THE UNIVERSITY OF CHICAGO MEDICINE

Treating AML: Other Molecular Targets

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September 2017

Disclosures – Richard A. Larson, MD

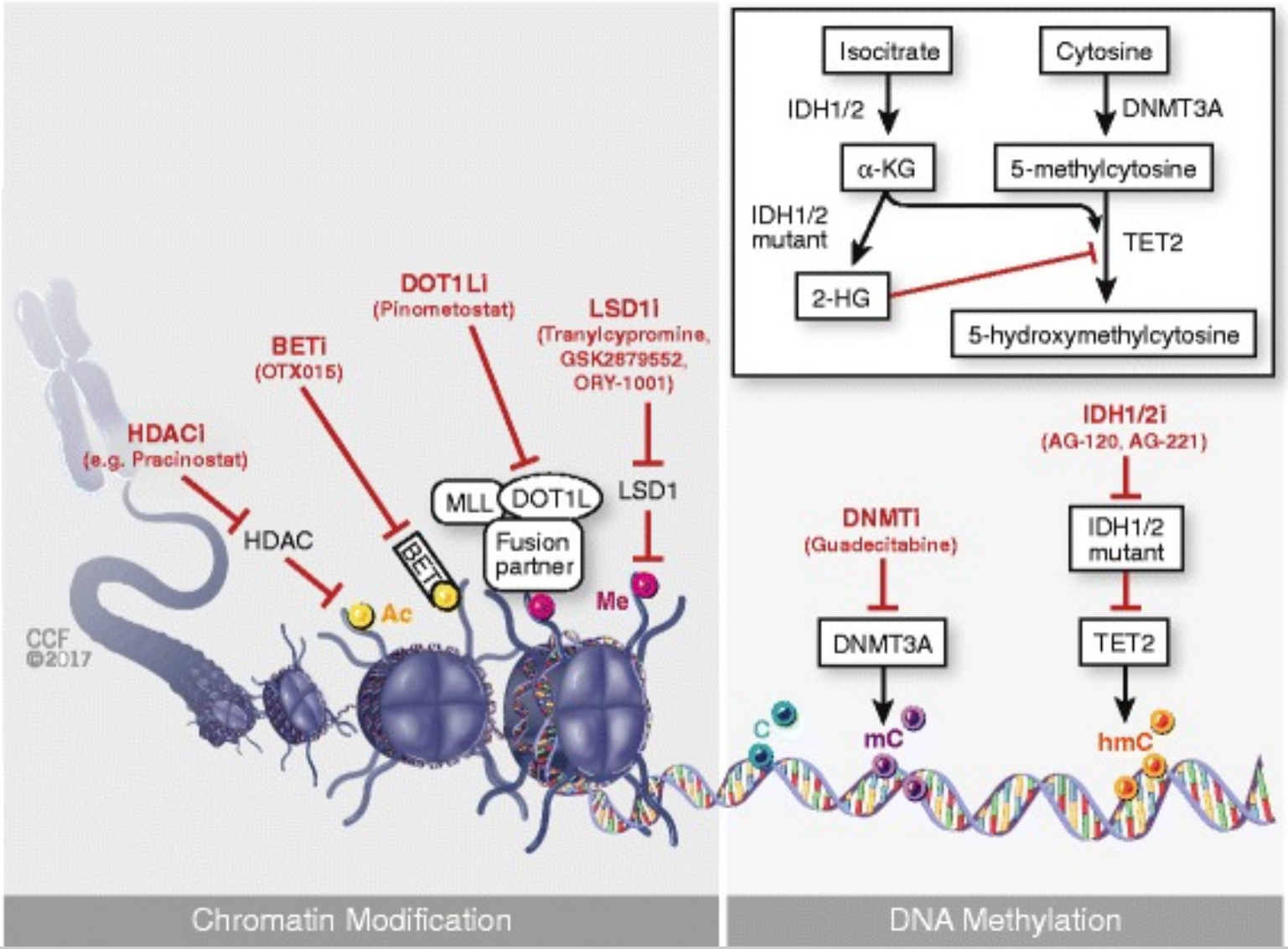
- Research funding to the University of Chicago:
  - Astellas
  - Celgene
  - Daiichi Sankyo
  - Erytech
  - Novartis
- Equity ownership: none
- Royalties: UpToDate, Inc

- Consultancy/ Honoraria:
  - Amgen
  - Ariad (DSMB)
  - Astellas
  - Bristol Myers Squibb (DSMB)
  - Celgene (DSMB)
  - CVS/Caremark
  - Jazz
  - Novartis
  - Pfizer

