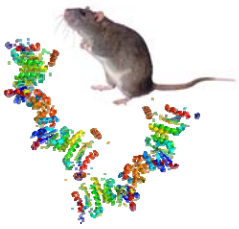
NMDP Symposium
Atlanta, Georgia; December 2012



Drug therapy for MDS: targets and biomarkers

David Steensma, MD FACP
Associate Professor of Medicine, Harvard Medical School
Adult Leukemia Program, Dana-Farber Cancer Institute
Hematological Oncology Service, Brigham & Women's Hospital

What do we mean by "targeted therapy" in the MDS context?

- A 'buzzword' – cliché?
- We don't really know the 'target' of the current FDA-approved therapies
  - 'epigenetic' and 'immunomodulatory' = *handwaving*
- Challenges:
  - Like most other neoplasms, MDS is heterogeneous
  - Unlike most other neoplasms, this extends even to basic pathophysiology (e.g., immune dysregulation)
  - Multiple clones in individual patient
  - Many somatic mutations described, but none exceed 25% frequency overall

What are the "targets" that the existing MDS therapies are hitting?

Current "standard" therapy for MDS

Supportive care for all (transfusions and antimicrobials PRN, ?iron chelation)

Lower-risk MDS (*assessed using IPSS, etc.*)

Cytopenia(s)	Disease feature	First-line therapy
Anemia only	Del (5q)	**Lenalidomide**
	No del(5q), sEPO <500	**ESA** ± G-CSF
	No del(5q), sEPO >500	?Immunosuppressive therapy
Neutropenia or **thrombocytopenia** or both		None established; observation, growth factors, aza/decit all reasonable

Higher-risk MDS

Allogeneic SCT candidate?	Therapeutic approach
Yes	**Proceed to transplant ASAP**; a hypomethylating agent (HMA) or cytotoxic chemotherapy may be useful as a "bridge"
No	**Azacitidine; decitabine** as alternate

Partly based on 2012 NCCN guidelines; see www.nccn.org

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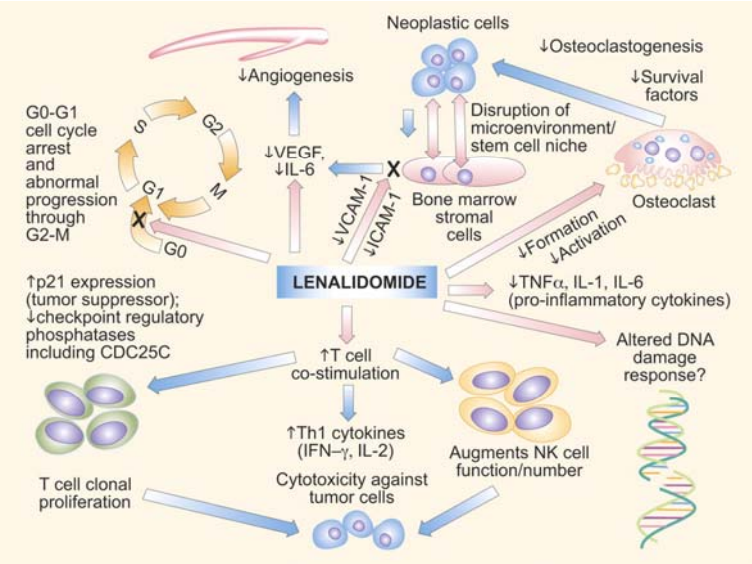
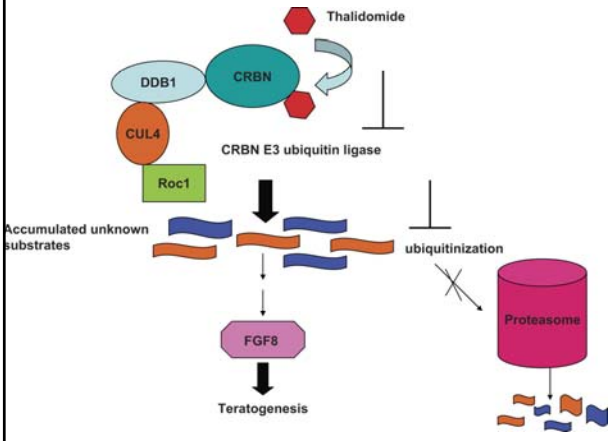
Proposed molecular and cellular targets of lenalidomide with potential relevance to human neoplasia



Steensma D P , Stone R M Blood 2011;118:481-482

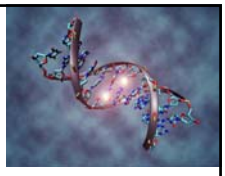
New insights into lenalidomide mechanism

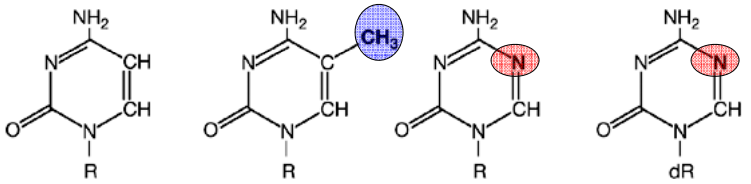


- Thalidomide and derivatives binds to **cereblon (CRBN)**
- IMiDs inhibit CRBN-associated **E3 ubiquitin ligase** activity
- E3 UL inhibition results in accumulation of unknown substrates

Ito T et al *Science* 2010 ; 327 : 1345 – 1350.
Zhu Y X et al *Leukemia & Lymphoma, 2012;* Early Online: 1–5 .

