Target molecolari e metabolici per la terapia della AML

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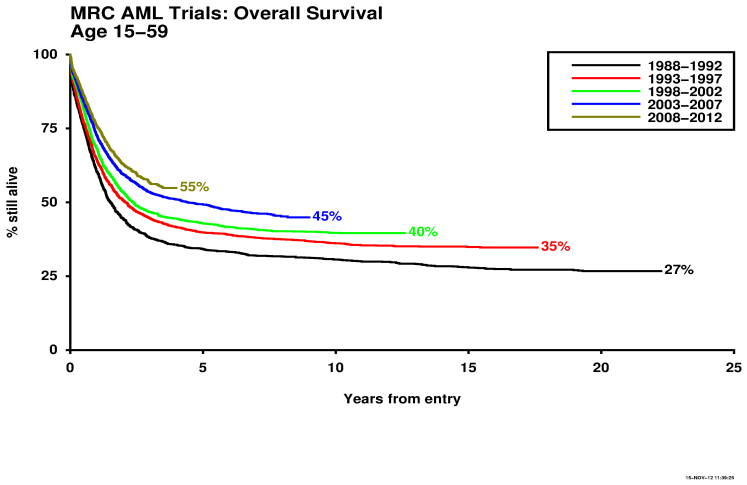
FONDAZIONE PTV
POLICLINICO TOR VERGATA

