Targeted therapeutic approaches for high risk myeloid malignancies

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Disclosures
Olatoyosi Odenike, MD

I disclose the following financial relationship(s):

- **Celegene, Advisory Board or Panel, Grants/Research Support**
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- **CTI-Biopharma, Grants/Research Support**
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- **Membership on the ABIM Med Onc Governance Board**
- **Membership on the ABIM Med Onc Exam Committee**

High Risk Myeloid Malignancies

Acute Myeloid Leukemia

- **Poor risk clinical, molecular or cytogenetic features**
- **Relapsed refractory**

Myelodysplastic syndromes

- **Higher risk disease**

Myeloproliferative neoplasms

- **Advanced Myelofibrosis**

Propensity to evolve to AML

Objectives

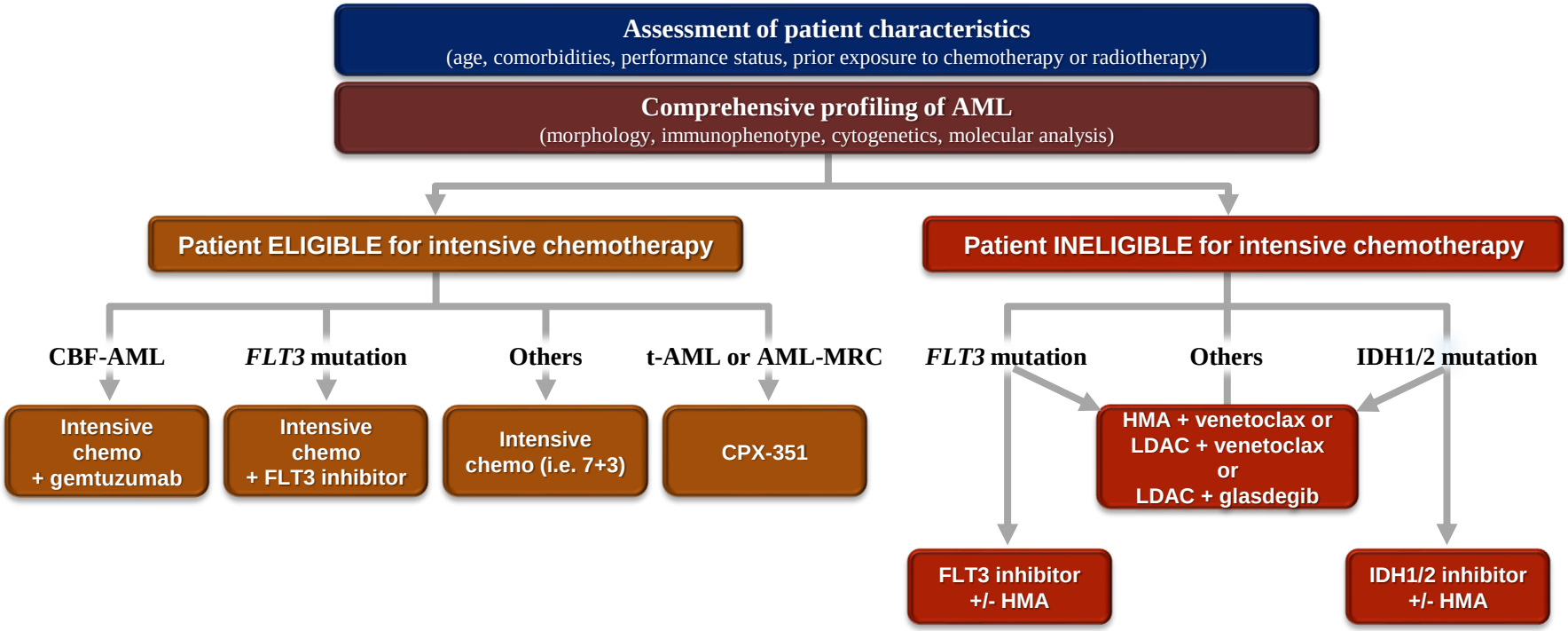
- **Highlight significant ongoing areas of unmet need in high risk myeloid neoplasms**

- **Review promising therapeutic approaches that span the spectrum of myeloid malignancies**

FDA Approvals for AML since 2017

- **In 2017, 4 new drugs were approved:**
  - **Midostaurin (newly-diagnosed FLT3-mutant AML)**
  - **CPX-351 (Vyxeos™) (therapy-related AML, or AML with MDS-related changes)**
  - **Gemtuzumab ozogamicin (CD33+ AML)**
  - **Enasidenib (IDH2mutant Rel/Ref AML)**
- **20 July 2018: Ivosidenib (IDH1mut Rel/Ref AML)**
- **21 Nov 2018: Glasdegib & Venetoclax (newly dx AML ≥75 or unfit)**
- **28 Nov 2018: Gilteritinib (FLT3mut Rel/Ref AML)**
- **21 Dec 2018: Tagraxofusp (SL-401) for BPDCN**

Evolving treatment paradigm for Newly Dx AML



Targeting the leukemia stem cell

BCL2 inhibition

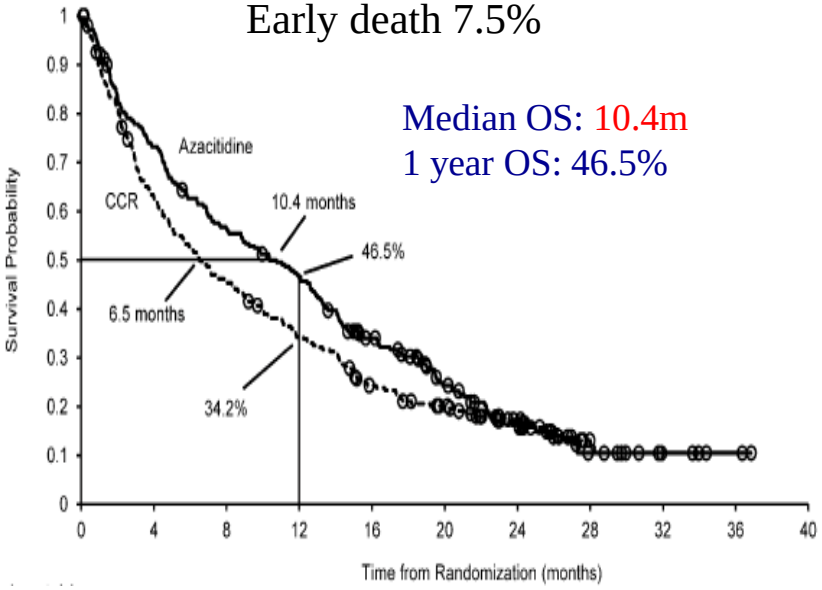
Background: Experience with AZA alone and AZA + venetoclax in older adults with AML