DNA methyltransferase inhibitors ("Hypomethylating" or "epigenetic" agents)





Cytidine | 5-Methyl-cytidine | 5-Aza-cytidine | 5-Aza-2'-deoxycytidine

(azacitidine) *Incorporates into **RNA***

(decitabine) *Incorporates into **DNA***

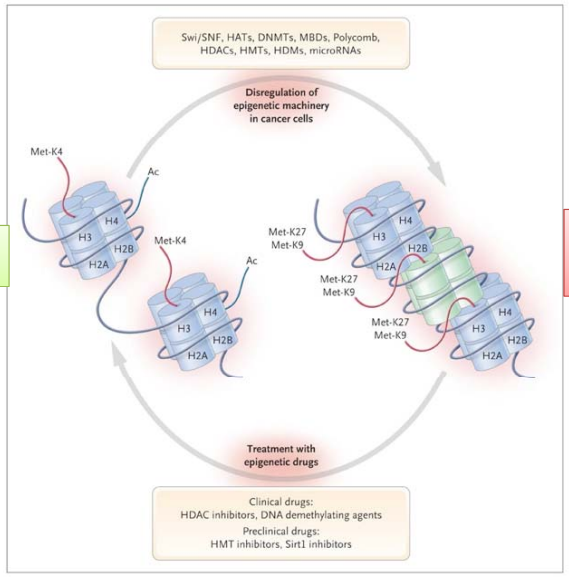
DNMT1

can't make new methyl-cytosine

Binds to, and irreversibly inhibits, "maintenance" DNA methyltransferase 1 (DNMT1)

Epigenetics and cancer

Open chromatin; Transcription high

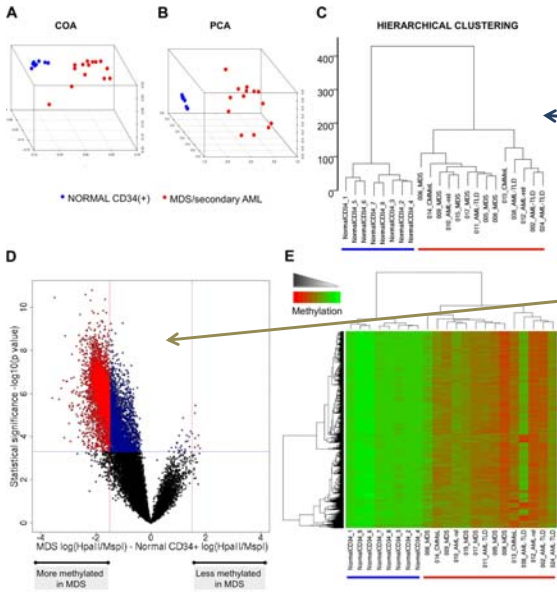


Compacted chromatin; Transcription low

Esteller M *NEJM* 2008 358;1148-1159

MDS displays marked aberrant promoter DNA methylation

(*Hpa*II tiny fragment enrichment by ligation-mediated PCR, followed by MassARRAYEpiTyping)



Unsupervised clustering analysis of 14 MDS samples and 8 CD34+ normal controls with the use of 3 different algorithms

"Volcano" plot of methylation difference between MDS cases and normal CD34+ controls (x-axis) versus statistical significance (y-axis); trend to **higher methylation levels in the MDS cases.**

"Heatmap" 2-D hierarchical clustering of differentially methylated genes between MDS and normal CD34+ controls.
Cases = columns, and probe sets in the rows.

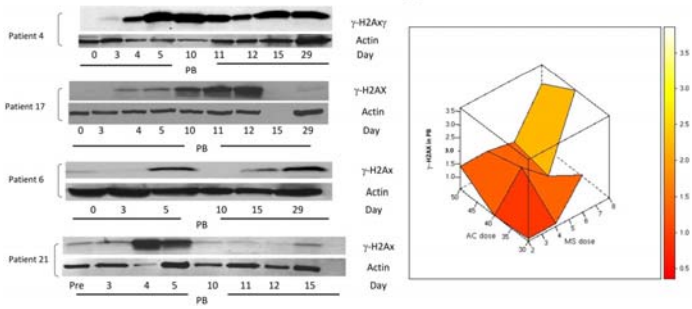
Figueroa M E et al. Blood 2009;114:3448-3458

Are "epigenetic" agents actually acting clinically via epigenetic mechanisms on tumor suppressors?

