Myelodysplastic syndromes 2020

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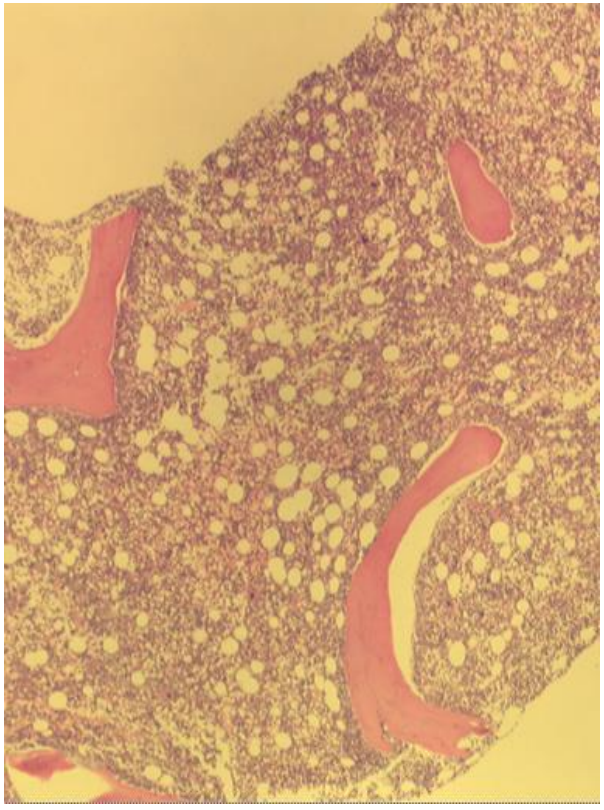
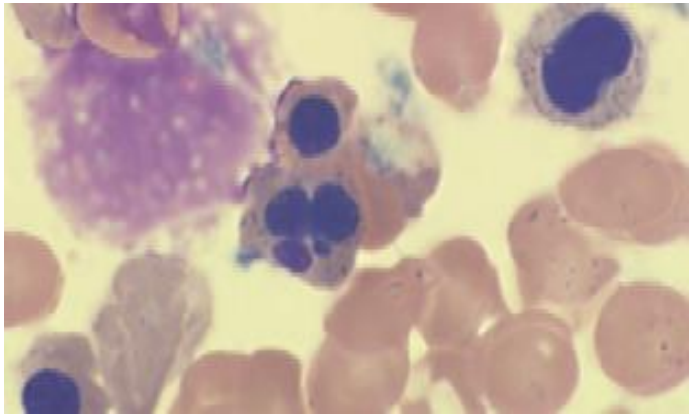
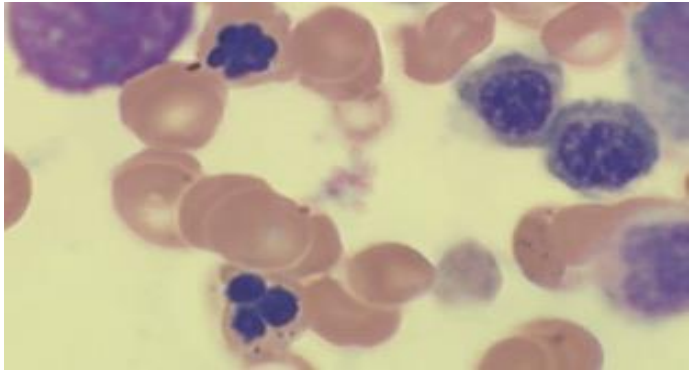
Diagnosis of MDS is based on morphology





