Antibody-driven therapy of AML

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Roma, 09/2017

Disclosures of SERGIO AMADORI

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						X	
Celgene						X	
Daiichi-Sankyo						X	
Janssen						X	
Novartis						X	

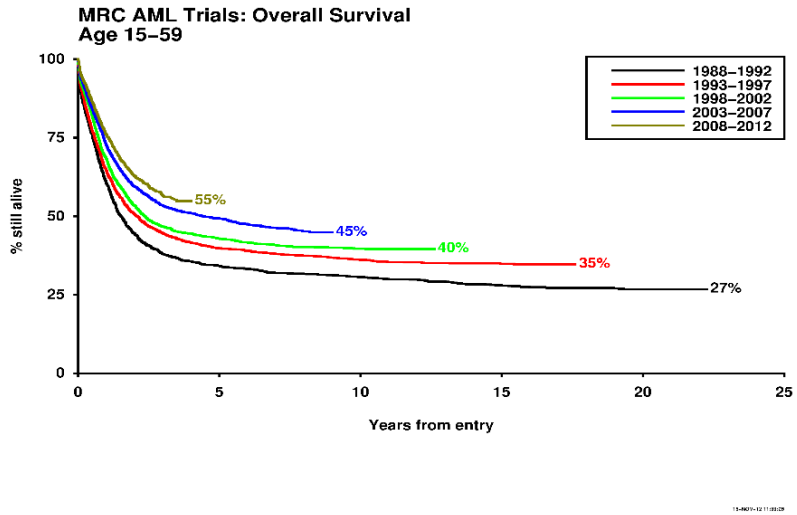
Why do we need antibody therapy in AML?

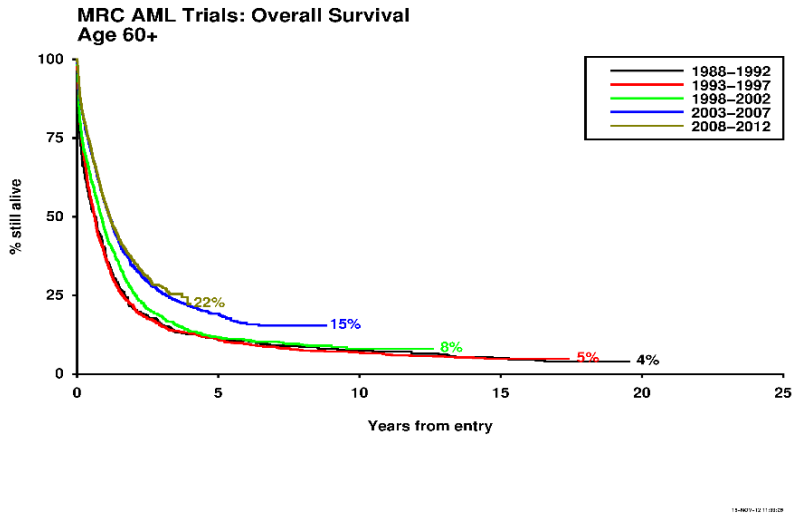
Heterogenous disease with poor outcomes, particularly in older patients

Conventional treatment has largely remained unchanged for decades

Drug resistance major obstacle to cure

Novel therapeutic approaches are needed





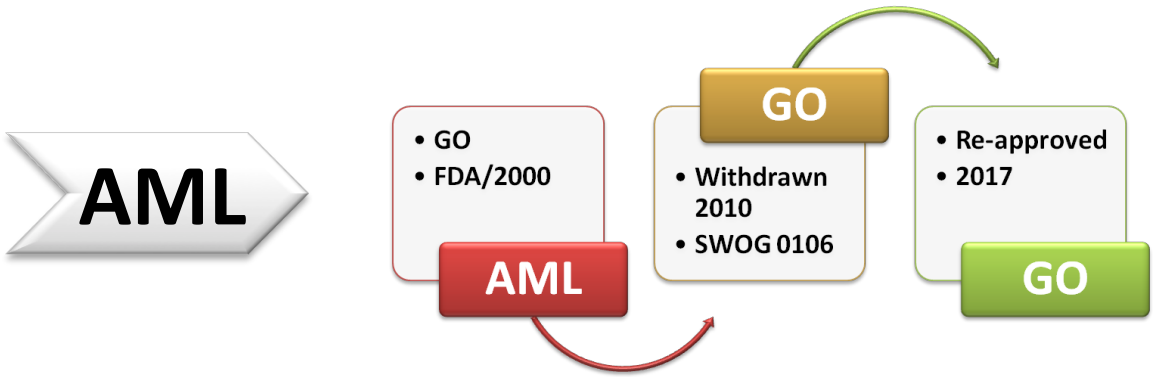
Burnett AK, ASH 2012

Antibody-based therapy

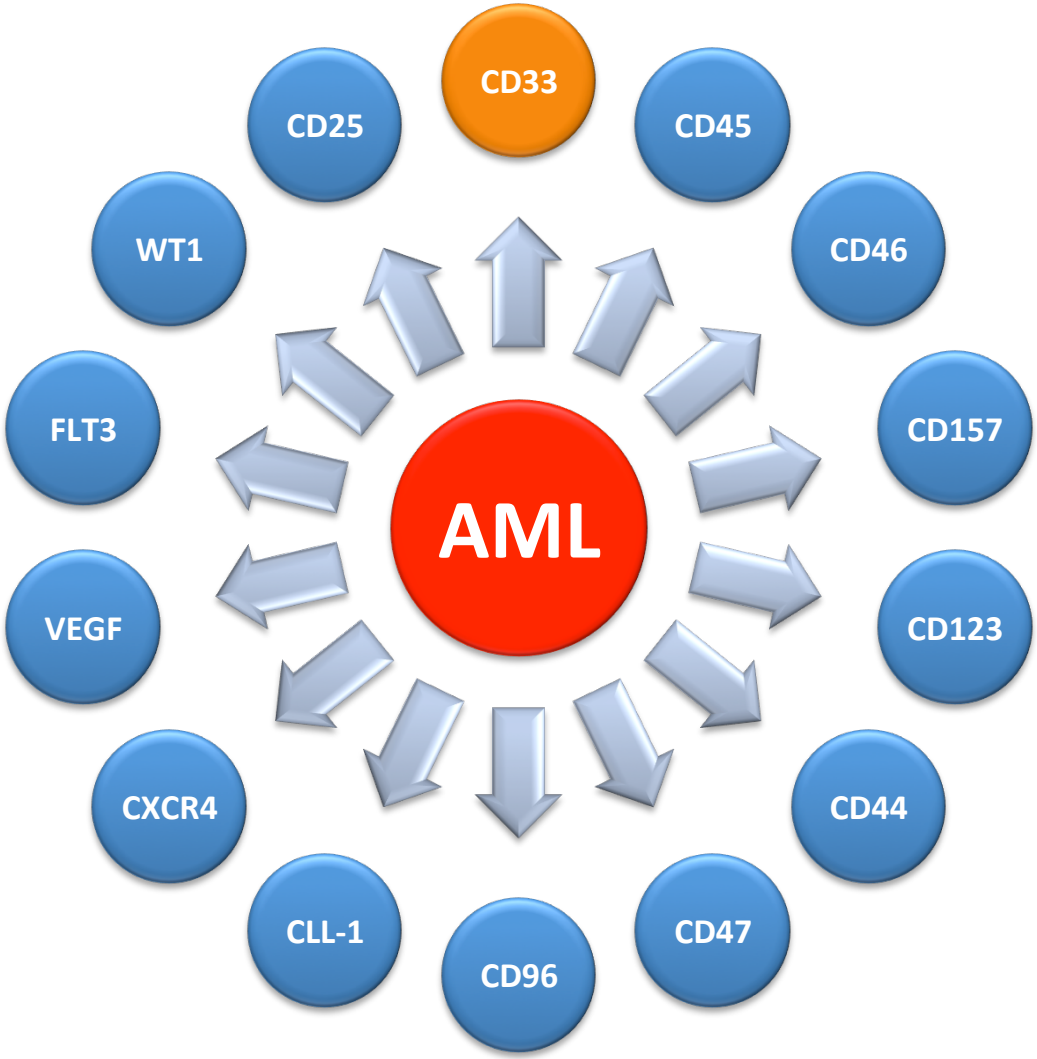
An effective strategy in many hematologic cancers…