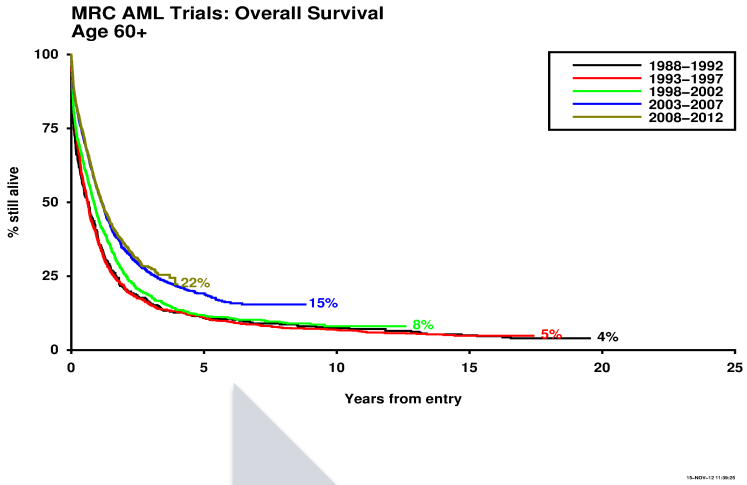
Bari, 10/2016

Survival in AML by time period

Younger patients



Older patients

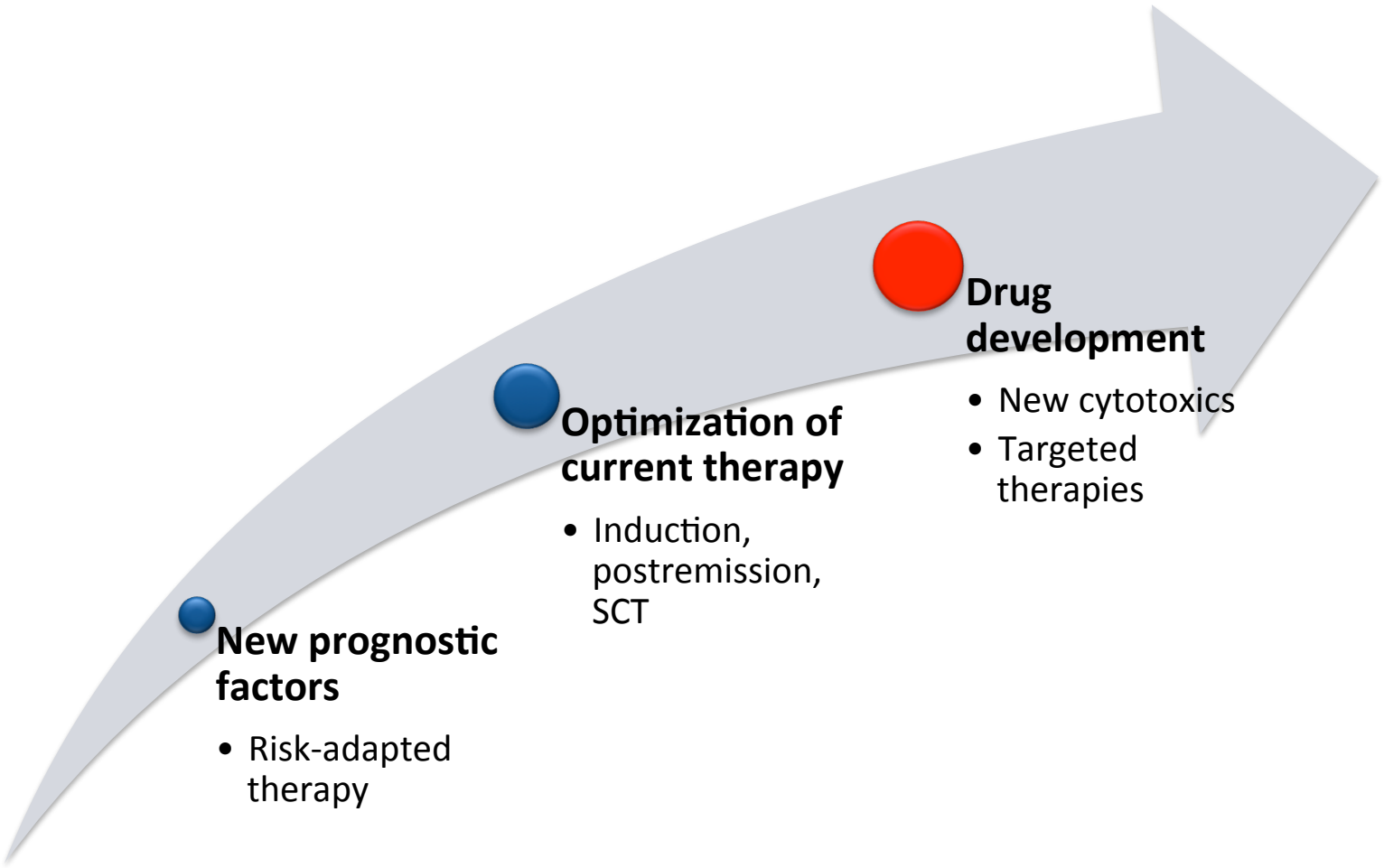


Drug resistance

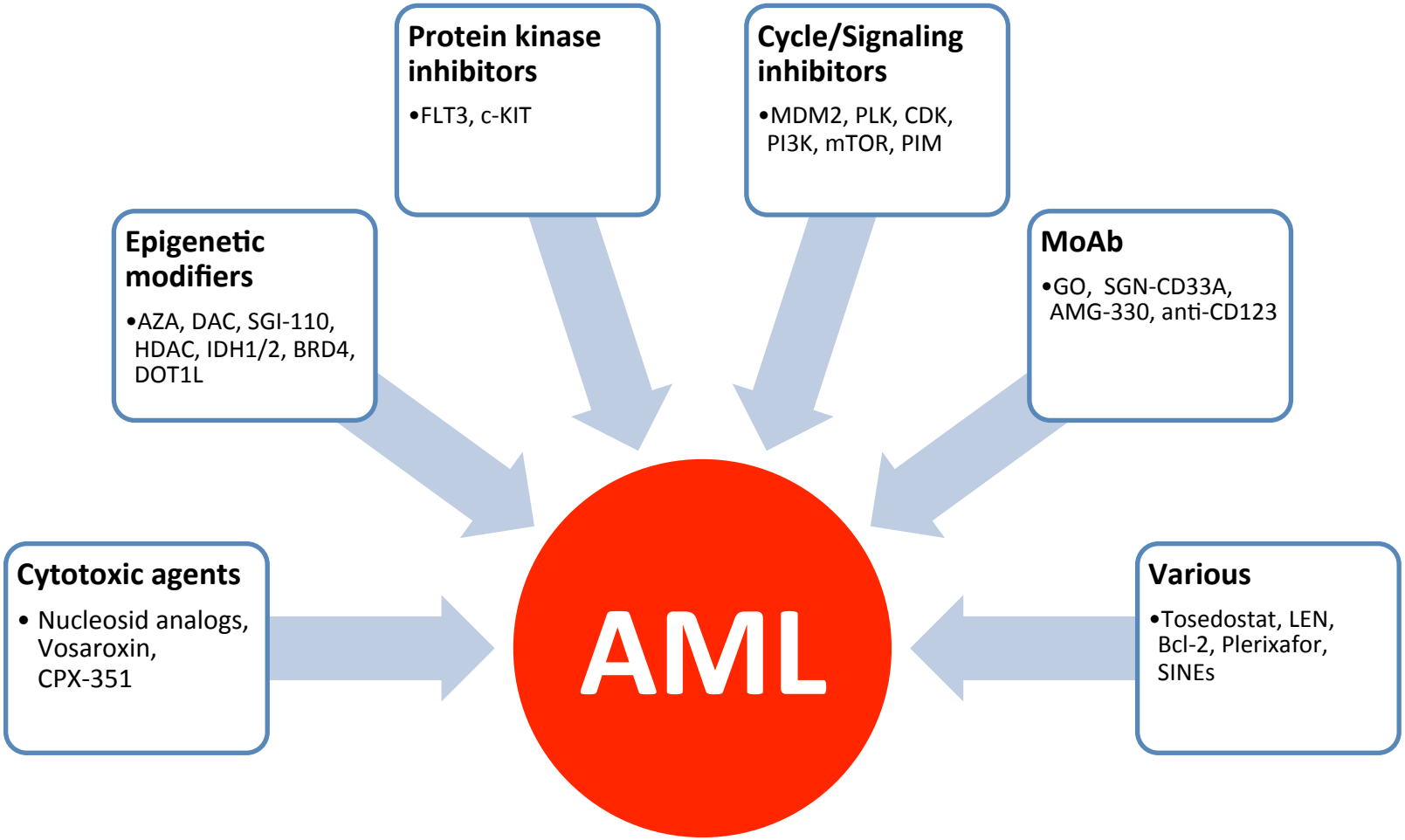
Major obstacle to cure

Burnett AK, ASH 2012

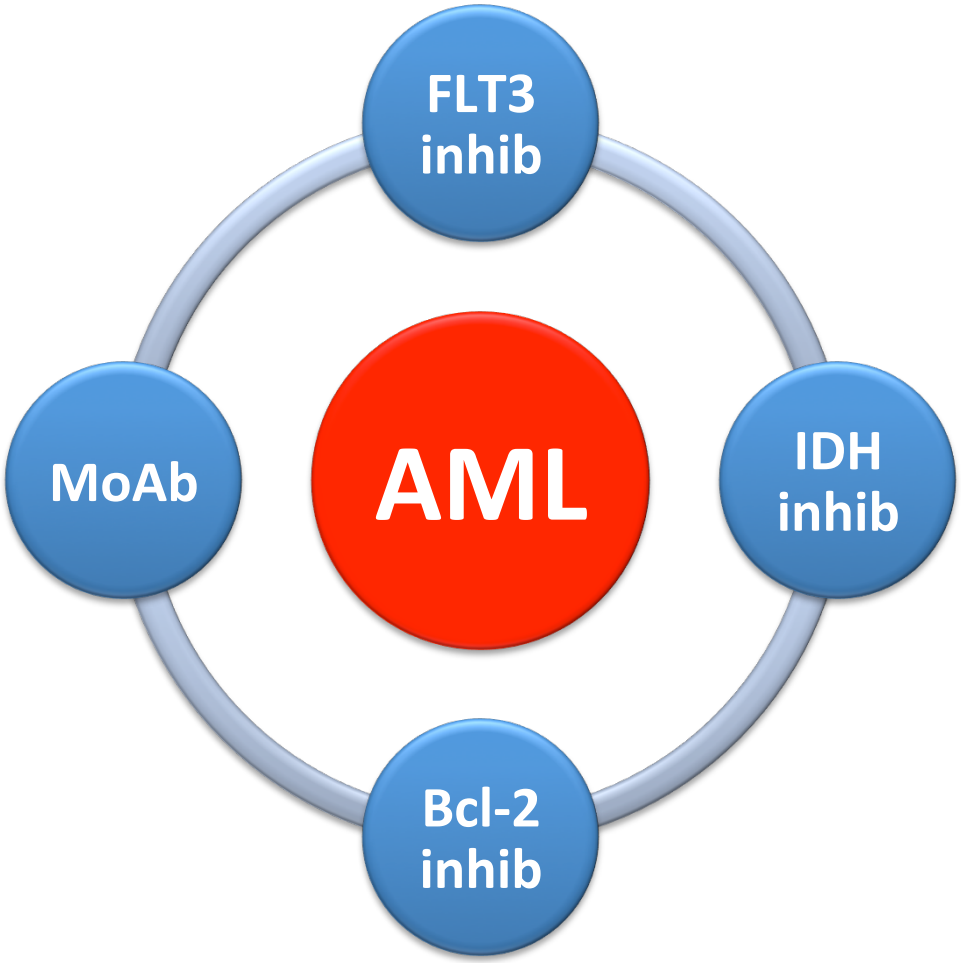
Prospects for improvement



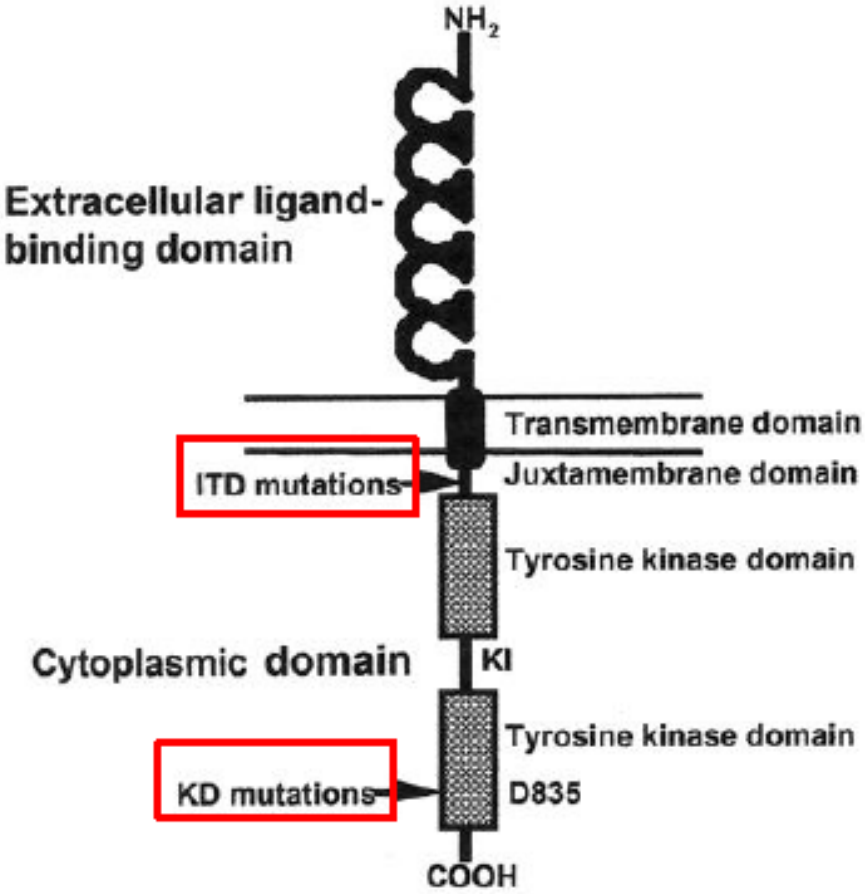
Drug development



Novel targeted therapies to watch….