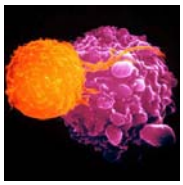
No correlation of HMA response with <u>pre-treatment DNA methylation</u> status -
- Shen L et al *JCO* 2010 (JP Issa lab); also studied for numerous candidate genes

No correlation with early <u>on-therapy DNA methylation changes</u> or DNA damage
- Fandy T, Herman JG et al *Blood* 2009 and others

Induction of **DNA damage-associated** variant histone gamma-H2AX is observed during therapy with HMA
- Fandy T, Herman JG et al *Blood* 2009



An alternative hypothesis: *"epigenetic" agents are immunomodulatory*



- Suggestive evidence:
  - HMAs augment CD4+CD25+FOXP3+ **Tregs** by increasing *FOXP3* expression
  - HMAs augment KIR expression and thereby increase GvL effect of **NK cells**
  - HMAs induce **cytotoxic CD8$^+$ T-cell response** to candidate tumor antigens (post-SCT)

Goodyear O C et al. *Blood* 2012;119:3361-3369
Reviewed in: Engel N, *Clin Epigenetics.* 2011 August; 2(2): 411–416.

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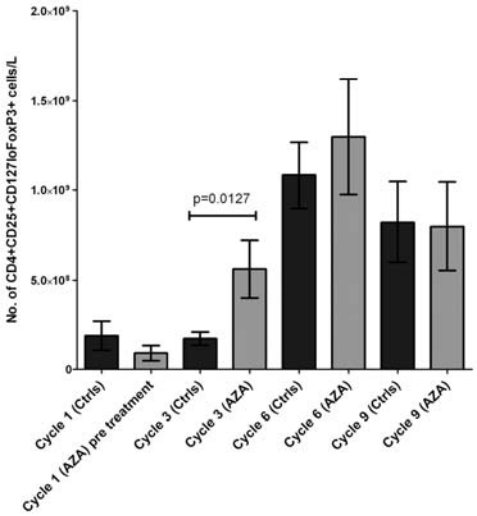
Comparison of the number of CD4+CD25+CD127^{lo}FoxP3+ Treg T cells per liter after transplantation in post RIC - AZA treated patients compared with time-matched samples from RIC controls.



Goodyear O C et al. Blood 2012;119:3361-3369

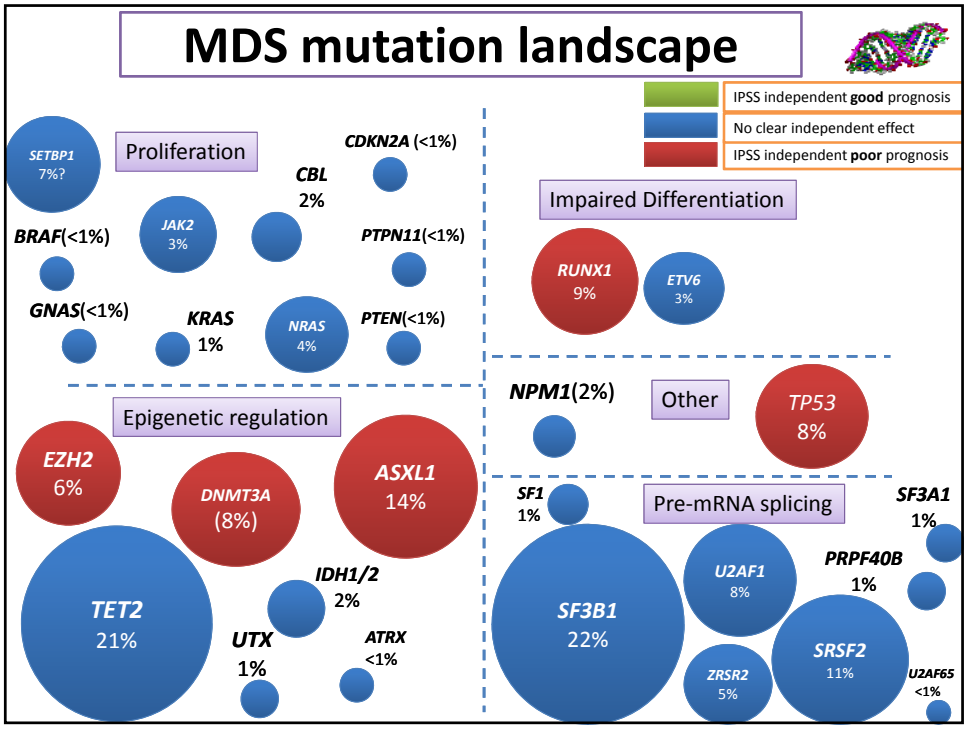
What other "targets" might there be in MDS?