FDA-approved antibodies in blood cancers

CLL	NHL	MM	HL	ALL
Rituximab	Rituximab	Elotuzumab	Brentuximab	Blinatumomab
Ofatumumab	Obinutuzumab	Daratumumab		Inotuzumab
Obinutuzumab	Ibritumomab			



Selected antigen targets for therapy in AML



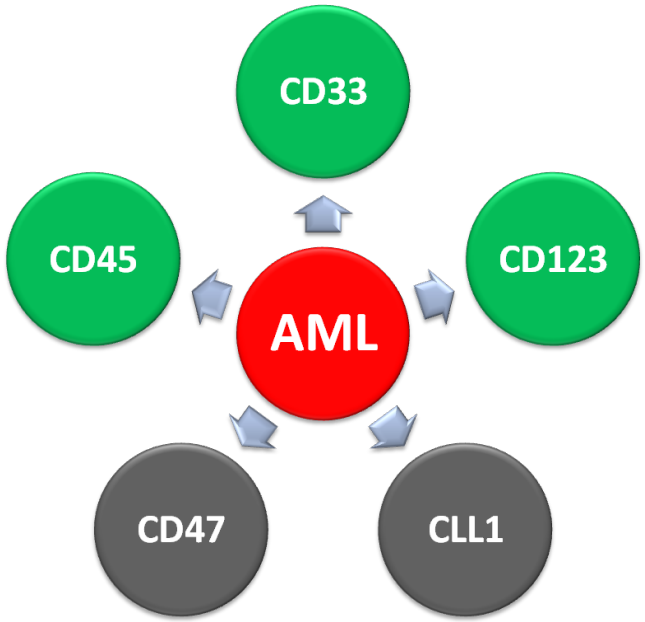
Buckley and Walter, Hematology 2015

The quest for novel AML antigens continues…

"The ideal target antigen"

- High level of expression on all AML cells including LSCs
- Minimal to no expression in normal tissues
- Important role in AML pathogenesis
- Not shed into the circulation
- Sufficiently immunogenic (in case of active immunization strategies)

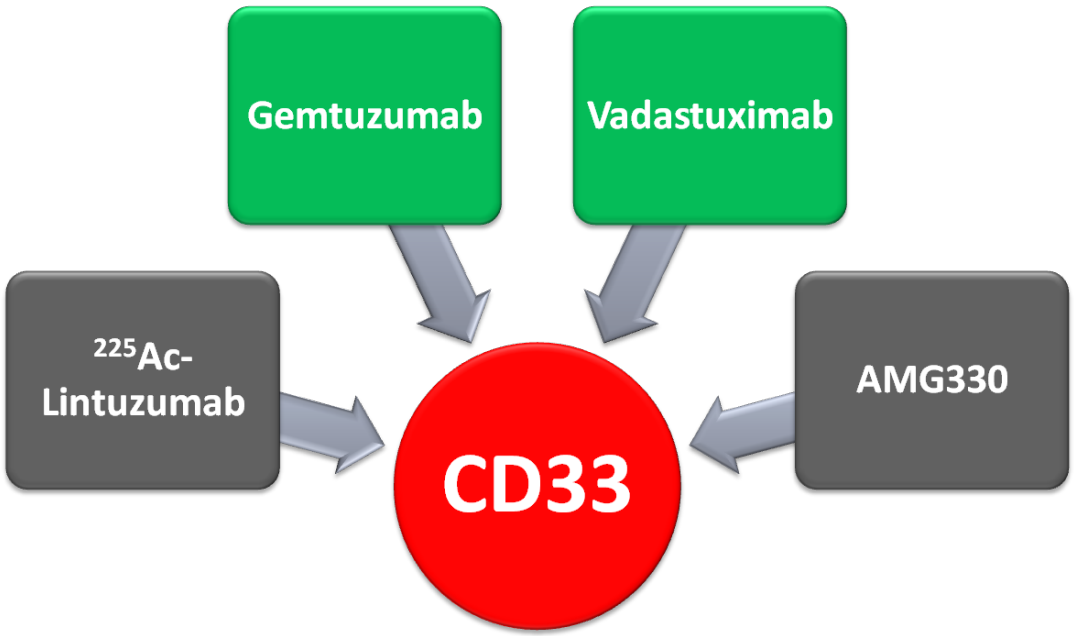
Focus on



Buckley and Walter, Hematology 2015

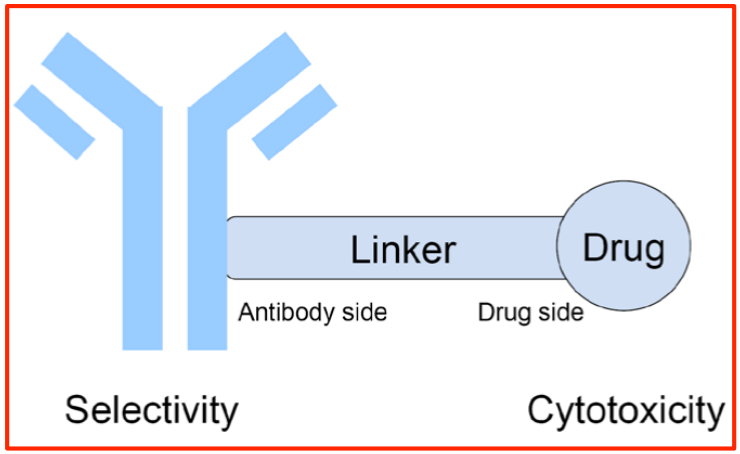
Targeting CD33

- Myeloid differentiation antigen broadly expressed in AML (> 90% of pts)[1]
- In some myeloid leukemias, CD33 thought to be expressed on LSCs[2]
- Function of CD33 poorly understood (cell adhesion and activation)



[1]Pollard JA et al, Blood 2012; [2]Walter RB et al, Blood 2012

Anti-CD33 drug conjugates



Gemtuzumab ozogamicin (Mylotarg)

- **Ab**: humanized anti-CD33 IgG4
- **Linker**: acyl hydrazone (sensitive to acidification)
- **Drug**: calicheamicin derivative, binds DNA, P-gp efflux

