Combinational therapy and newer agents in MDS-

Prof Ghulam .J.Mufti
MDS foundation

ASH 2011

My Disclosures

- Advisory board member of GSK, Novartis, Roche and Celgene
- Unrestricted educational grants from Celgene

Spectrum of MDS

Asymptomatic,IPSS Low/Int-1 **Symptomatic,IPSS Int-2/High Risk**

BM function

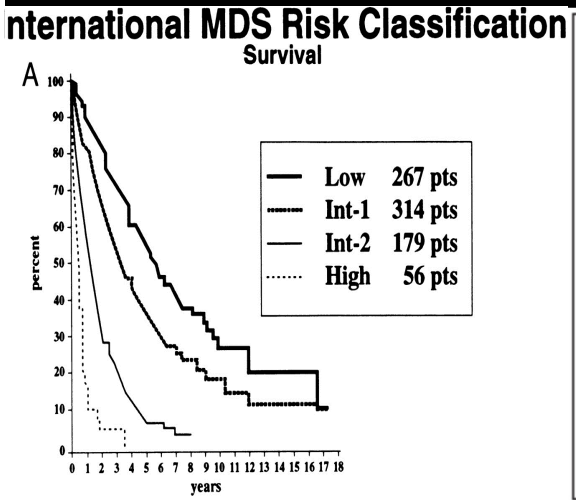
Transfusion

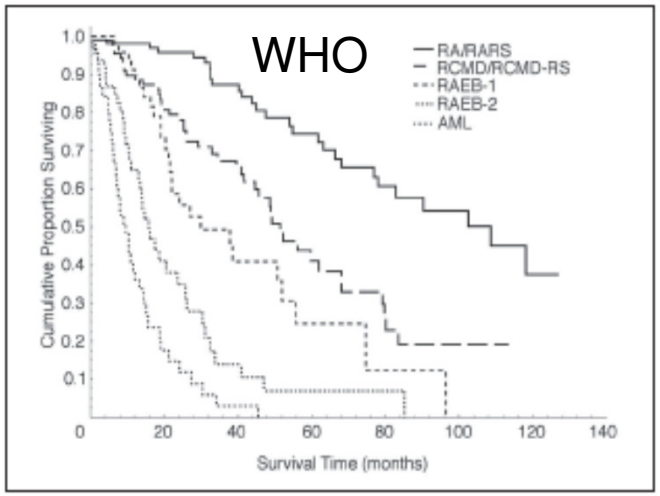
Differentiation

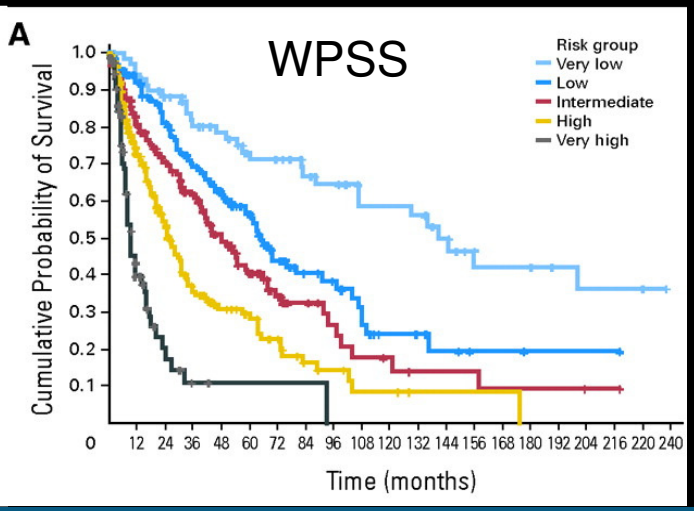
Apoptosis

IPSS-R

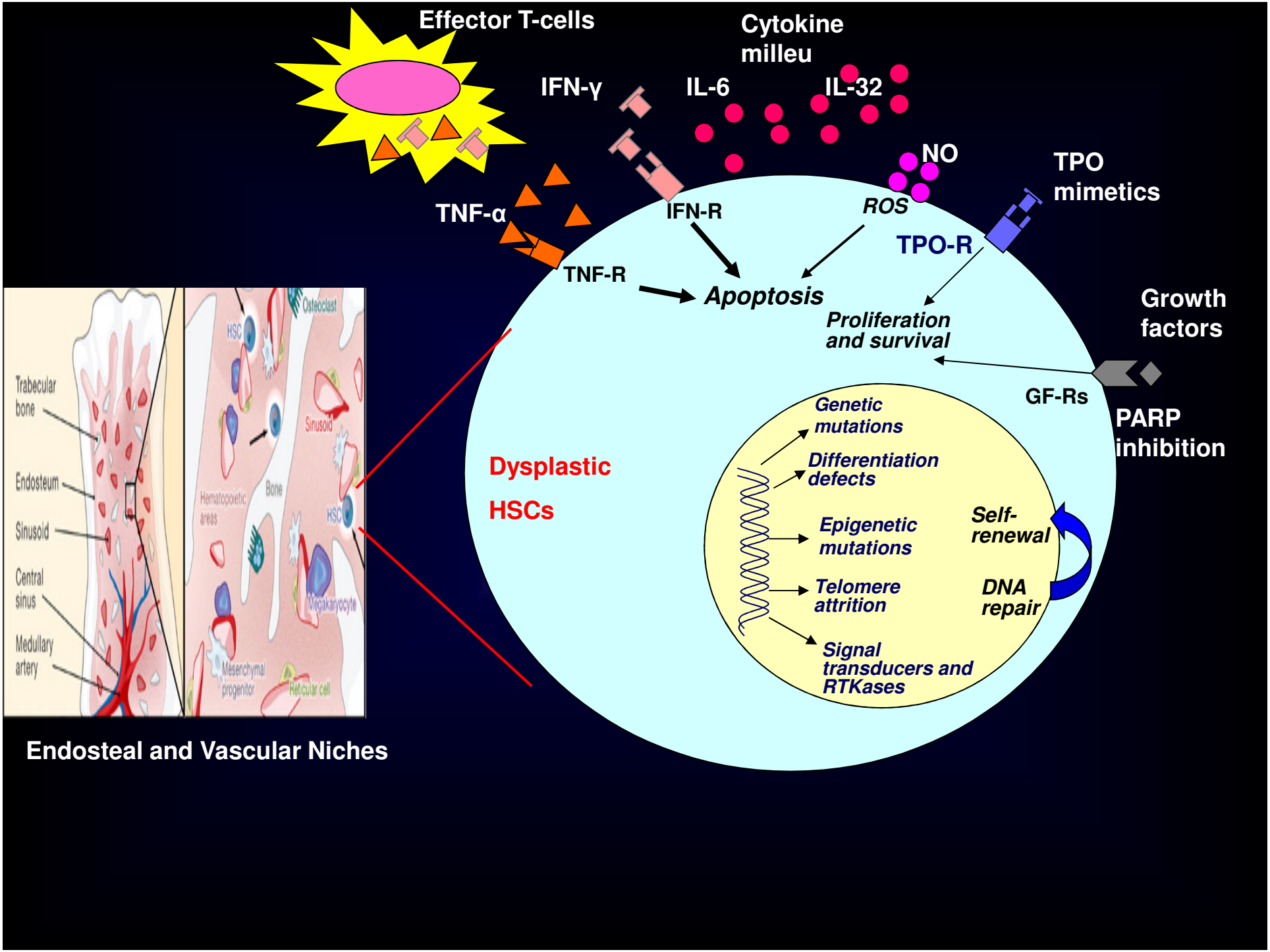
Median (Years)	1	2	3	4	5
(Score)	Very Low (0-2)	Low (3-5)	Intermediate (6-7)	High (8-9)	V. High (10-18)
Survival	6.8	4.3	2.3	1.5	0.9
25% AML Transform	NR	10.1	2.8	1.2	0.7







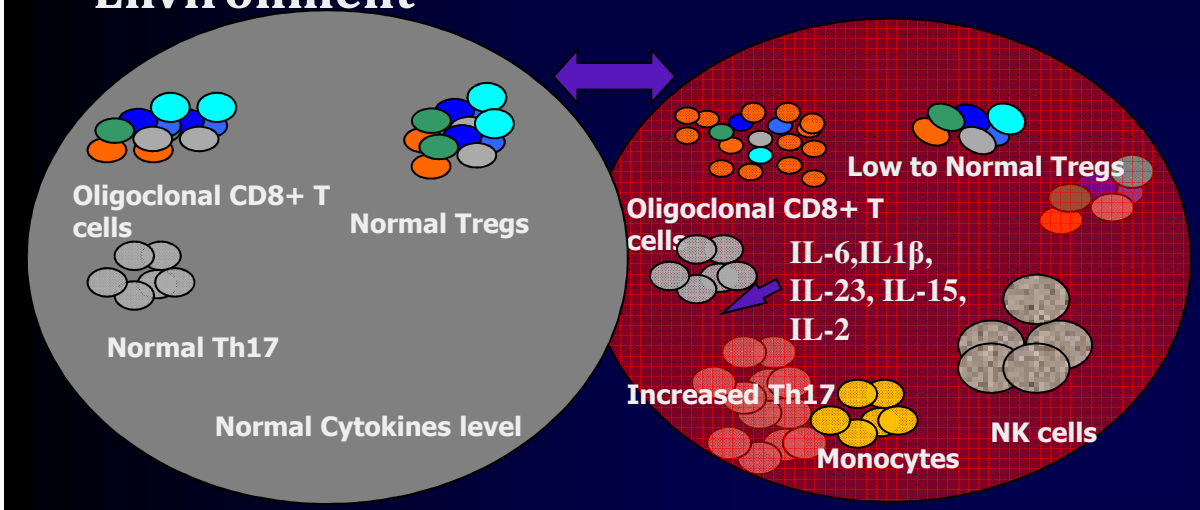
Greenberg, Blood 1997, Malcovati,JCO 2009,Greenberg Leuk.Research 2011


Effector T-cells
Cytokine milleu
IFN-γ
IL-6
IL-32
NO
TPO mimetics
TNF-α
IFN-R
ROS
TPO-R
TNF-R
Apoptosis
Proliferation and survival
Growth factors
GF-Rs
PARP inhibition
Dysplastic HSCs
Genetic mutations
Differentiation defects
Epigenetic mutations
Telomere attrition
Signal transducers and RTKases
Self-renewal
DNA repair
Trabecular bone
Endosteum
Sinusoid
Central sinus
Medullary artery
Osteoclast
HSC
Sinusoid
Hematopoietic areas
Bone
HSC
Megakaryocyte
Mesenchymal progenitor
Reticular cell
Endosteal and Vascular Niches

‘Low risk’ MDS

Normal **Low Risk**

Normal Environment **Inflammatory Environment**



Immune mediated

IST- ATG, CyA
Anti-TNF (Etanarcept)
Anti-IL6 (Siltuximab)
?Lenalidomide
Campath
P38α MAPK inhibitors(**SCIO-469)**

Growth and Differentiation factors

Epo plus GCSF
Eltrombopag/Romiplostim

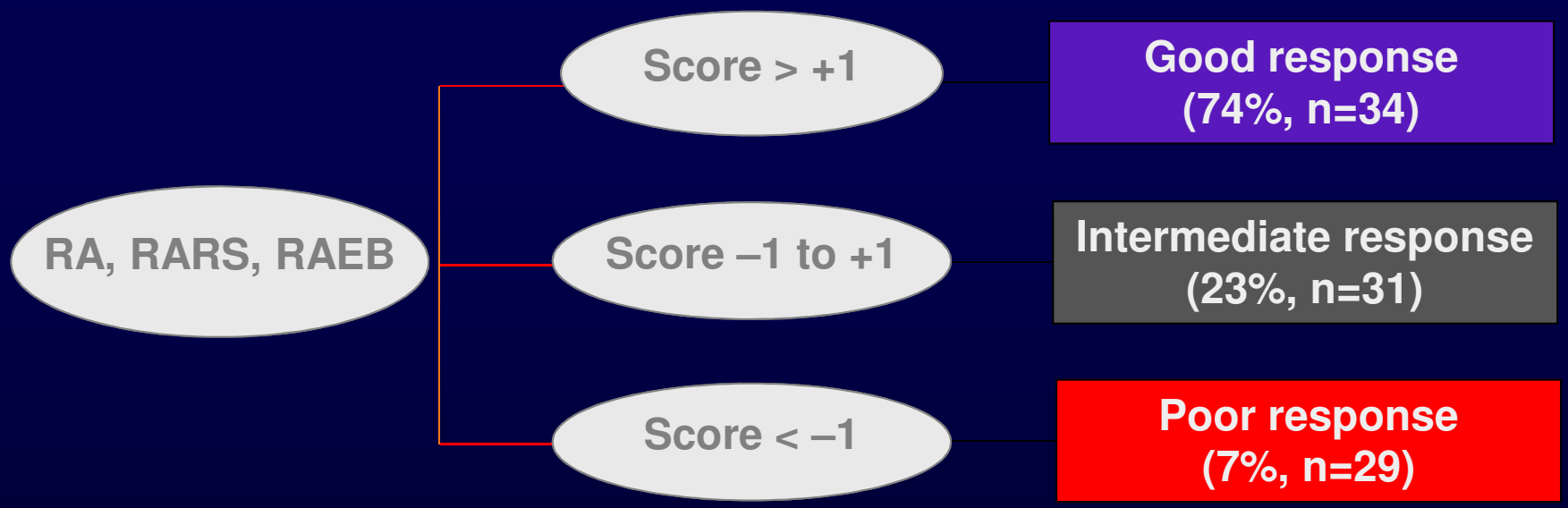
Stromal modulation

Myeloid derived suppresor Cells (MDSCs) and IDO1 inhibitor (INCB24360)

Others

Ezatiostat Hydrochloride (Telintra®, TLK199)- GSTP1 inhibitor
Neddylation inhibitors
Kinase Inhibitors- ON-01910 (PLK1 & Cdc25C Inhibition), Sorafanib,Erlotinib

Erythropoietin ± G-CSF in MDS-



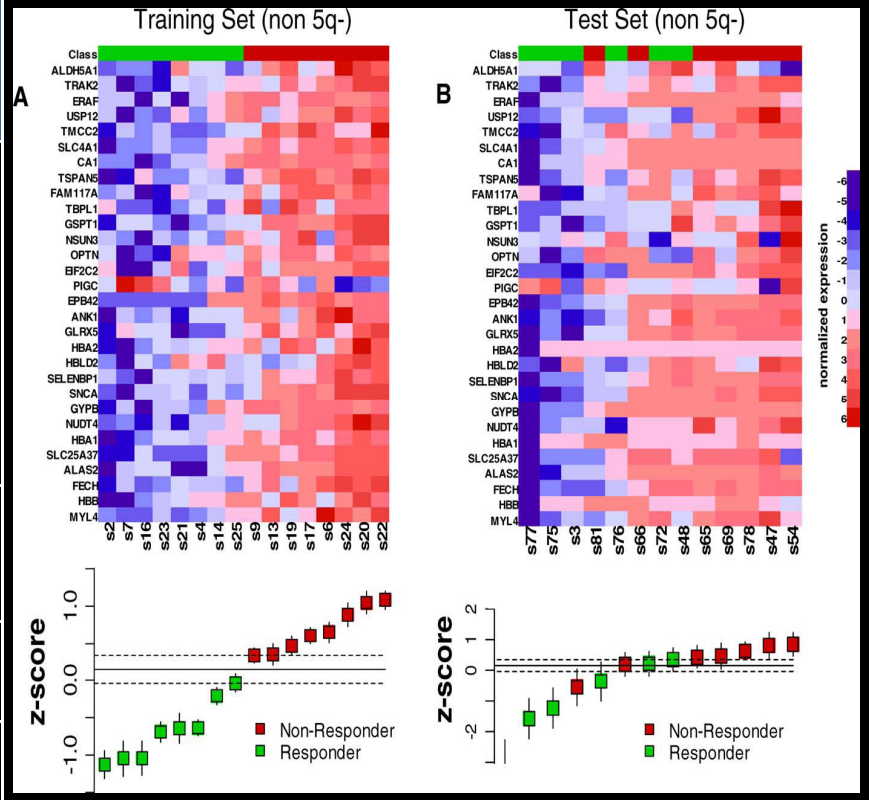
Treatment response score

s-epo	<100	+2
U/L	100–500	+1
	>500	–3
Transf	<2 units/m	+2
U RBC/m	= or >2 units/m	–2

Hellström-Lindberg , *Br J Haematol*. 2003.