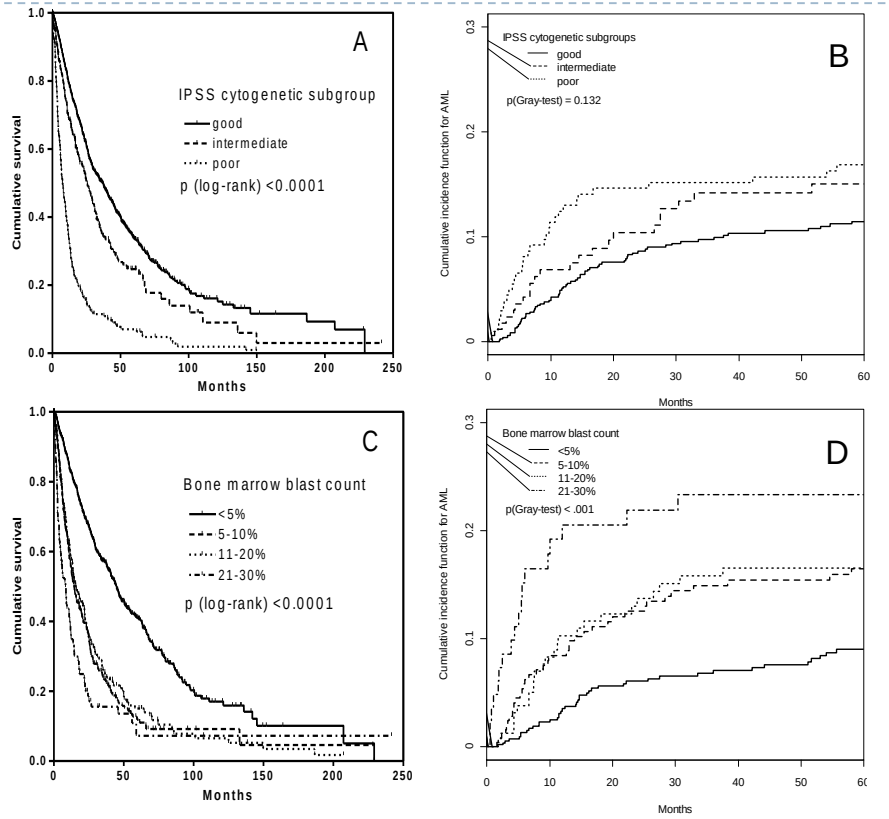


Courtesy of Dr. Carlos Bueso-Ramos

Slow progress in MDS

- **Chronological order of discoveries in MDS:**
- **IPSS classification: 1997**
- **Approval of azacitidine: 2004**
- **Approval of lenalidomide: 2005**
- **Approval of decitabine: 2006**
- **Improved cytogenetic classification: 2012**
- **Application of NGS assays in MDS: 2013**

Weighting of Cytogenetics in Relation to BM blast counts in IPSS

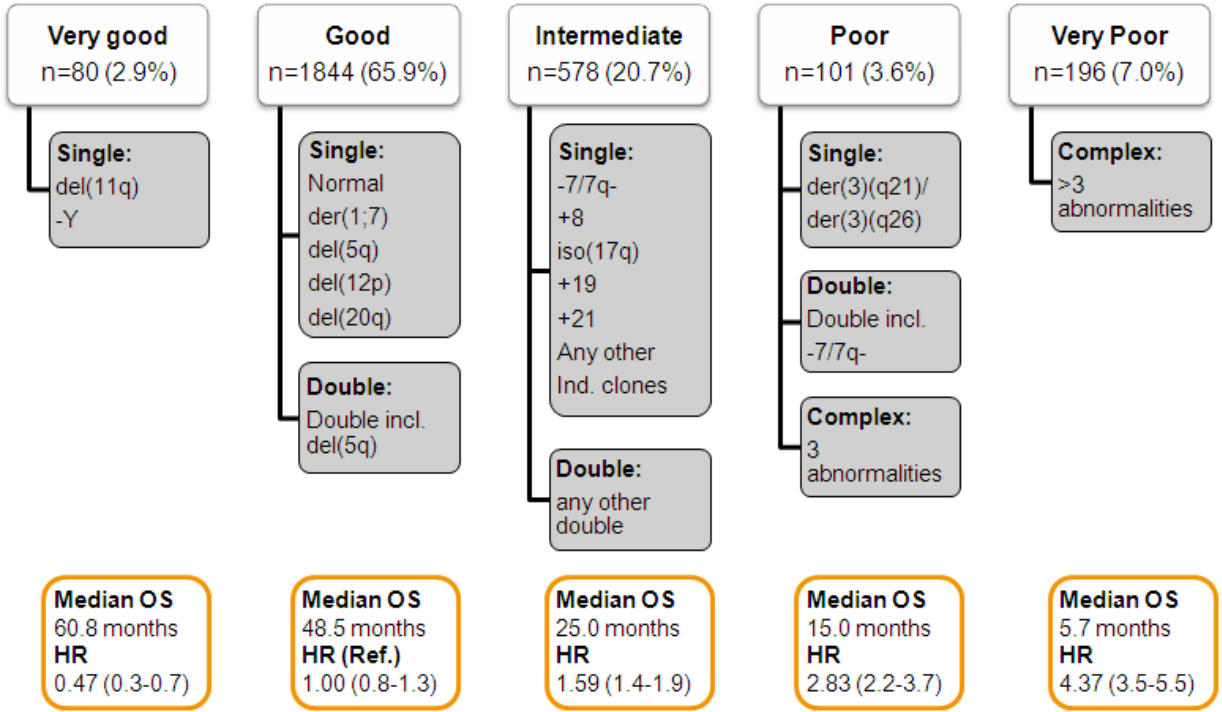


Category	OS (months)	OS (HR)
Poor (IPSS)	7.5	3.2
Complex (non 5/7)	7.4	3.0
Complex (5/7)	5.6	5.4
Blasts (21-30%)	7.4	3.2