Vadastuximab Talirine (SGN-CD33A)

- **Ab**: humanized anti-CD33 IgG1, with engineered cysteine residues to allows uniform drug loading
- **Linker**: dipeptide (sensitive to proteases)
- **Drug**: pyrrolobenzodiazepine (PBD) dimer, binds DNA, no P-gp efflux

GO + Induction chemotherapy

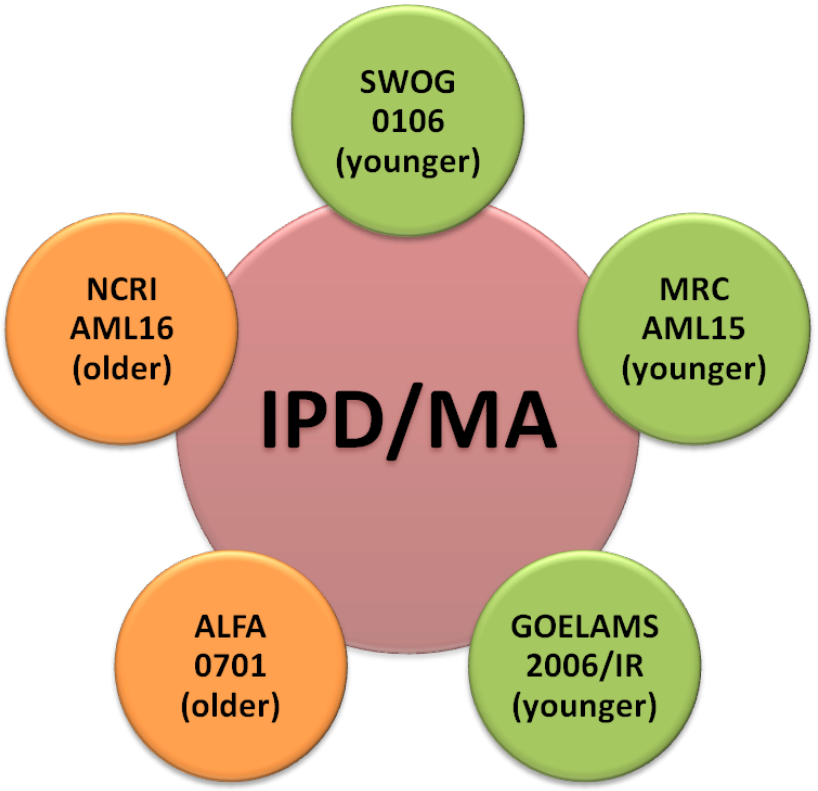
First antibody-targeted agent for the treatment of AML

CR/CRp rate 30%; rare VOD/SOS

Approved for older adults in first relapse in 2000

Withdrawn from market in 2010

5 RCT (N=3325 pts)



Hills et al, Lancet Oncol 2014

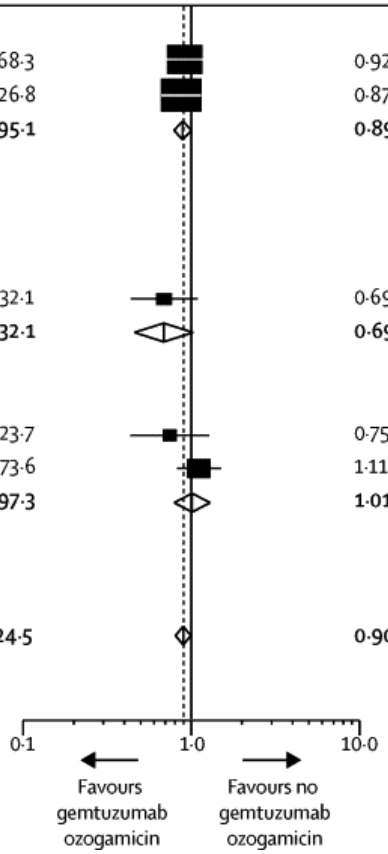
GO+IC: meta-analysis of RCT

Trial	GO dose/sched	Induction Chemo	No. of patients	Median age (years)	CG Risk (MRC)
MRC AML15	**3 mg/m^2 d1**	ADE,DA, FLAG-Ida	1099	50 (15-71)	All
NCRI AML16		DA, DClo	1115	67 (51-84)	All
SWOG-0106	**6 mg/m^2 d4**	DA (3+7)	595	47 (18-60)	All
GOELAMS AML2006/IR		DA (3+7)	238	50.5 (18-60)	Inter
ALFA-0701	**3 mg/m^2 d1,4,7**	DA (3+7)	278	62 (50-70)	Inter/Adv

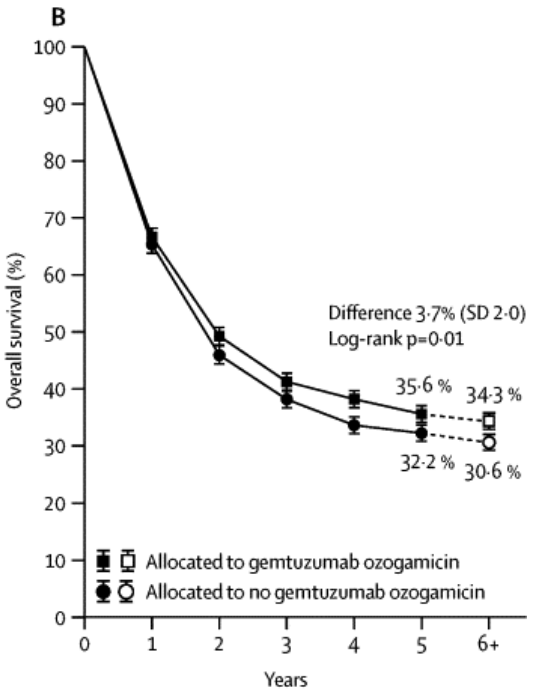
Overall Survival

A

	Events/patients		o–e	Variance	OR (CI*)	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
3 mg/m² single dose						
MRC AML15	326/548	348/551	−14·7	168·3	0·92 (0·75–1·12)	
NCRI AML16	447/559	466/554	−31·1	226·8	0·87 (0·73–1·03)	
Subtotal	**773/1107**	**814/1105**	**−45·7**	**395·1**	**0·89 (0·81–0·98)**	**0·02**
Test for heterogeneity between trials χ^2=0·2; p=0·6						
3 mg/m² fractionated						
ALFA-0701	59/139	72/139	−11·8	32·1	0·69 (0·44–1·09)	
Subtotal	**51/113**	**72/139**	**−11·8**	**32·1**	**0·69 (0·49–0·98)**	**0·04**
6 mg/m² dose						
GOELAMS AML2006 IR	41/119	54/119	−7·0	23·7	0·75 (0·44–1·27)	
SWOG 0106	151/295	144/300	8·0	73·6	1·11 (0·83–1·50)	
Subtotal	**192/414**	**198/419**	**1·0**	**97·3**	**1·01 (0·83–1·23)**	**0·9**
Test for heterogeneity between trials χ^2=2·9; p=0·09						
Total	**1024/1660**	**1084/1663**	**−56·6**	**524·5**	**0·90 (0·82–0·98)**	**0·01**
Test for heterogeneity (five trials) χ^2=6·7; p=0·2						
Test for heterogeneity between subtotals χ^2=3·6; p=0·2						