Novel therapies for AML

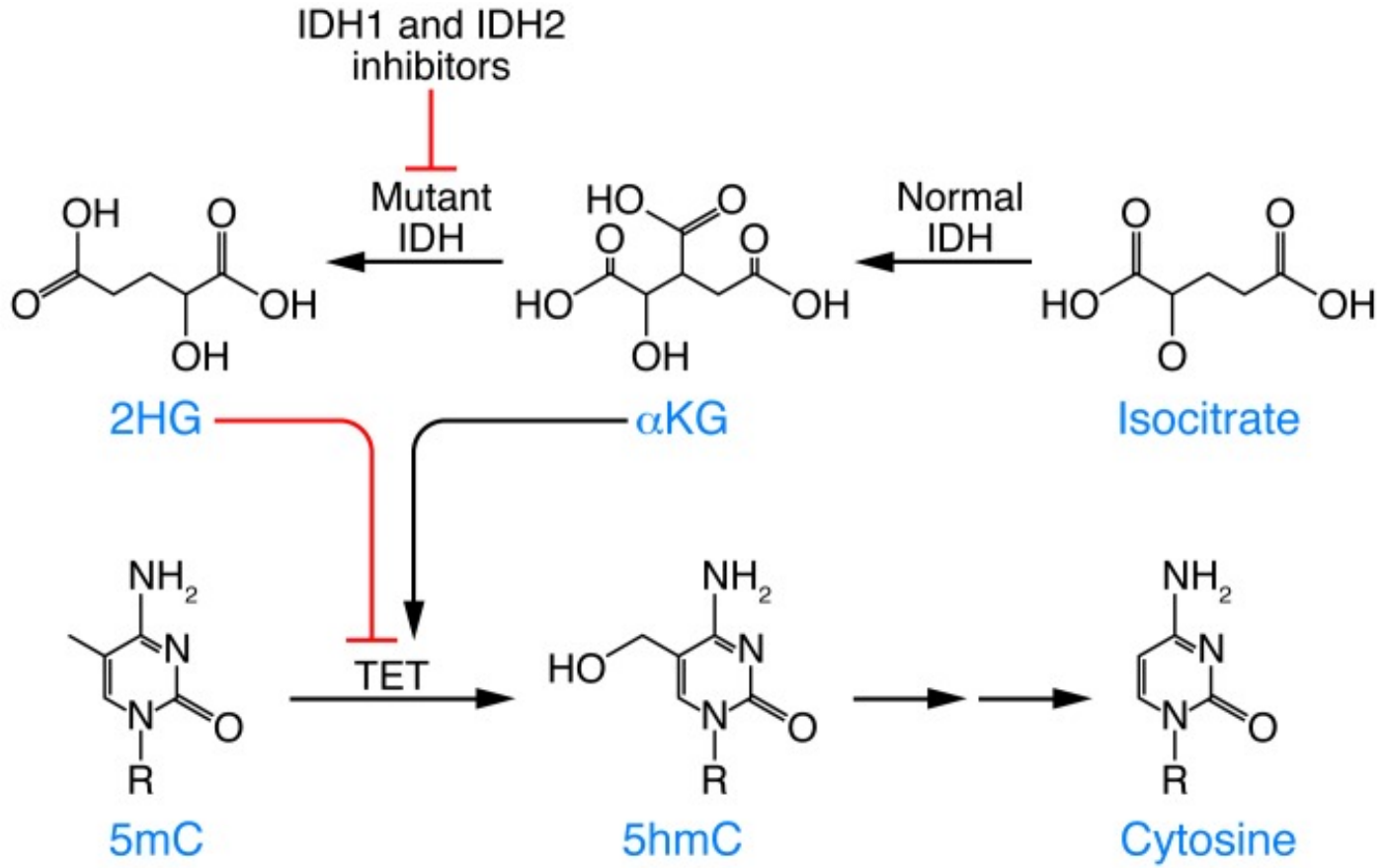
- FLT3 inhibitors
- Monoclonal antibody-based agents
- Other Molecular Targets
  - IDH2: enasidenib (AG-221)
  - BCL2: venetoclax (ABT-199)
  - IDH1: AG-120, IDH305, FT-2102
  - DNMT: guadecitabine (SGI-110)
  - HDAC inhibitors: panobinostat, vorinostat
  - Aminopeptidase inhibitor: tosedostat
  - Polo-like kinase inhibitor: volasertib
  - BET inhibitor: OTX015
  - XPO1 inhibitor: selinexor

Multiple vulnerabilities



Saygin & Carraway. J Hematol Oncol 2017

Normal IDH functions to convert isocitrate to α-ketoglutarate in the Krebs cycle.