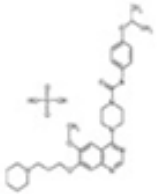
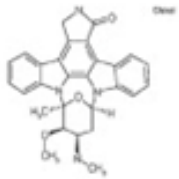
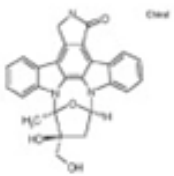
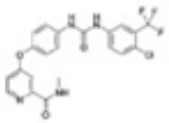
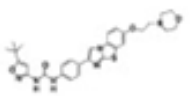
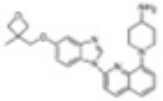
Targeting FLT3

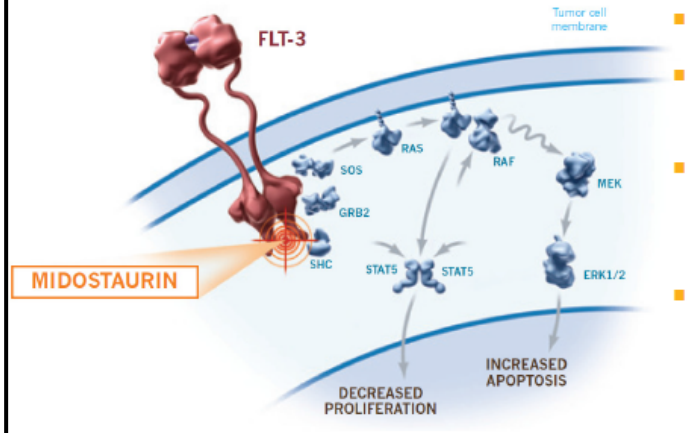


- Occur in **20% of all AML** and 28-34% of normal karyotype AML
- Result in constitutive activation of FLT-3 kinase and growth-related signaling pathways
- Internal tandem duplications (ITD) in 25-30%
- Point mutations in the D835 activation loop of the kinase domain (TKD) in 7%

Poor prognosis

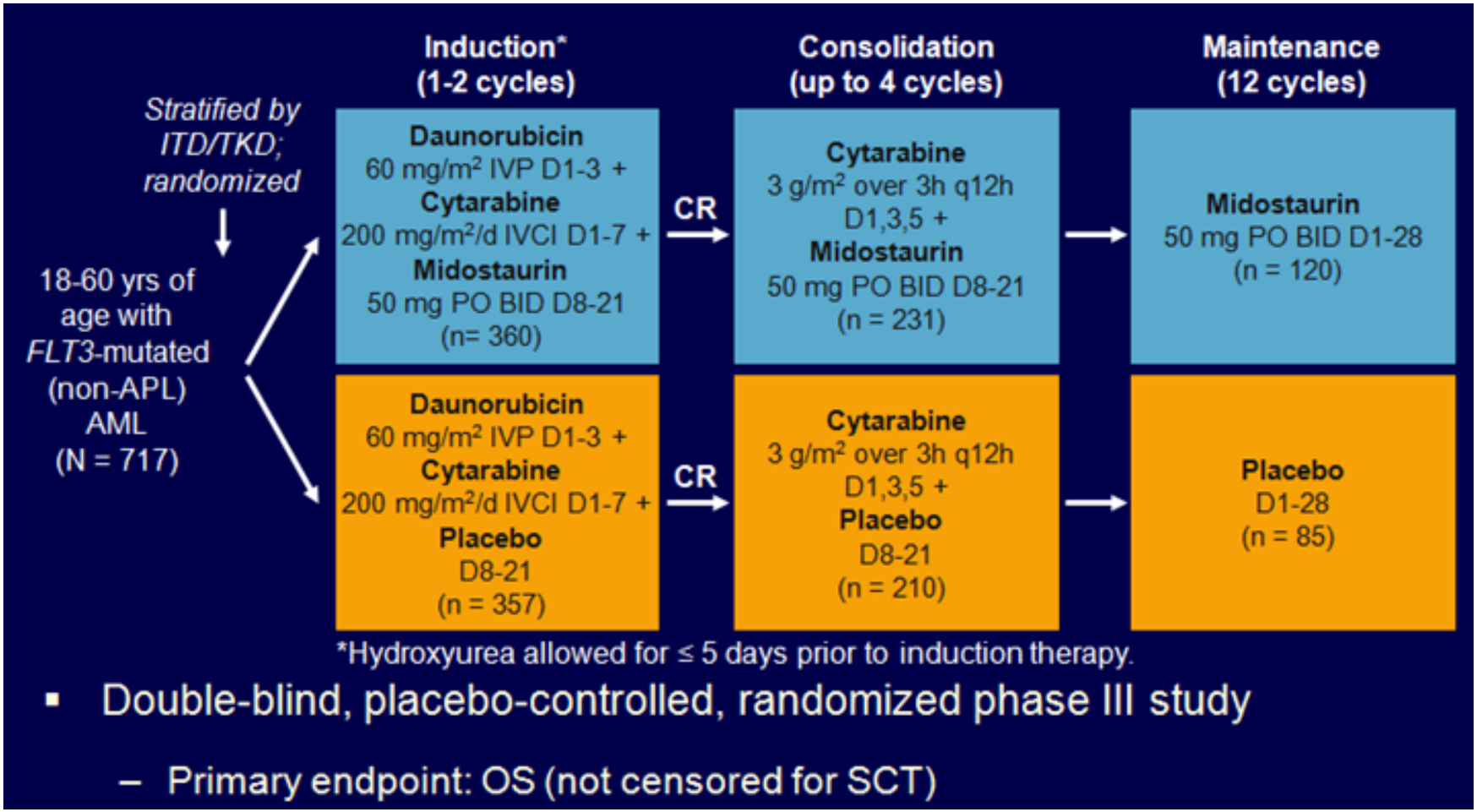
FLT3 inhibitors

FLT3 inhibitors	Tandutinib	Lestaurtinib	Midostaurin	Sorafenib	Quizartinib	Crenolanib
FLT3 inhibition (IC50, nM)	220	3	<10	58	1.1	0.15
Structure						



- Oral, Multi-target kinase inhibitor
- Potent inhibitor of a spectrum of FLT-3 mutants
- Also inhibits other molecular targets important for AML (VEGFR-2, PDGFR, c-KIT, Pgp-mediated MDR)
- Current development efforts are focusing on FLT3-AML and Agressive Systemic Mastocytosis