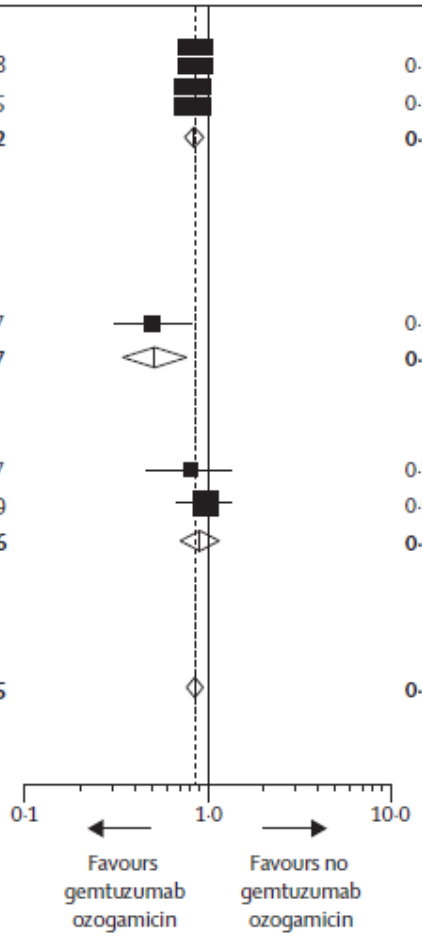
B



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	26·7 % SD 0·8	3·5 % SD 0·8
No gemtuzumab ozogamicin	29·5 % SD 0·9	5·2 % SD 1·0

Relapse

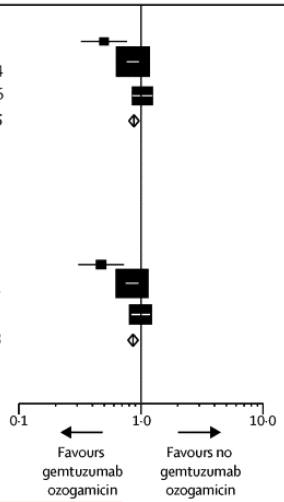
	Events/patients		o–e	Variance	OR (CI*)	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
3 mg/m² single dose						
MRC AML15	282/466	314/478	–20·8	148·8	0·87 (0·70–1·07)	
NCRI AML16	325/396	321/376	–27·2	159·5	0·84 (0·69–1·03)	
Subtotal	**607/862**	**635/854**	**–48·0**	**308·2**	**0·86 (0·77–0·96)**	**0·006**
Test for heterogeneity between trials χ^2=0·1; p=0·8						
3 mg/m² fractionated						
ALFA-0701	51/113	69/104	–19·1	28·7	0·51 (0·32–0·83)	
Subtotal	**51/113**	**69/104**	**–19·1**	**28·7**	**0·51 (0·36–0·74)**	**0·0004**
6 mg/m² dose						
GOELAMS AML2006 IR	43/109	48/102	–4·9	22·7	0·81 (0·47–1·39)	
SWOG 0106	118/222	122/222	–2·5	59·9	0·96 (0·69–1·34)	
Subtotal	**161/331**	**170/324**	**–7·4**	**82·6**	**0·91 (0·74–1·14)**	**0·4**
Test for heterogeneity between trials χ^2=0·5; p=0·5						
Total	**819/1306**	**874/1282**	**–74·4**	**419·5**	**0·84 (0·76–0·92)**	**0·0003**
Test for heterogeneity (five trials) χ^2=8·2; p=0·08						
Test for heterogeneity between subtotals χ^2=7·7; p=0·02						

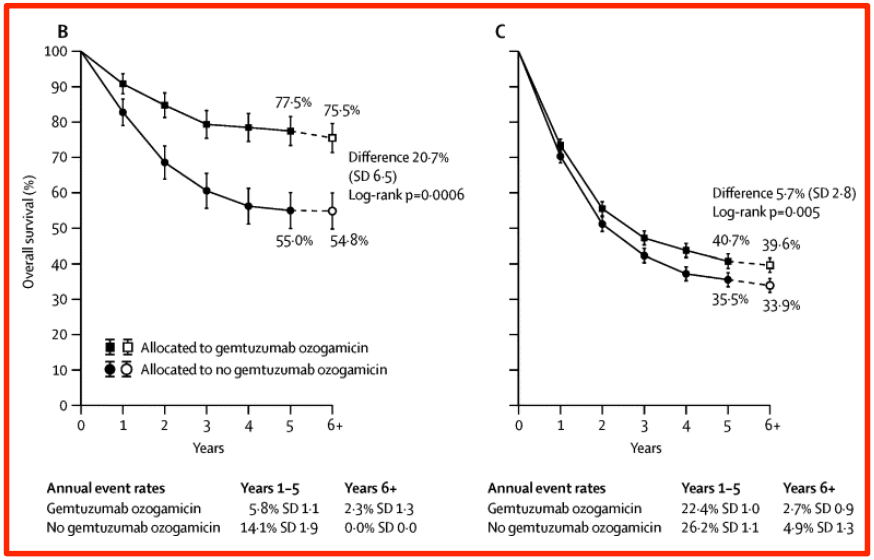


Survival by cytogenetics

A

	Events/patients: Gemtuzumab ozogamicin group	Events/patients: No gemtuzumab ozogamicin group	o–e	Variance	OR (95% CI)	p value
Original coding						
Favourable	32/125	54/126	−14·3	20·5	0·50 (0·32–0·77)	
Intermediate	549/962	596/964	−44·2	284·4	0·86 (0·76–0·96)	
Adverse	223/261	227/256	3·1	110·6	1·03 (0·85–1·24)	
Subtotal	**804/1348**	**877/1346**	**−55·4**	**415·5**	**0·88 (0·79–0·96)**	**0·007**
Test for heterogeneity between subgroups: χ^2=9·6; p=0·008						
Test for trend between subgroups: χ^2=7·8; p=0·005						
Revised MRC coding[12]						
Favourable	30/122	54/124	−15·5	20·6	0·47 (0·31–0·73)	
Intermediate	506/911	559/916	−45·3	264·6	0·84 (0·75–0·95)	
Adverse	260/299	258/284	−1·2	127·6	0·99 (0·83–1·18)	
Subtotal	**796/1332**	**871/1324**	**−61·9**	**412·8**	**0·86 (0·78–0·95)**	**0·002**
Test for heterogeneity between subgroups: χ^2=10·1; p=0·006						
Test for trend between subgroups: χ^2=7·7; p=0·006						





Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

GO back on market!