Figure 1 A-D
Overall survival and cumulative risk of AML-transformation in IPSS cytogenetic and FAB bone marrow blast count subgroups (univariate analysis; pts. treated with supportive care exclusively)

(Schanz et al., JCO, 2011)

Cytogenetic Scoring System in MDS



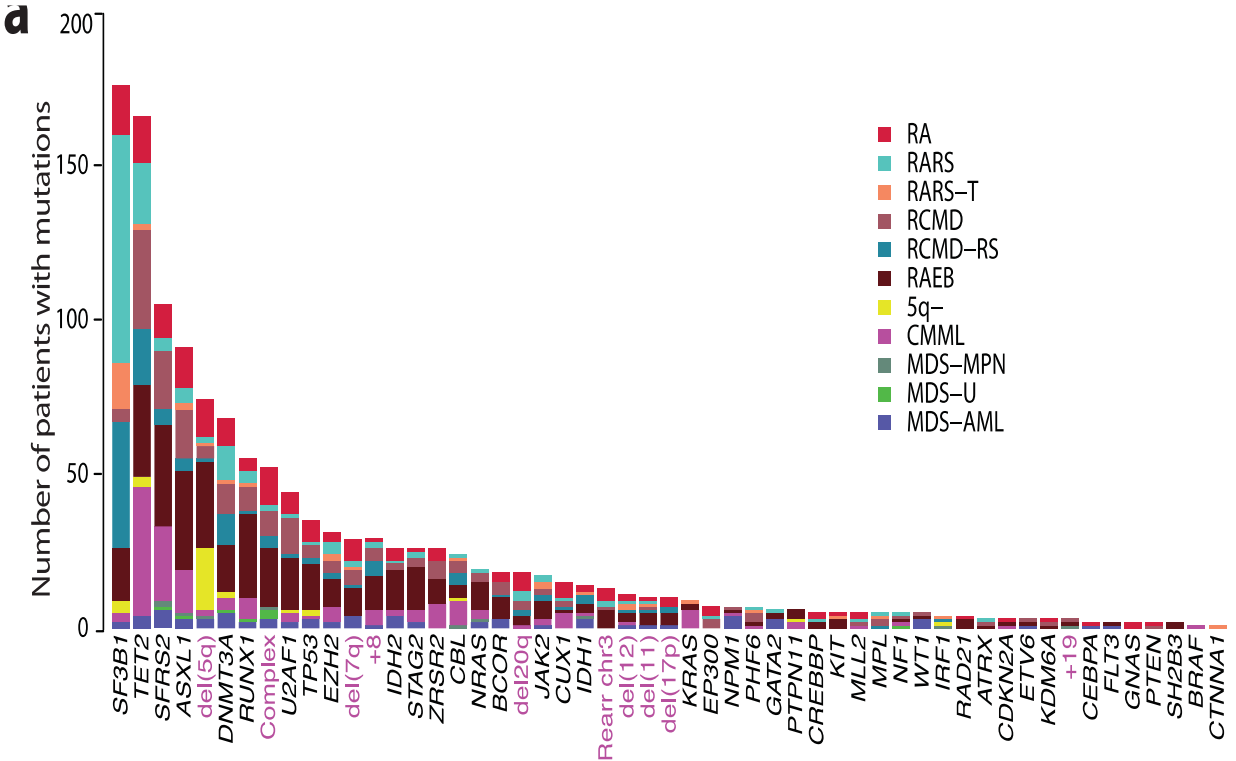
(Schanz et al., JCO, 2011)