Karyotypes have given limited insight into MDS pathobiology

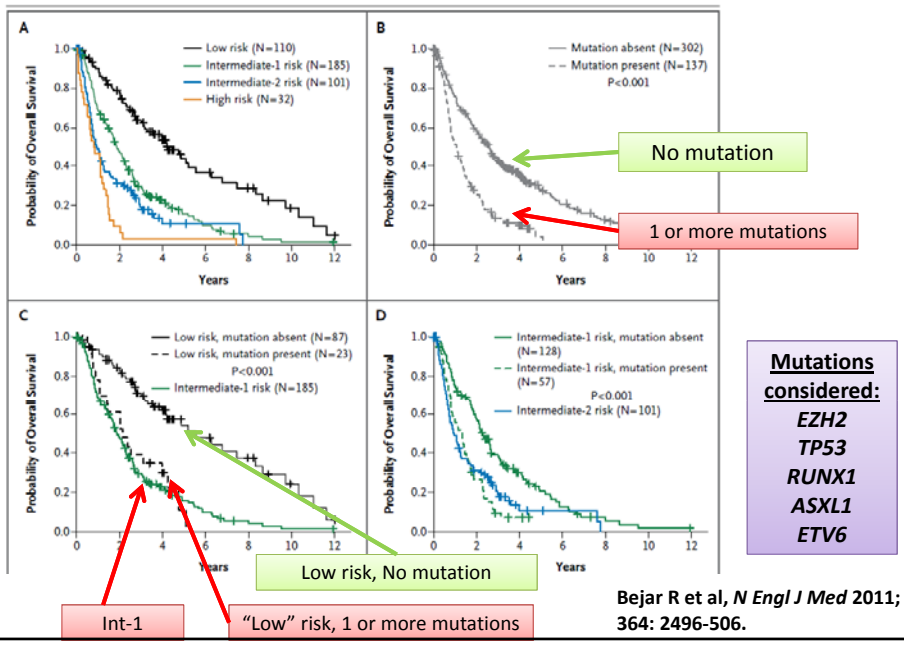
Risk group	Included karyotypes	Median survival, years	25% of patients to AML, years	Proportion of patients in this group
Very good	del(11q), -Y	5.4	N/R	4%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	4.8	9.4	72%
Intermediate	+8, del(7q), i(17q), +19, any other single or double abnormality not listed	2.7	2.5	13%
Poor	Abnormal 3q, -7, double abnormality include -7/del(7q), complex with 3 abnormalities	1.5	1.7	4%
Very poor	Complex with >3 abnormalities	0.7	0.7	7%

From: Greenberg P et al *Blood* ePub 27 Jun 2012

MDS mutation landscape



Impact of mutations on IPSS risk modeling in MDS



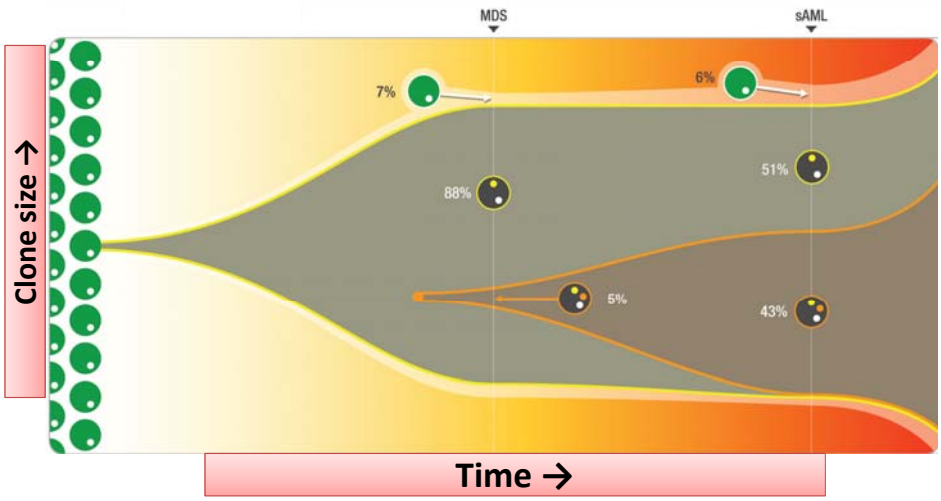
Mutations considered:
EZH2
TP53
RUNX1
ASXL1
ETV6

Bejar R et al, *N Engl J Med* 2011; 364: 2496-506.

