escalation**

- Highest daily dose 650mg
- Dose-escalation ended, MTD not reached

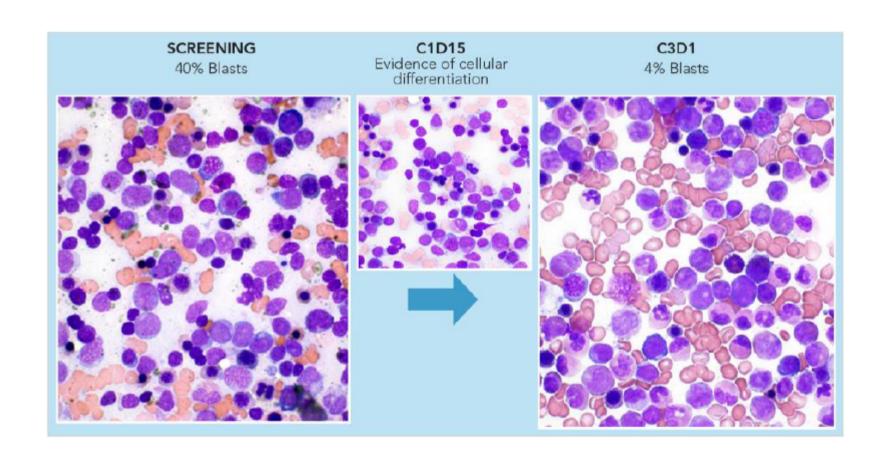
## Durable responses in pts with R/R AML

- ORR 37%
- Median DOR 6.9 mo

#### **Safety**

- 23% of pts had SAEs
- Diff syndrome (4%), leukocytosis (4%), nausea (2%)
- Grade 5: pericardial effusion (2), respiratory failure (1)

## Differentiation effect in the BM



Differentiation syndrome in 4% of pts: manageable with steroids

## **Next Steps**

#### **Combination studies**

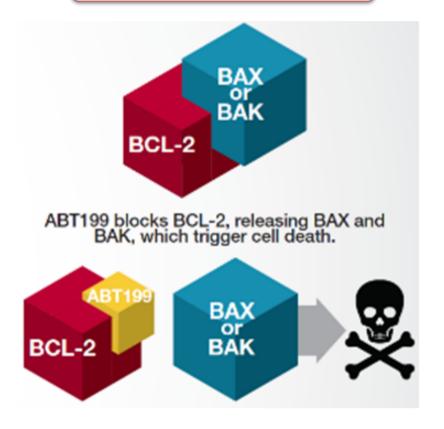
- Induction chemotherapy (ongoing)
- Hypomethylating agents (ongoing)

#### **Maintenance therapy**

- Post-induction/consolid for pts in CR (ongoing)
- Post-transplant

## **Targeting Bcl-2**

**ABT-199 (Venetoclax)** 



## **Bcl-2: a promising therapeutic target in AML**

- Overexpression enhances survival of AML cells
- Associates with poor survival and chemoresistance

## ABT-199: selective, oral Bcl-2 inhibitor

- Single-agent activity in pts with R/R AML
- Preclinical synergy with HMAs and cytarabine

Tzifi F et al, Adv Hematol 2012; Pan R et al, Cancer Discov 2014; Tsao T et al, Ann Hematol 2012; Konopleva M et al, Cancer Discov 2016

## **VEN+HMA** in elderly AML

## Open-label, nonrandomized, 2-arm, 2-stage phase lb study

Pats with untreated AML, 65 yrs of age or older, adverse or intermediate-risk cytogenetics, ineligible for standard induction therapy

(N = 34)

Safety, PK, dose finding

Venetoclax\* + Decitabine 20 mg/m² Days 1-5, IV 28-day cycles (n = 18)

Venetoclax\* + Azacitidine 75 mg/m² Days 1-7, IV/SC 28-day cycles (n = 16)

\*In each arm, 1 cohort received venetoclax 400 mg and 2 cohorts received 800 mg.

Expansion stage: safety and efficacy confirmation

1 HMA

combo

(RP2D)

Venetoclax + HMA (n = 40)

- Endpoints
  - Safety: MTD, DLTs, RP2D, AEs, early deaths, PK
  - Efficacy: ORR per IWG AML criteria, response duration, TTP, PFS, OS, MRD (assessed after cycles 1 and 4, then every 12 weeks)
  - Exploratory: mutational profiling and BCL-2 characterization, molecular markers, ex vivo testing of pt samples

## **Outcomes**



Response, n (%)	Venclexta + decitabine (n=23)	Venclexta + azacitidine (n=22)	Total (n=45)	
ORR	16 (70)	12 (55)	28 (62)	
CR/CRi	15 (65)	12 (55)	27 (60)	
CR	5 (22)	7 (32)	12 (27)	
CRi	10 (44)	5 (23)	15 (33)	
PR	1 (4)	0 (0)	1 (2)	

# The state of the s

"Patients non-evaluable, did not complete cycle 1

#### Phase Ib results

- · 90% of patients achieved significant reduction in bone marrow blast counts
- · ORR of 62% taking both hypomethylating agent combinations together
- Tolerable safety profile for treatment-naive chemo-unfit patients aged ≥65y
- Safety expansion with both hypomethylating agents at 2 Venclexta doses ongoing (n=100)

Median time to CR/CRi 30 days; 4 relapses

6 deaths <30d of last VEN dose (3 PD, 3 infect)