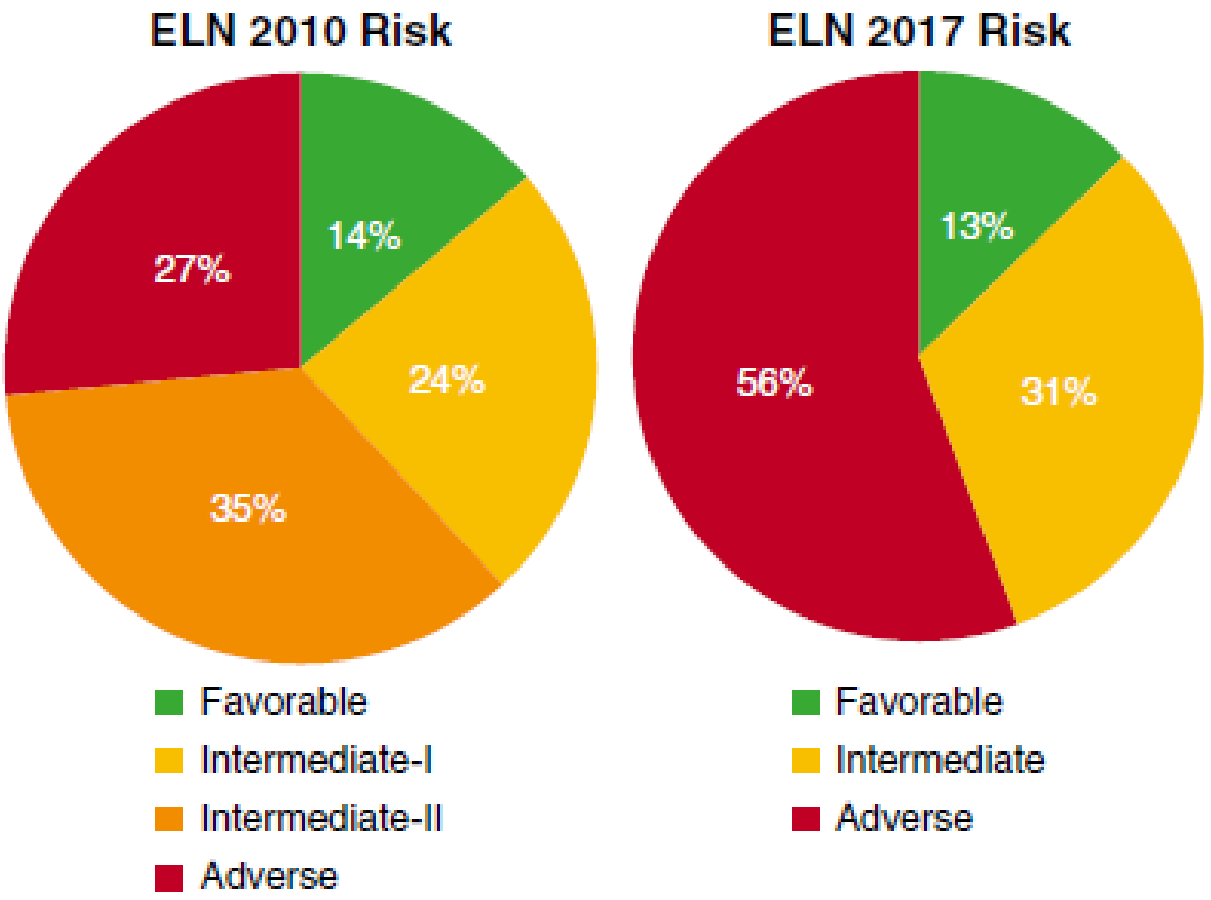
Oncogenic mutations in IDH induce neomorphic function to produce the oncometabolite 2HG. In leukemias, 2HG affects the TET family of proteins, which results in impaired hydroxymethylation of DNA and disrupted epigenetic control.

McKenney & Levine. J Clin Invest. 2013

IDH1/2 mutations: the crossroads between tumor metabolism and epigenetics

- *IDH2* is found in the mitochondria
  - Mutated in 10-15% of adult AML
  - More commonly found in cytogenetically normal AML, but 30% will have abnormal karyotypes
  - Mutated in 5-6% of MDS
- *IDH1* is found in the cytoplasm
  - Mutated in 5-10% of adult AML
- WT enzymes: catalyze conversion of isocitrate to α-ketoglutarate.
- Mutant enzymes result in increased β-hydroxyglutarate (2HG) and hypermethylation of target genes, blocking myeloid differentiation

Proportion of m*IDH2* AML patients by ELN risk categories



Amatangelo et al. Blood 2017; 130: 732-741

Clinical Outcome of Patients With *IDH1* or With R140 *IDH2* Mutations (n=345 with cytogenetically normal AML)

Outcome Endpoint	*IDH1*-Mutated (n = 49)		R140 *IDH2*-Mutated (n = 56)		*IDH1*/*IDH2*wt (n = 240)	
	%	95% CI	%	95% CI	%	95% CI
Complete remission	73		70		75	
Overall survival:						
Median, years	1.3		1.4		1.4	
Alive at 3 years	29	17 to 41	39	26 to 52	33	27 to 39
Disease-free survival:						
Median, years	1.1		1.3		1.1	
Disease-free at 3 years	28	14 to 43	28	15 to 43	32	25 to 39