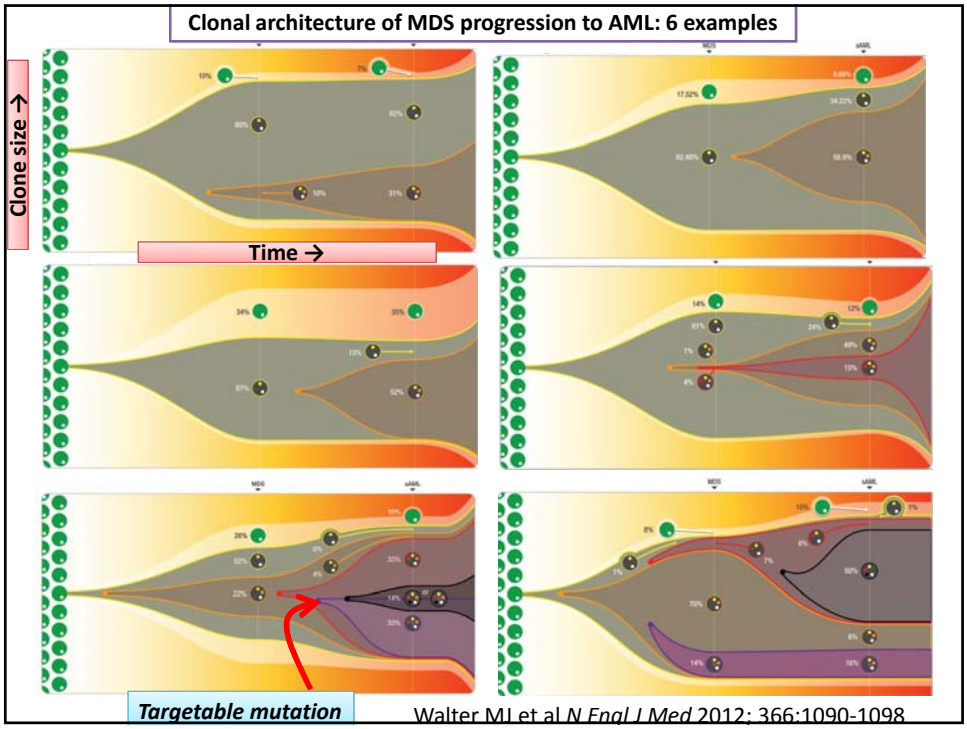
Effect of mutations on MDS outlook: not simple!

- Allele burden matters
- Potential for meaningful interactions (high combinatorial power!)
- Specific mutation matters (e.g. IDH2 R140 vs. R172)

Clonal architecture of MDS



Walter MJ, Shen D et el *NEJM* Mar 22;366(12):1090-8



Are there biomarkers that predict treatment response (not just prognosis) in MDS?

Clinical response predictors to drug therapy in MDS

Drug	Parameters predicting favorable response
Erythropoiesis stimulating agents	•Serum EPO level <500 IU/L •RBC transfusion needs <2 U/8 weeks •Non-RARS subtype •Less than 5% marrow blasts
Lenalidomide	•Del(5q) •Platelet count >100 x 10^9/L •Evolution of cytopenias during therapy
Immunosuppressive therapy (ATG, calcineurin inhibitors)	•Normal karyotype or trisomy 8 •HLA-DR15 •Hypocellular marrow •<5% marrow blasts •PNH clone •Short duration of transfusion needs
Hypomethylating agents	•Treatment earlier in the course of disease •Early platelet increment during therapy •No previous LDAC; blasts <15%; normal karyotype or trisomy 8

Who the patient is matters as much in outcome as the biology of the disease

TET2 mutant status and azacitidine response

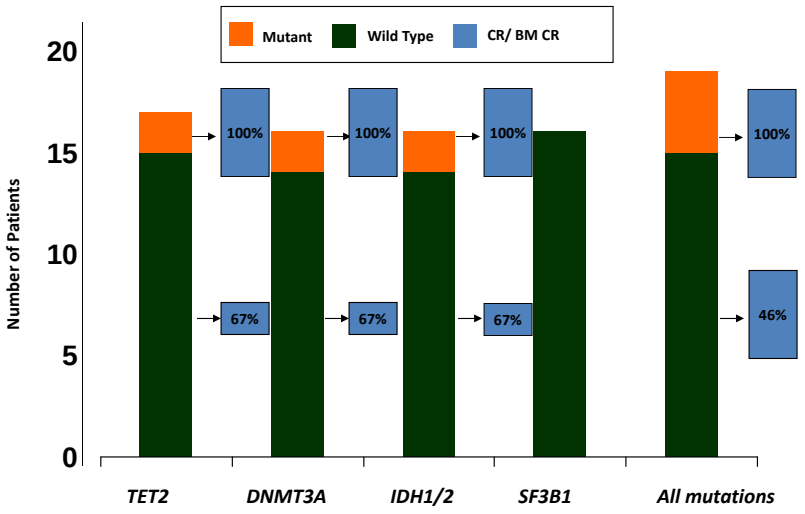
- n=86 with MDS [73%] or oligoblastic AML (i.e., 20-30% blasts) [27%] treated with azacitidine
- 13/86 (15%) had TET2 mutations
- TET2 mutant patients had: lower hemoglobin, better-risk karyotypes (61% vs. 40%), longer duration from diagnosis to therapy