AZA

CR/CRi 28%

N=241, median age 75

Early death 7.5%



Median OS: 10.4m

1 year OS: 46.5%

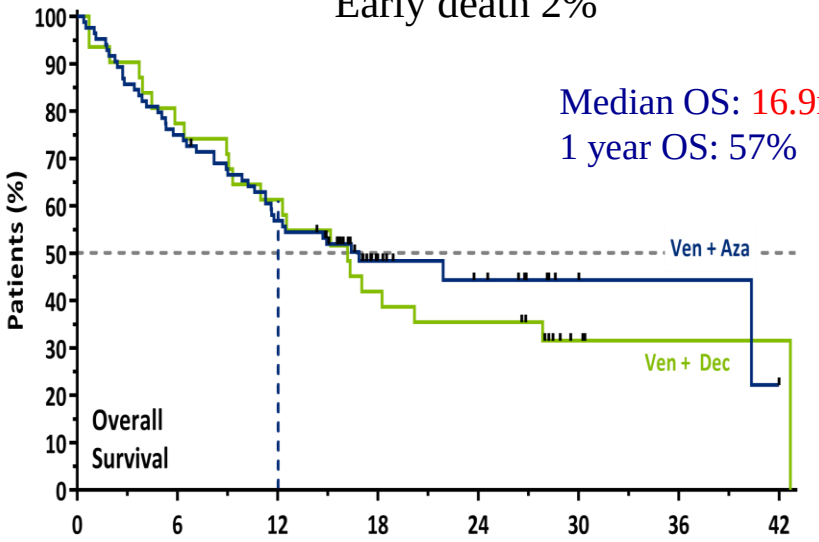
Dombret H et al, Blood 2015

AZA+VEN

CR/CRi 71%

N=84, median age 75

Early death 2%



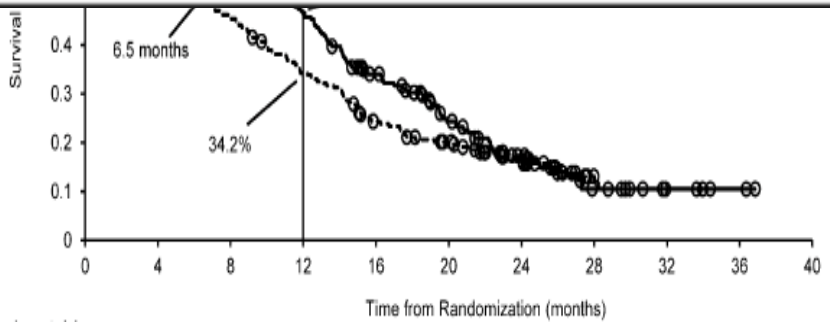
Median OS: 16.9m

1 year OS: 57%

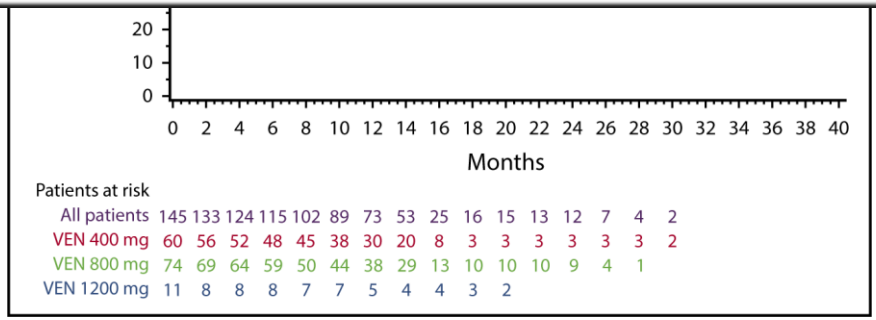
DiNardo CD et al, Lancet Oncol 2018

Background: Expectations with AZA alone and AZA + venetoclax

Cohort	N	Composite Response Rate, (CR+CRi) n (%)	Overall Response Rate (CR+CRi+PR) n (%)	Median Duration of CR+CRi (95% CI)	Median OS (95% CI)
All patients	145	97 (67)	99 (68)	11.3 (8.9-NR)	17.5 (12.3-NR)
VEN 400 mg + HMA	60	44 (73)	44 (73)	12.5 (7.8-NR)	NR (11.0-NR)
VEN 800 mg + HMA	74	48 (65)	50 (68)	11.0 (6.5-12.9)	17.5 (10.3-NR)

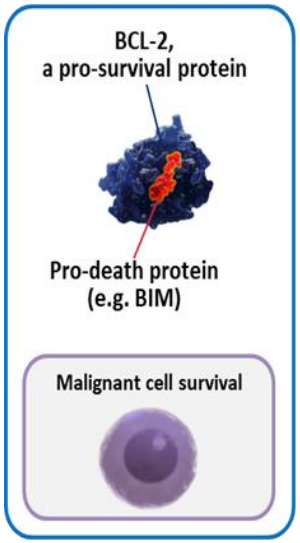


Dombret H et al, Blood 2015

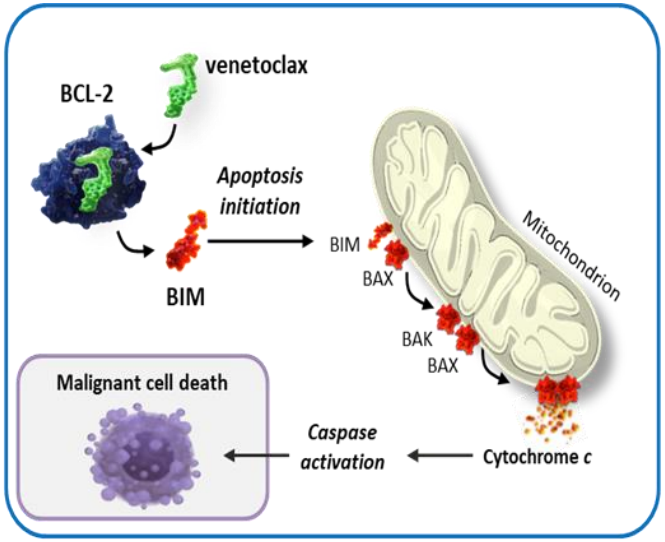


DiNardo CD et al, Blood 2019

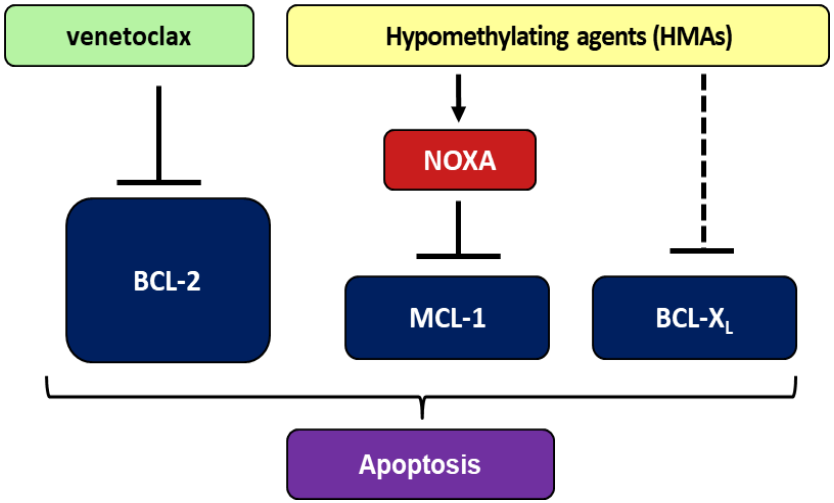
Venetoclax is a potent and selective BCL2 inhibitor



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins [1-3]