- No significant differences in any comparison

Marcucci et al (CALGB). J Clin Oncol 2010

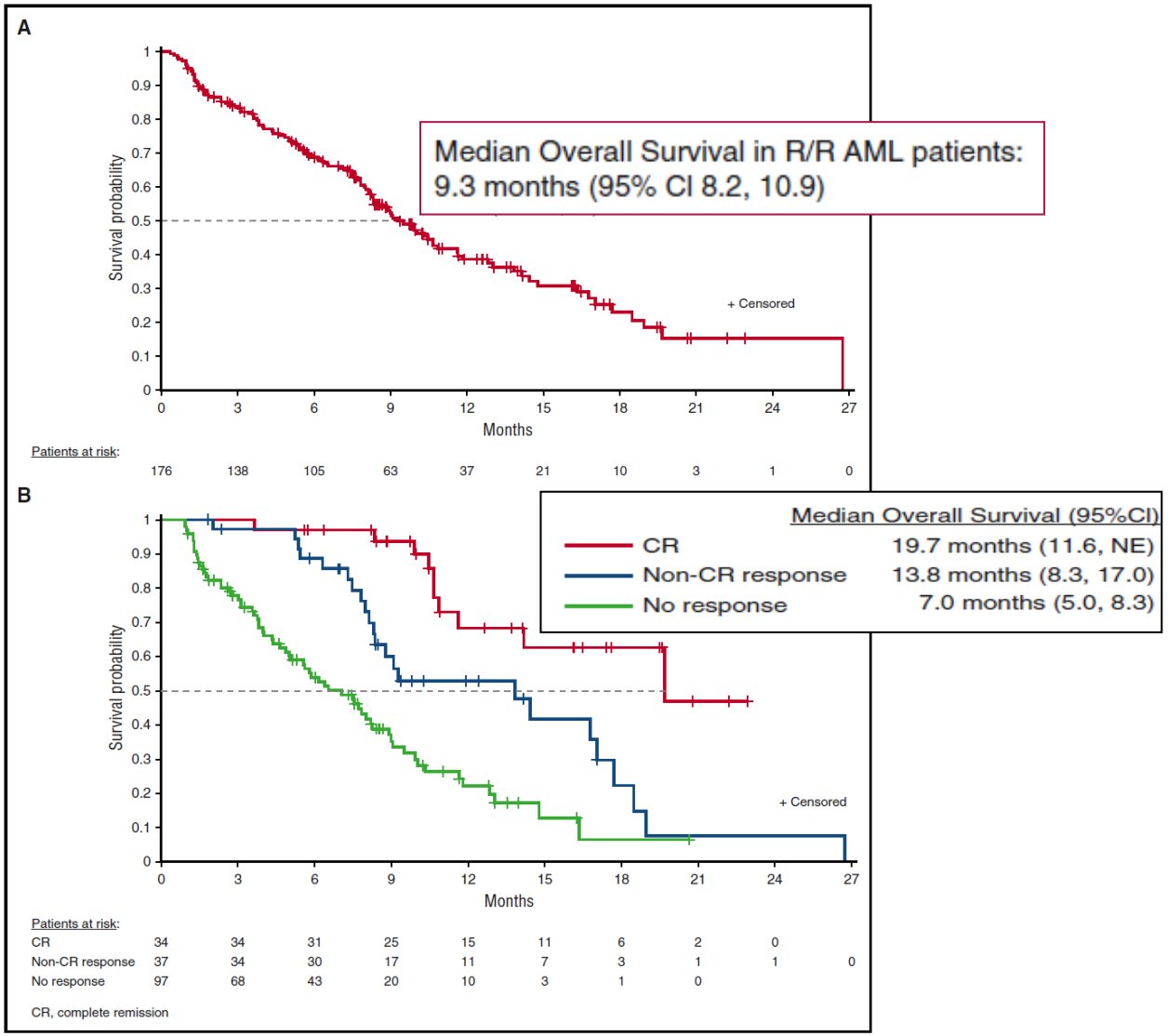
Enasidenib (AG-221): Oral inhibitor of mutant-IDH2 enzymes

- 239 patients with relapsed/refractory AML: Phase 1/2
- Median age, 70 (range, 19-100)
- Dose-escalation study (50 → 650 mg/day)
- No MTD was reached.
- 100 mg daily selected for expansion studies.
- Overall responses observed in 40%
- Median duration of 5.8 months
- Cellular differentiation and maturation without aplasia

Stein et al. Blood 2017; 130: 722-731

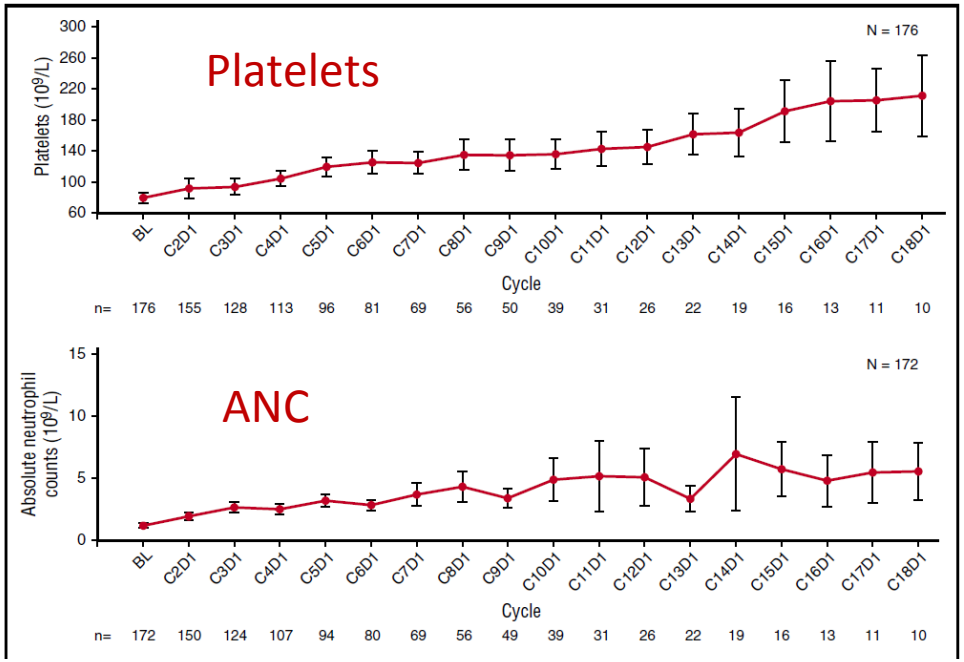
(A) Overall survival; (B) Overall survival by response to enasidenib