Sept 1, 2017

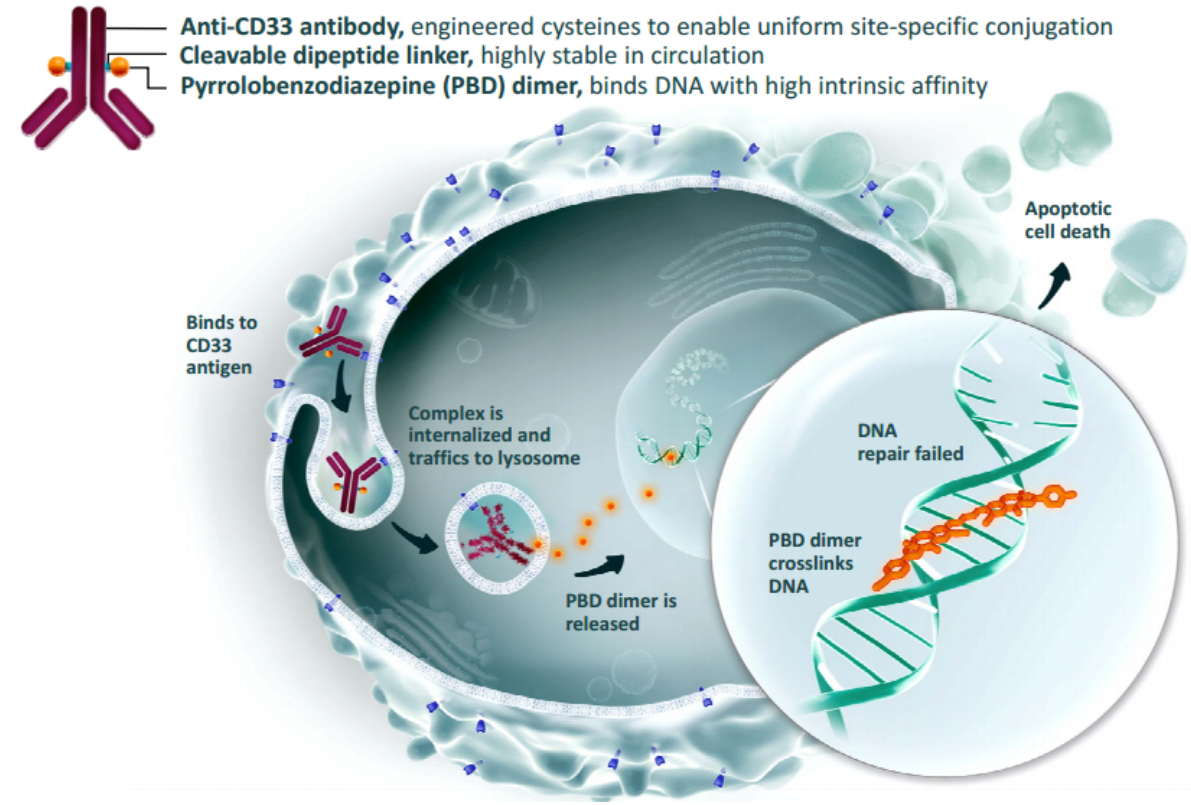
Adults with CD33+ ND-AML

- In combo with chemo
- Stand-alone treatment

R-R CD33+ AML

- Children
- Adults

Vadastuximab talirine



Humanized anti-CD33 MoAb linked to a pyrrolbenzodiazepine dimer, which binds DNA with high intrinsic affinity[1]

Synergy with HMAs to enhance antileukaemic activity[2]

CR rate 29% in a phase I study for R/R AML with no liver toxicity (VOD)[3]

[1]Sutherland et al, Blood 2013; [2]Sutherland et al, ASH 2014; [3]Stein et al, ASH 2014

VT: early studies in ND-AML

[1]Phase 1 single agent (older pts)

- N=26 (median 74y) treated at 40 mcg/kg q3wk x 2 cycles
- **CR+CRi 54% (46% MRDneg by flow)**
- 30/60-d mortality 0%15%, no VOD

[2]Phase 1 in combo with HM

All ongoing trials discontinued

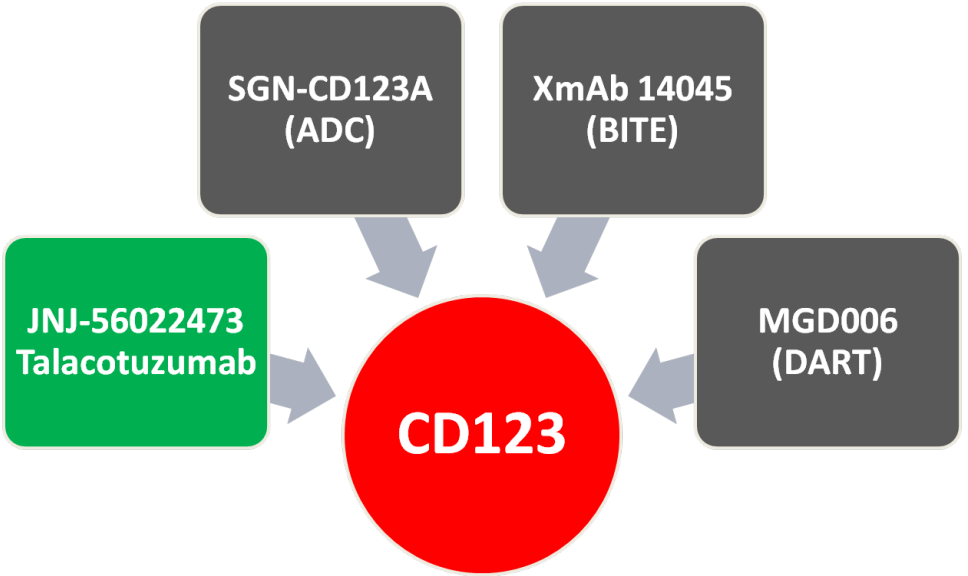
[3]Ph (younger pts)

- N=42 (median 45y) treated at 10+10 or 20+10 mcg/kg on day 1 and 4 of "3+7" (Split-dose)
- N=25 (median 58y) treated at 30 or 40 mcg/kg on day 1 of "3+7" (Single-dose)
- **Across schedules: CR+CRi 73% (mostly @1 cycle); 79% MRDneg by flow**
- Median OS not reached by either schedule
- 30/60-d mortality 1%/7%, no VOD

[1]Bixby DL et al, ASH 2016; [2]Ravandi F et al, EHA 2017; [3]Levy MY et al, EHA 2017

Targeting CD123

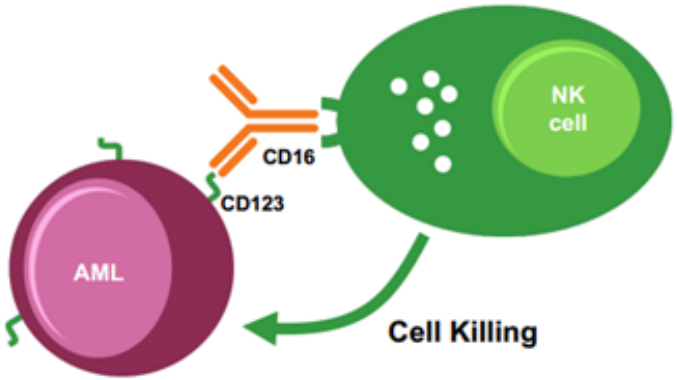
- CD123 (IL-3 receptor α chain) is a key mediator of cell proliferation, differentiation and suvival
- Expressed on >90% in LSCs in nearly 90% of AML patient samples
- Very low expression on normal HSCs
- Promising target for antibody therapy of AML