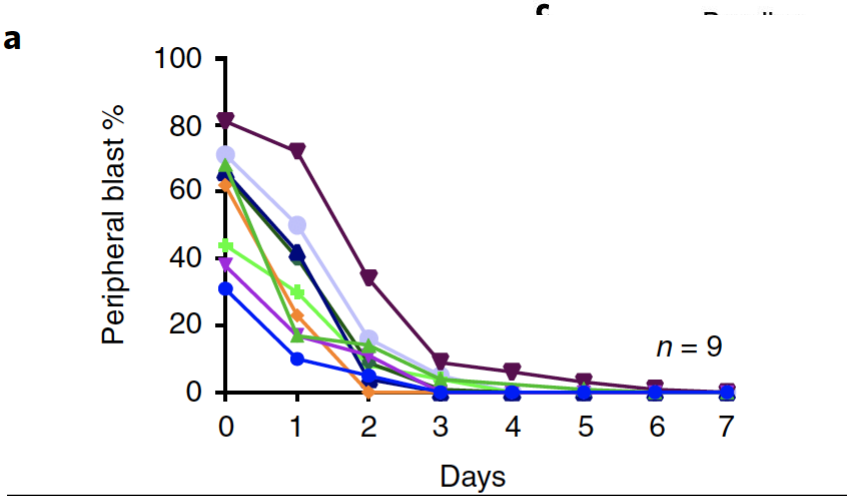
Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis)[4-6]



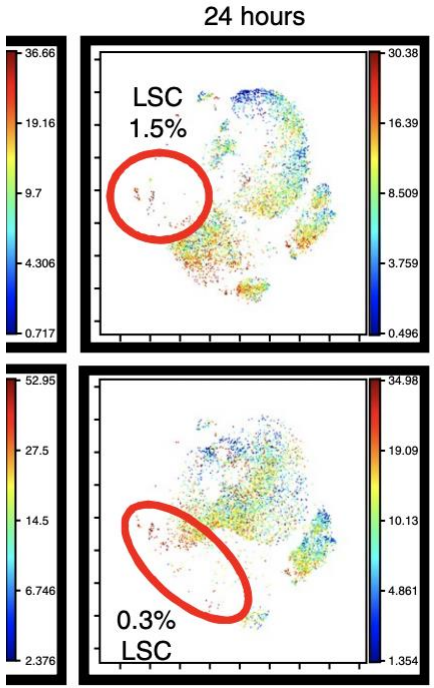
Azacitidine and decitabine indirectly increase sensitivity to BCL-2 inhibition in AML cells by modifying the relative levels of BCL-2 family members[2,3]

1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296. 4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

Azacitidine + Venetoclax Targets LSCs in Vivo

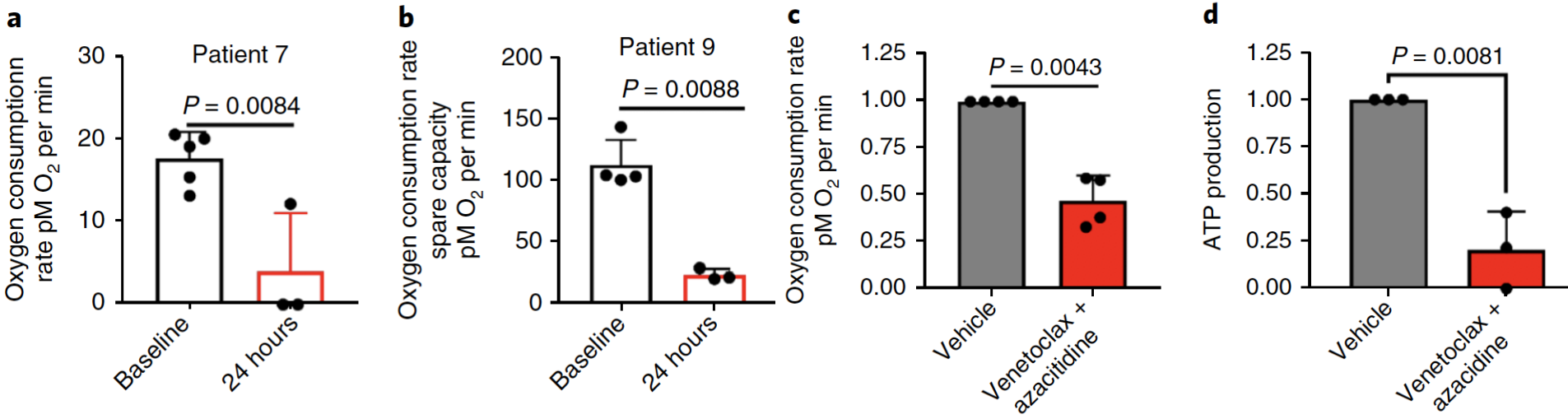


Day	1	2	3	4	5	6	7
Blast reduction to 0%	0 of 9	1 of 9	4 of 9	7 of 9	7 of 9	9 of 9	9 of 9
Average % reduction in blasts (+/-S.D)	45.36 (+/–21.0)	81.3 (+/–12.3)	96.1 (+/–4.5)	99 (+/–2.5)	99 (+/–1.3)	100 (+/–0.4)	100 (+/–0)



Pollyea*, Stevens*, Jones* et al. Nature Medicine 2018

Rapid Drop in OXPHOS and ATP

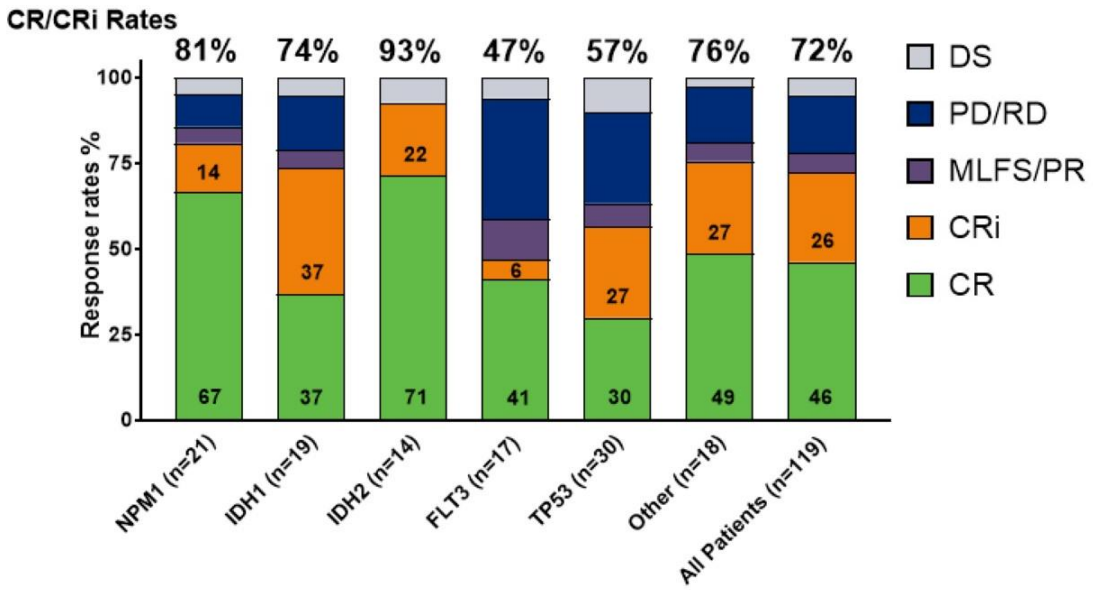


Pollyea*, Stevens*, Jones* et al. Nature Medicine 2018.