**Grade 3-4 febrile neutropenia** 

## **VEN+LDAC** in elderly AML

Phase lb/II dose escalation/expansion study

Treatment-naive AML
pts aged 65 yrs or
older who are
ineligible for
standard induction;
ECOG PS 0-2
(N = 68)

Venetoclax QD\* + LDAC 20 mg/m² D1-10 28-day cycles (n = 18)

Phase I (3 + 3 design)

Phase II

Venetoclax 600 mg QD + LDAC 20 mg/m<sup>2</sup> D1-10 28-day cycles (n = 50)

\*Venetoclax dosing phase lb: dose escalation to 600 or 800 mg daily

- Started 24 hrs after LDAC; escalated to target dose from 50 mg/day over first 6 days of cycle 1
- Phase I objectives
  - Safety, pharmacokinetics, MTD, determine recommended phase II dose
  - Efficacy, response rates, DoR, OS
  - Exploratory biomarker analyses



## Outcomes

Response, n (%)	Venclexta + LDAC All patients (n=26)	Venclexta + LDAC Patients with no prior MPN (n=22)	Venclexta + LDAC Patients with no prior HMA (n=21)
ORR	15 (58)	15 (68)	13 (62)
CR/CRi	14 (54)	14 (64)	12 (57)
CR	6 (23)		
CRi	8 (31)		
PR	1 (4)		
BM blast count < 5%	21 (81)		

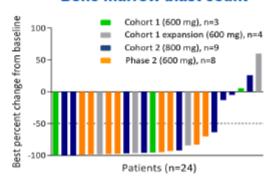
#### Phase Ib results

- Majority of patients achieved significant reduction in BM and peripheral blast counts
- · ORR of 68% in patients with not prior MPN
- Combination demonstrates a tolerable safety profile for treatment-naive chemo-unfit patients aged ≥65y
- Ph2 expansion on-going (n=50)

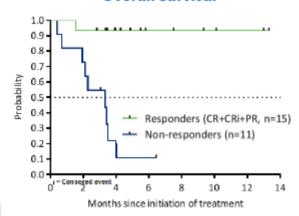
Median OS: 4 mos (non-resp) vs NR (resp)

**Grade 3-4 febrile neutropenia** 

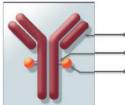
#### Bone marrow blast count



#### Overall survival

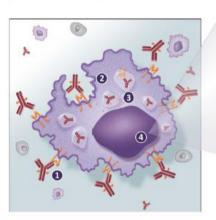


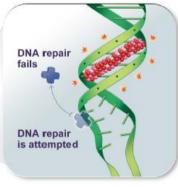
## **Targeting CD33: SGN-CD33A**



Engineered cysteine anti-CD33 antibody, enables uniform site-specific conjugation
Cleavable dipeptide linker, highly stable in circulation

Pyrrolobenzodiazepine (PBD) dimer, binds DNA with high intrinsic affinity





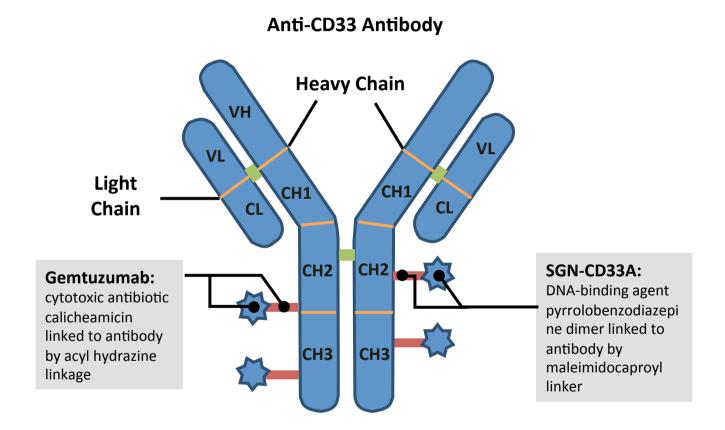
- SGN-CD33A binds to CD33
- ② Complex is internalized and transported to lysosomes
- PBD dimer released via proteolytic cleavage of linker & diffuses inside cell
- PBD dimer crosslinks DNA, overwhelms DNA repair mechanisms & triggers a cascade of events leading to cell death

© 2014 Seattle Genetics, Inc.

Phase 1	

Trial	Pt Population	N	Treatment	Results
Cohort 1 <sup>[1]</sup>	CD33+AML with relapse or declined conventional induction/consolid ation	93	Vadastuximab talirine	<ul> <li>27% overall CR/CRi</li> <li>41% CR/CRi with 40 μg/kg dose</li> <li>58% CR/CRi in tx-naive pts with 40 μg/kg dose</li> <li>75% CR/CRi in patients with NPM1+/FLT3-</li> <li>Most common AEs: febrile neutropenia, fatigue, thrombocytopenia, anemia</li> </ul>

## 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)

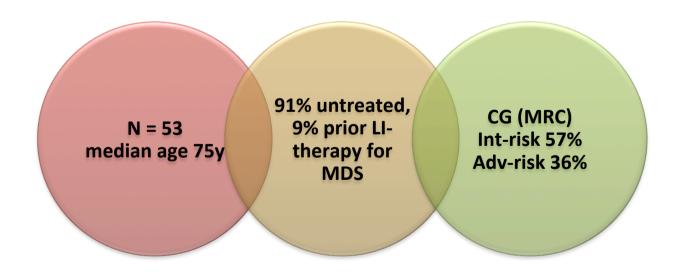


#### SGN-CD33A

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



Responders may continue until relapse or toxicity



## 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...