	TET2 mutant (n=13)	TET2 wildtype (n=73)	Nominal p value
Response rate (IWG 2006, HI or better)	**82%**	**45%**	0.007
Response duration, median	12.1 months	9.5 months	0.04

Itzykson R, Kosmider O et al. *Leukemia* 2011; 25:1147-52

BMFC Phase II Lenalidomide-Azacitidine trial

Correlation of mutational status and clinical responses (n=36, ORR 72%, CR 42%, duration >16 months)

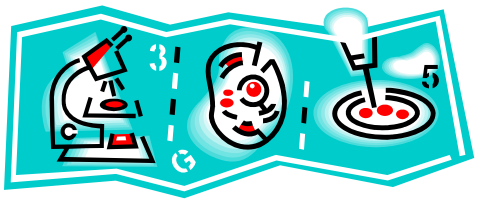


Sekeres M, List A et al. *Blood* 2011; 118:607a

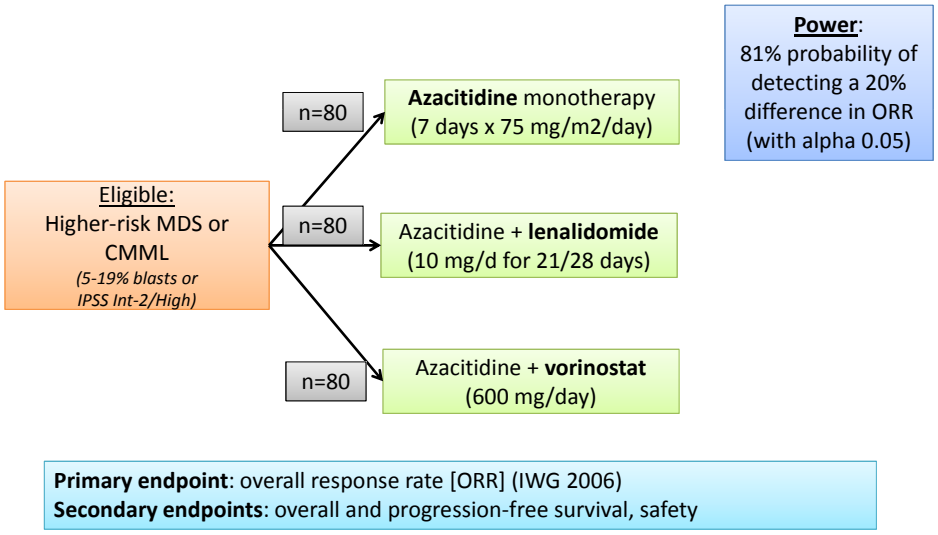
Abstract #311, Rafael Bejar et al:
"Detection of Recurrent Mutations by Pooled Targeted Next-Generation Sequencing in MDS Patients Prior to Treatment with Hypomethylating Agents or Stem Cell Transplantation"

- Assessment of 4 patient cohorts:
  - 48 MDS patients treated with HMA at DFCI
  - 83 MDS patients from the ADOPT study of decitabine
  - 109 MDS patients treated with HMA at MDACC
  - 76 patients who underwent SCT at DFCI 2004-2009
- 74 genes sequenced in each sample on an Illumina HiSeq 2000 at Broad Institute
- >90% had mutations
- Correlation between clinical response and genotype assessed

Newer approaches



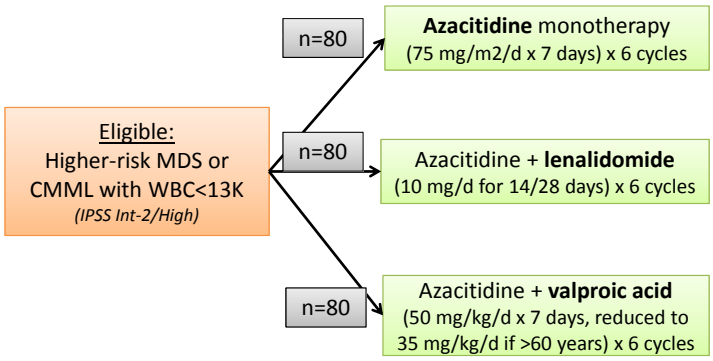
S1117 (US/Canada Intergroup) study



Primary endpoint: overall response rate [ORR] (IWG 2006)
Secondary endpoints: overall and progression-free survival, safety

Principal investigator: Mikkael Sekeres, Cleveland Clinic

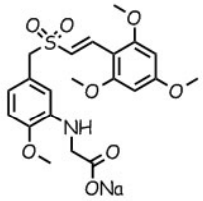
AZA-PLUS (GFM) randomized phase II study