Azacitidine+venetoclax in AML: Response according to mutational profile

Subgroup	CR + CRi, n (%)
All patients	97 (67)
Cytogenetic risk	
Intermediate	55 (74)
Poor	42 (60)
Age	
≥75 y	40 (65)
<75 y	57 (69)
AML	
De novo	73 (67)
Secondary	24 (67)

DiNardo et al, Blood 2019



Chyla et al, ASH 2019

Other venetoclax based strategies being investigated in AML

- 10 day decitabine+venetoclax
  - TP53 mutated subset
- Enasidenib+venetoclax
  - IDH2 mutated subset
- Venetoclax+CDK inhibition
- Venetoclax+ intensive chemotherapy
  - FLAG-IDA+ven
  - 7+3+venetoclax
- Venetoclax incorporation into transplant conditioning regimen

Higher Risk MDS

Stratification based on IPSS/IPSS-R

IPSS (N=816)	Score	Risk Group	Median Survival in years
	0	Low	5.7
	0.5-1.0	Intermediate-1	3.5
	1.5-2.0	Intermediate-2	1.2
	≥ 2.5	High	0.4

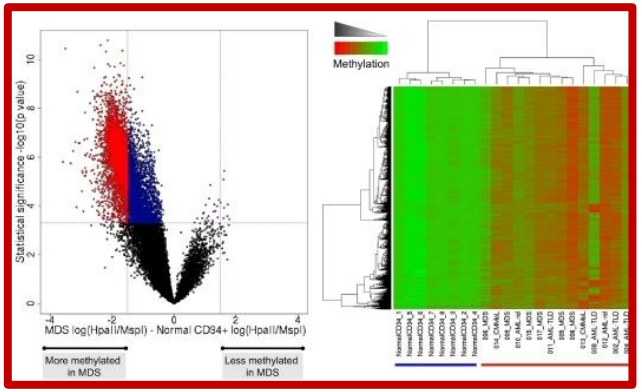
Score=>1.5: Higher risk MDS

IPSS-R (N=7,012)	Points	Risk Score	Median survival in years
	≤ 1.5	Very Low	8.8
	> 1.5-3	Low	5.3
	>3-4.5	Intermediate	3.0
	>4.5-6	High	1.6
	>6	Very high	0.8

*Score=>3.5: Higher risk MDS

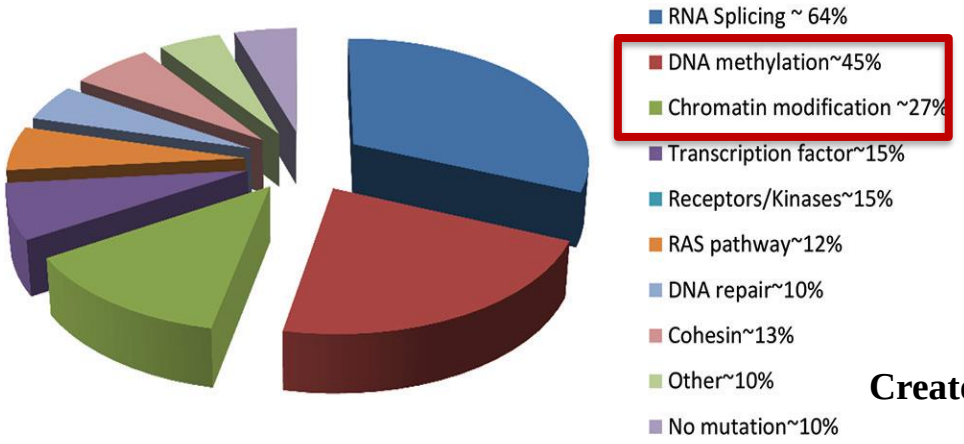
Adapted from: Greenberg P, Blood 1997, 89:2079, Greenberg PL, Blood 2012, 30:820, *Pfeilstocker M, Blood 2016, 128:902-910

Rationale for targeting the epigenome in MDS?



- **MDS is associated with a hypermethylator phenotype**

Mutational Spectrum of MDS



- **Mutations in epigenetic modifiers occur frequently in MDS**

Figueroa, Blood, 2009; 114:3448

Created from data in Haferlach T, Leukemia; 2014, 28: 241

Selected Phase II/III Hypomethylating Agent Trials in MDS

Agent	*N	Overall Response Rate (CR/PR/HI)	Duration of response (months)	Overall Survival (months)	Author
Azacitidine	99	47%	13.1	20	Silverman
Azacitidine	179	49%	13.6	24.5	Fenaux
Decitabine	89	30%	10.3	14	Kantarjian
Decitabine	99	30%	10	19.4	Steensma
Azacitidine	75	46%	12	18	Prebet
Azacitidine	92	38%	10	15	Sekeres

Silverman , JCO,2002, 2006
Fenaux, Lancet Oncol, 2009
Kantarjian, Cancer, 2006
Steensma, JCO, 2009
Prebet, JCO, 2014
Sekeres, JCO, 2017

CR rate in the 10-20% range across studies;
*N=number on hypomethylating agent arm of trial