Lenalidomide MDS-002 Study
Erythroid Responses at 24 wks

		MDS-002 Non-del(5q) (n=215)
Erythroid response	**Transfusion indep**	58 (27%)
	Minor (>50% ↓)	36 (17%)
	Transfusion indep + minor	94 (44%)
Median duration of transfusion independence		43 wk
Median Hgb rise		3.3 g/dL (1.0–9.8)
Median time to response		4.5 wk (0.3–39.1)



- GEP from Lenalidomide–responsive patients lacking 5q deletions have a defect in erythroid differentiation analogous to the ineffective erythropoiesis in patients with 5q deletiions..

- Ongoing Lenalidomide + EPO trials

Raza, Blood 2007 and Ebert ,PLOS Medicine 2007

Phase 1 Dose-Ranging Study of Oral Ezatiostat Hydrochloride (Telintra®, TLK199) in Combination with Lenalidomide (Revlimid®) in Patients with Non-Deletion(5q) Low to Intermediate-1 Risk Myelodysplastic Syndrome (MDS)

Ezatiostat, a glutathione S-transferase P1-1 (GST P1-1) inhibitor, activates Jun kinase and MAPK.

- promoting the growth and maturation of hematopoietic progenitors
- induces apoptosis in malignant cells

- Proven to be an effective single agent therapy for low/Int1 risk MDS (n=75)
- Induces transfusion independence in 30% of patients.
- HI-E 19% and HI-N 16%.
- Median duration of response 34 weeks (2-63 wks)
- Grade 1 to 2 – nausea, vomiting and diarrhoea

- Combination therapy with Lenalidomide is well tolerated
- HI-Erythroid response of 43%
- Ezatiostat may also have the potential to enhance lenalidomide's efficacy.
- ‘Go forward’ dose is ezatiostat/lenalidomide 2000/10 mg

Raza et al,ASH abstract 2778,Sun, Dec 11,2011 and Raza,Cancer, 2011

Romiplostim-Single agent and combination

Study	N	End Point	Bleeding events	Blasts	AML
Romiplostim 4w / Extension 1 year	44	46% durable response	4.3/100 patient week	4	2
Azacitidine + Placebo/Romiplostim	40	85% Vs 62-71% Thromocytopenic events			2
Lenalidomide+ Placebo/ Romiplostim	39	67% vs 57% Thromocytopenic events			1
Decitabine + Placebo/Romiplostim	29	79% Vs 80% Thromocytopenic events	43% Vs 27%		1
Romiplostim Vs Placebo	250	Eff	NR	NR	NR

Kantarjian, JCO 2009, Kantarjian Blood 2010,Lyons ASH 2009,Greenberg ASH 2009 and Amgen Protocol

Responders to ATG

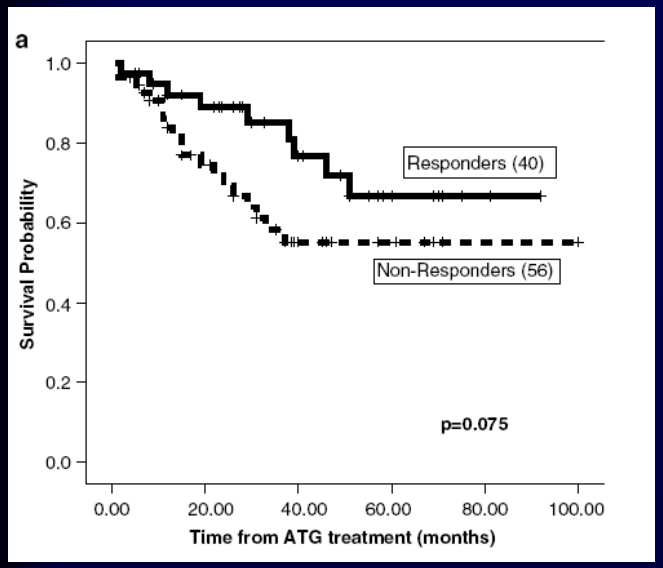
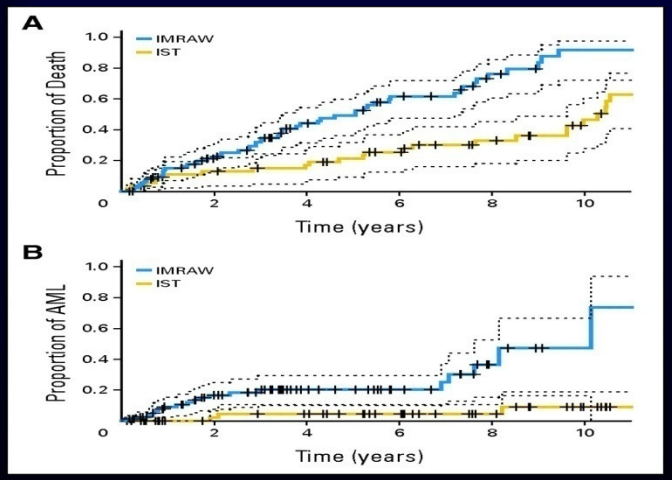


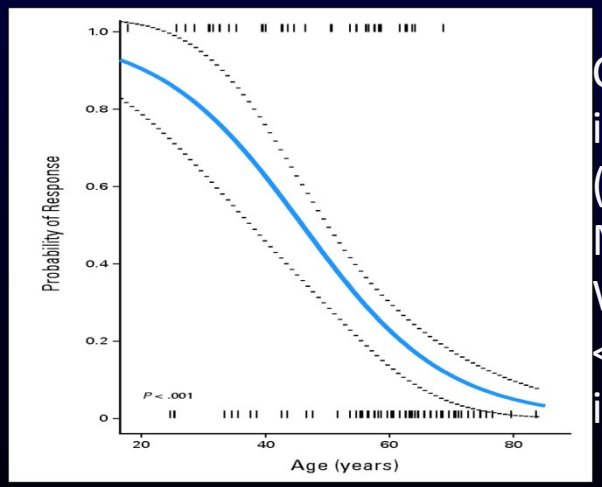
Table 3 Univariate and multivariate analysis of factors predicting response to ATG

	OR (95% CI)	*Significance (P-value)*
Univariate analysis variables		
Disease stage	0.46 (0.13-1.55)	0.21
IPSS	0.09 (0.01-0.68)	0.02
BM cellularity	0.51 (0.29-0.87)	0.01
Age	0.64 (0.28-1.47)	0.30
HLA-DR15 status	0.75 (0.19-2.96)	0.68
Cytogenetics[a]	0.78 (0.31-1.97)	0.59
Transfusion dependence	1.74 (0.61-4.99)	0.30
Platelet dependence	1.06 (0.47-2.40)	0.89
Multivariate analysis variables[b]		
IPSS		0.02
Low/Int-1[c]	—	
Int-2/High	0.08 (0.01-0.65)	
BM cellularity		0.01
Hypocellular[c]	—	
Normo/Hypercellular	0.49 (0.28-0.86)	

Effect of IST on survival of 96 MDS patients and predictive factors for the response to treatment

ZY Lim et al Leukemia 2007





Clinical outcomes of 89 NIH immunosuppressive therapy (IST) and 55 International Myelodysplasia Risk Analysis Workshop (IMRAW) patients <= 60 years of age with intermediate-1 MDS

Sloand. E et al JCO 2009

Phase II Studies of Etanarcept and Siltuximab (Anti-IL6) in Lower Risk MDS

Etanarcept

Etanarcept	Soluble fusion protein against TNF alpha
Eligibility	RBC-TD, Low/Int-1 risk IPSS
Design	25mg sc twice weekly 16 weeks
No. Patients	N=12
Responses	HI-E-3, HI-N=2 and HI-P=2

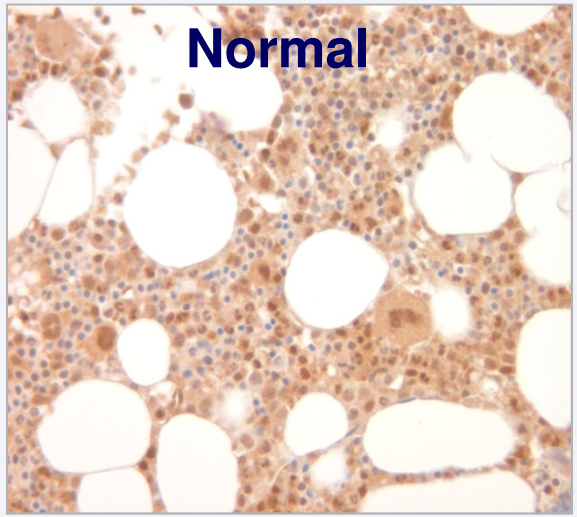
Siltuximab

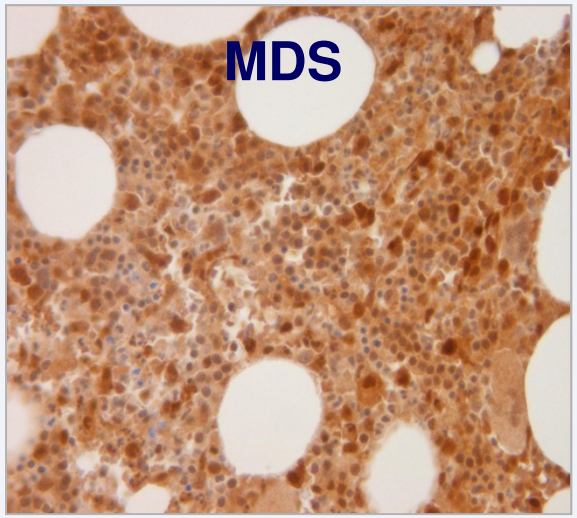
Siltuximab (CNTO 328)	Chimeric mur/hu-monoclonal
Eligibility	RBC-TD, Low/Int-1 risk IPSS
Design	Randomized 2:1 vs Placebo q 4 wk
No. Patients	N=75
Primary Endpoint	HI-Erythroid

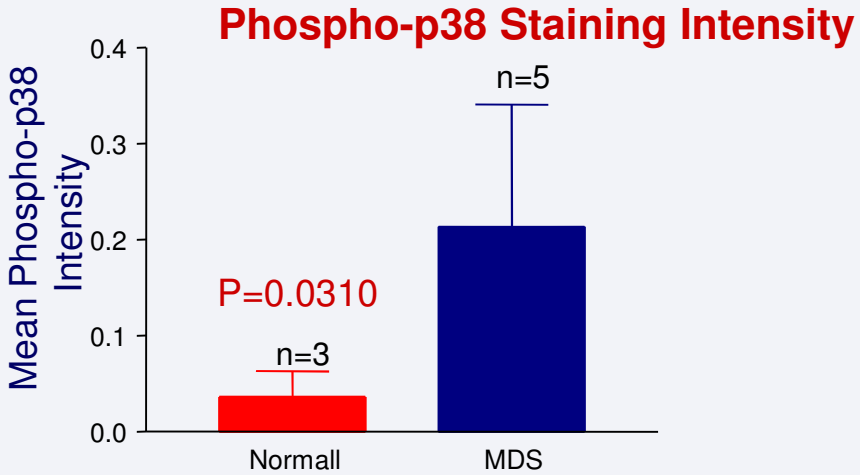
Deeg,Leukaemia 2002 and CNTO328 courtesy of Alan List

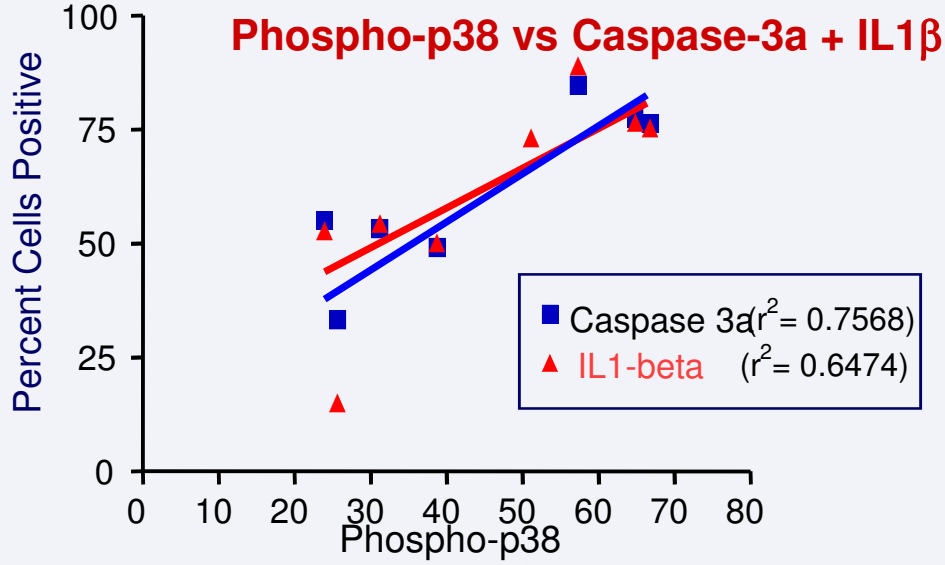
Medullary p38α/MAPK Phosphorylation

Relationship to Apoptotic Fraction









Navas T, et al. Blood 2004; 104, #3424.
Mohindru M, et al. Blood 2004;104, #470.