RATIFY: study design



Stone RM et al, ASH 2015

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

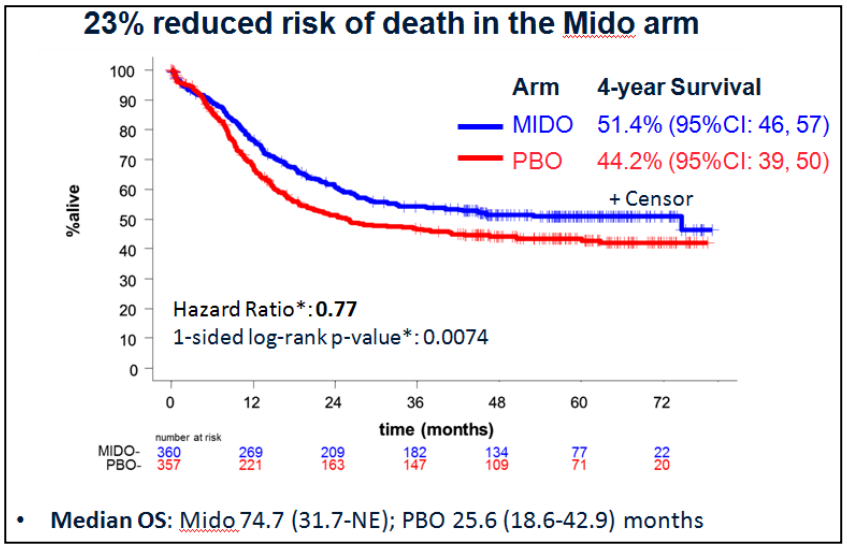
	MIDO	PBO	p *
	% (n= 360)	% (n=357)	
Febrile Neutropenia	81%	82%	0.92
Infection	40%	38%	0.49
Diarrhea	15%	16%	1.00
Hypokalemia	13%	17%	0.17
Pain	13%	13%	0.91
Infection - Other	12%	12%	1.00
ALT, SGPT	12%	9%	0.23
Rash/desquamation	13%	8%	0.02
Fatigue (asthenia, lethargy, malaise)	9%	11%	0.53

Grade 5 AEs during treatment

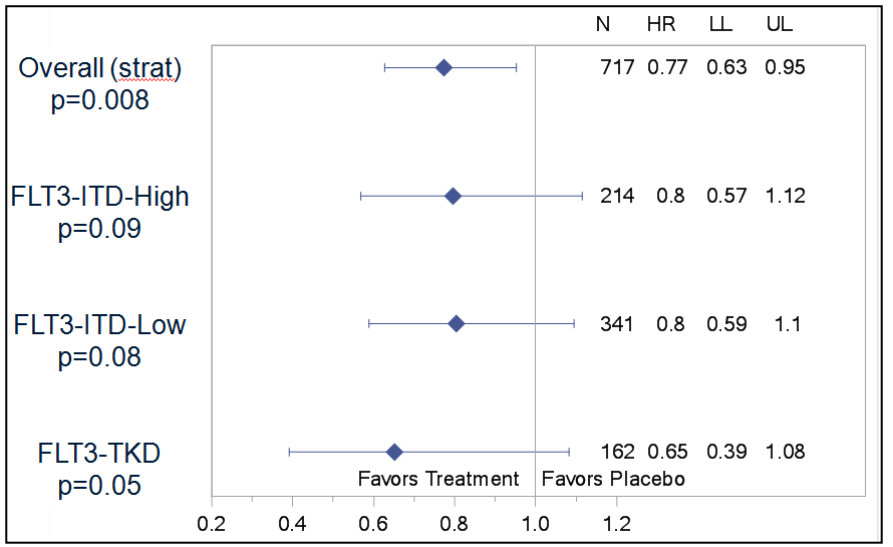
- Mido 5% vs PBO 5.3%

Overall Survival

OS (ITT analysis)