Azacitidine+venetoclax in MDS

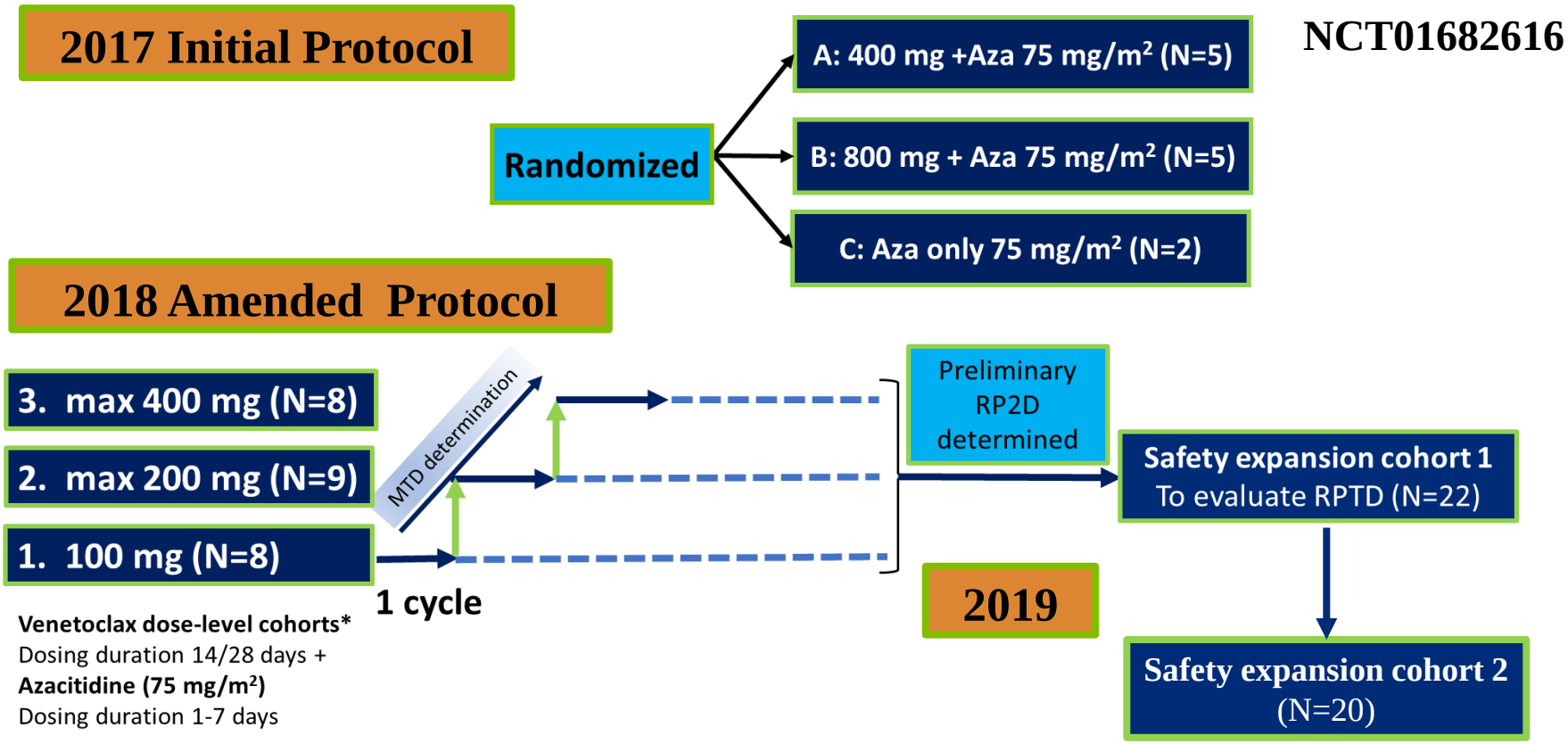
A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax in Combination with Azacitidine in Treatment-Naïve Patients with Higher-Risk Myelodysplastic Syndrome

Andrew H Wei[1], Jacqueline S Garcia[2], Uma Borate[3], Chun Yew Fong[4], Maria R Baer[5], Florian Nolte[6], Pierre Peterlin[7], Joseph Jurcic[8], Guillermo Garcia-Manero[9], Wan-Jen Hong[10], Uwe Platzbecker[11], Olatoyosi Odenike[12], Ilona Cunningham[13], Martin Dunbar[14], Ying Zhou[14], Jason Harb[14], Poonam Tanwani[14], Sathej Gopalakrishnan[15], Johannes Wolff[14], Meagan Jacoby[16]

[1]Department of Haematology, Alfred Hospital and Monash University, Melbourne, Australia, [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [3]Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA
[4]Olivia Newton John Cancer Research Institute, Austin Health, Melbourne, VIC, Australia, [5]Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, University of Maryland, Baltimore, MD, USA, [6]Department of Hematology and Oncology, Charité University Hospital, Campus Benjamin Franklin, Berlin, Germany, [7]Hematology Department, Nantes University Hospital, Nantes, France, [8]Myelodysplastic Syndromes Center, Columbia University Medical Center, Columbia University, New York, NY, USA, [9]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [10]Genentech, South San Francisco, CA, [11]Medical Clinic and Policlinic 1, Hematology and Cellular therapy, University Hospital Leipzig, Germany , [12]University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, [13]Concord Clinical School, University of Sydney, Sydney, Australia
[14]AbbVie Inc, North Chicago, IL, USA, [15]AbbVie Deutschland GmbH & Co KG, Germany, [16]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, MO, USA

American Society of Hematology (ASH) – 61th Annual Meeting
Orlando, FL, USA ● December 9, 2018

Study Design, Dosing, and Enrollment



RP2D: Recommended Phase 2 dose

Baseline Characteristics

Characteristics	N=57
Male, n (%)	14 (25)
Age	
Median (range)	71 (26-85)
≥60 years, n (%)	51 (90)
ECOG Performance Score, n (%)	
0	22 (39)
1	29 (51)
2	6 (11)
Bone marrow blast, n (%)	
<5%	3 (5)
≥5% to <10%	15 (26)
≥10% to <20%	37 (65)
≥20%	2 (4)[#]
IPSS-R score, median (range)	7 (4-10)

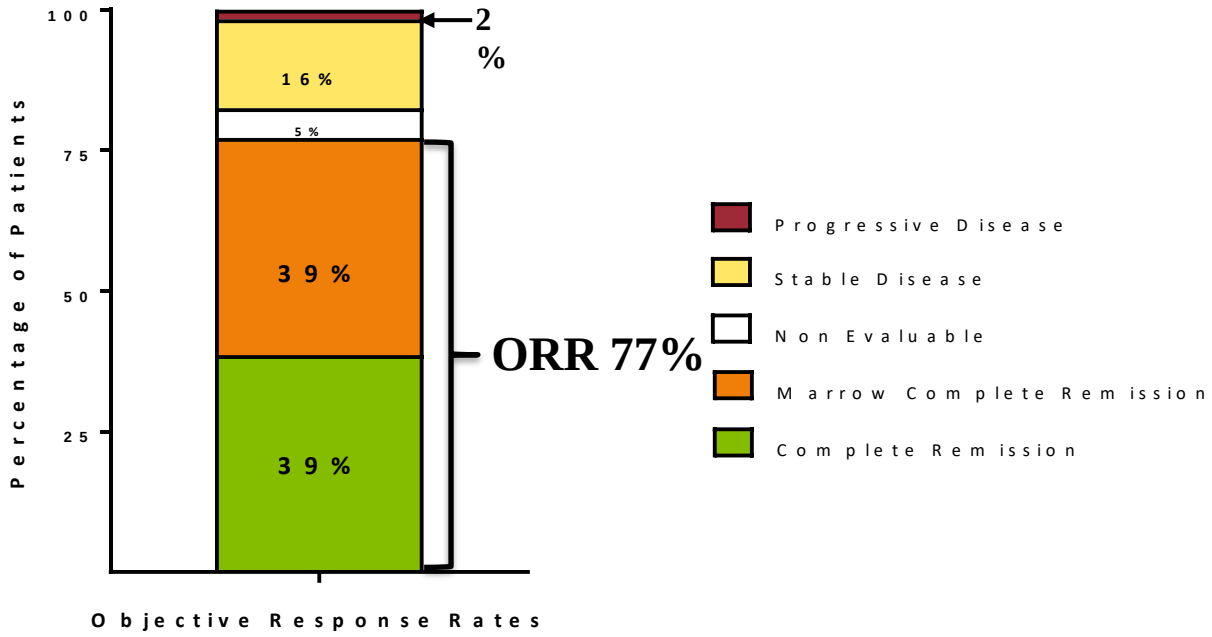
Characteristics	N=57
Cytogenetic risks n (%)	
Good	23 (40)
Intermediate	10 (18)
Poor	24 (42)
Baseline cytopenia (Grade ≥3), n (%)	
Neutropenia[a]	32 (56)
Thrombocytopenia[b]	19 (33)
Leukopenia[c]	23 (40)
Anemia[d]	7 (12)

a. Includes neutrophil count decreased
b. Includes platelet count decreased
c. Includes white blood cell count decreased
d. Includes hemoglobin count decreased