N = 176

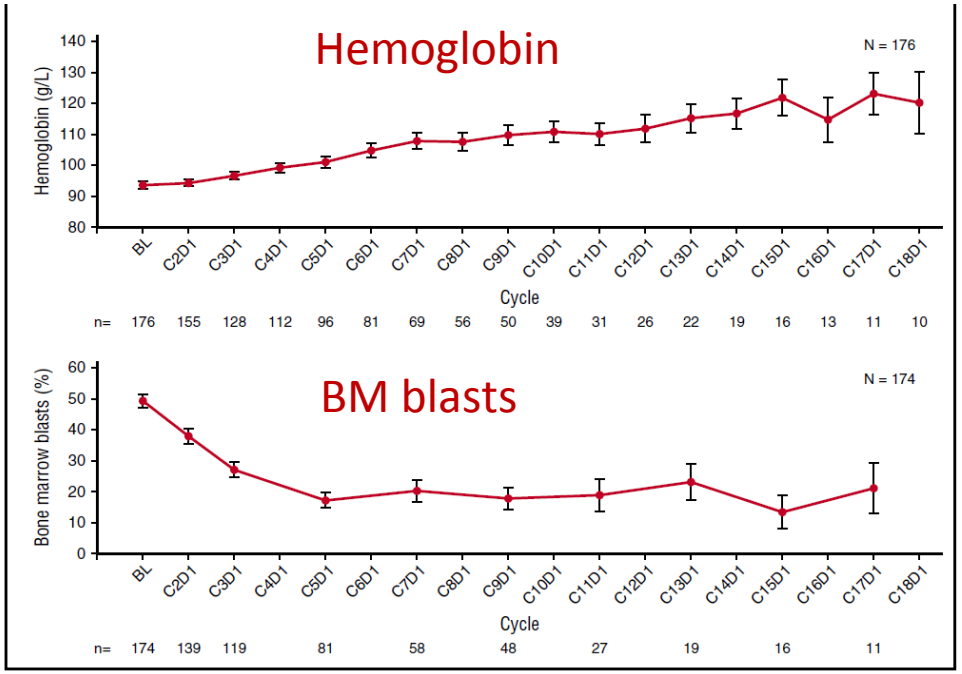


Stein et al. Blood 2017; 130: 722-731

Mean platelets, ANC, hemoglobin and BM blasts over time on enasidenib

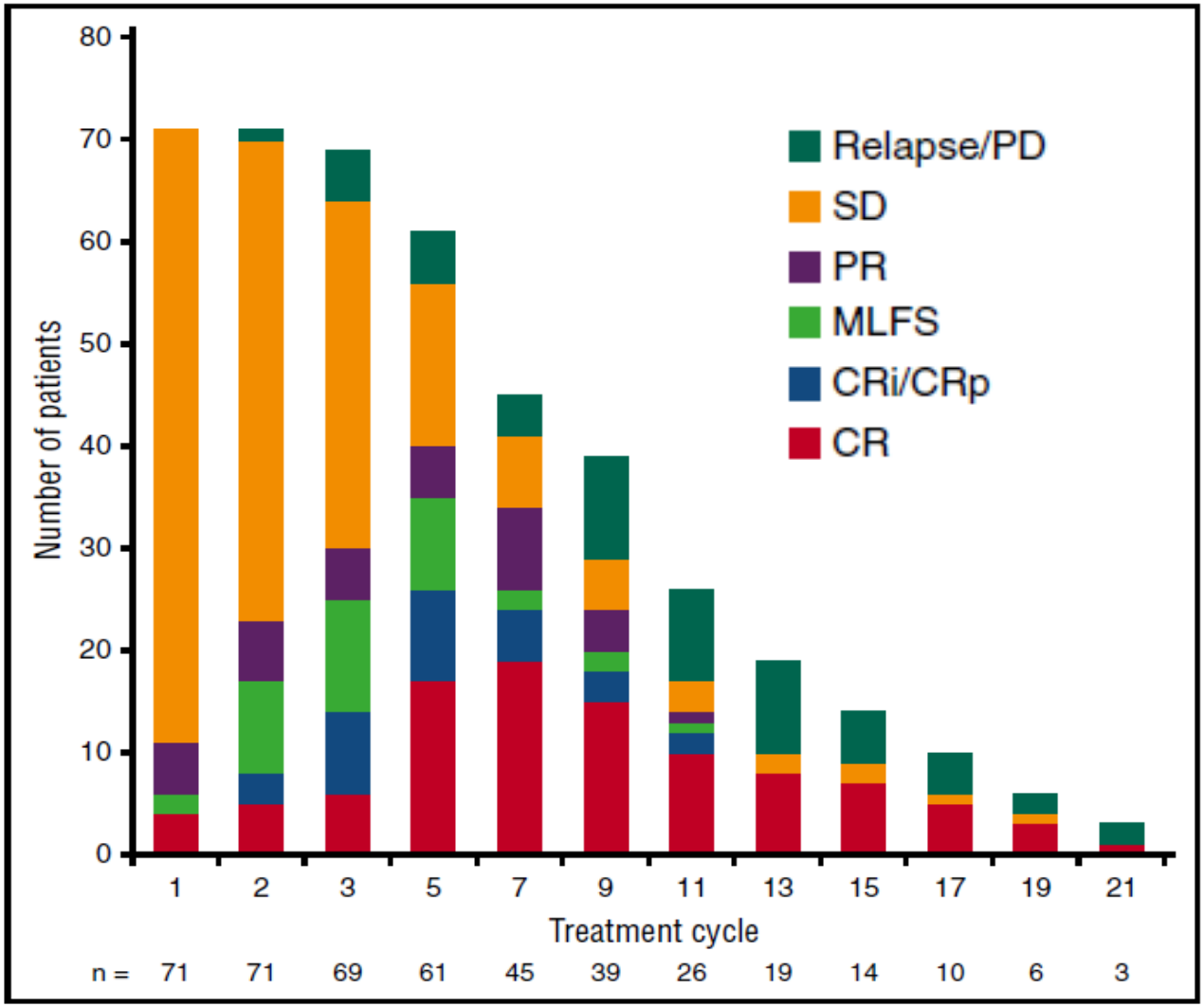


N = 176 (all dose levels)



Stein et al. Blood 2017; 130: 722-731

Evolution of response by treatment cycle (N = 71)



Stein et al. Blood 2017; 130: 722-731

Responses, time to response, and duration with enasidenib (100 mg daily; N= 109)

Response	No. of patients	%	95% CI
Overall response rate	42	39	29 - 48
Complete remission	22	20	13 – 29
Complete remission w/incomplete	7	6	
Partial remission	3	3	
Morphologic leukemia-free state	10	9	
Stable disease	58	53	