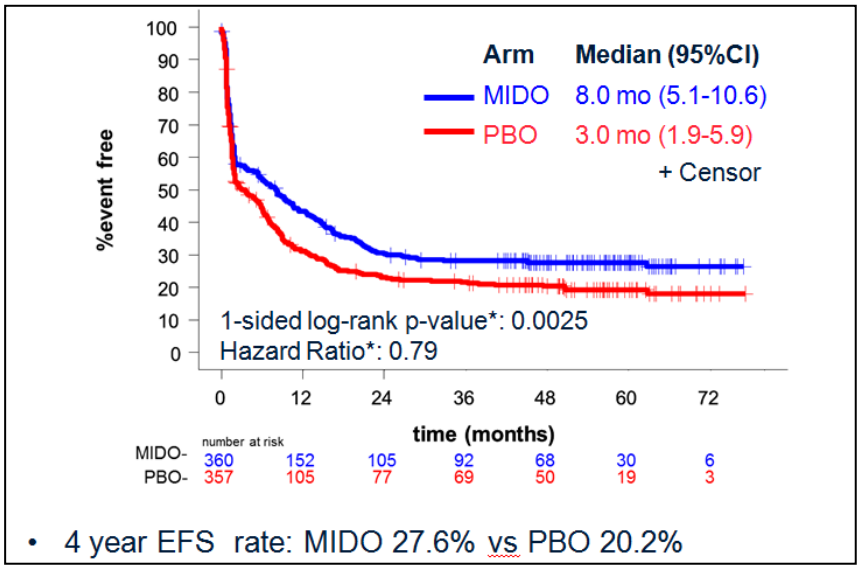


OS by FLT3 status



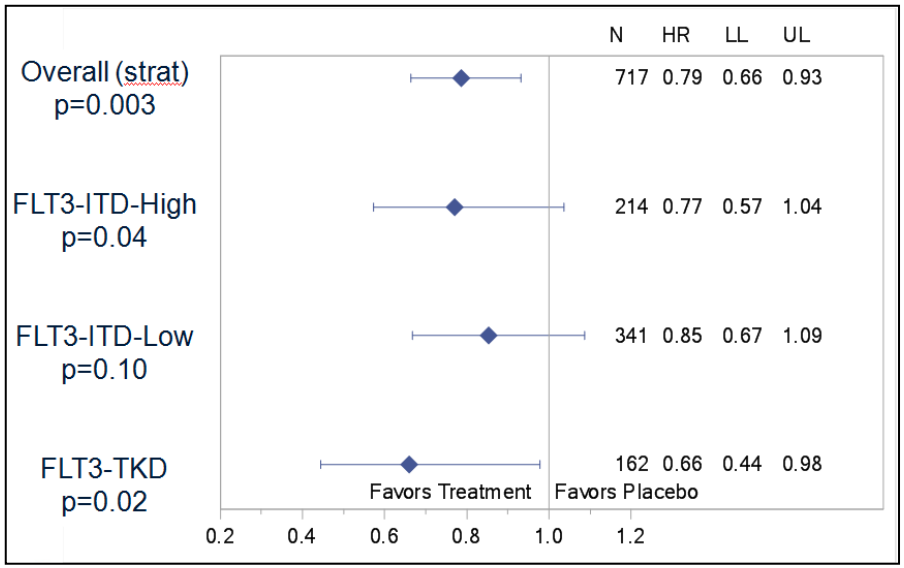
Event-free Survival

EFS

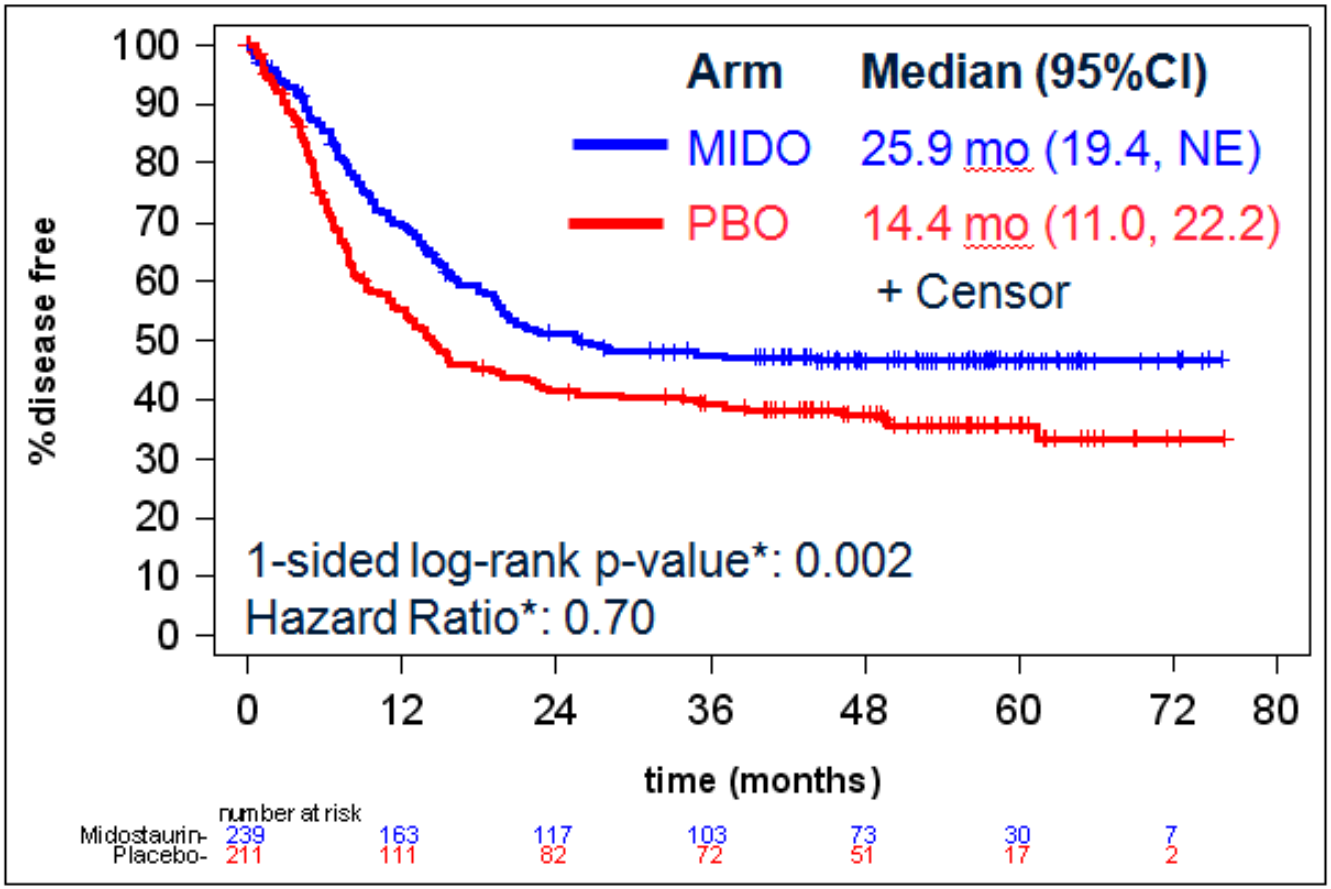


- 4 year EFS rate: MIDO 27.6% vs PBO 20.2%

EFS by FLT3 status



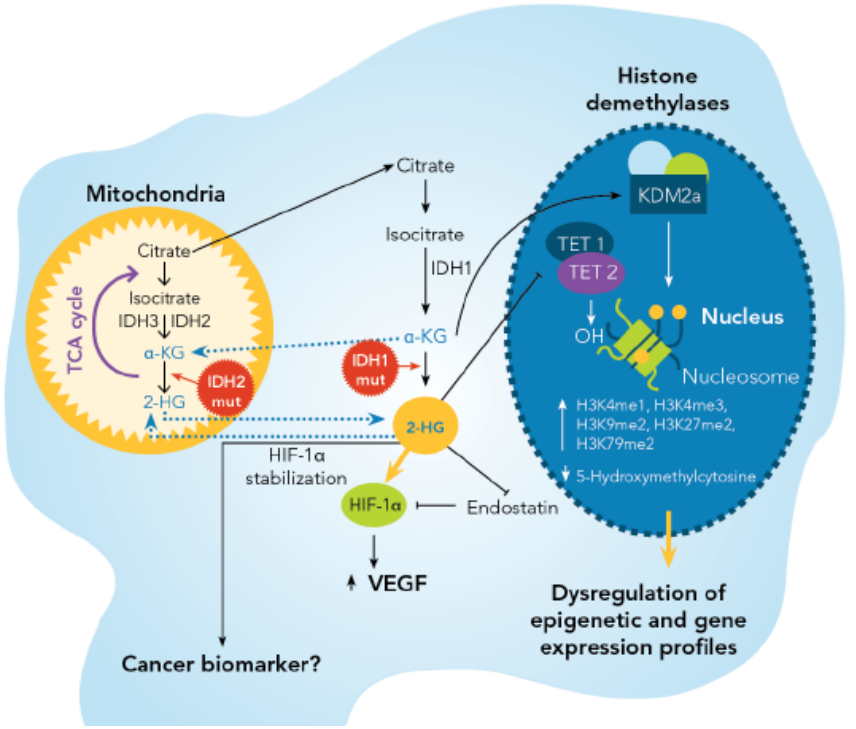
Disease-free Survival



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

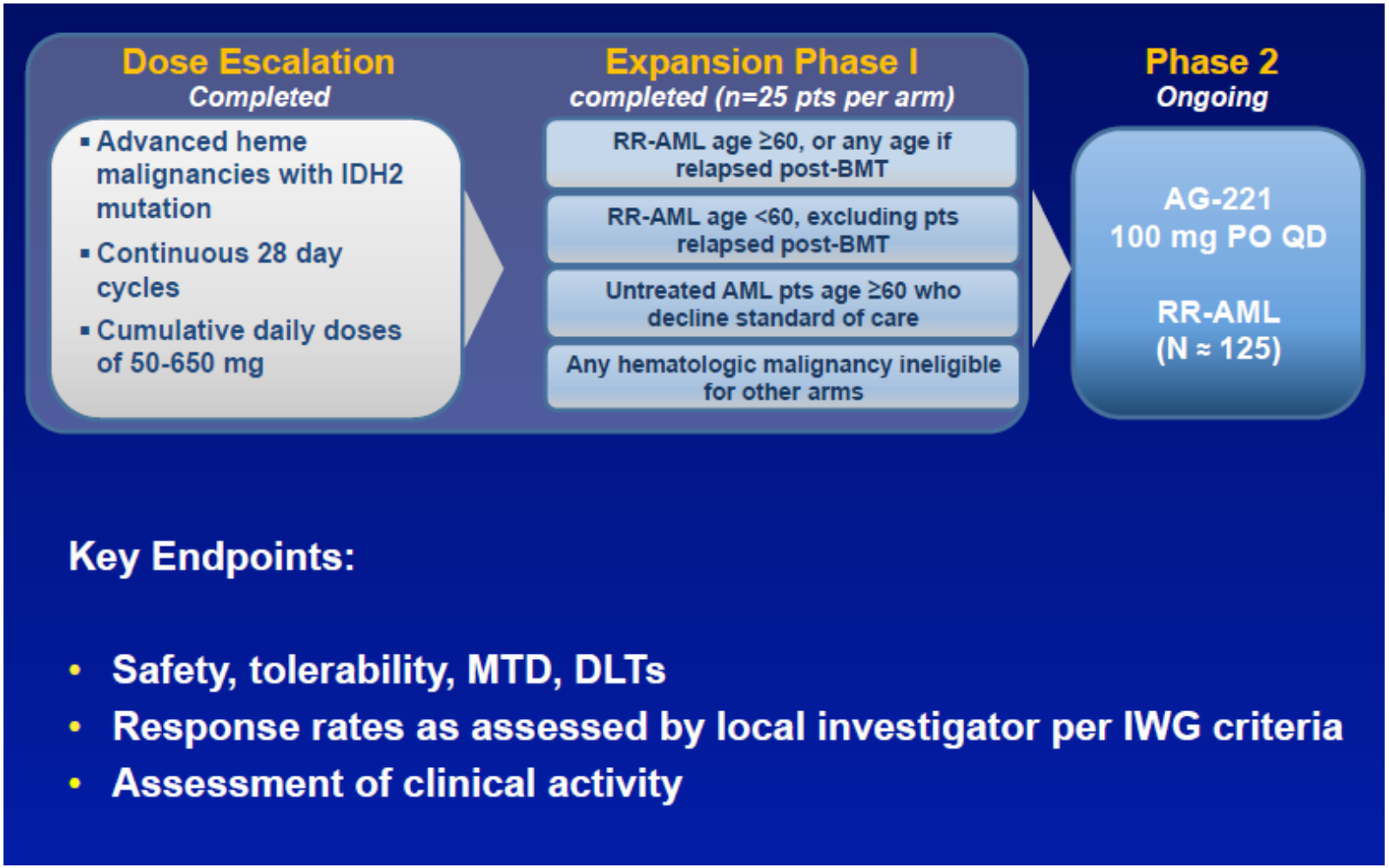
Targeting IDH mutations

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)