Macauley MS et al, Nat Rev Immunol 2014

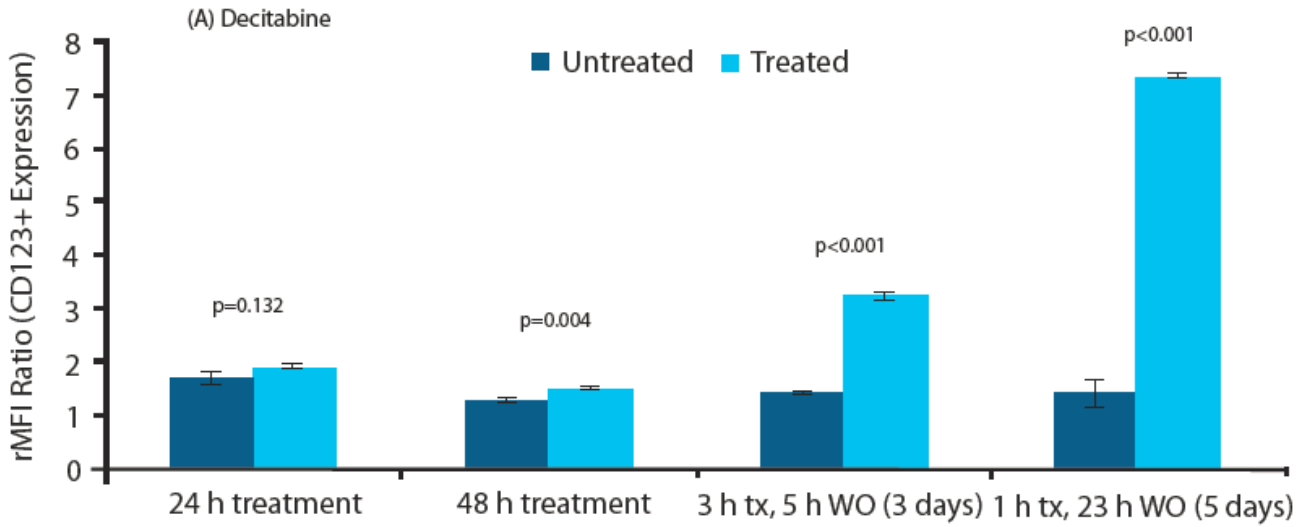
Talacotuzumab (JNJ-56022473)

Novel Anti-CD123 antibody with enhanced ADCC function



Single agent safety observed in AML pts in CR/CRp at high risk of relapse (phase 1)[1]

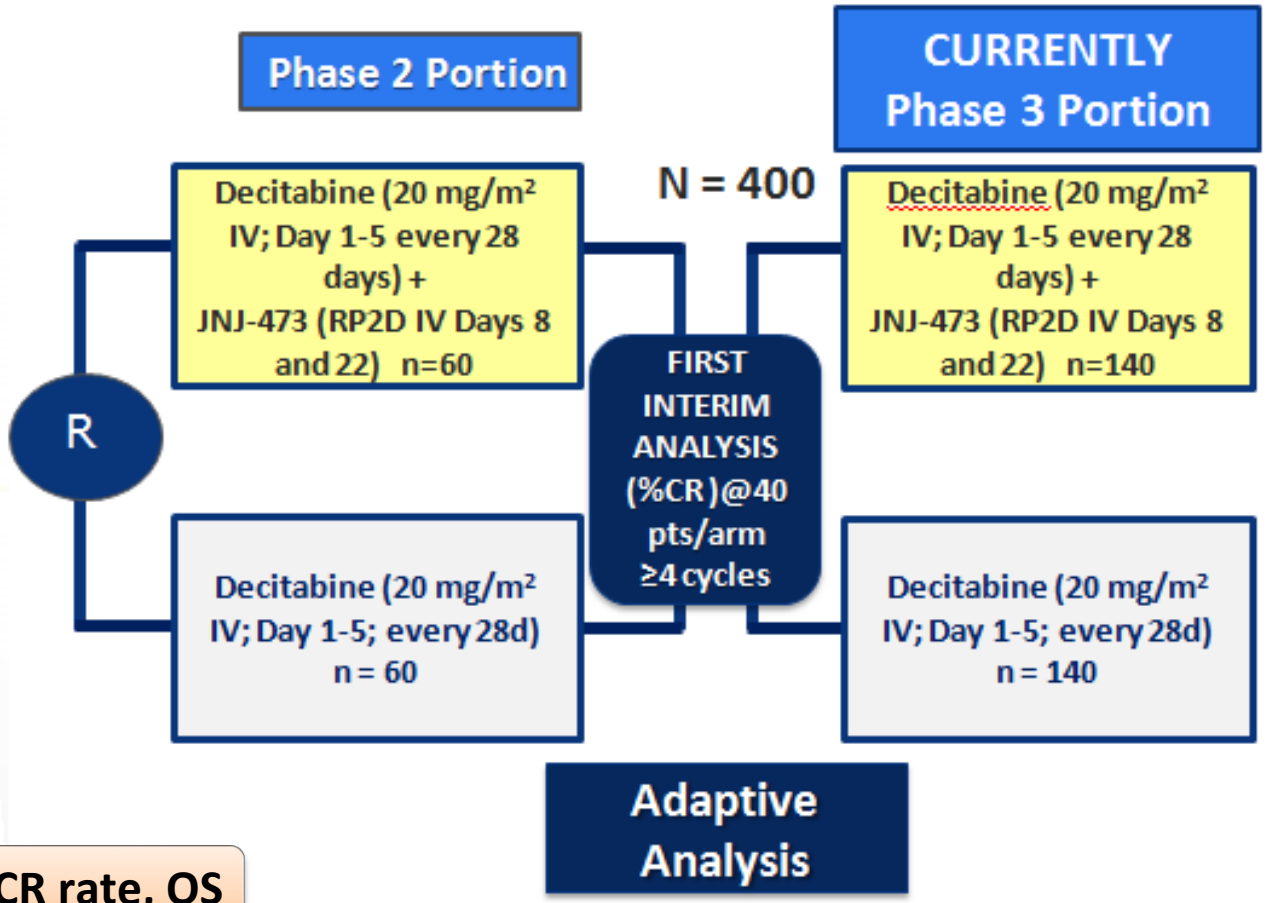
DAC (3-5 days) increases CD123 expression[2]



[1]Smith BD et al, Blood 2014; [2]Syed K et al, ASH 2015

DAC + TALA study

A Randomized Phase 2/3 Study of Decitabine Plus Talacotuzumab (JNJ-56022473; Anti CD123) Versus Decitabine Alone in Patients With AML Ineligible for Intensive Chemotherapy



Primary E-P: CR rate, OS

Targeting CD45

CD45 (LCA) is a tyrosine phosphatase expressed at high density on lymphohematopoietic cells

Not expressed on nonhematopoietic tissues

Some 85% to 90% of acute leukemias express CD45

Anti-CD45 radioimmunoconjugates in clinical development as part of RIC-HSCT for patients with advanced AML

Lomab-B

- Combines anti-CD45 MoAb with a radionuclide (β-emitting ^{131}I)
- Offers target-specific ablation as a conditioning regimen prior to HSCT
- Directs radiation to leukemic and immune cells
- Does not bind other normal tissues