ECOG: Eastern Cooperative Oncology Group, IPSS: International Prognostic Scoring System
[#]Patients recruited under 2017 Initial Protocol

Data Cut-off: 21 AUG 2019

Response Rates (IWG 2006)

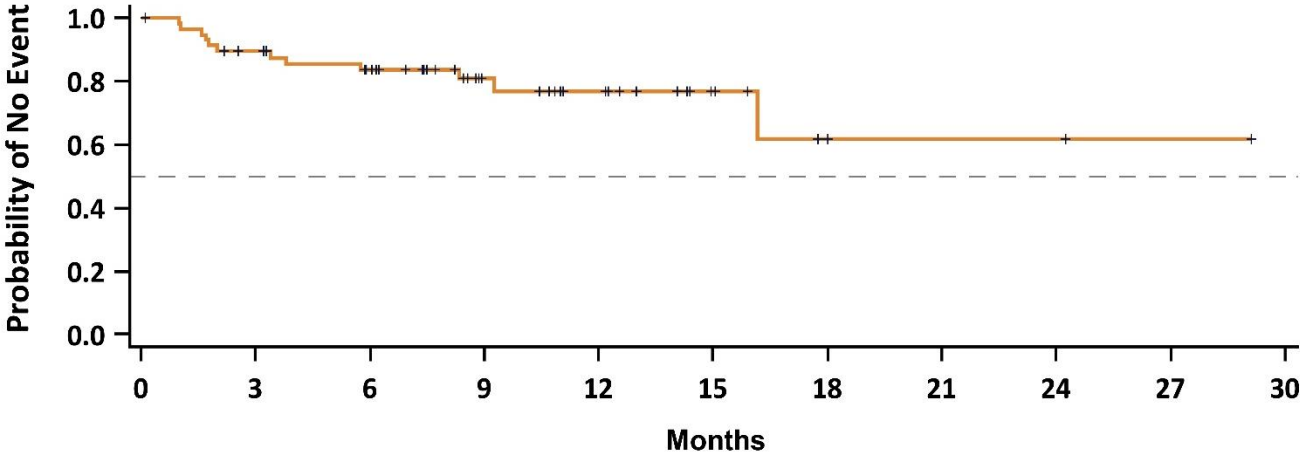


Excludes patients of arm C (Aza only); ORR includes CR+mCR+ PR; # of patients with PR=0

Data Cut-off: 21 AUG 2019

Overall Survival

Survival estimates* (95% CI)	
Month 18	**62%** (28%, 83%)



Number at Risk											
All Patients	57	47	40	22	16	7	3	2	2	1	0

* Median Overall Survival time not reached; Includes all patients that received Ven+Aza (excluding arm C) N=57

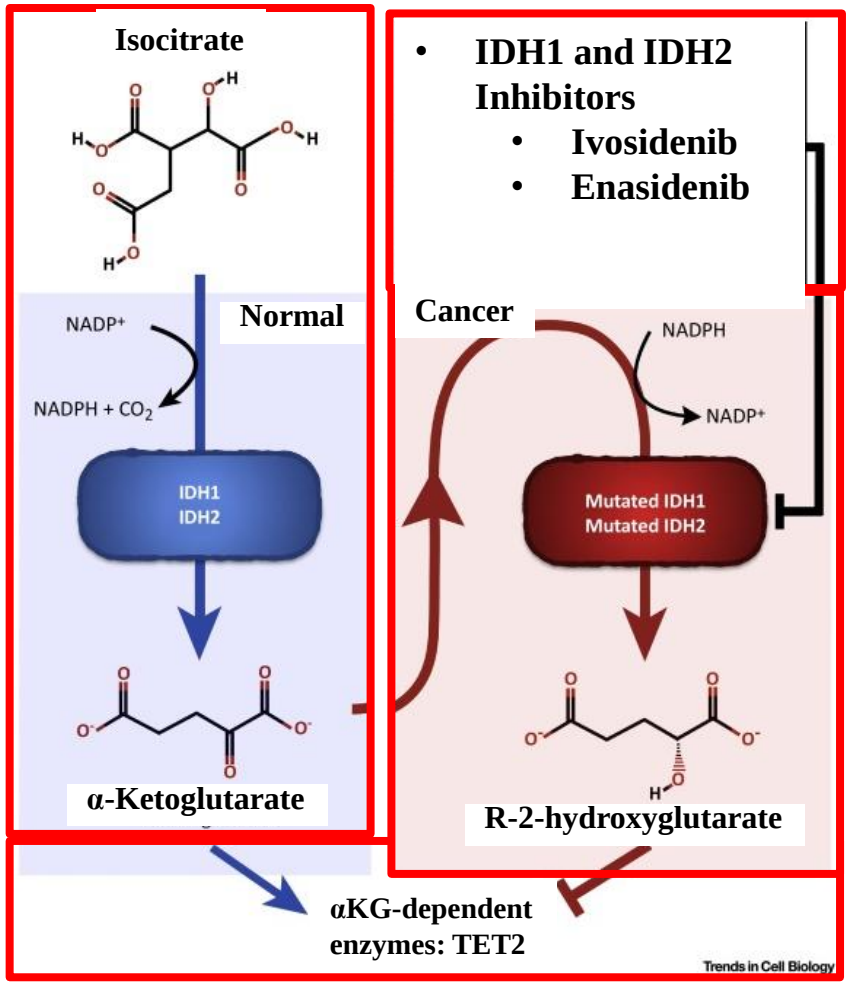
Data Cut-off: 21 AUG 2019

Summary-azacitidine+venetoclax in MDS

- The recommended dose of Venetoclax is 400 mg for days 1-14 of a 28-day cycle when combined with azacitidine (75mg/m^2, days 1-7)
- The emerging safety profile indicates that the combination of Venetoclax and Azacitidine is manageable
- The observed CR rate is 39% with Venetoclax in combination with Azacitidine, ORR>70%
- Overall survival rates are encouraging
  - Follow up is still short
- Impact of baseline mutations on response?