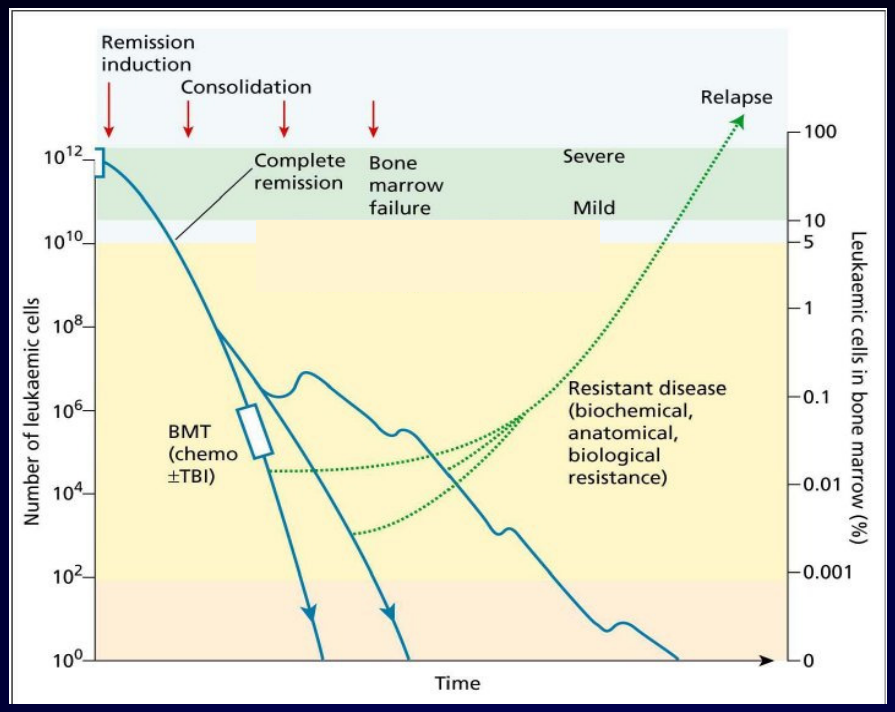
Courtesy of Alan List

Phase I/II Study of SCIO-469 in Low/Int-1 MDS

Parameter	Number (%) or Feature
Drug class	P38α MAPK inhibitor
Eligibility	Low/Int-1 MDS with ESA failure
Design	TID oral (90.180, 270 & 360 mg/d)
No. Patients	N=62
AEs all grades	GI (constipation, nausea, diarrhea ≤15%)
DLT	None defined
Week 16 Response	HI-P (12%), HI-N (28%), 1CR, 1 cytogenetic-CR

Sokol and List, 2011.

Paradigm of ‘cancer’ chemotherapy



- Synergism if not at lease additive, hope not antagonistic!
- Reduce toxicity and dose, non overlapping actions

Combination Therapies in MDS

Intensive chemotherapy (n=42)			AZA-001
Azacitidine (n=17)	Intensive chemotherapy (n=25)	HR (95%CI)	p value
25·1 (10·0–NR)	15·7 (8·2–24·1)	0·76 (0·33–1·74)	0·51
23·1 (6·4–25·4)	10·7 (4·6–15·4)	0·48 (0·16–1·45)	0·19

MDACC ,Courtesy GG Manero

Alternating schedule

Induction:

Clofarabine 20mg/m^2 IV QD x 5 d
Cytarabine 20mg SC BID x 10 d

Induction ± Re-Induction

⇩

Consolidation:

Clofarabine 20mg/m^2 IV QD x 3 d
Cytarabine 20mg SC BID x 5 d

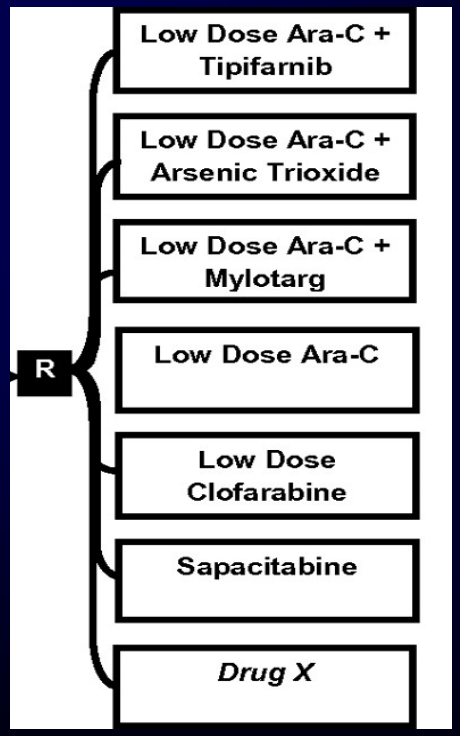
Courses 1-2, 6-8,12-14

alternating with

Decitabine 20 mg/m^2 IV QD x 5 d

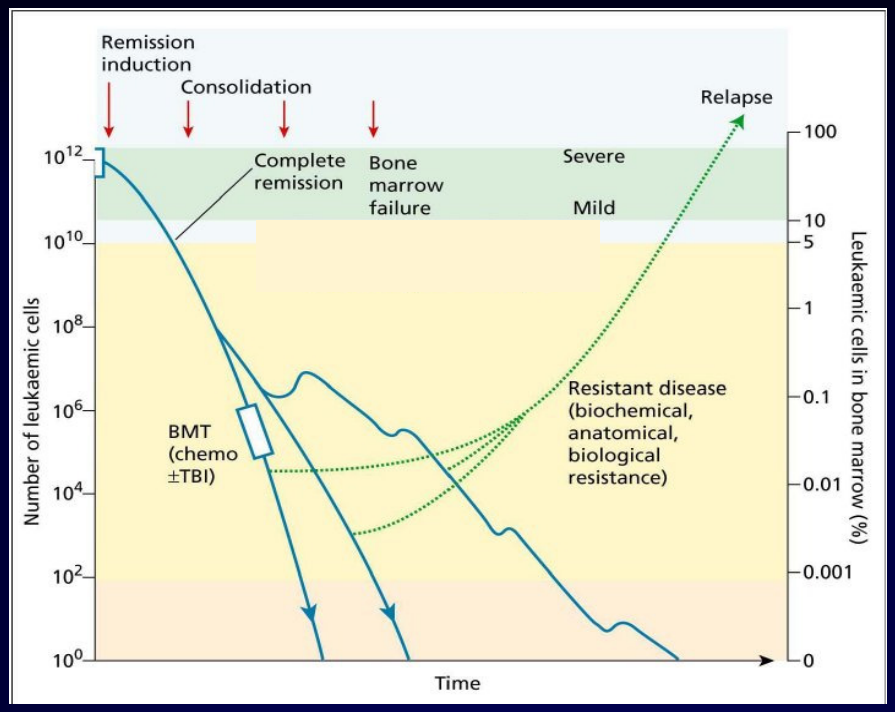
Courses 3-5, 9-11,15-17

Pick a winner AML 16 non-intensive



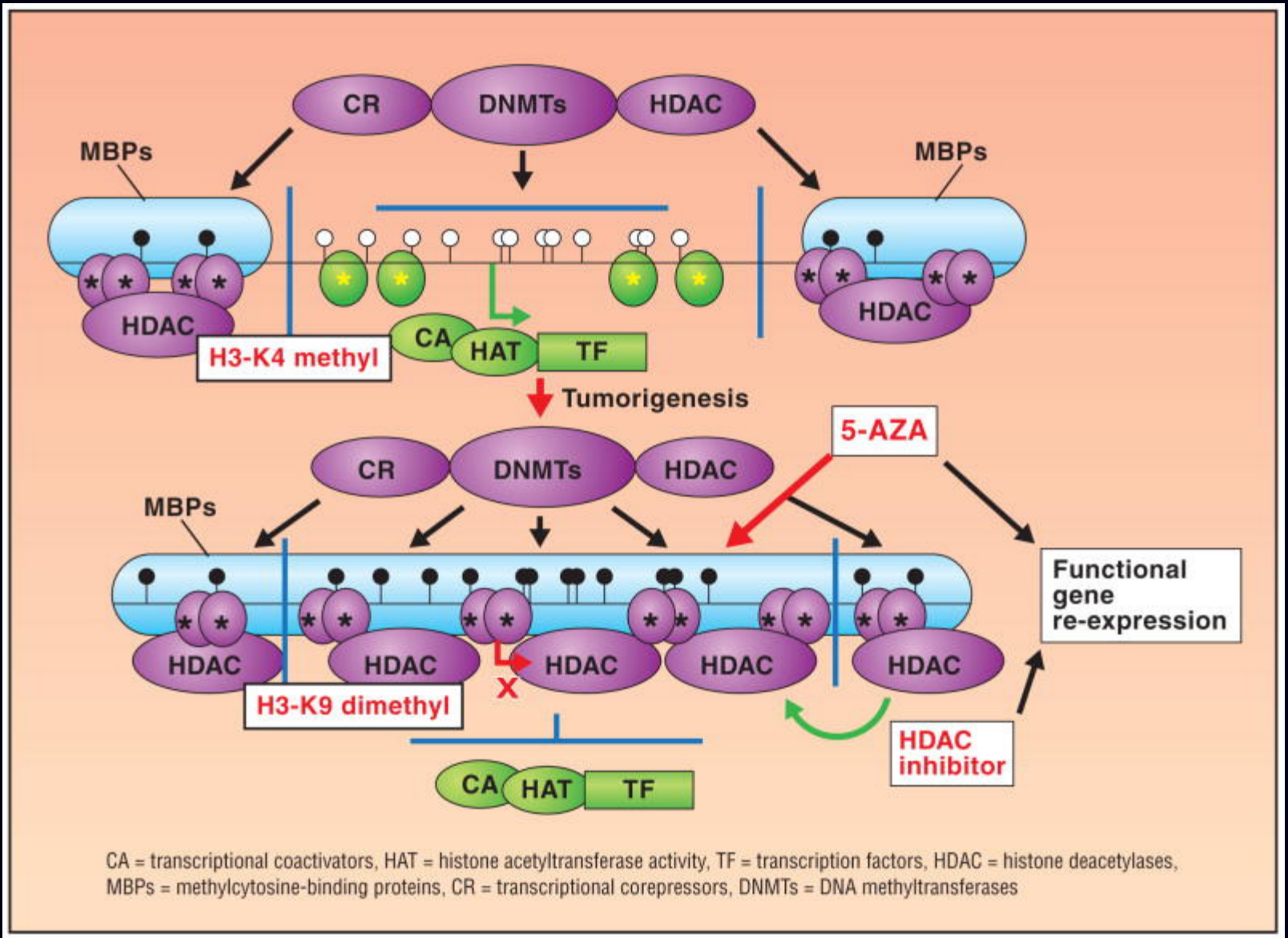
Fenaux,Lancet Oncol, 2009, and Burnett &Hills, Blood 2011

Paradigm of 'cancer' chemotherapy



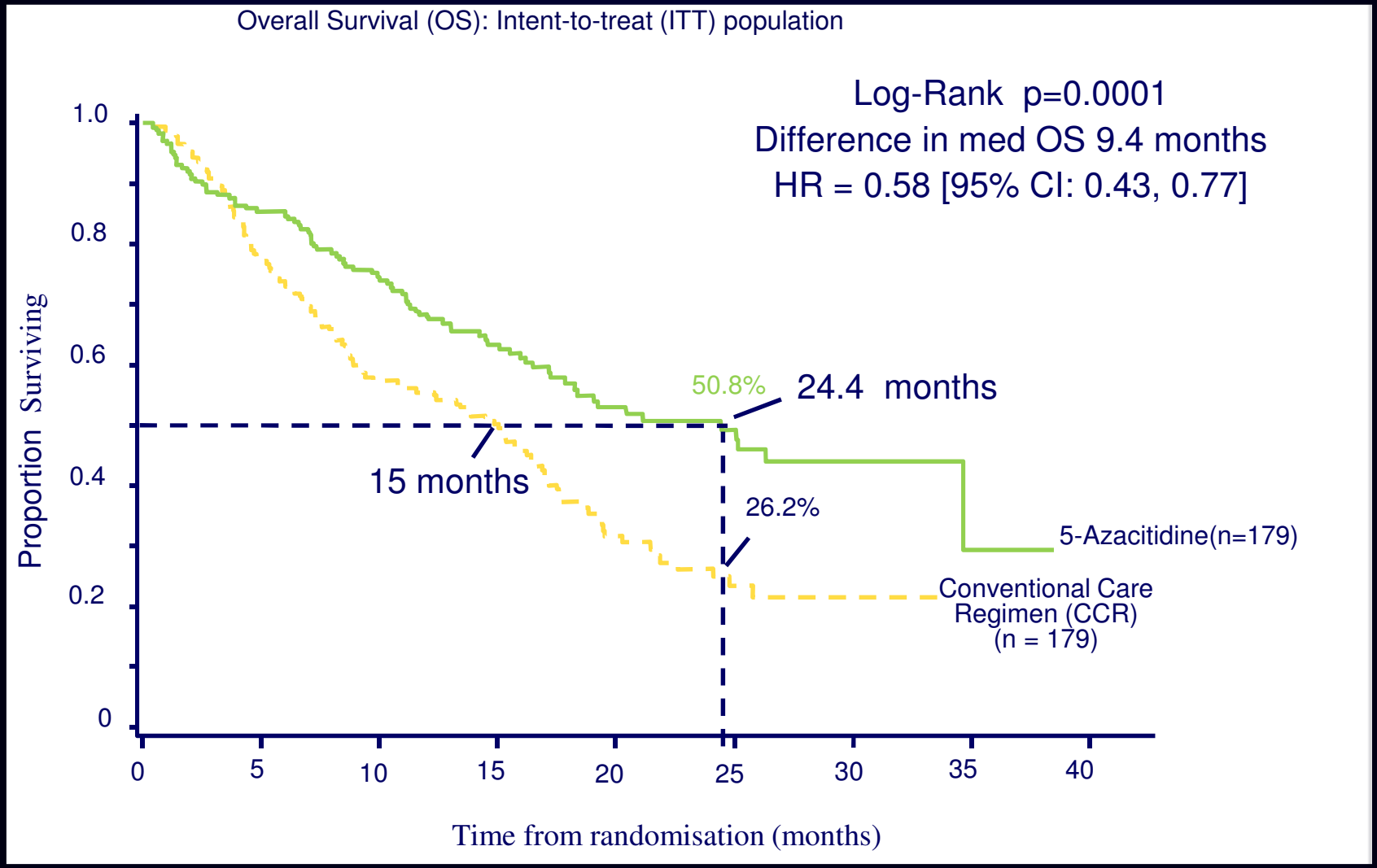
- Synergism if not at lease additive, hope not antagonistic!
- Reduce toxicity and dose, non overlapping actions.
- Epigenetic models and genetic mutation directed therapy

Normal and Tumour cells- DNA methylation and chromatin modifications



Herman and Baylin,NEJM 2003

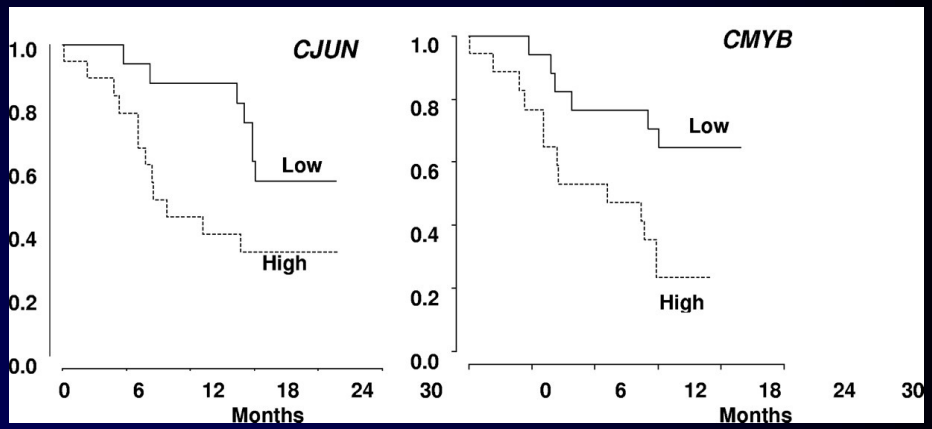
Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study.