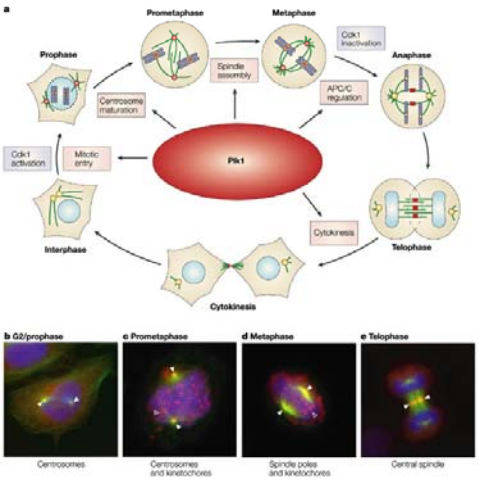
Primary endpoint: overall response rate [ORR, CR + mCR + PR] (IWG 2006)
Secondary endpoints: SD/HI, OS and PFS, response duration, safety

Principal investigator: Pierre Fenaux, Avicenne Hospital, Bobigny, France

ON 01910.Na (rigosertib) - multikinase inhibitor



Cell-cycle functions and localizations of Plk1



ON 01910.Na

Multikinase inhibitor

Polo-like kinase 1 modulator?

PI3Kab/Akt/ERK pathway inhibitor

Induces Bim, inhibits Mcl-1 activation

Reduces cyclin D1 levels

Barr F et al *Nature Reviews Molecular Cell Biology* 2004; 5: 429-441

Rigosertib (ON01910.Na) randomized trial for post-HMA failure

Eligible patients:

- **MDS (FAB)** *with 5-30% blasts and at least one cytopenia; WBC < 25x10^9/L*
- **No response or progression after ≥6 cycles azacitidine or ≥4 cycles decitabine**
- **Not an allogeneic stem cell transplant candidate, or refused transplant**
- **No low-dose cytarabine within last 2 years**
- **Bilirubin <1.5 and creatinine <2 mg/dL**

Randomize 2:1

n=180 → **ON 01910.Na 1800 mg/24 hr as a 72-hr continuous infusion on Days 1, 2, and 3 of a 2-week cycle**

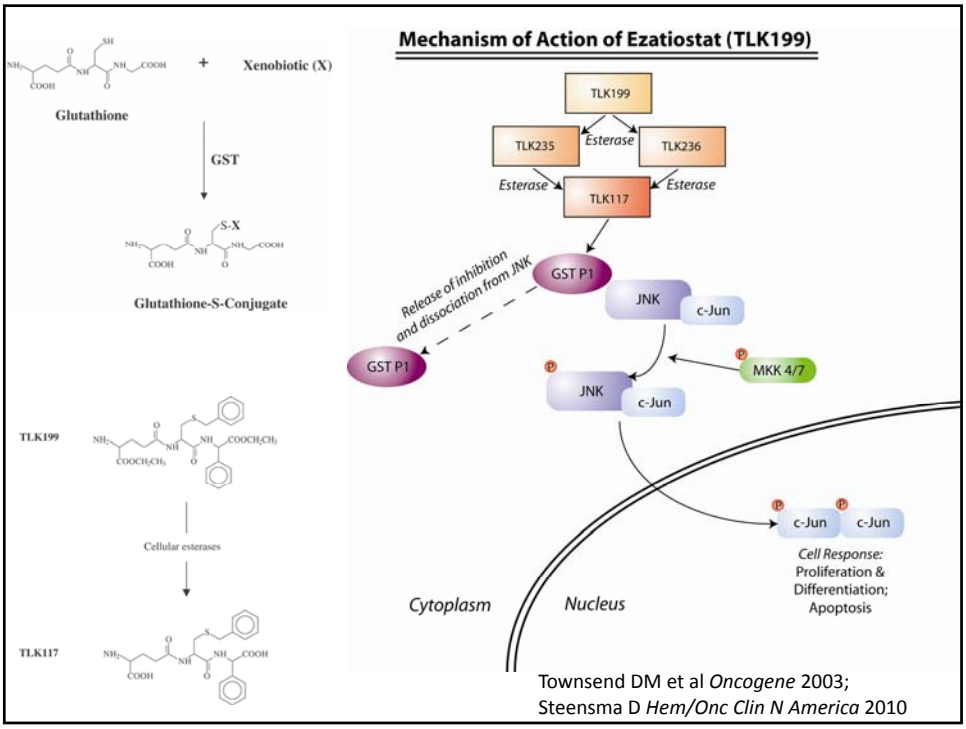
Primary Endpoint:
Overall survival
Secondary Endpoints:
IWG 2006 response, AEs, etc

n=90 → **Best Supportive Care (BSC) or Low-Dose Cytarabine (LDAC)**

Other novel "targeted" therapeutics

- **Sapacitabine** (CYC682)
  - Oral nucleoside analogue prodrug
  - Interferes with DNA synthesis and induces G2 arrest
  - Phase II ongoing in MDS (and Ph 3 in AML)
    - Median overall survival to date (Oct 12 2012) for all 63 patients is **252 days (8 months)**; 27 received 6 cycles of drug

- **ARRY-614**
  - Oral inhibitor of p38MAPK / Tie2 / VEGFR2
  - 38% HI (IWG 2006) in Phase I at highest dose (1200 mg/day)
  - Randomized trial planned