IDH inhibition

Targeting mutant IDH1/2

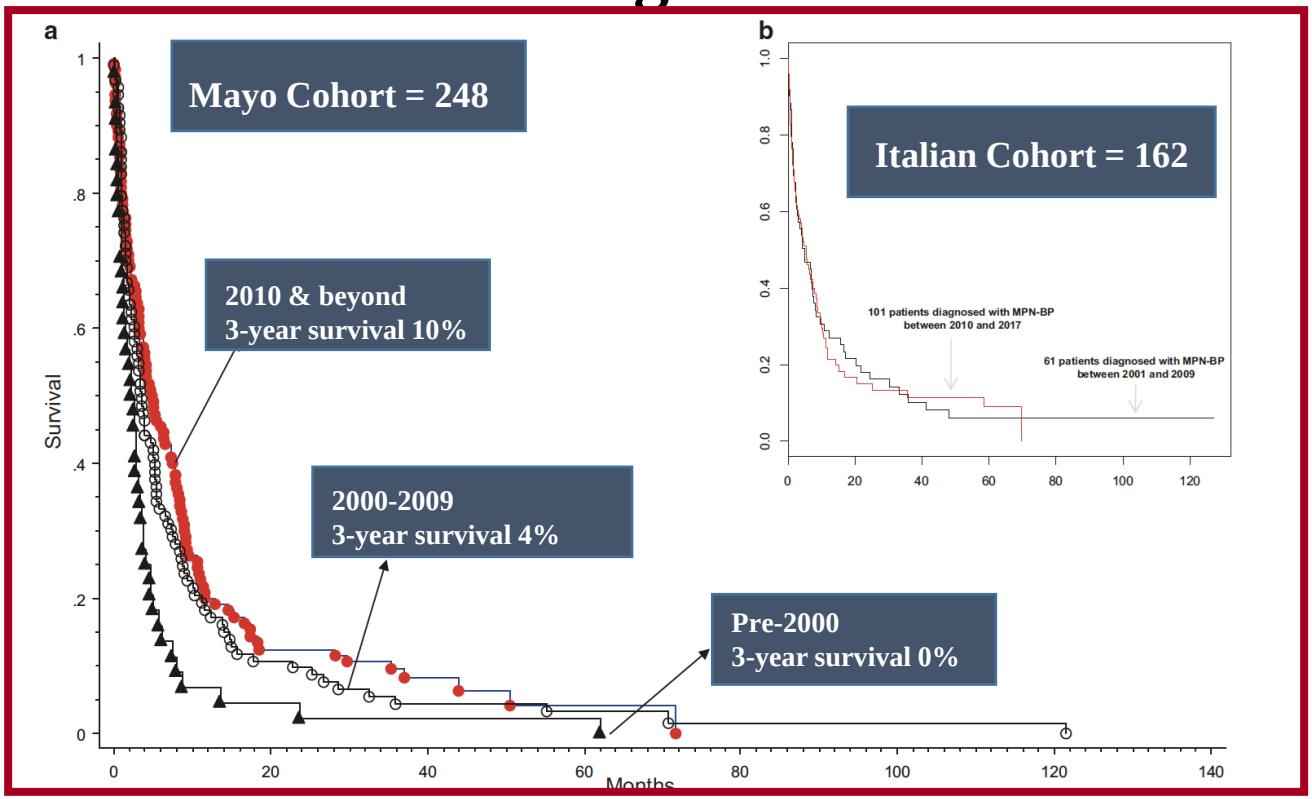


Adapted from: Gagne et al, Trends in Cell Biology, 27; 738-52

- **Mutations in IDH1/2**
  - Lead to elevated 2HG and inhibition of αKG enzymes and epigenetic dysregulation
  - Occur in 6% of MDS, incidence rises with leukemic transformation [1]
  - Occur in 20% of patients with MPN-BP
- **IDH1/2 inhibitors active in IDH mutant AML**
- **Preliminary evidence of activity in MDS**
  - 6 of 15 patients (1CR, 1PR, 4HI) responded in an early phase trial [3]
- **Combination trials with HMA or chemo ongoing in treatment naïve setting in AML.**

1.Dinardo CD, Leukemia, 2016; 30: 980
2.Stein EM, Blood 2017 E-pub
3.Stein EM, Blood, 2016, ASH annual meeting abstracts # 343
4. Dinardo CD, ASH, 2019, abstract # 343

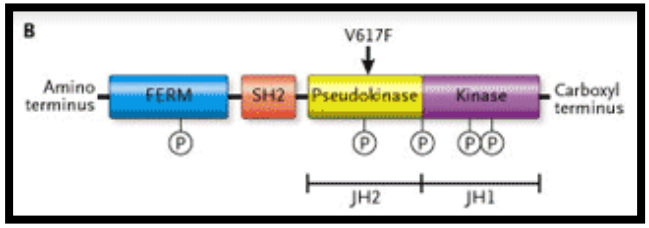
Outcomes in Ph neg Blast-Phase MPNs



Tefferi et al. Leukemia 2018

Advances in MPN Pathogenesis

JAK2V617F mutation

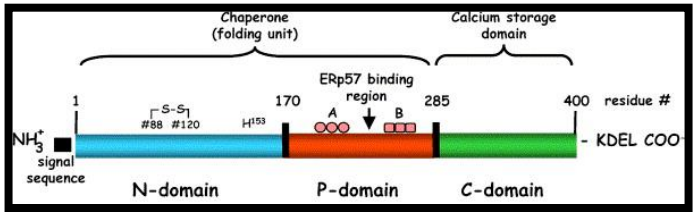


Polycythemia Vera (95%)
Essential Thrombocythemia (50%-60%)
Myelofibrosis (50%-60%)

Mutation confers constitutive activation of JAK/STAT signaling

James C et al, Nature 2005, 434:1144-8
Kralovics R et al, NEJM 2005, 352:1779-90

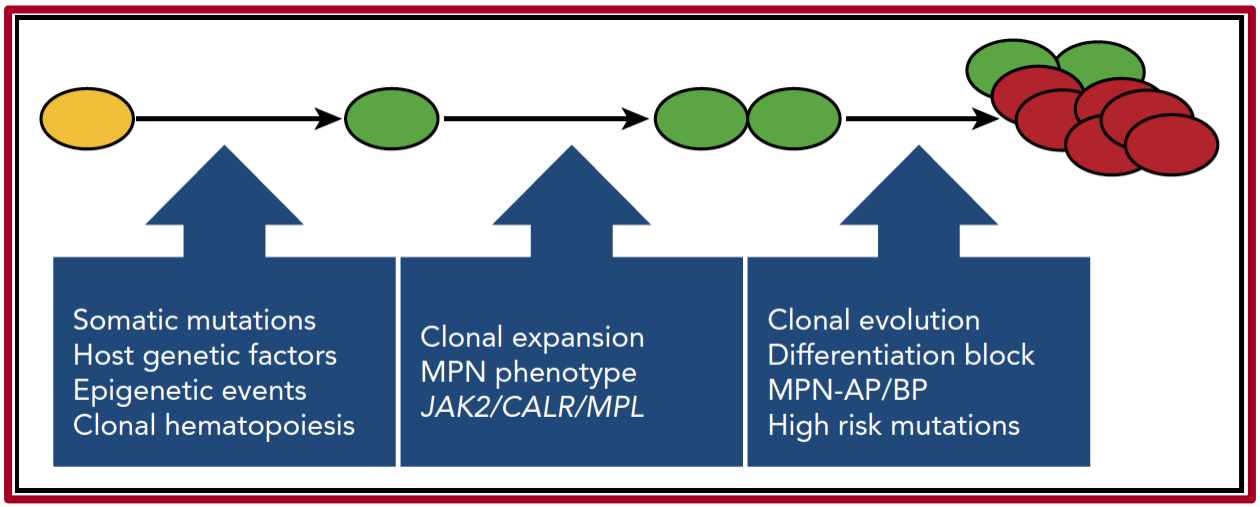
Calreticulin mutation



Essential thrombocythemia (20-30%)
Myelofibrosis (30-40%)

CALR mutations result in activated JAK/STAT signaling

Klampfl T et al, NEJM 2013, 369:2379-90
Nangalia J et al, NEJM 2013, 369:2391-405



An Evolutionary pathway to MPN-BP

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Odenike O, Blood 2018

University of Chicago series: IDH mutated MPN-BP treated with enasidenib or ivosidenib