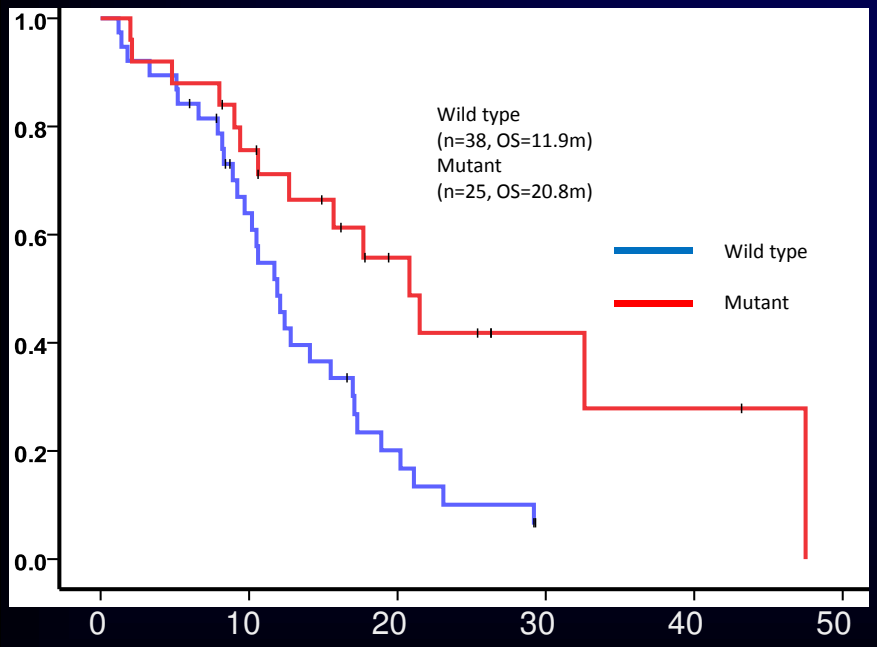


Fenaux, Lancet Oncol, 2009

Molecular predictors of response to DAC and AZA

- GFM(DAC)- 39 advanced CMML
- ORR of 38%
- 8 gene mutations did not predict response or survival (incl *ASXL1/TET2/RUNX1,RAS*)
- **Lower *CJUN* and *CMYB* expression predicted improved OS**





- Kings(Aza)- 63 high risk MDS
- ORR of 49%
- 10 gene mutations incl. *TP53*
- **Presence of EZH2 mutations associated with response**
- Better OS in patients with EZH2/ASXL1 mutation.
- P53 mutations adversely affected survival

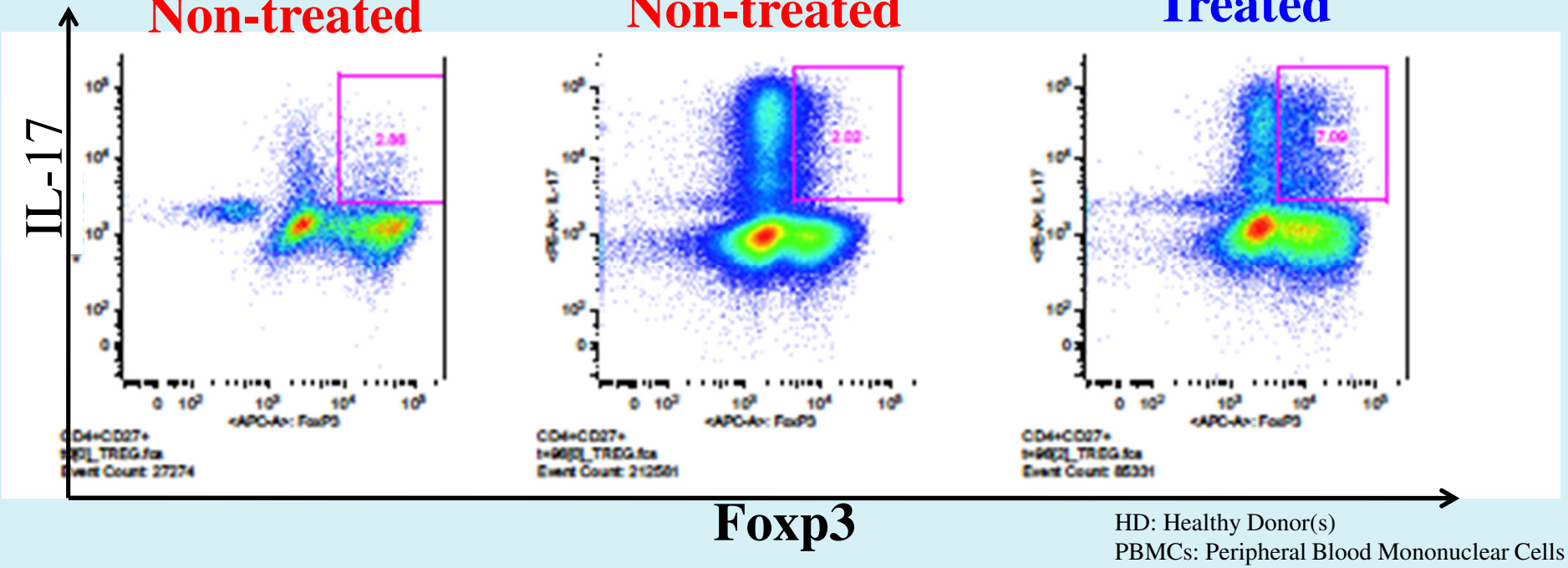
Braun, Blood, 2011 and Kulasekararaj ,ASH,2010

Foxp3 expression increased BUT more IL-17 secretion

HD PBMCs
t0
Non-treated

HD PBMCs
t+96 h
Non-treated

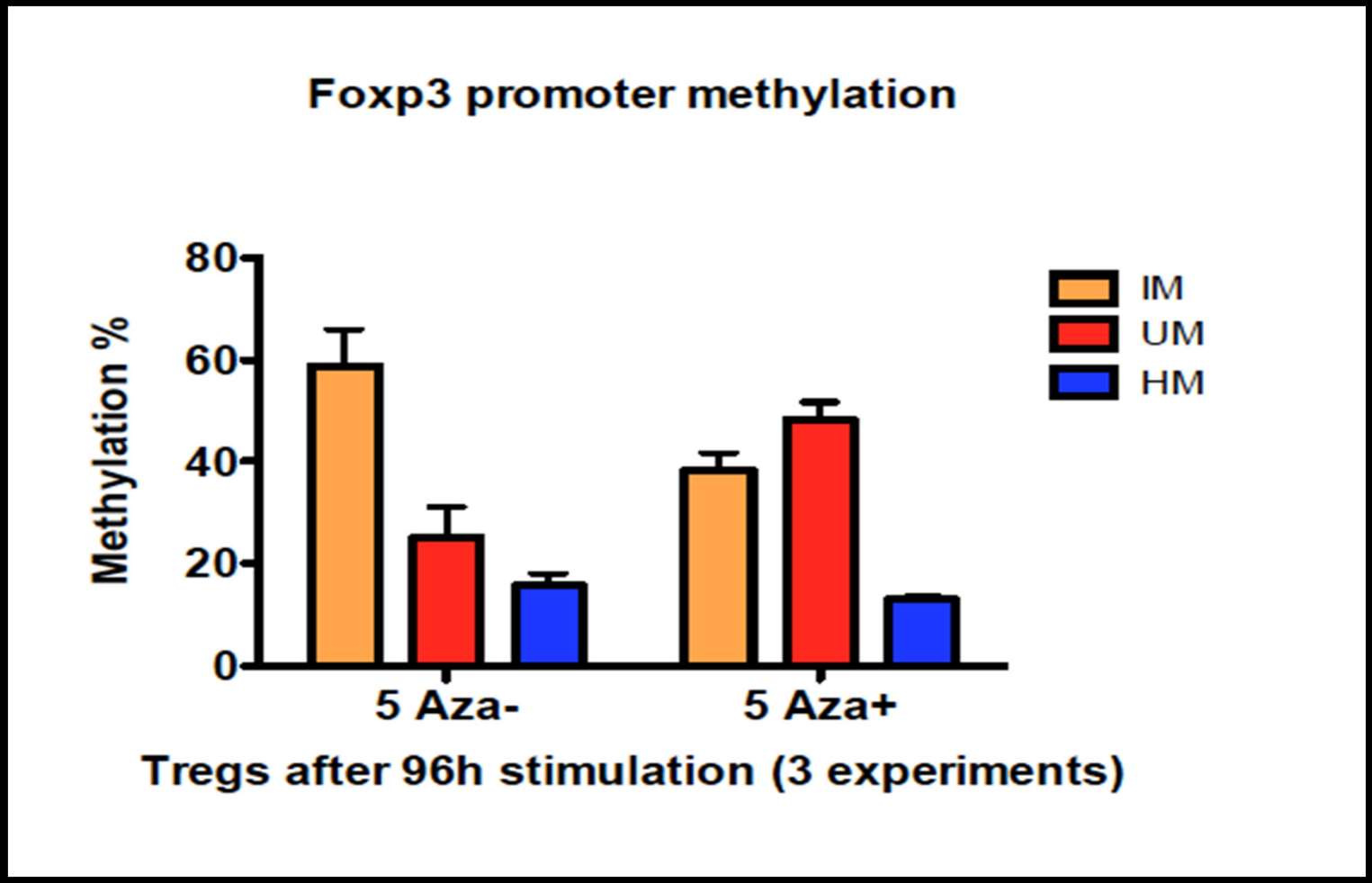
HD PBMCs
t+96 h
Treated



HD: Healthy Donor(s)
PBMCs: Peripheral Blood Mononuclear Cells
5-aza treatment: 2 µM

5-Azacytidine Specifically Depletes Regulatory T Cells (Tregs) in Myelodysplastic Syndrome (MDS) Patients (Abstract 276)

Benedetta Costantini, Shahram Y Kordasti, Austin G Kulasekararaj, Jie Jiang, PhD, Thomas Seidl, Pilar Perez Abellan, Janet Hayden, Farzin Farzaneh and Ghulam J. Mufti.



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Phase I Combination Trial of Lenalidomide and Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes and Update from Phase II

Table 1. Dose Escalation Scheme

Dose Level	
1	75
2	75
3	75
4	50
5	50
6	50

NOTE. Each cycle of
maximum of seven cy
Abbreviations: SC, su

ase II)
7-78)
veeks(2-106)

/36
2-60)

ORR

- 14
- 11

Median time to response -3 months(range 1-7 months)

Median OS for responders is 27 months(range,7-55)

Sekeres et al. JCO 2010 and ASH abstract 607,Mon, Dec 12,2011

Toxicity of combinaton-Len plus Aza

- No DLTs reached through all dosing cohorts in Phase I
- Grade 3/4 non-hematologic AEs -cardiac (11%), febrile neutropenia (31%), other infection (8%), pulmonary (11%), vascular access-related thrombosis (6%), CNS hemorrhage (6%).
- Median ANC decrease 35% and median Plt decrease 18%

Sekeres et al. JCO 2010 and ASH abstract 607,Mon, Dec 12,2011

Triple Negatives(!) respond better

Sub	Cytogenetics#	c-Cbl/b-Cbl/Jak2	TET2	Response
1	47, xy, +8 [20] UPD19p13-11p12	Wt	Wt	NR
2	**46, xy [20]**	**Wt**	**Wt**	**CR**
3	**46, xy [20]**	**Wt**	**Wt**	**CR**
4	**46, xx [20] 46,x, iXp10 [2]**	**Wt**	**Wt**	**CR**
5	**46, xy [20]**	**Wt**	**Wt**	**CR**
6	**46, xy [20]**	**Wt**	**Wt**	**CR**
7	46,xy del(5q31q35)[2] 46,xy,[18] UPD6P25-3P22.1, UPD8q24.3	Wt	Wt	CR
8	46, xy [20]	Wt	Heterozygous T1078P	CR
9	Complex, UPD11q24.2-q25	Wt	Wt	NR
10	46,xx [20]	Wt	Wt	HI
11	46,xy [20]	Wt	Wt	HI
12	Complex ^	Wt	N.D	HI
13	Complex ^	Wt	Wt	NR
14	47, xx, +8 [20]	Wt	Heterozygous V1417F	NR

Sekeres et al. JCO 2010 . Slides courtesy M.Sekeres

Azacitidine plus HDACi

- Aza/DAC +SAHA-**(ORR approx=60%)** Silverman ASH 2008
- Aza +Entinostat- E1905 (US leukaemia Intergroup trial)
- Aza + Panabinostat (LBH 589)- abstract 1529
- Aza/DAC + Valproic acid (+/- ATRA)
- Aza + MS-275
- Aza + MGCD0103

Other Combinations

- Possible combination with effective Oral Nucleoside analogues like Clofarabine and Sapacitabine
- Aza plus Romiplostim
- Aza plus Etanarcept
- Aza plus EGFR-TKIs (Abstract 2790)

5-Azacitidine and Vorinostat in Patients (pts) with Newly Diagnosed MDS or AML Not Eligible for Clinical Trials Because Poor Performance and Presence of Other Comorbidities

- Untreated AML/MDS

  -Not eligible for other clinical trials
- 5-azacitidine 75 mg/m^2 IV daily x 5 every 3 to 6 weeks and Vorinostat 200 mg orally TID

Gracia –Manero et al, Blood 2010 and Abstract 608,Monday, Dec 12 ,ASH,2011

Responses: Aza +SAHA

- 24 (80%) survived longer than 60 days with median survival of 7 months (1 to 16).
- ORR 9 (30%)-CR 8 +m CR 1
- Additionally, 8 had stable disease of the 16 non-responding patients.
- No correlation with pharmacodynamic end points.