Prensner JR and Chinnaiyan AM, Nature 2011

AG-221: phase 1/2 study

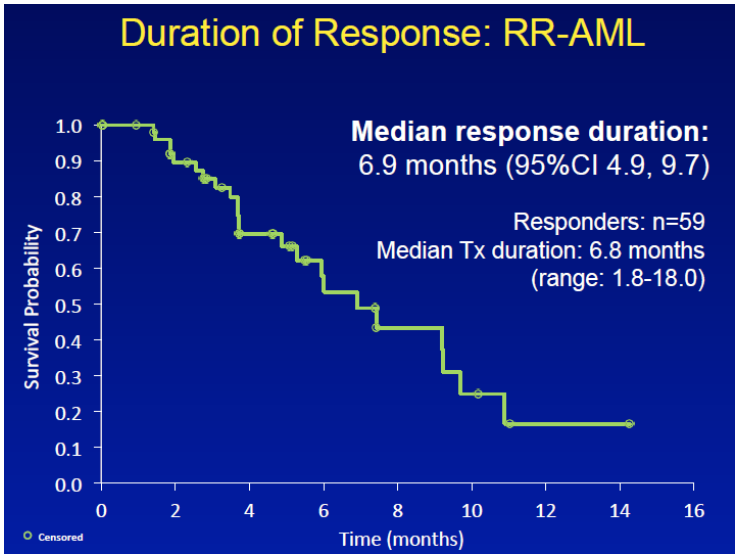


Stein EM et al, ASH 2015

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

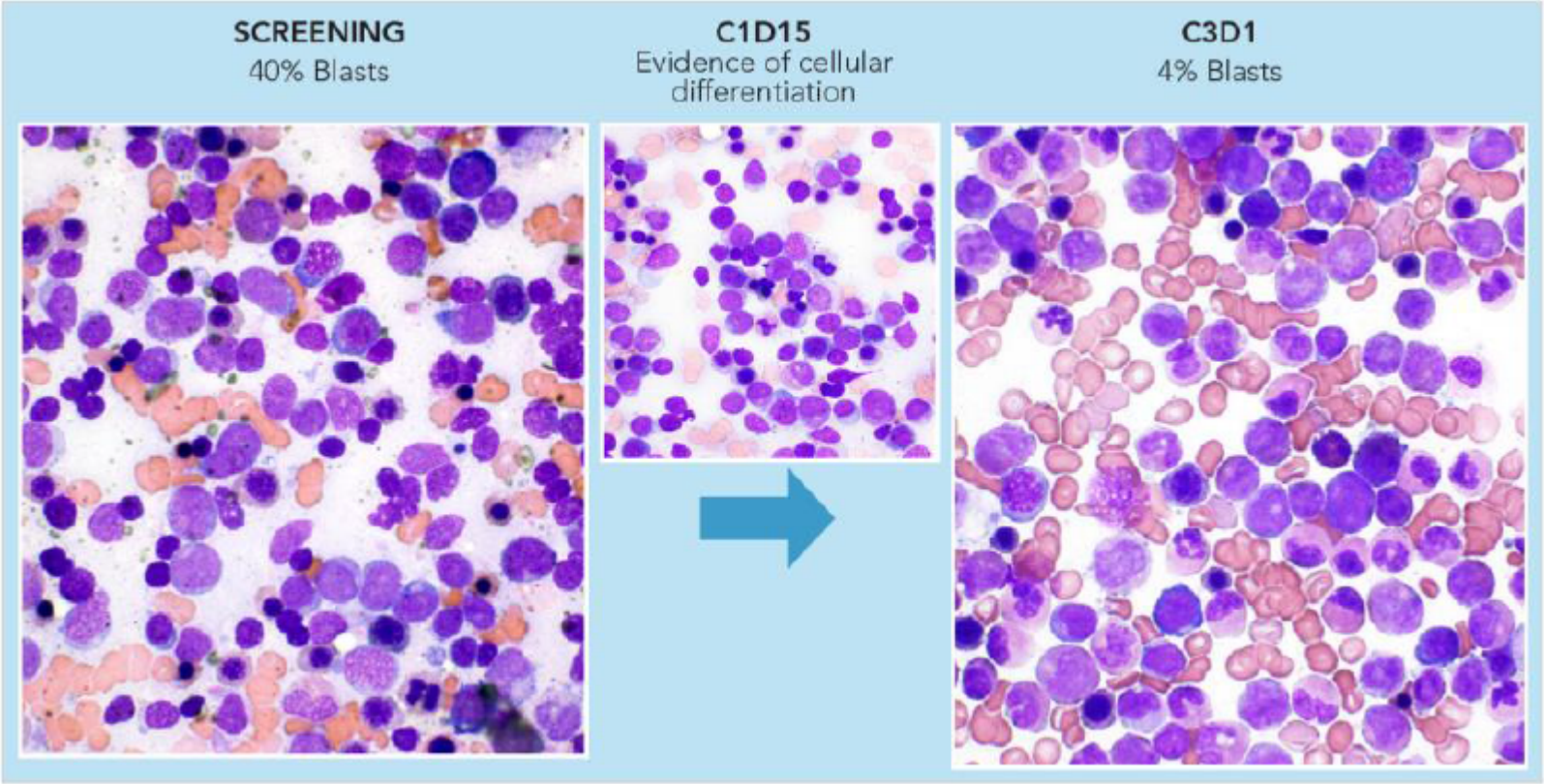
Durable responses in pts with R/R AML

- 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

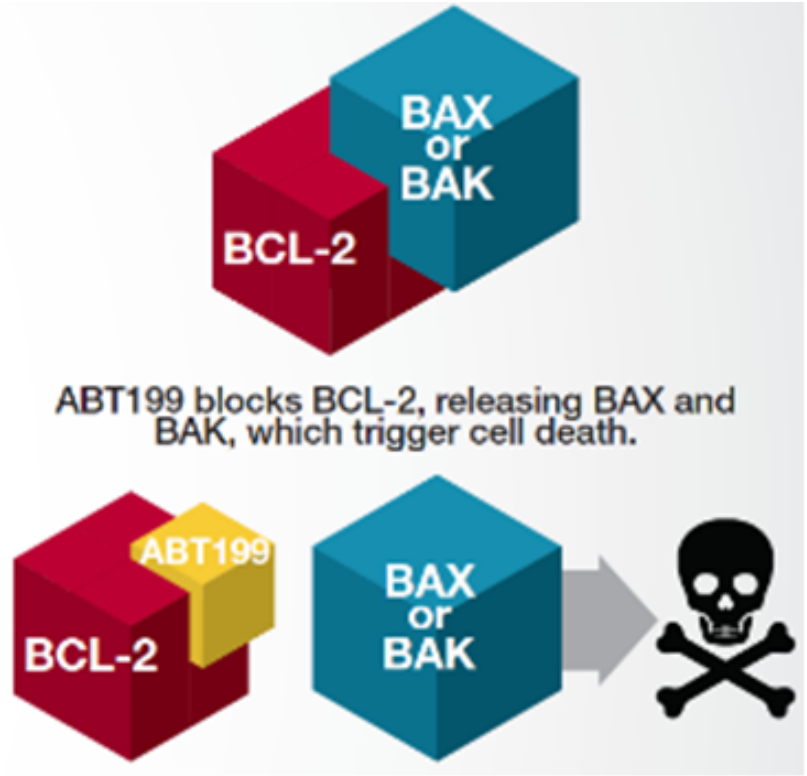
- Induction chemotherapy (ongoing)
- Hypomethylating agents (ongoing)