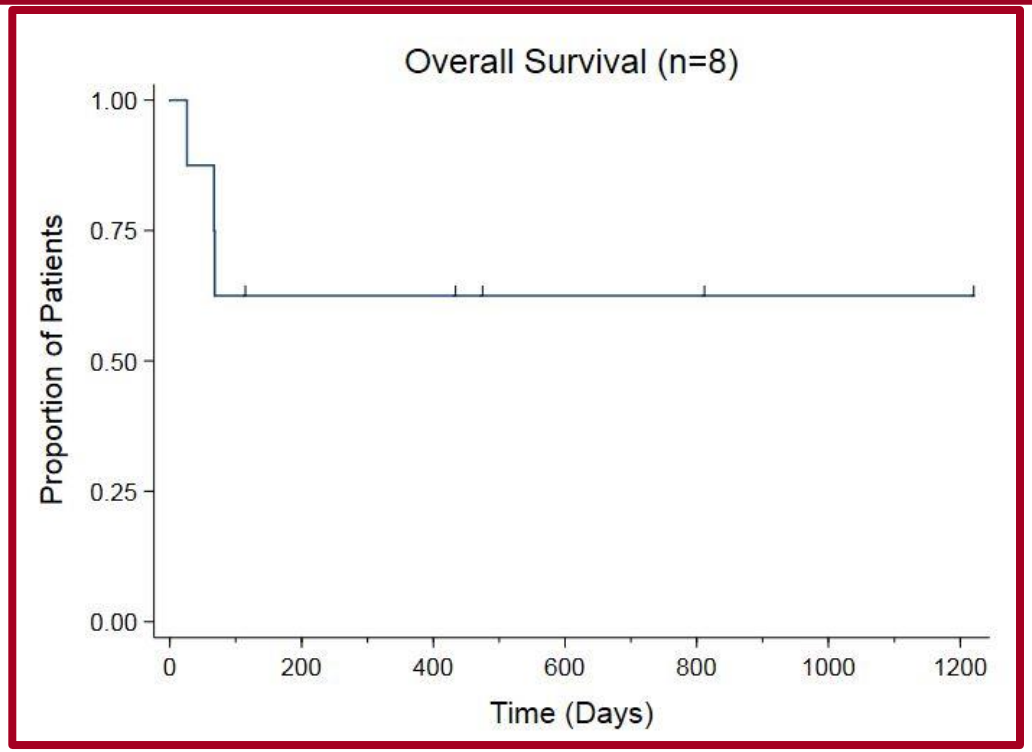
Response by 2003 AML IWG Criteria	All Patients (n=15)	MPN-BP Patients (n=8)
CR	1 (7%)	1 (12.5%)
PR	1 (7%)	1 (12.5%)
MLFS	2 (14%)	1 (12.5%)
TF	11 (53%)	5 (62.5%)
ORR (CR+PR+MLFS)	4 (27%)	3 (37.5%)

Response by 2012 MPN-BP Criteria	MPN-BP Patients (n=8)
CCR	0 (0%)
ALR-C	2 (25%)
ALR-P	4 (50%)
SD	1 (12.5%)
PD	1 (12.5%)
ORR (CCR+ALR-C+ALR-P)	6 (75%)

CR = complete remission; PR = partial remission; MLFS = morphologic leukemia-free state; TF = treatment failure; ORR = overall response rate; SD = stable disease; PD = progressive disease; CCR = complete resolution of acute leukemia and MPN component with normal karyotype; ALR-C = acute leukemia response-complete; ALR-P = acute leukemia response-partial

Patel A et al, In Press, BJH

Survival outcomes :University of Chicago series IDH2 mutated MPN-BP treated with enasidenib



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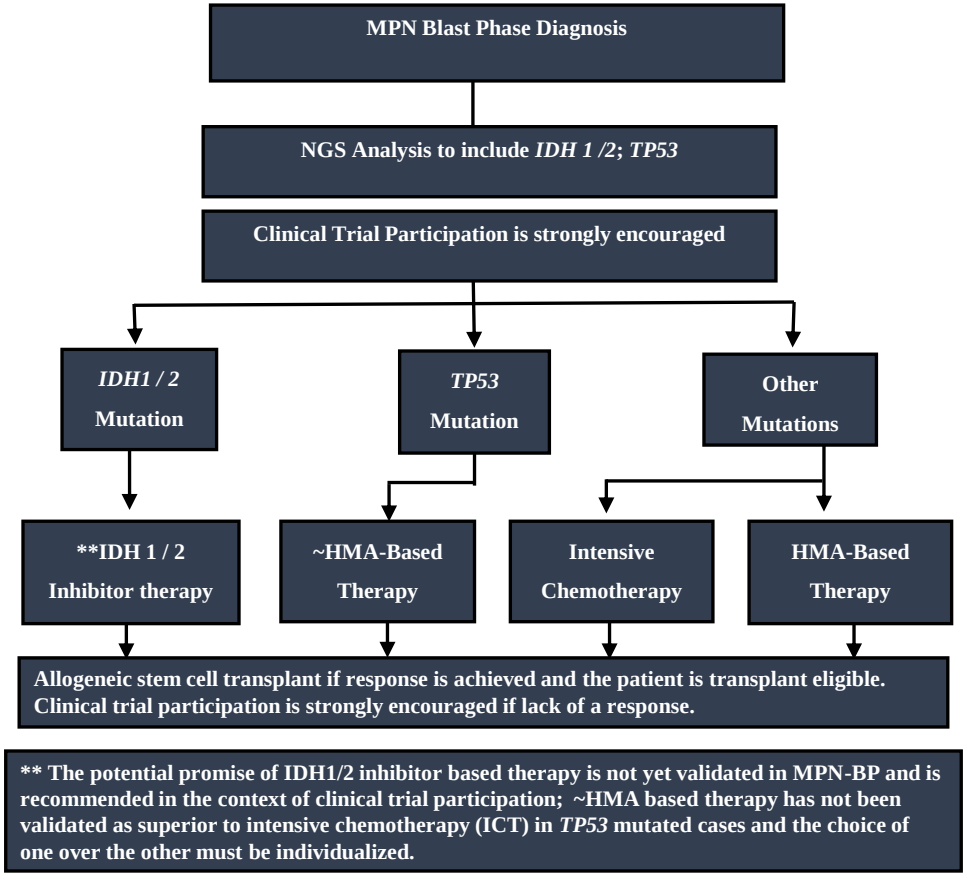
Patel A et al, In Press, BJH

How I treat Ph -MPN in the Blast Phase



Odenike O, Blood 2018

Other novel agents in myeloid neoplasms:

- **Epigenetic therapies**
  - **BET inhibition**
  - **LSD1 inhibition**
  - **DNMT inhibition**
    - **ASTX727, CC-486**
- **TP53 modulators**
  - **APR-246**
- **Checkpoint inhibitors**
  - **Anti-CD47**
  - **Anti-TIM3**
- **TGFbeta inhibitors**
  - **Luspatercept**
- **Non JAK kinase inhibitors**

Conclusions

- **Comprehensive genomic profiling is an integral aspect of the diagnostic work up of patients with myeloid malignancies**

- **Several promising targeted therapeutics are in development which span the spectrum of myeloid malignancies**

- **Potential impact on the natural history of these malignancies is an evolving story**