Gracia –Manero et al, Blood 2010 and Abstract 608,Monday, Dec 12 ,ASH,2011

Single agent Lenalidomide in high risk MDS with del 5q -Prognostic factors for achieving CR

N=47
ORR of 27% and 25% achieved TI

Factor	Category	n	No. of CRs	CR, %	*P*
Cytogenetic					
	Isolated del 5q	9	6	67	< .001
	Single additional abnormality	11	1	9	
	> 1 additional abnormalities	27	0	0	
Bone marrow blasts, %					
	< 20%	29	6	21	.16
	> 20%	18	1	5	
Baseline platelet count, G/L					
	> 100	20	7	35	< .001
	< 100	27	0	0	

L.Ades,Blood 2009.

SPMs in Lenalidomide treated Low or Int-1 risk MDS patients

n=557

Median age 71 (range 27-95 yrs)
MDS-001 to -004 & -007
88(16%) had prior history of malignancies

Median Time 13.5 m

Invasive SPM
n=17

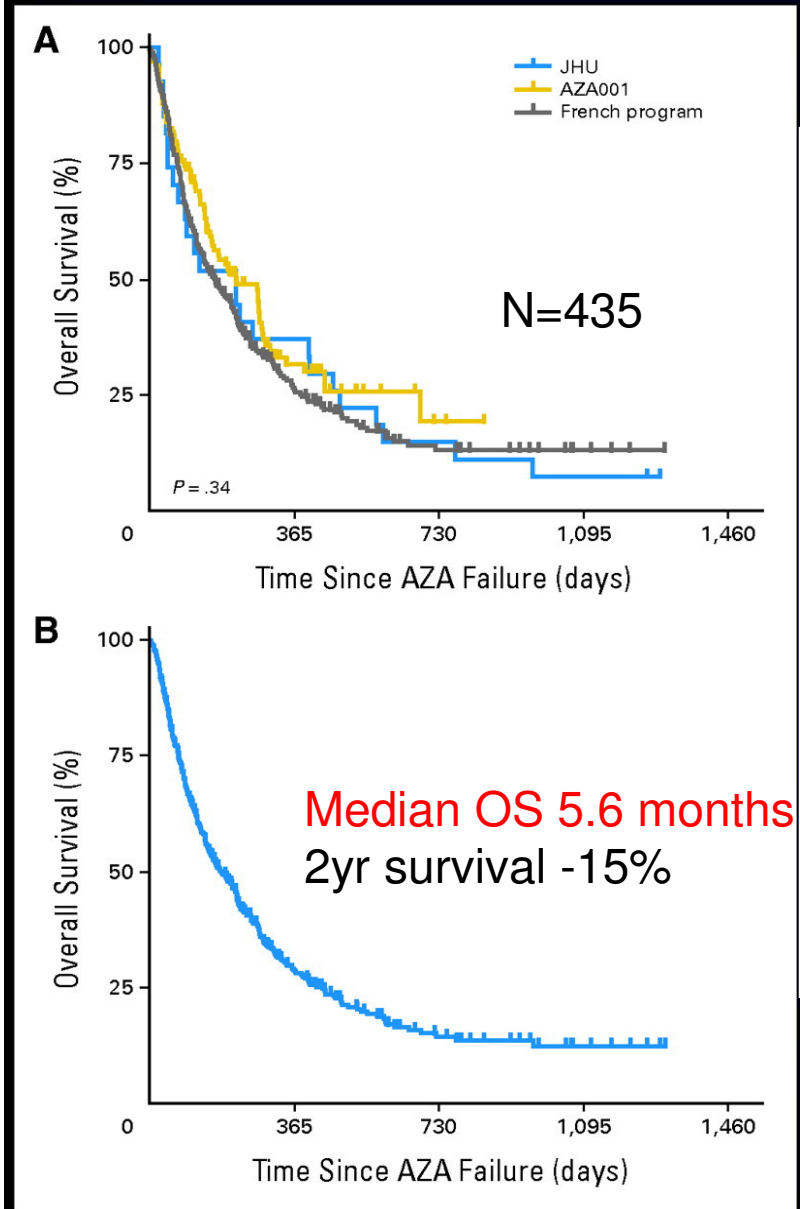
B cell malignancies(n=2)
Solid tumours (n=15)

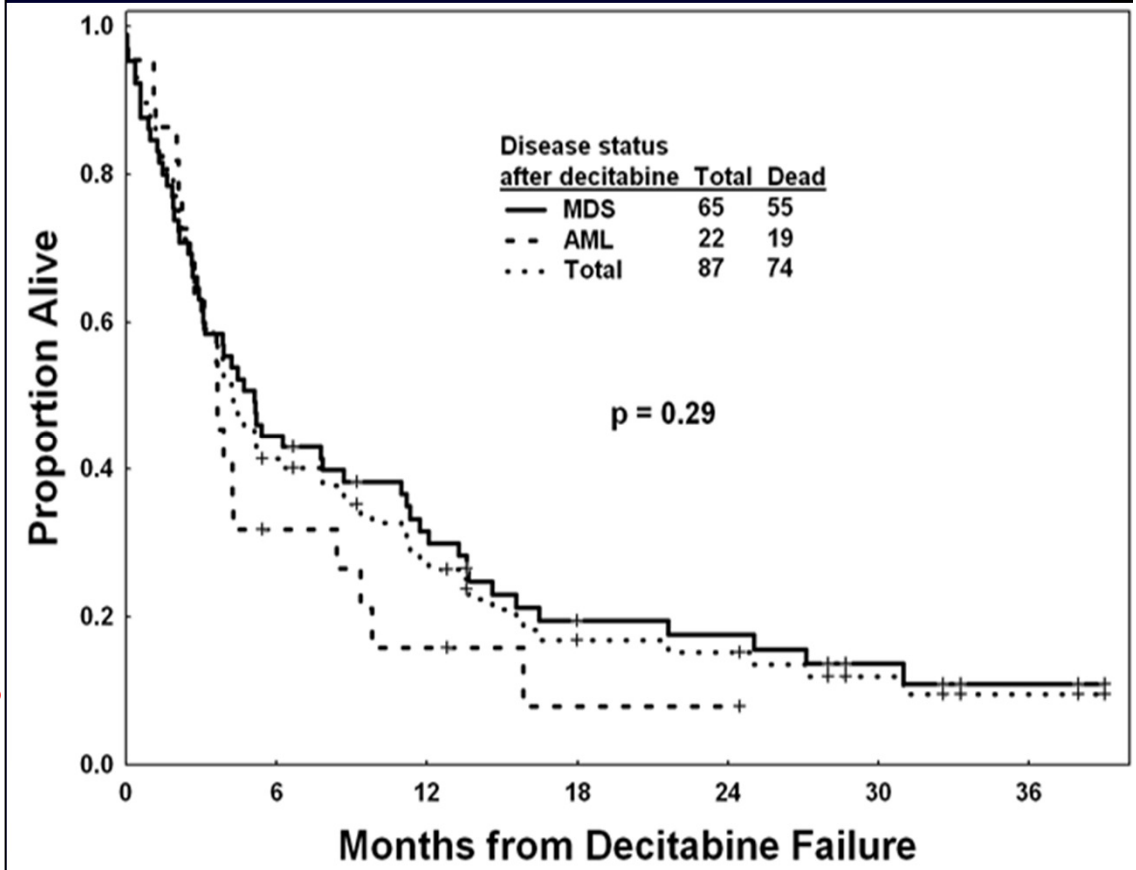
Non Melanoma skin cancer
n=12

Incidence rate is 2.6/100 patient years
(SEER data 2.1/100 patient years for >65 years)

Giagounidis et al,Abstract 1704,Saturday,Dec 10 ,ASH,2011

Outcomes after 5-Azacitidine (AZA) or Decitabine(DAC) failure



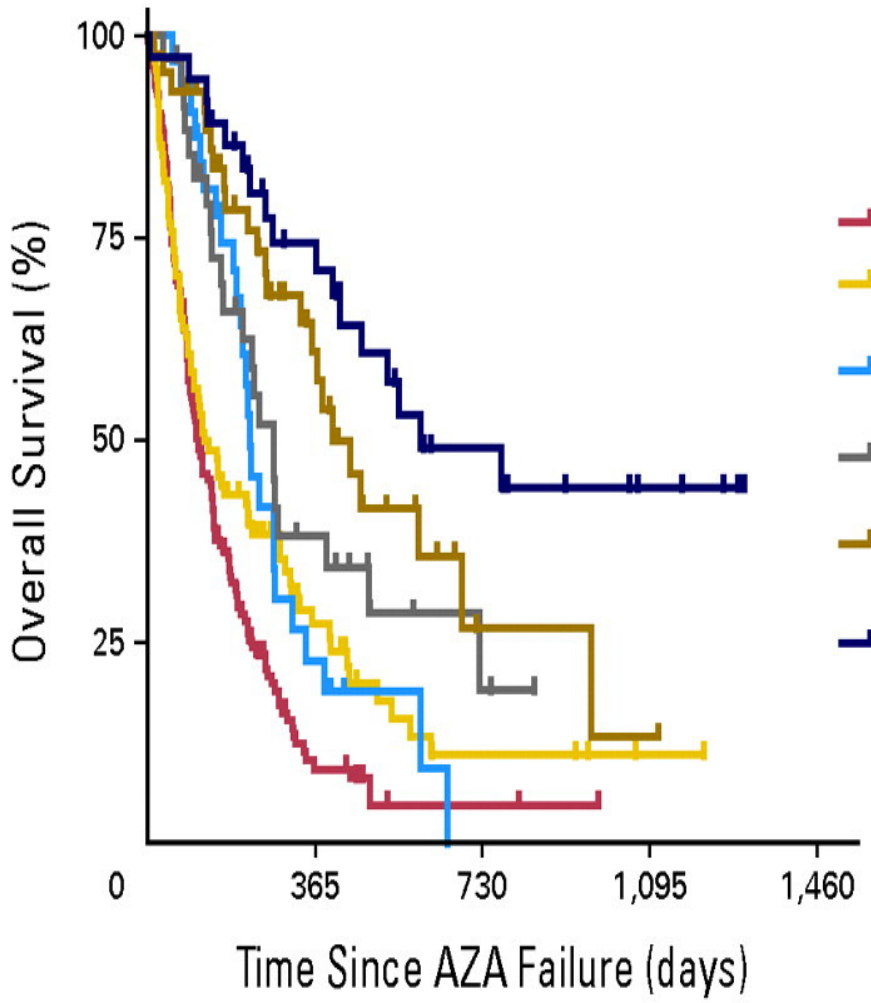


Median survival 4.3 months
1 year survival 28%
ORR to Cytarabine salvage 20%

Prébet T et al. JCO 2011

Jabbour, Cancer 2010

Outcomes after salvage therapy post 5-azacitidine failure



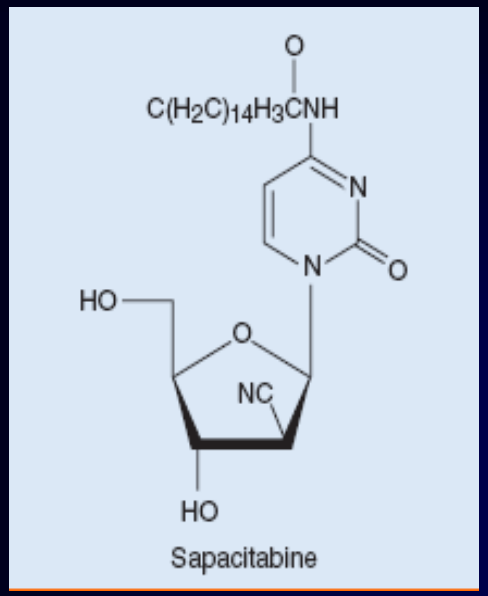
Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

Prébet T et al. JCO 2011

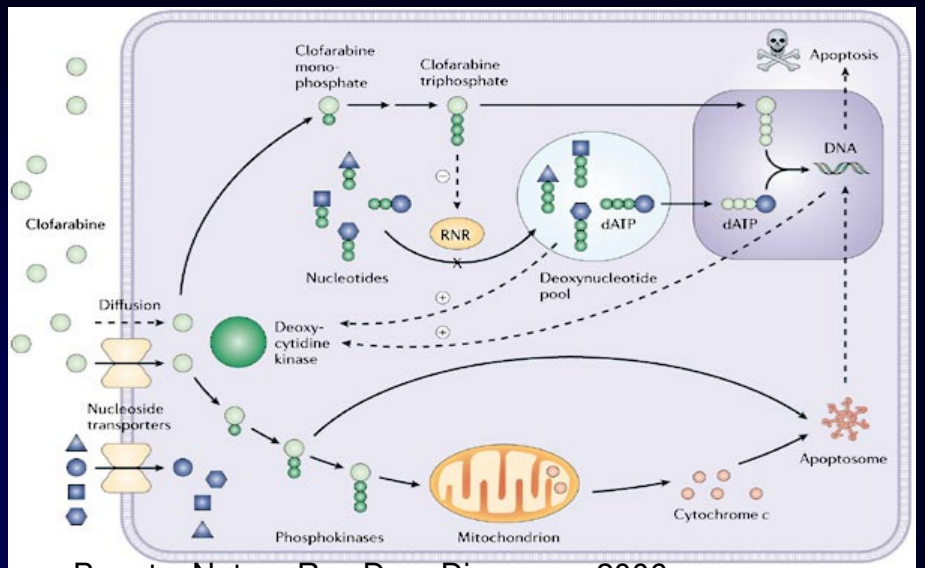
NOVEL Nucleoside analogues

-Response Rates of around 30%.