Townsend DM et al *Oncogene* 2003;
Steensma D *Hem/Onc Clin N America* 2010

Novel therapies being tested in MDS (1)

Nucleoside analogs

Compound name (former)	Route of administration; feature	Sponsor
Clofarabine	IV; approved for pediatric ALL in 2004, oral in development; purine analogue resistant to deamination/disruption of glycosidic link	Genzyme / Sanofi
Sapacitabine (CYC682)	Oral; single-strand DNA breaks and G2 arrest	Cyclacel

Kinase inhibitors

Compound name (former)	Kinase(s) inhibited	Sponsor
Rigosertib/ON 01910.Na	PI3Ka, ?Plk-1	Onconova
ARRY-614	p38 MAPK, Abl, Tie2 and VEGFR2	Array Biopharma
Midostaurin (PKC412)	FLT3, PKC	Novartis
MLN4924	Nedd8 activating enzyme	Millennium / Takeda
KB004 antibody	EphA3 oncofetoprotein	KalosBios
CYT387	JAK1/JAK2	YM Biosciences

*375 interventional studies listed as recruiting on clinicaltrials.gov as of Nov, 2012

Novel therapies being tested in MDS (2)

Epigenetic modifiers

Compound name (former)	Comments	Sponsor
Oral azacitidine	DNMT1 inhibitor	Celgene
SGI-110	PDE-linked dinucleotide of decitabine and deoxyguanosine, resistant to deamination	Astex (Supergen)
5-Fluoro-2'-Deoxycytidine With tetrahydrouridine	THU is a cytidine deaminase inhibitor; prevents FdCyd from being deaminated	NIH/CTEP
Panobinostat (LBH589)	DACi	Novartis
Vorinostat (SAHA)	DACi	Merck
Belinostat (PXD101)	No activity as monotherapy	Curagen
Entinostat (MS-275)	May be “dead” in MDS after E1905	Syndax

Monoclonal antibodies

Compound name (former)	Target	Sponsor
Siltuximab (CNTO-328)	IL-6 antibody	J & J
Etanercept	TNFα chimeric antibody	Pfizer
Alemtuzumab	Anti-CD52 monoclonal	Genzyme / Sanofi
Lintuzumab (SGN-33)	Anti-CD33	Seattle Genetics

Novel therapies being tested in MDS (3)

Proteasome/Amino Acid recycling inhibitors

Compound name (former)		Sponsor
Tosedostat (CHR-2797)	Aminopeptidase inhibitor	CTI
Bortezomib	Proteasome inhibition	Millennium / Takeda

Immunomodulation / Disruption of immune tolerance

Compound names		Sponsor
Vaccine-based approaches (WT1, dendritic cells/PD-1, etc)	Disruption of immunotolerance	Various
Umbilical cord/placental-derived mesenchymal stem cells	Disruption of immunotolerance	Various
AS-101	Tellurium(IV)-based immunomodulator / redox	BioMAS
Maitake mushroom extract	Immunomodulatory (beta-D-glucan induces T/NK cells and IL-1/2)	Yukiguni

Novel therapies being tested in MDS (4)

Miscellaneous

Compound name (former)	Mechanism	Sponsor
Ezatiostat (TLK199)	Glutathione analog; augments JNK signaling	Telik
BP100-1.01	GRB2 inhibitor, liposomally delivered antisense nucleotide	Bio-Path Holdings
PM01183	IV; DNA minor groove covalent binder	PharmaMar
PF-04449913	Hedgehog pathway inhibitor	Pfizer
OXi4503 (combretastatin A1 diphosphate, CA1P)	Vascular disrupting agent	OXiGENE
Ganetespib (STA-9090)	Hsp90 inhibitor	Synta
TXA127	Pharmaceutical-grade angiotensin; increases hematopoiesis	Tarix / US Biosciences
Sodium stibogluconate	Antimony derivative; inhibits PTPase1, SHP-1, PTP1B	GlaxoSmithKline
CPI-613	Lipoic acid analog; inhibits mitochondrial energy metabolism	Cornerstone
Omacetaxine / homoharringtonine	Marine-derived alkaloid; apoptosis induction by inhibition of Mcl-1 etc.	ChemGenex
Plerixafor (AMD3100)	CXCR4 signaling blockade; ?chemosensitizing	Genzyme/Sanofi

A vision for the future…

…it may be closer than we think

Thank you!

Boston Harbor skyline at dusk

Harvard Medical School quadrangle

Yawkey Center (2011), Dana-Farber

Research Collaborators:
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Benjamin Ebert MD PhD
Mark Fleming MD DPhil
Corey Cutler MD
Robert Soiffer MD

DFCI Adult Leukemia Clinical Program:
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Daniel Deangelo MD PhD
Martha Wadleigh MD
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Gregory (Goyo) Abel MD MPH