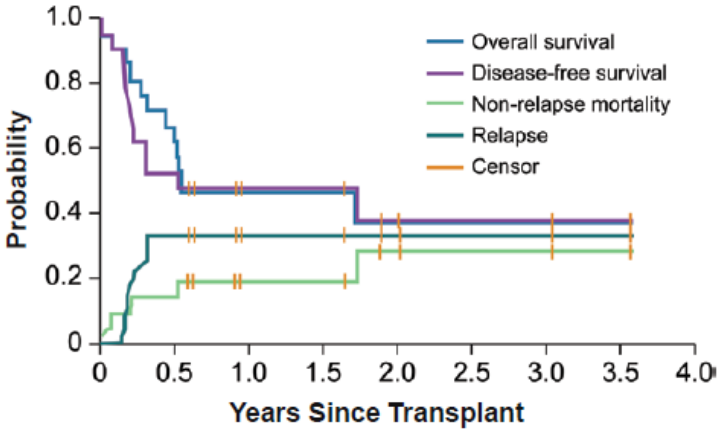
Pagel JM et al, Blood 2009

Lomab-B + RIC in AML

- Phase 2 study: Iomab-B safe in combination with RIC; associated with encouraging overall survival in patients >50 years with advanced AML and high-risk MDS[1]

FHCRC[1]

- Patients received Iomab-B + RIC → HCT
- N = 21; patients treated at MTD



Ongoing

Phase 3 SIERRA Trial: Iomab-B Prior to HCT vs CCR in Relapsed/Refractory AML[1]

- **Patients with relapsed or refractory AML >55 years**
- **Estimated N = 150**

R

Iomab-B + RIC → HCT

CCR (physician's choice of chemotherapy)

- Primary endpoint: dCR[a]
- Secondary endpoint: OS

[a] CR or CRp lasting 180 days or more from time of initial CR or CRp is documented with evidence of subsequent relapse.
1. https://clinicaltrials.gov/ct2/show/NCT02665065. Accessed January 31, 2017.

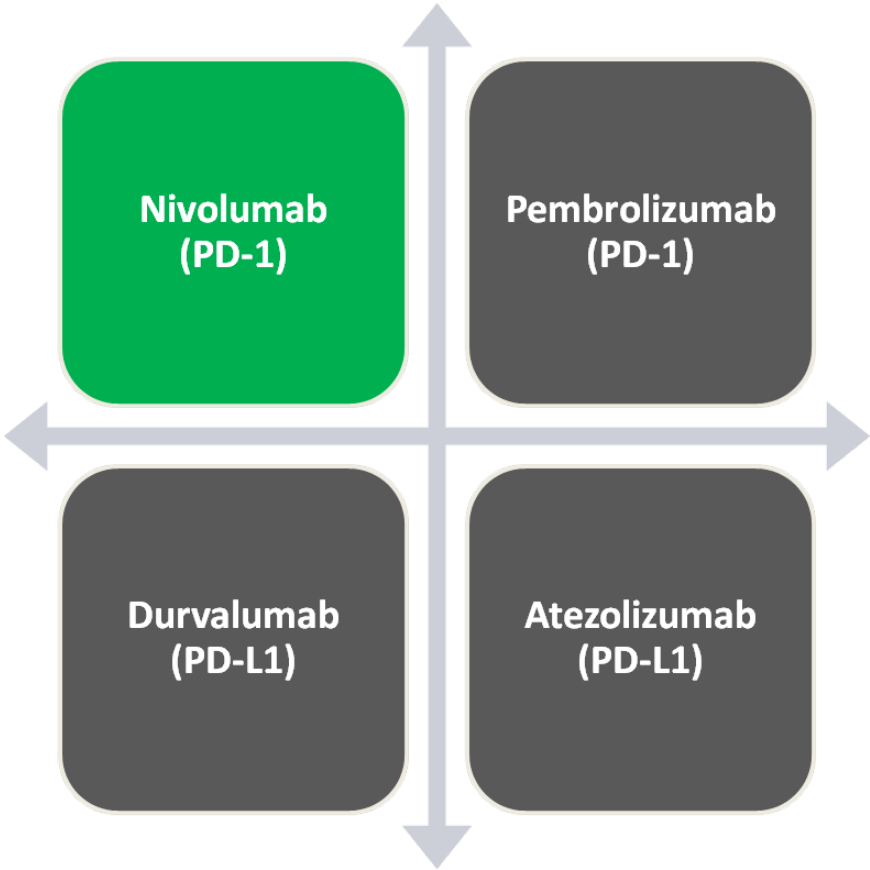
[1]Pagel JM et al, Blood 2009

Targeting immune checkpoints

Tumors take advantage of immune checkpoints as mechanism of immune evasion[1]

PD-1/PD-L1 axis upregulated in AML (poor prognosis)[2]

Clinical evaluation of PD-1/PD-L1 blockade in AML ongoing



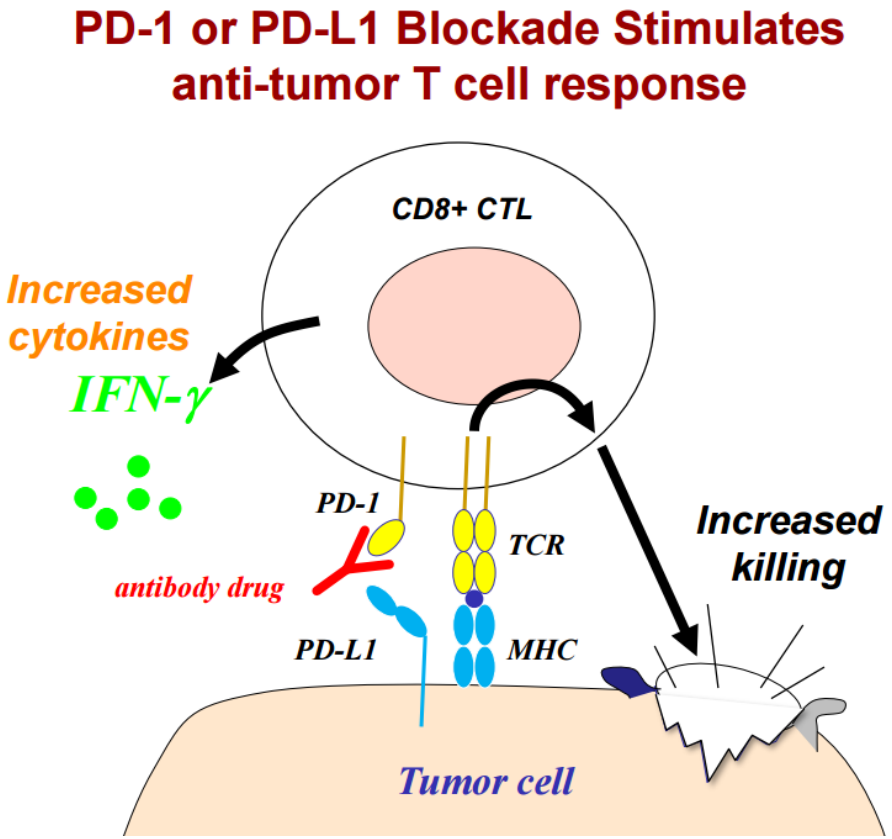
[1]Pardoll DM , Nat Rev Cancer 2012; [2]Yang H et al, Leukemia 2013