SAPACITABINE

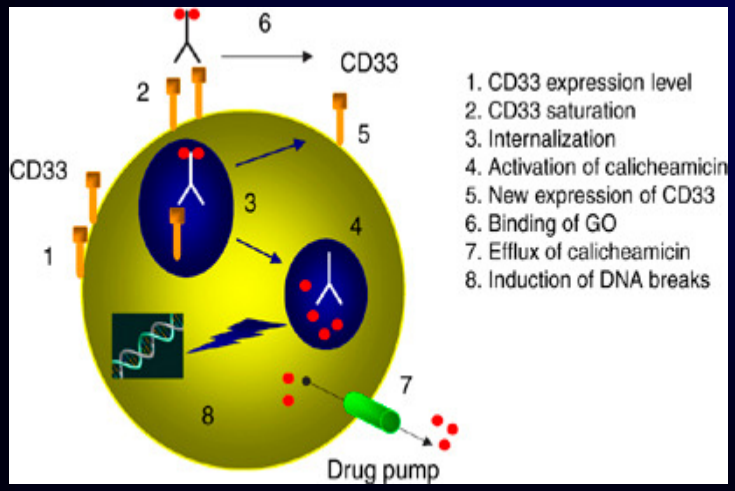


CLOFARABINE



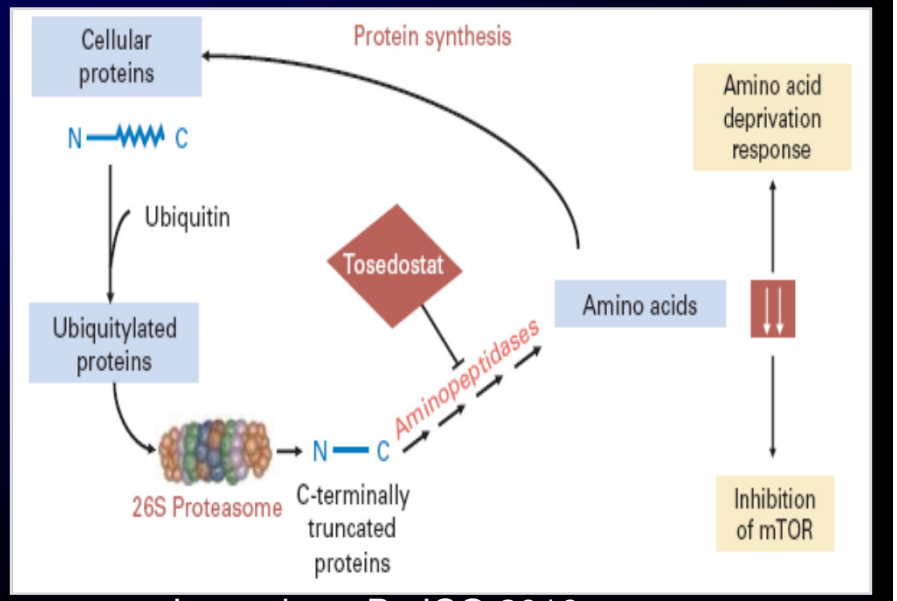
Bonate, Nature Rev Drug Discovery, 2006

Is there a role for GO ?



Pagano,Oncogene, 2007.

Tosedostat-Aminopepdidase inhibitor



Lowenberg B, JCO 2010.

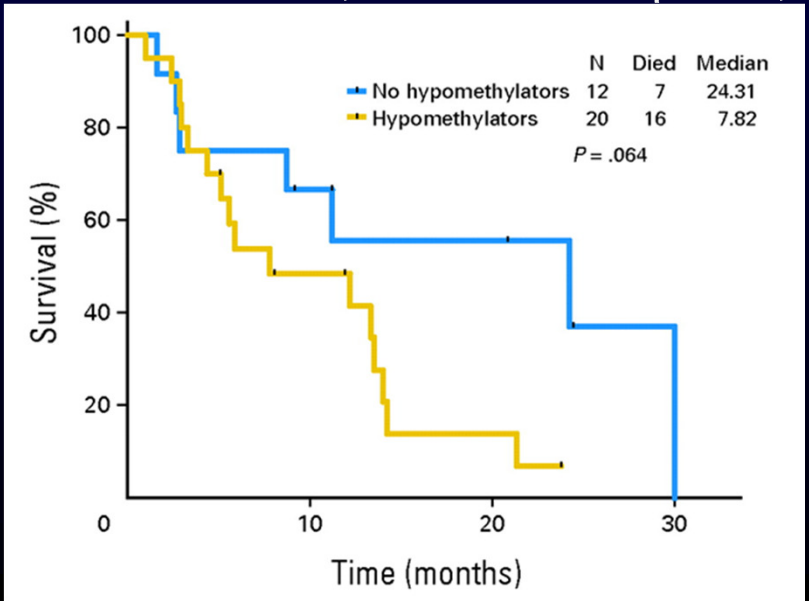
Clofarabine

- Clofarabine for 5 days every 4-6 weekly

  Oral 40/30/20 mg/m2 –*Faderl,JCO 2010*

  IV 15/30 mg/m2 –*Kantarjian,JCO 2010*

  Fixed oral dose-*Sekeres,ASH 2010*
- CR rates 25%, with ORR 43%(ORAL) and 36%(for IV)
- Median OS 5-9 months
- Med OS in Complete Responders is 20-24 months
- ORR is only 25% in AZA/DAC failure group.
- Side-effects-Transaminitis,febrile neutropenia,Nausea



Sapacitabine

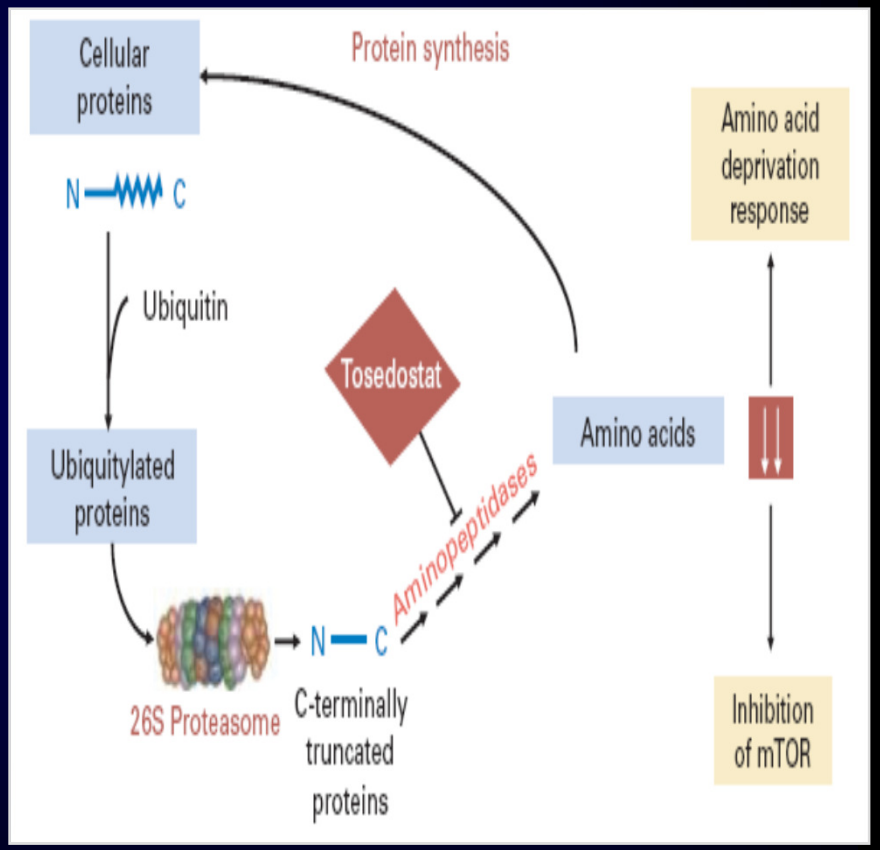
Orally Bioavailable and resistant to deamination

Drug class	Nucleoside analogue
Eligibility	Phase I,Relapsed AML or high risk MDS
Design	Daily oral BD X 3-4 wk
No. Patients	N=47
MTD	Arm A 325(7 days) Arm B 425mg(6 days)
DLT	GI and Hepatic
Response	28%: 9%CR, 4%CRp,15%CRi
4 wk mortality	4%

Kantarjian, JCO 2010

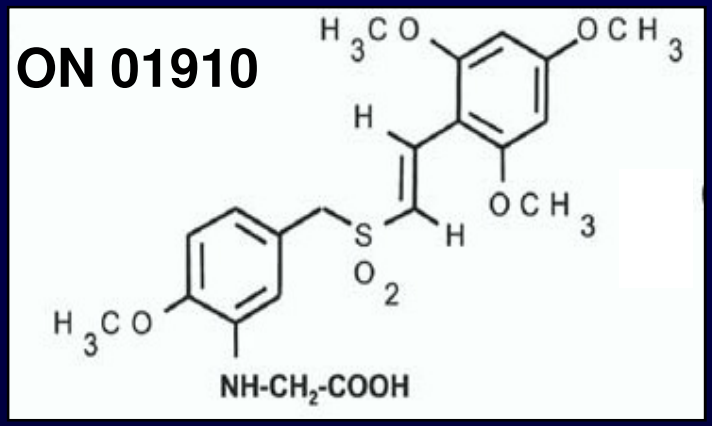
Phase I/II Study of Tosedostat in MDS & AML

Drug class	Amintopeptidase inhibitor
Eligibility	Relapsed AML or high risk MDS
Design	Daily oral (60-180mg/d)
No. Patients	N=44
MTD	180 mg (130 mg phase II)
DLT	Hepatic (ALT)
Response	14 (32%): 3CR, 4mCR, 7PR

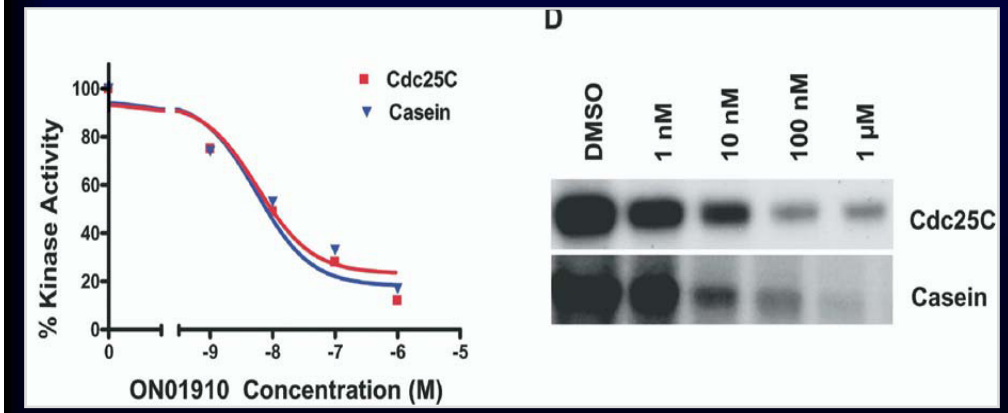


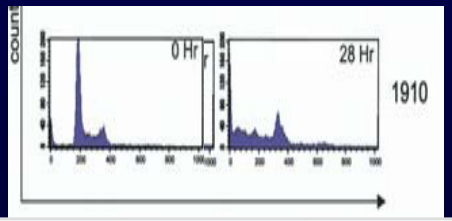
Lowenberg B, et. al.JCO 2010; 28:4333.

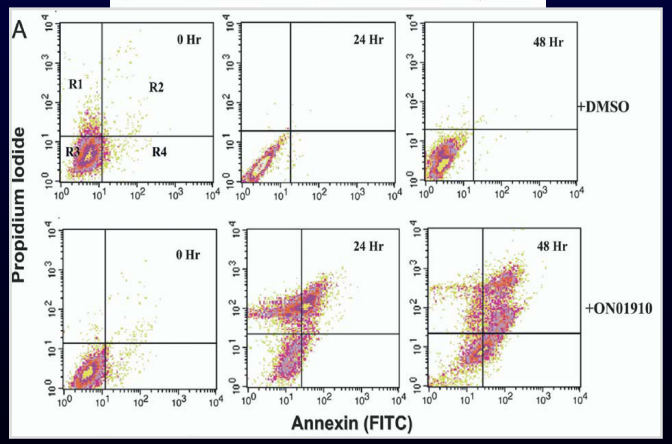
ON-01910 -Multikinase Inhibitor



- PLK1 and Cdc25C inhibitor
- ON 01910 inhibits PLK1 activation of Chk1 & Cdc25C $\rightarrow G_2$/M arrest







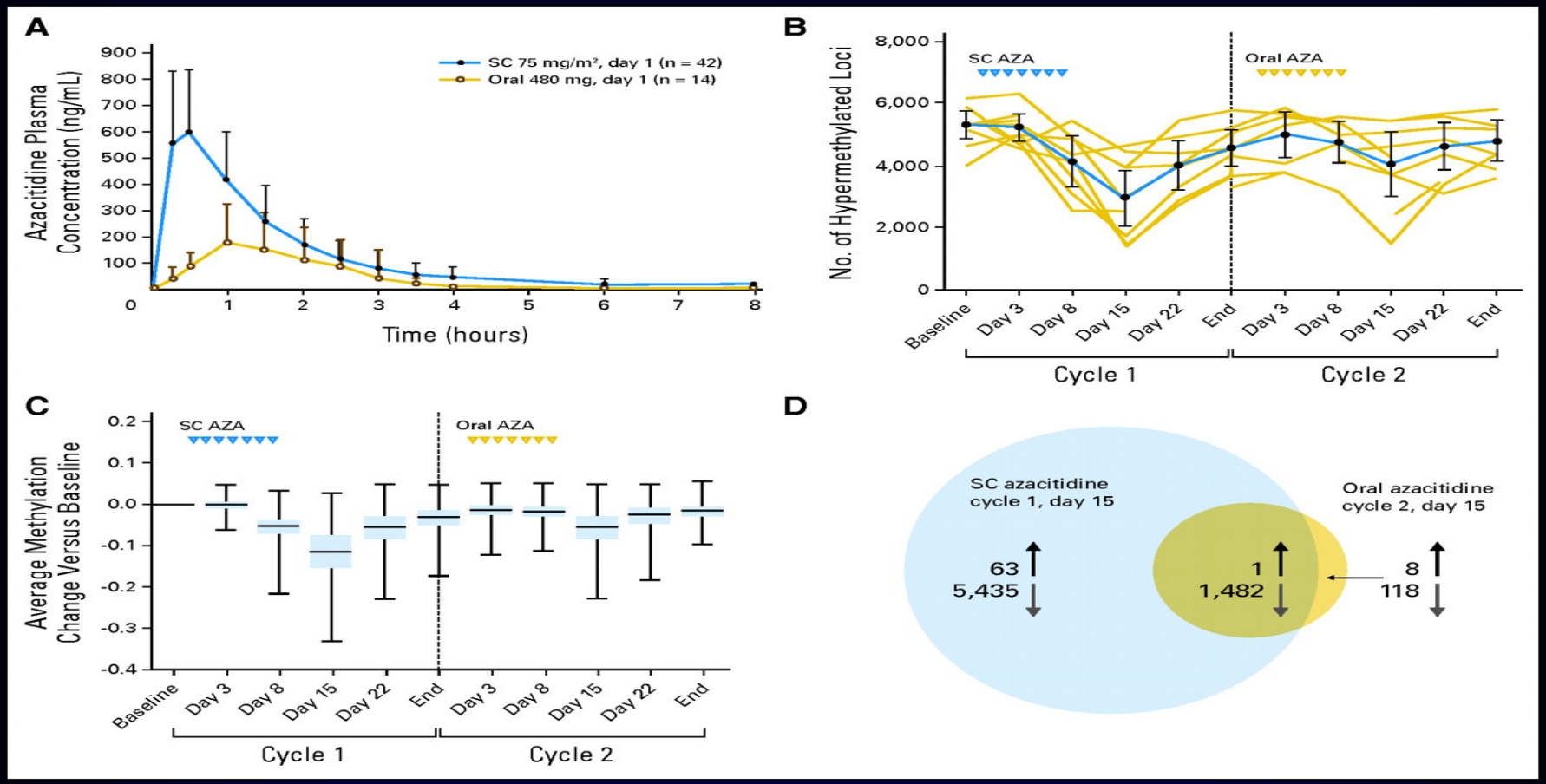
Gumireddy K, Cancer Cell 2005.