	Median	Range	95% CI
Time to 1st response (mo)	1.9	0.5 – 9.4	
Duration of response (mo)	5.6		3.8 – 9.7
Time to CR (mo)	3.7	0.7 – 11.2	
Duration of CR (mo)	8.8		5.3 - NR

Stein et al. Blood 2017; 130: 722-731

Enasidenib-related differentiation syndrome

- ~12% of patients with relapsed/refractory *mIDH2* AML
- Dyspnea, unexplained fever, pulmonary infiltrates, hypoxia, effusions, edema, weight gain, hypotension
- Median time to onset was 30 days (7 – 129)
- ~40% also had leukocytosis
- Managed with corticosteroids
- Did not impact the response rate

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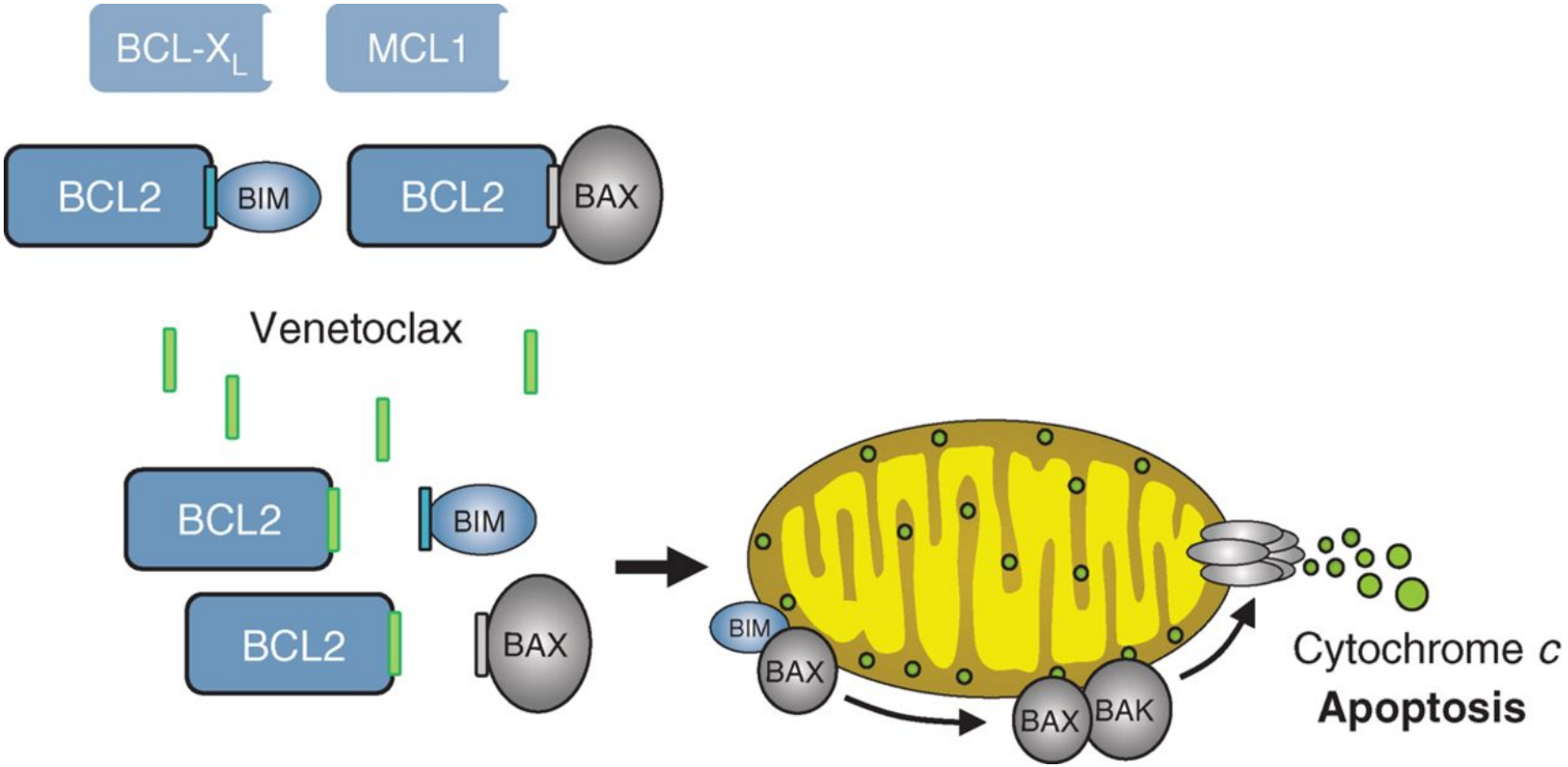
Targeting BCL2 -- venetoclax