Nivolumab: an anti-PD-1 MoAb

HMAs upregulate PD-1 and PD-L1 genes promoting resistance to epigenetic therapy

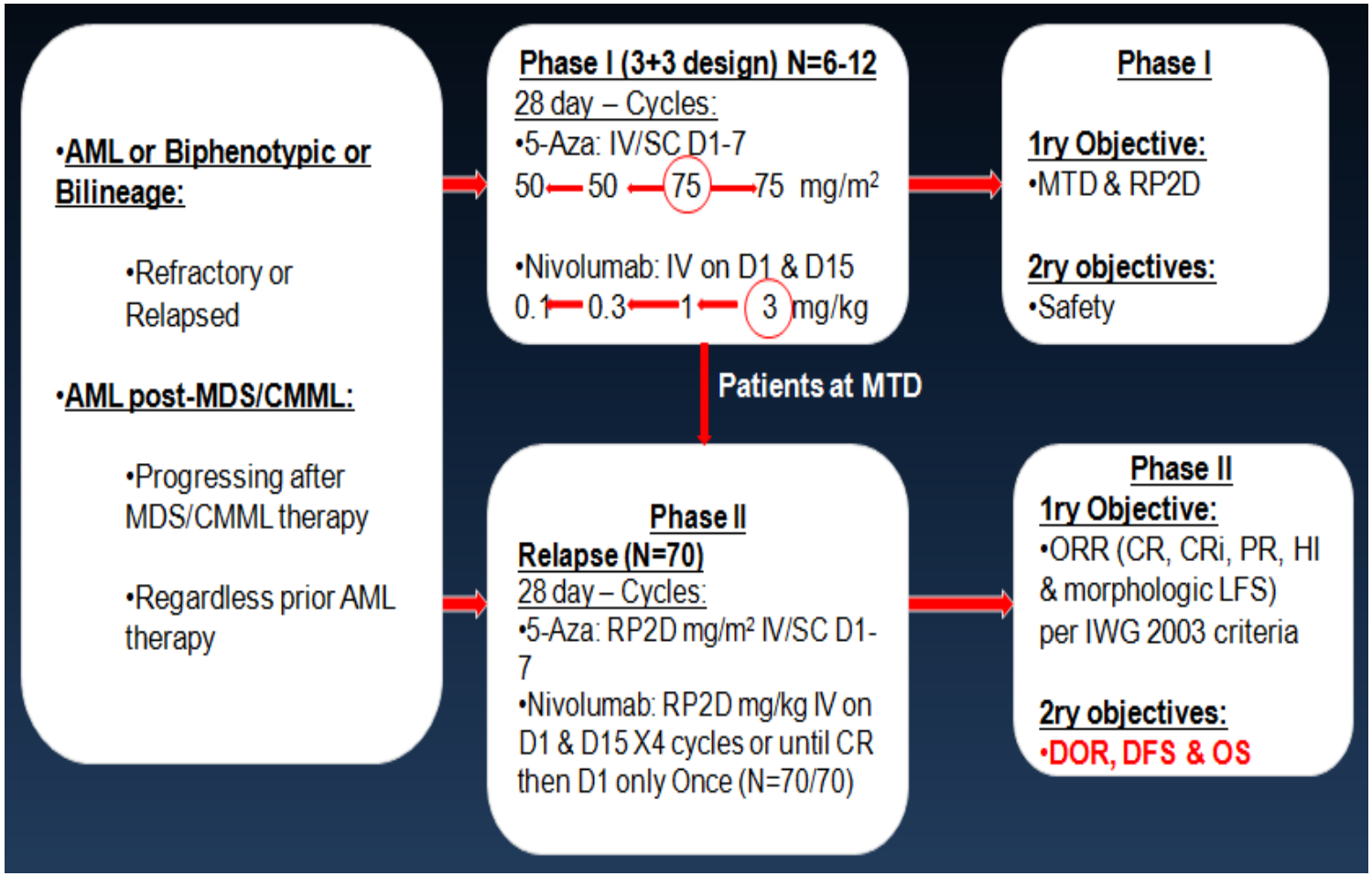
PD-1/PD-L1 blockade may improve response and abrogate resistance to HMAs

Nivolumab (OPDIVO) is a fully human MoAb that binds PD-1



Orskov AD et al, Oncotarget 2015

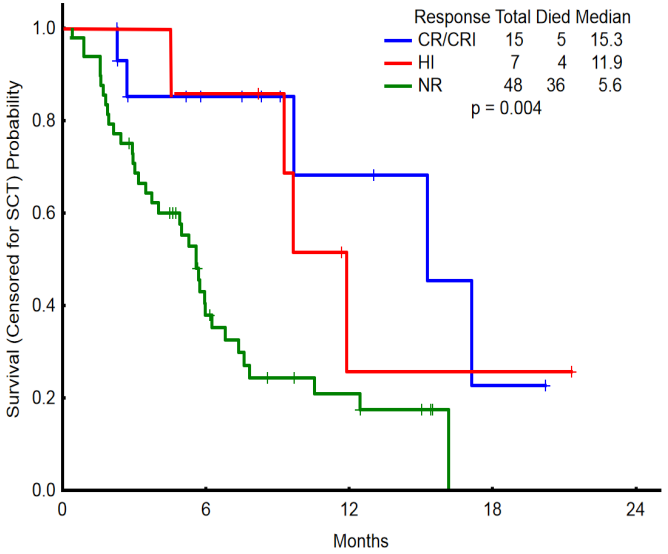
AZA + NIVO (phase 1b/2)

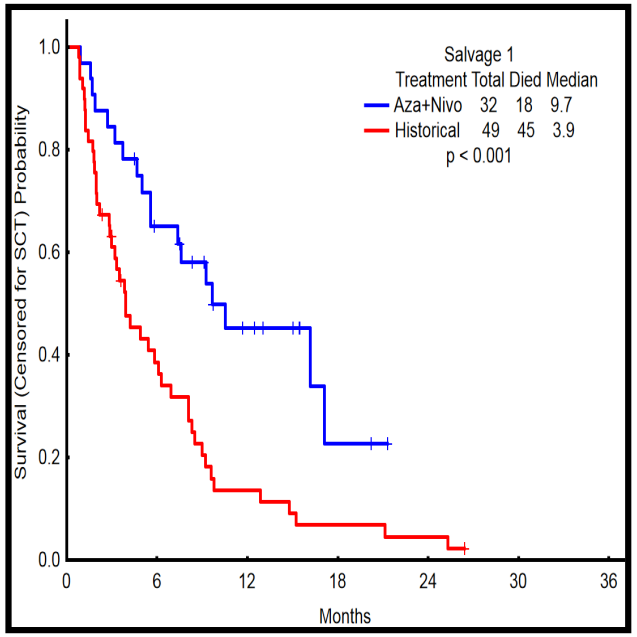


Daver N et al, EHA 2017

Outcomes (N=70)

Best response / Outcome	N (%) / Med [Range]
Evaluable	70
ORR	22 (32)
CR/CRi	15 (22)
HI + 50% blast reduction (6mo+)	7 (10)
50% reduction in blast	17 (24)
Progression/Stable dis (6 mo+)	26 (37) [21/5]
8-week mortality	5 (7)
Median cycles to response	2 [1 - 13]
Median follow-up	8.6 mo [2.8 – 21.3]





G2-4 immune tox → **26% (< 6 wks)** → **Respond to steroids**

Conclusions