Phase I Study of Oral Azacitidine in MDS,CMML and AML

- Cycle 1 sc Aza followed by Oral Aza(Cycle 2 onwards) at doses of 120 to 600mg (7days of 28 day cycle)
- 41 patients received SC and oral azacitidine (MDS, n = 29; CMML, n = 4; AML, n = 8)
- DLT(diarrhoea) at the 600mg dose and MTD was 480 mg
- Most common grade 3/4 adverse events were diarrhoea (12.2%), nausea (7.3%), vomiting (7.3%), febrile neutropenia (19.5%), and fatigue (9.8%)
- Overall response rate was 35% in previously treated patients and 73% in previously untreated patients.

Garcia-Manero G et al. JCO 2011

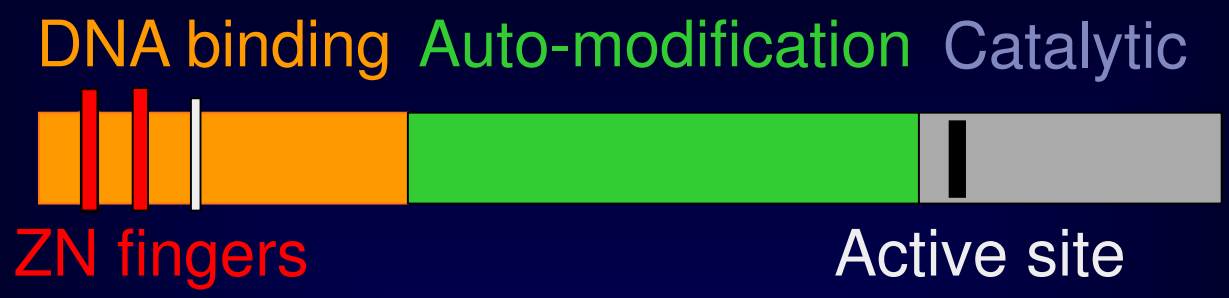
Plasma concentration and Blood Methylation patterns.



- Azacitidine exposure increased with escalating oral doses.
- Mean relative oral bioavailability ranged from **6.3% to 20%.**
- Oral and SC azacitidine decreased DNA methylation in blood, with maximum effect at day 15 of each cycle

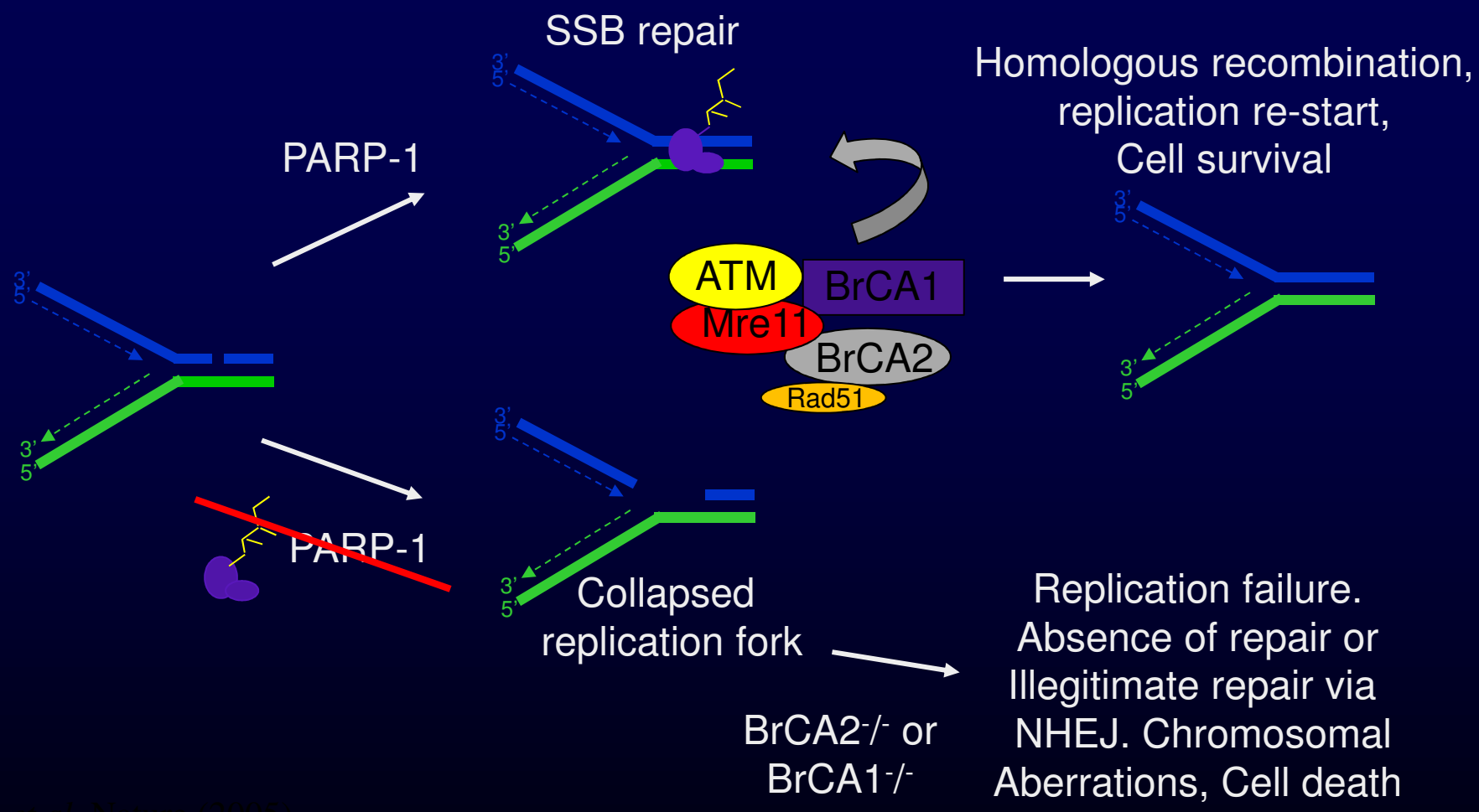
Garcia-Manero G et al. JCO 2011

Poly ADP-ribose polymerase 1 (PARP-1)



- Polymerization of ADP-ribose onto surrounding histones, transcription factors and itself
- DNA damage sensor of single strand breaks (SSB) involved in base excision repair
- ADP-ribose polymerization results in relaxation of chromatin and active recruitment of SSB repair factors to SSB.

Targeting of specific homologous recombination defects in cancer, 'synthetic lethality'

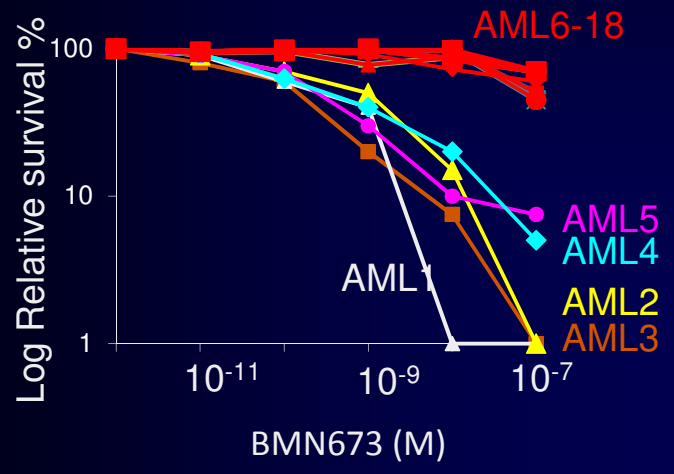


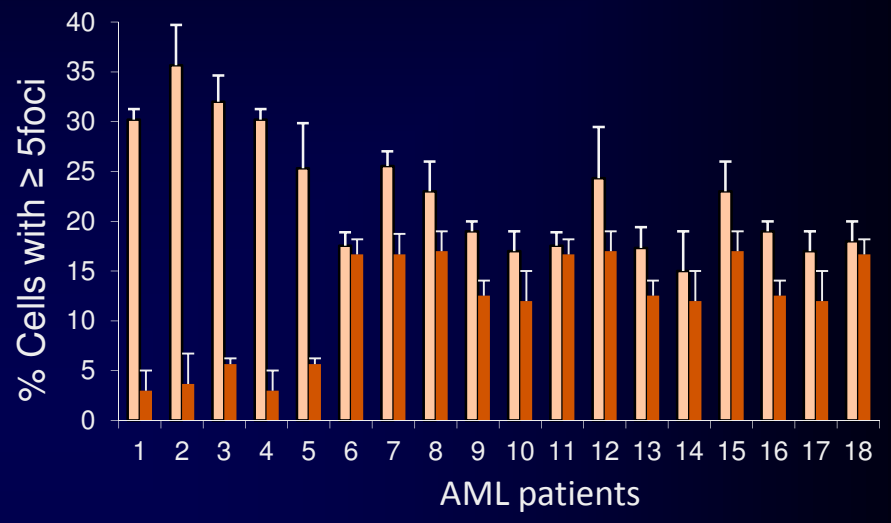
Bryant *et al.* Nature (2005)

Farmer *et al.* Nature (2005)

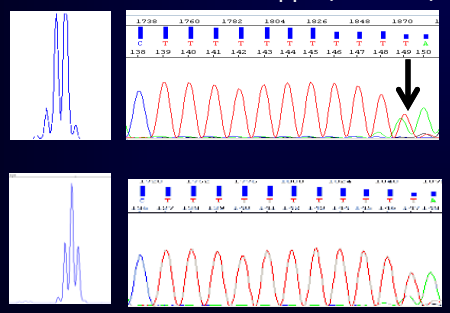
Microsatellite Instability Induced Mutation in DNA Repair Genes, *CTiP* and *Mre11* Confer Hypersensitivity to PARP Inhibitors in Myeloid Malignancies (Abstract 276)-Gaymes et al

Correlation of PARPi sensitivity in primary AML to MSI dependent abrogation of DNA repair, n=18





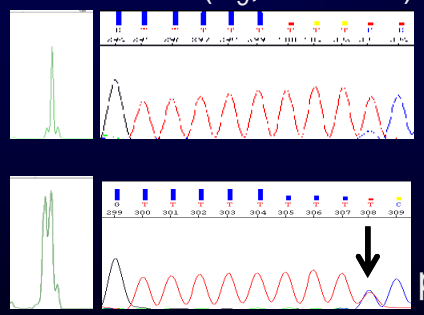
Mre11 T_{11}, (intron)



AML patient 2, $T_{10,11}$

AML patient 5, T_{11}

CTiP (T_9, exon 11)



AML patient 2, T_9

AML patient 5, $T_{8,9}$

Microsatellite Instability Induced Mutation in DNA Repair Genes, *CTiP* and *Mre11* Confer Hypersensitivity to PARP Inhibitors in Myeloid Malignancies (Abstract 276)-Gaymes et al

Post-Transplant combination strategies for relapse

- DLI plus chemotherapy
- DLI plus vaccination studies
- Post transplant Azacitidine +/- DLI (*Azarale study, Abstract 656*)
- Post Transplant Lenalidomide
- Adoptive immune therapy
- WT1 peptide Vaccination

Conclusions

- Combination therapy needs to be optimised especially in ‘high risk’ MDS patients
- Further large prospective studies might help identify molecular predictors of response to therapy.
- Non-overlapping mechanisms of actions and toxicities is important.
- Emerging efficacy of novel nucleoside analogues as single agents is promising
- PARP inhibitors are a novel class of agents and their efficacy in myeloid malignancies is been assessed