BCL2 – “guardian of mitochondrial integrity”

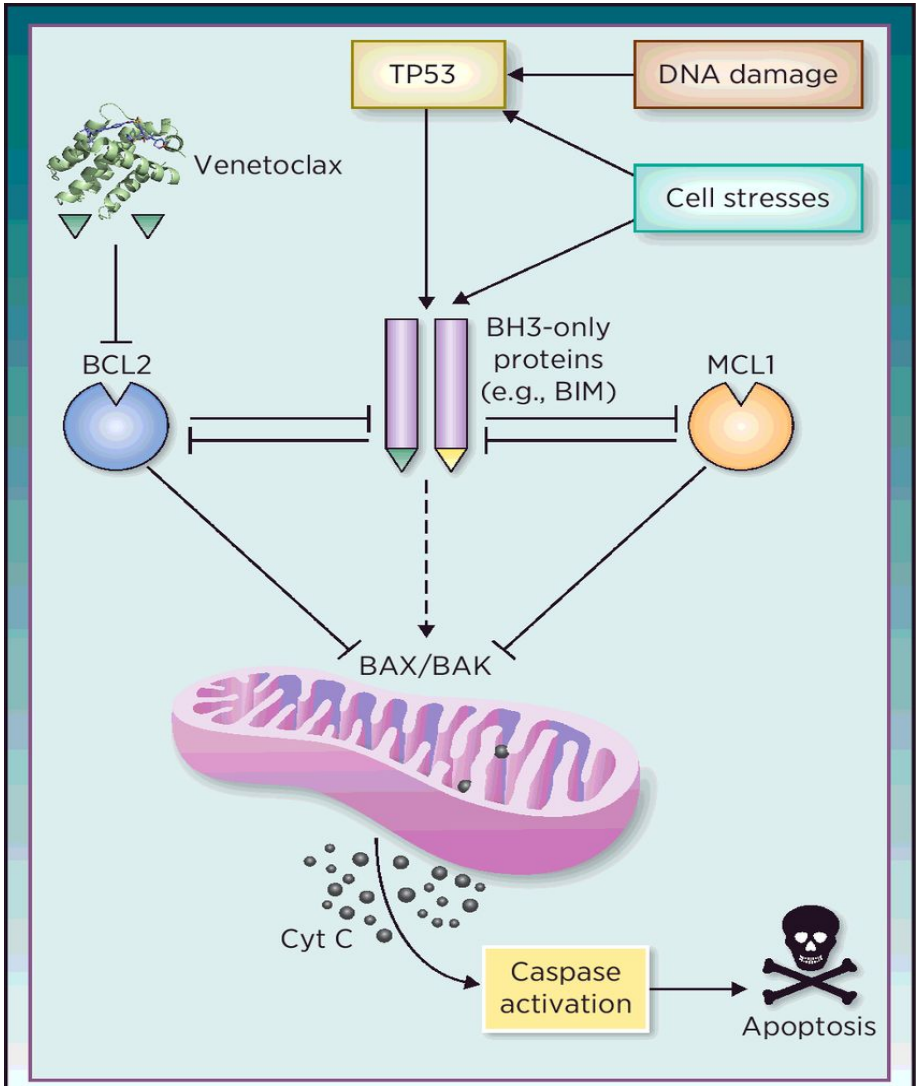
- The BCL2 family of anti-apoptotic proteins: BCL2, BCL-XL, MCL-1
- Aberrant overexpression of *BCL2* is associated with tumorigenesis and resistance to chemotherapy.
- These potent anti-apoptotic proteins protect cells from diverse challenges and stress after DNA damage.
- Pro-apoptotic proteins bind and inhibit BCL2, leading to cell death.
- The BH3-only proteins: BCL2L11 (BIM), BBC3 (PUMA), BAX, BAK, and BAD.