Maintenance therapy

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

Targeting Bcl-2

ABT-199 (Venetoclax)



Souers A et al, Nat Med 2013

Bcl-2: a promising therapeutic target in AML

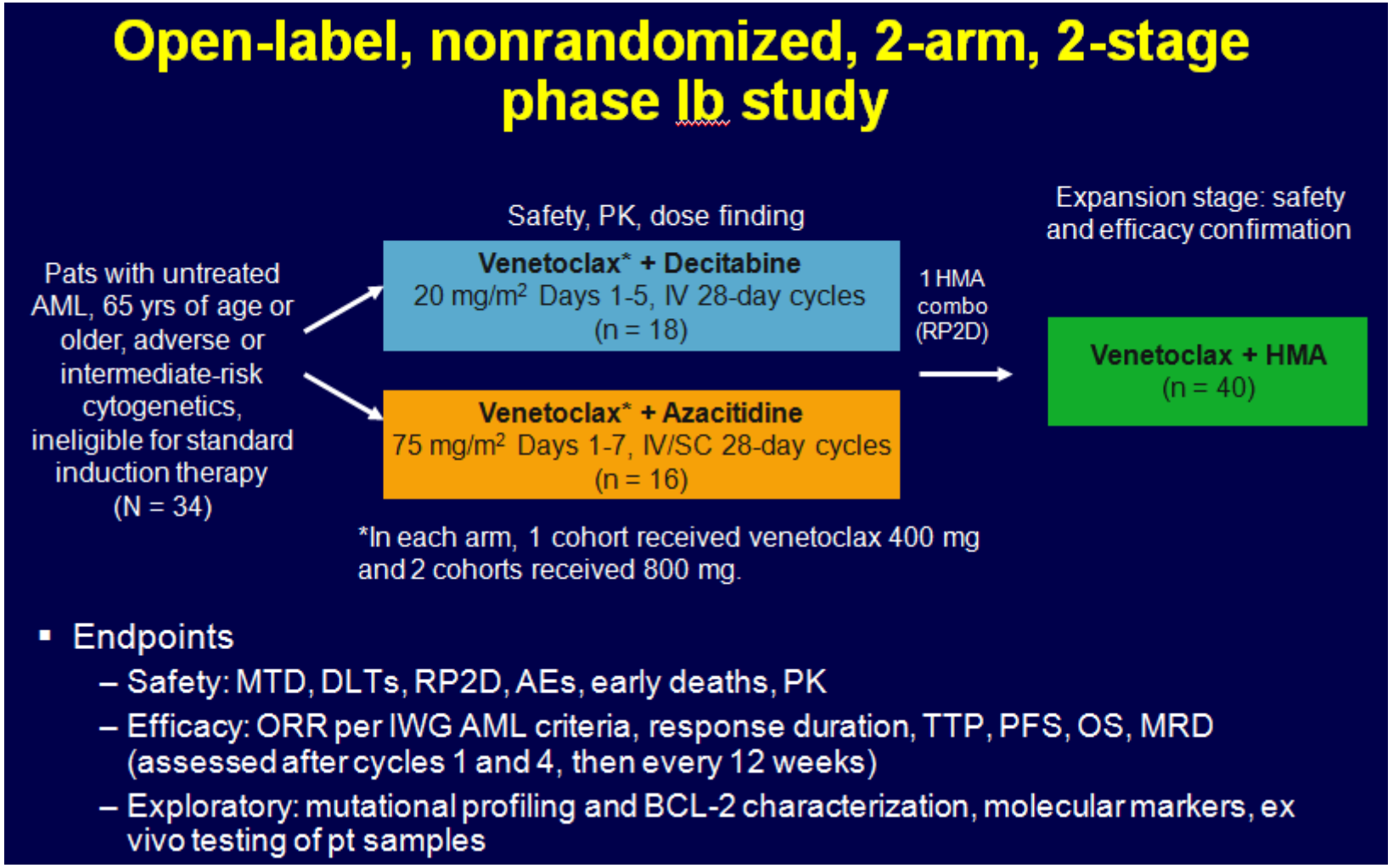
- Overexpression enhances survival of AML cells
- Associates with poor survival and chemoresistance

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



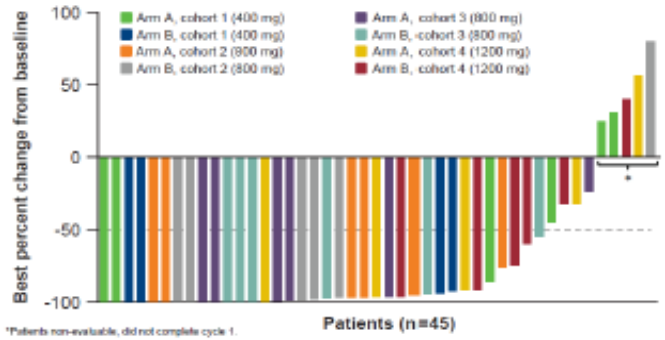
Pollyea D et al, ASCO 2016

Outcomes

FDA BTD

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)

Bone marrow blast count



*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 Ib/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)

Phase I (3 + 3 design)

Venetoclax QD* + **LDAC** 20 mg/m^2 D1-10 28-day cycles (n = 18)

Phase II

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

*Venetoclax dosing phase Ib: 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

Li TL et al, ASCO 2016

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)		

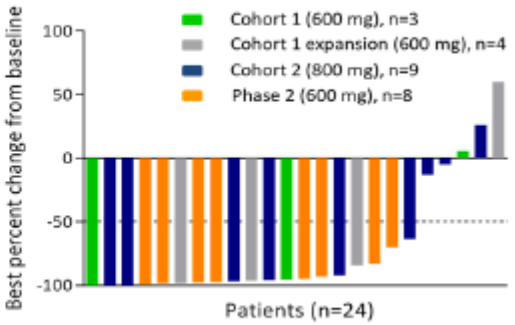
Phase Ib results

- 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)

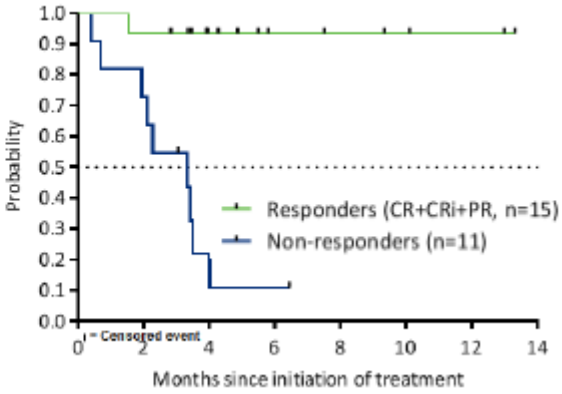
Median OS: 4 mos (non-resp) vs NR (resp)