Acknowledgements

Leukaemia & Lymphoma Research
BEATING BLOOD CANCERS

Kings Health Partners

ELIMINATION OF LEUKAEMIA FUND
Advancing the cure and treatment of leukaemia

MRC Medical Research Council
Leading science for better health

DH Department of Health

EPSRC Engineering and Physical Sciences Research Council

CANCER RESEARCH UK

bbsrc

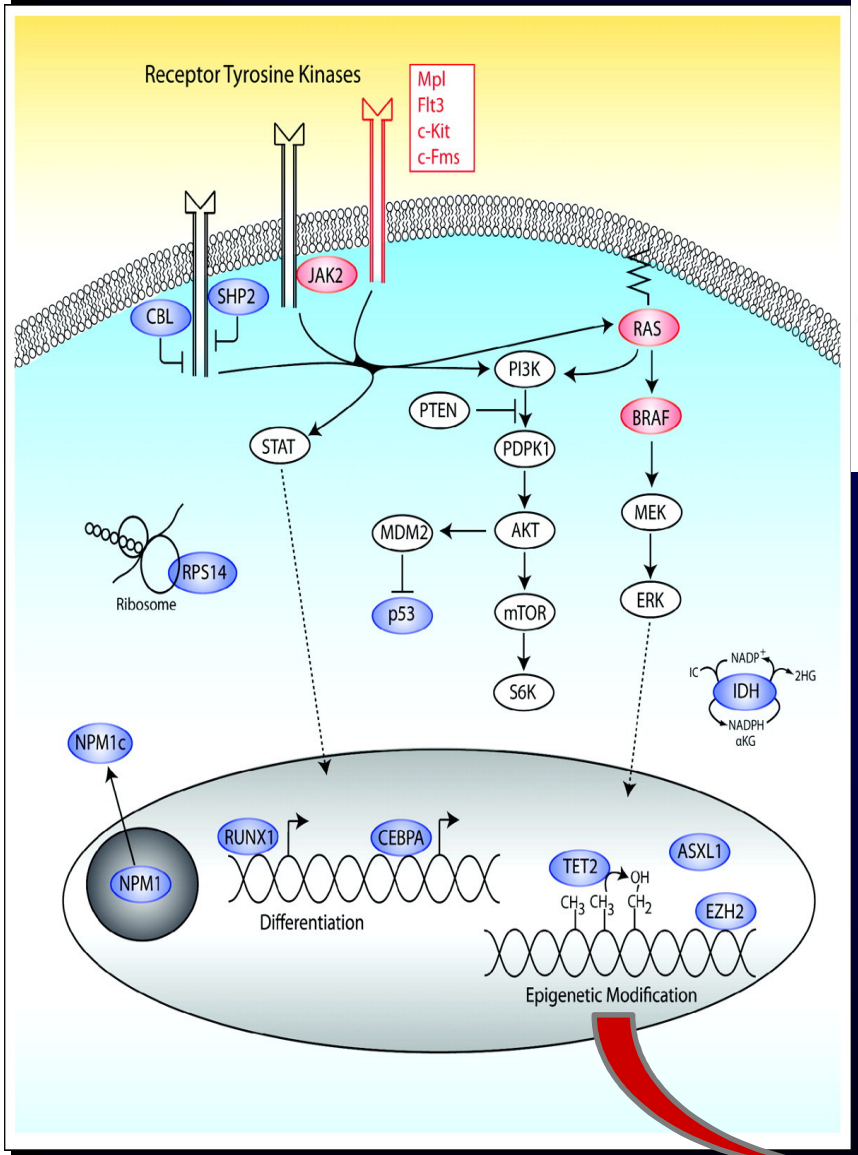
The Wellcome Trust

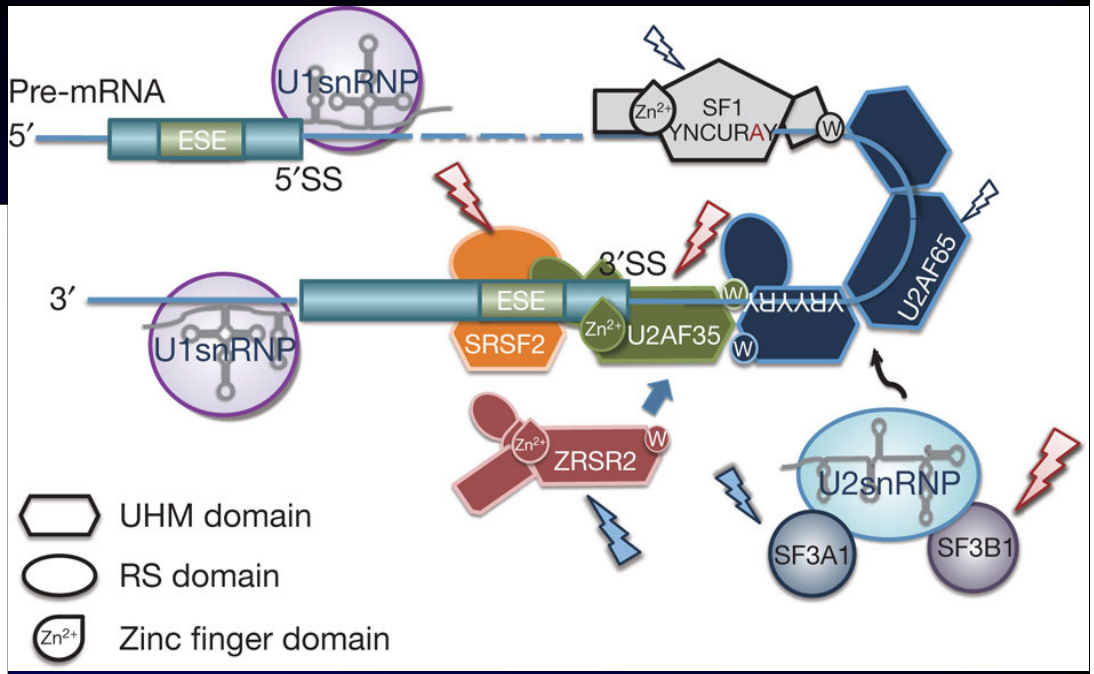
Charles Wolfson Trust
John and Holly Burton Trust

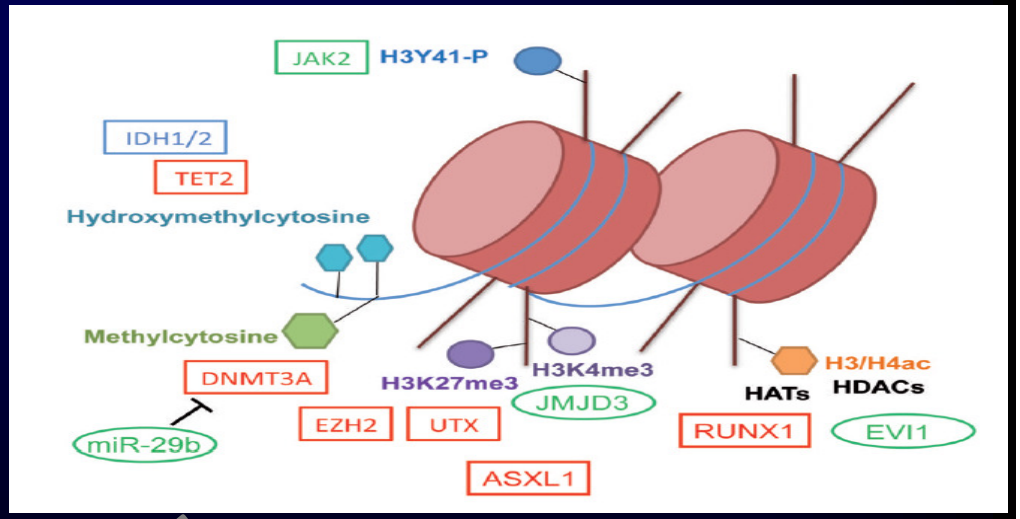
KING'S College LONDON
Founded 1829
University of London

THE KAY KENDALL LEUKAEMIA FUND

Mutations in MDS



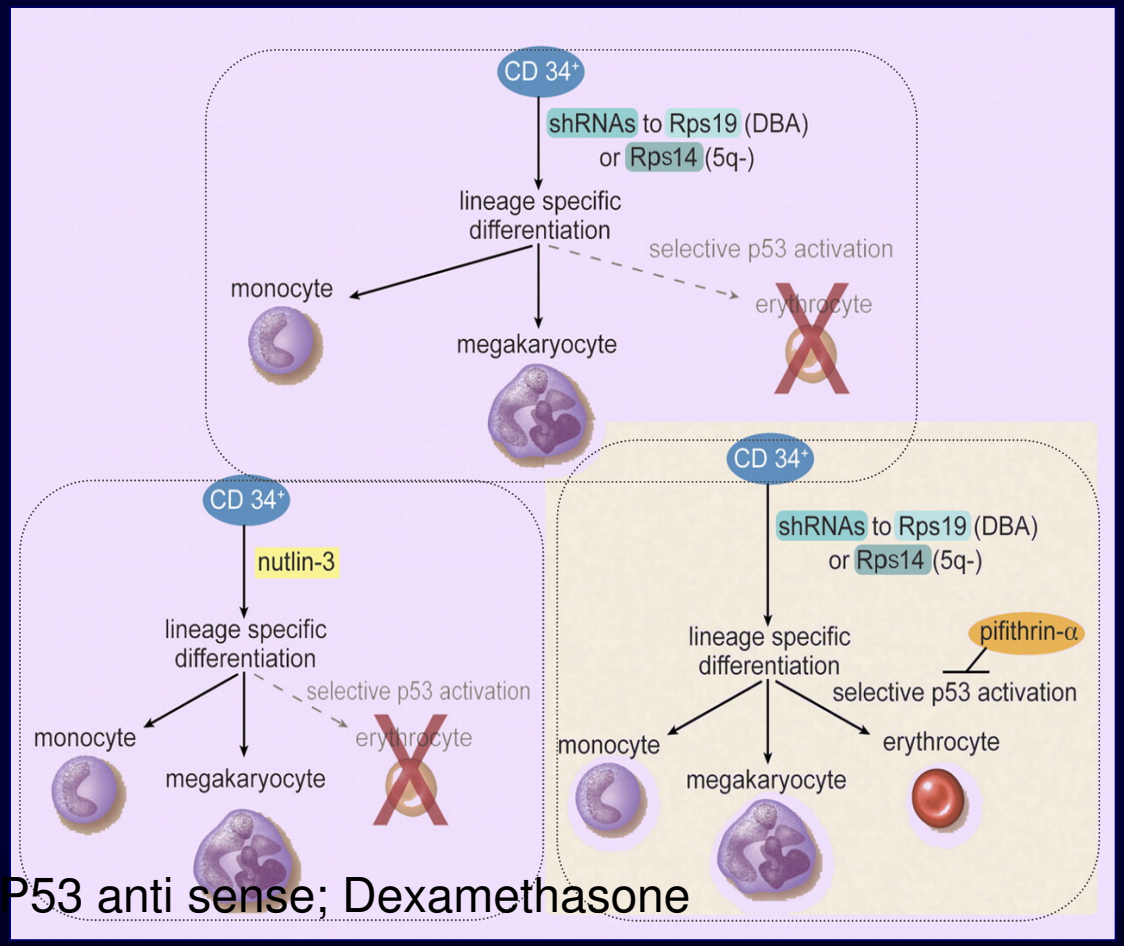




Modified from Bejar R ,JCO 2011, Levine 2010 Cancer cell and Yoshida Nature 2011

Effects of Reduced Expression of Ribosomal Proteins (RPs) on p53 Activation

P53 activation by Nutlin-3 mimics effect of ↓RPs



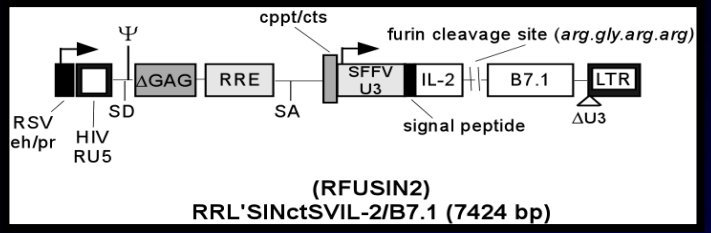
P53 inhibition rescues erythropoiesis

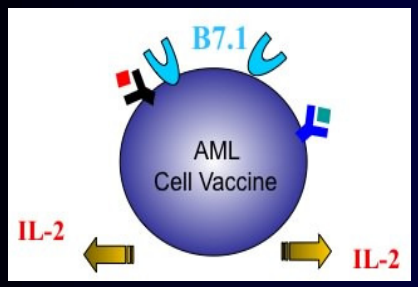
Neddylation Inhibition

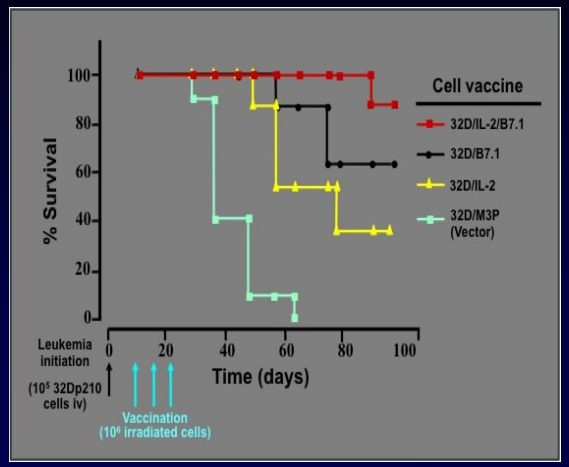
MLN4924

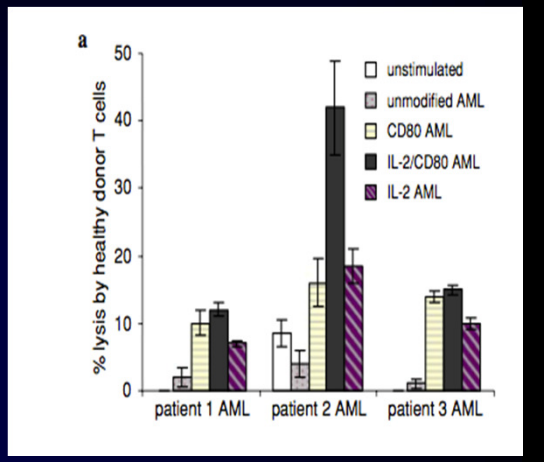
Adapted from Ellis, S. R. Blood 2011;117:2558.

RFUSIN2 Lentiviral Vector - B7.1/IL-2 transduced AML Cell Vaccine



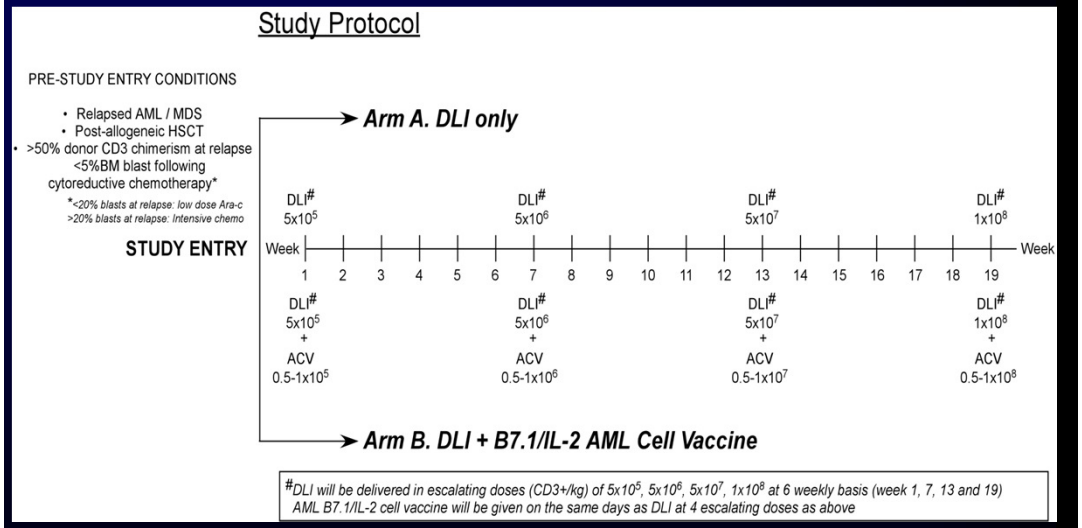






AML	FAB	Karyotype	Viability index	B7.1	IL-2/B7.1	IL-2 (10⁶cells/24 hrs)	IL-2
U937	*nd*	*nd*	1	99%	99%	11.8 ng	118 ng
NB4	*nd*	*nd*	1	97%	97%	9.5 ng	238 ng
Pat.1	TLD-AML	46,XY	0.8	96%	93%	14.6 ng	297 ng
Pat.2	RAEB-AML	45,XX,-7	1	85%	75%	15.6 ng	257 ng
Pat.3	M4	47,XY,+8	0.7	65%	41%	2.7 ng	4.7 ng
Pat.4	M5	46,XY,del(13)(q12q22),t(5;7)(p13;q34),del(13)(q12q22)	0.7	66%	44%	1.7 ng	*nd*
Pat.5	M5	46,XY,t(6;11)(q27;q23)	0.8	98%	98%	17.4 ng	362 ng
Pat.6	M2	46,XY	0.8	60%	50%	1.5 ng	5.4 ng
Pat.7	M5	46,XY,der(4),t(4;11)(q21;q23),der(11),del(11)(q13;q23),t(4;11),ins(19;11)(p13-3;q13;q23)	0.9	61%	48%	1.5 ng	14 ng
Pat.8	M1	46,XY,t(5;6)(p15;q15),t(16;21)(p13;q11)	1.2	71%	80%	7.7 ng	2 ng

Allogeneic – Post-transplant relapsed AML



Chan, Hardwick, Ingram et al:Mol Ther 2005;J. Virol 2006
BJ Haem 2009;Can Imm Immth 2010

Patient Characteristics: Aza +SAHA

Baseline	Total N=30
Median age (range)	74 (44-83)
Median WBC	3 K/Ul (0.6-112)
Median BM blasts	10% (1-78)
Complex cytogenetics	16 (53%)
Diagnosis	
MDS	16 (53%)
CMML	2 (7%)
AML	12 (40%)
Prior Malignancy	16(53%)

Gracia –Manero et al, Blood 2010 and Abstract 608,Monday, Dec 12 ,ASH,2011