Mechanism of action of venetoclax.
Venetoclax acts as a specific inhibitor of BCL2 and upon binding, releases proapoptotic proteins to induce apoptosis.
BIM, BCL2-like 11; BAX, BCL2-associated X protein; BAK, BCL2 antagonist/killer 1.

M Konopleva et al. Cancer Discov 2016;6:1106-1117

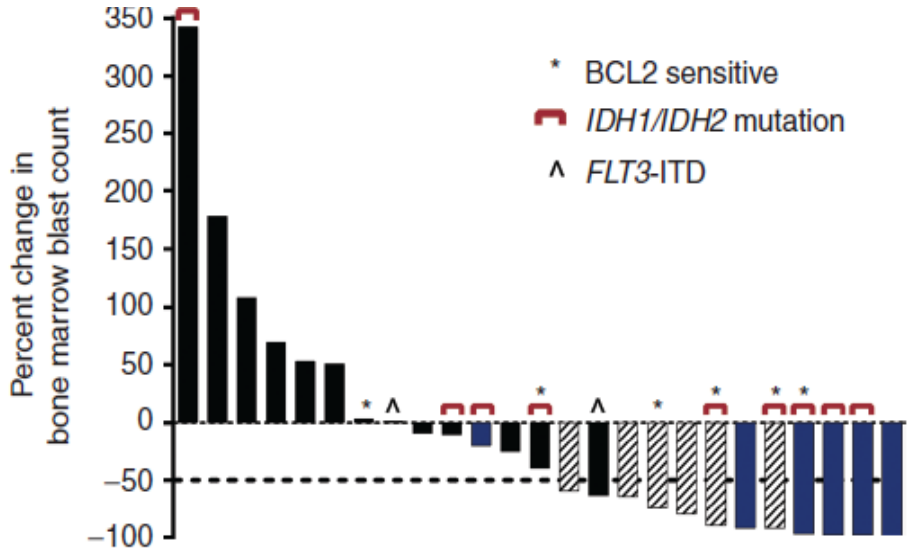
Venetoclax induces apoptosis by acting as a BH3 mimetic to inhibit BCL2



AW Roberts et al. Clin Cancer Res 2017;23:4527-4533

Venetoclax has single-agent activity in AML

- 32 adults with relapsed AML
- Median age, 71 years (range, 19-84)
- 62% had del(7q) or complex karyotypes
- 38% had *IDH* mutations and 13% *FLT3*-ITD
- CR n= 2 (6%)
- CRi n= 4 (13%)
- No serious unexpected toxicities.



Konopleva et al. Cancer Discovery; 6(10); 1106–17.

Venetoclax + low-dose cytarabine (LDAC)

- 61 adults >65 years with previously untreated AML
- Median age, 74 (range, 66-87)

Secondary AML	44%
Prior treatment with HMA	28%
Intermediate-risk cytogenetics	61%
Poor-risk cytogenetics	31%

- Venetoclax ramped up to 600 mg daily x 28 days
- Cytarabine 20 mg/m^2 SC daily on Days 1 - 10

Lin et al. EHA 2017; abstract #E911

Venetoclax + low-dose cytarabine (LDAC)

- Median time on study, 6 months (range, <1 to 19 months)

	CR + CRi	CR	CRi
Overall responses	65%	25%	38%
Intermediate-risk cytogenetics	76%		
Poor-risk cytogenetics	47%		
Age >75 years	70%		
Secondary AML	52%		
Prior HMA exposure	53%		

- Median time to response, 1 month (range, up to 9 months)

Lin et al. EHA 2017; abstract #E911

Venetoclax + low-dose cytarabine (LDAC)

- 30-day death rate 3%
- 60-day death rate 15%
- Median overall survival ~12 months

	Grade 3 or 4 Adverse Events	
	Hematologic	Non-hematologic
Thrombocytopenia	44%	
Febrile neutropenia	36%	
Anemia	28%	
Hypokalemia		16%
Hypophosphatemia		13%
Hypertension		12%

Lin et al. EHA 2017; abstract #E911

Venetoclax with azacitidine or decitabine

- 57 adults with untreated AML
- Median age, 75 years (range, 65-85)

Intermediate-risk cytogenetics	61%
Poor-risk cytogenetics	37%
Bone marrow blasts 20-50%	63%
Bone marrow blasts >50%	37%

- Azacitidine 75 mg/m^2 SC or IV on Days 1 – 7
  or Decitabine 20 mg/m^2 IV on Days 1-5
- Venetoclax was escalated in cohorts to 400, 800, or 1200 mg daily

Venetoclax with azacitidine or decitabine

- Median time to CR/CRi, 1.1 months (range, 0.8 – 5)

	CR + CRi
Overall responses	61%
Overall responses with azacitidine	59%
Overall responses with decitabine	61%
Responses with FLT3-ITD (n=4)	75%
Responses with TP53 mutation (n=11)	36%

- Median overall survival, 12.3 months
- No DLT events; MTD not reached
- 30-day mortality, 7%
- 60-day mortality, 16%

Conclusions

- Many novel agents that target specific molecular pathways in AML are currently under development.
- Challenges:
  - How to incorporate into the frontline therapy in order to shift remissions to cures?
  - Use as single agents or in combinations?
  - Sequence with other therapies?
    - Induction
    - Maintenance

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