Grade 3-4 febrile neutropenia

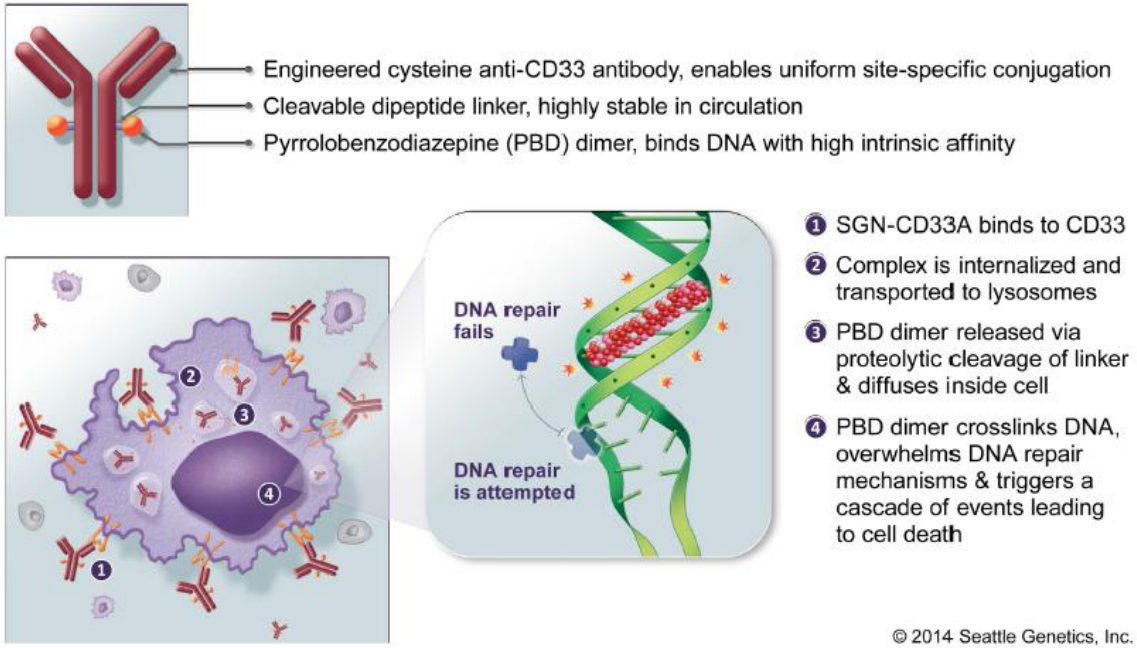
Bone marrow blast count



Overall survival



Targeting CD33: SGN-CD33A

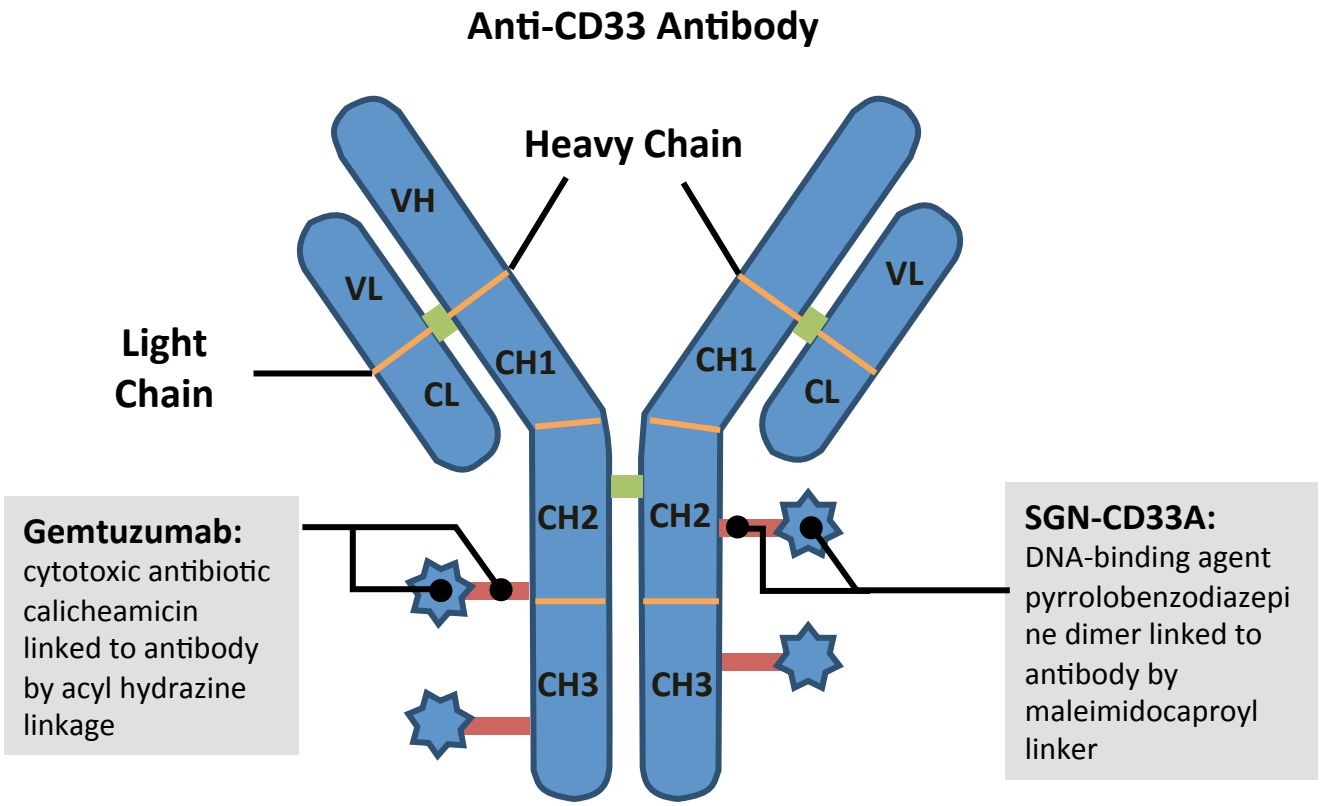


Phase 1

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

Stein A et al, ASH 2015

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

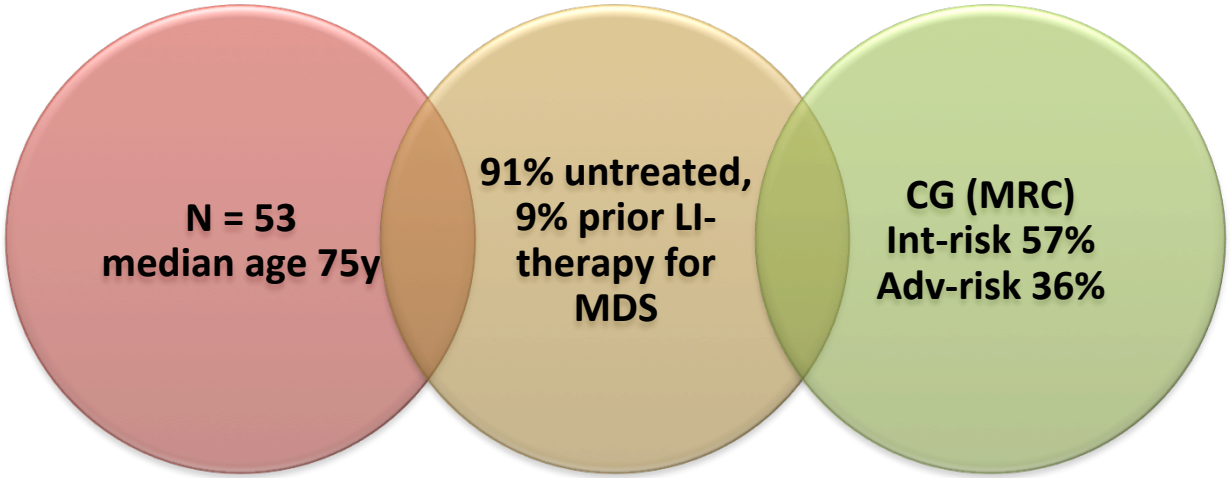
SGN-CD33A + HMAs: phase 1

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…