Revised IPSS

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

Greenberg et al. Blood 2012;120:2454-65

Genomics of MDS



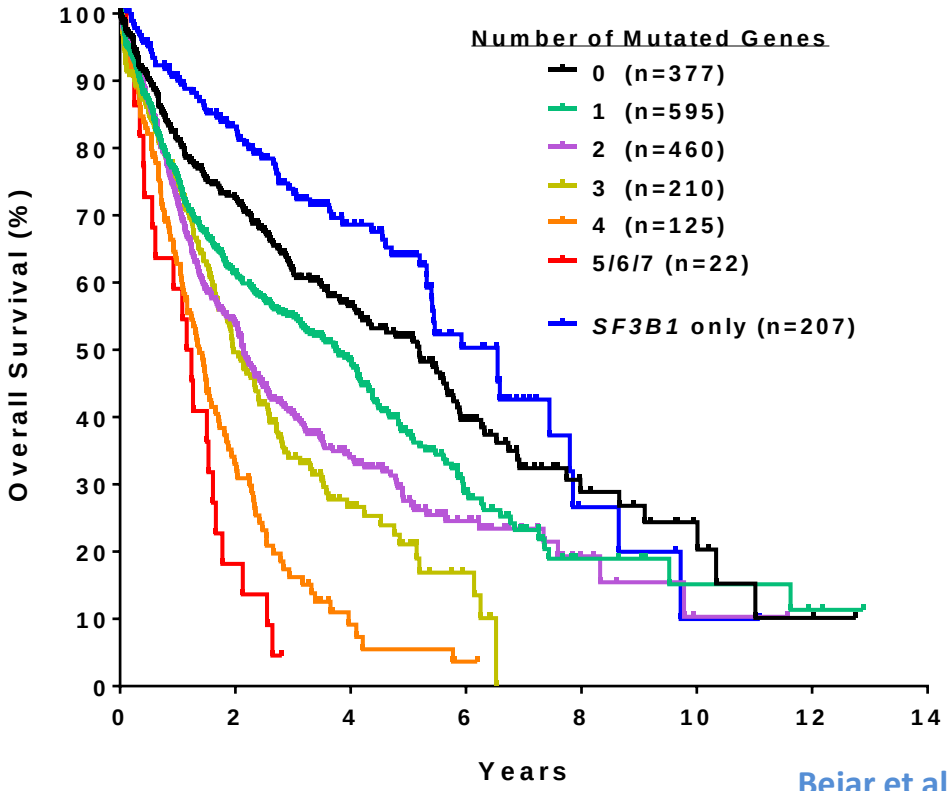
Papaemmanuil et al Blood 2013;122:3616-27

Overall Survival by Mutation Number

17 genes sequenced in 1996 patients with OS data

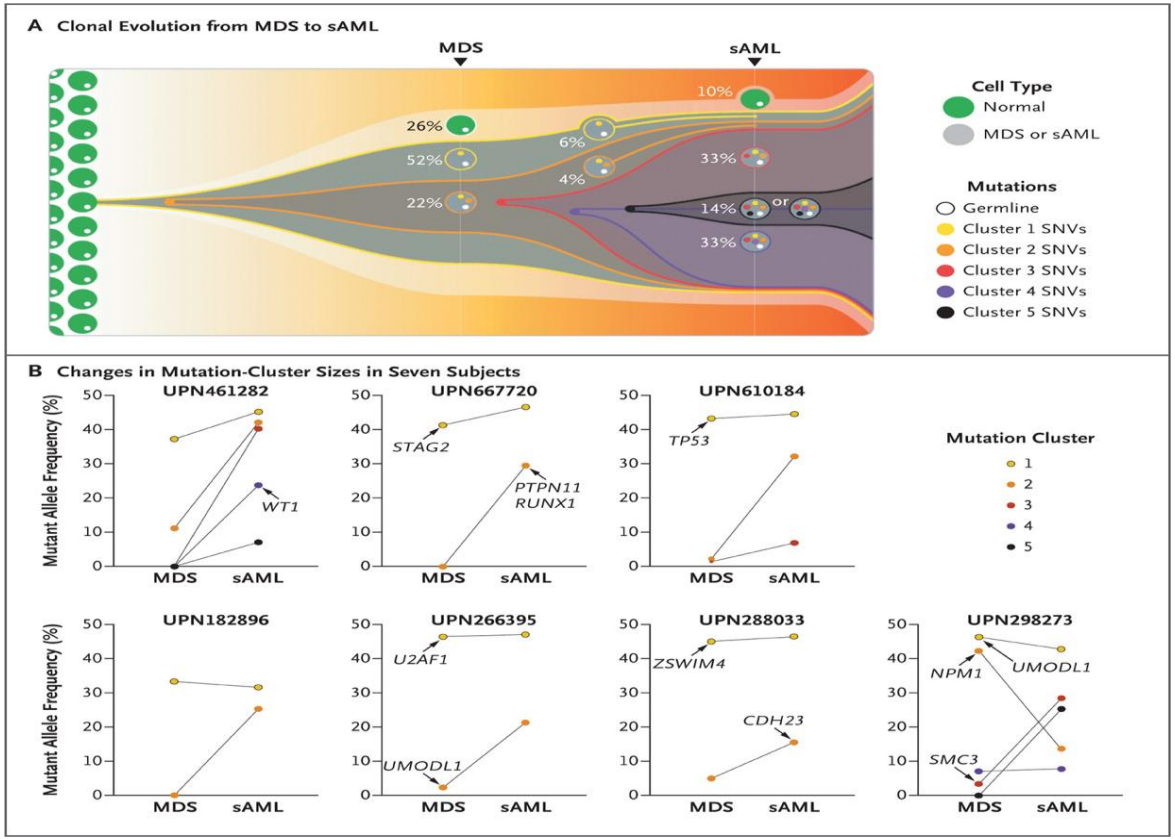
ASXL1
CBL
DNMT3A
ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1

SF3B1



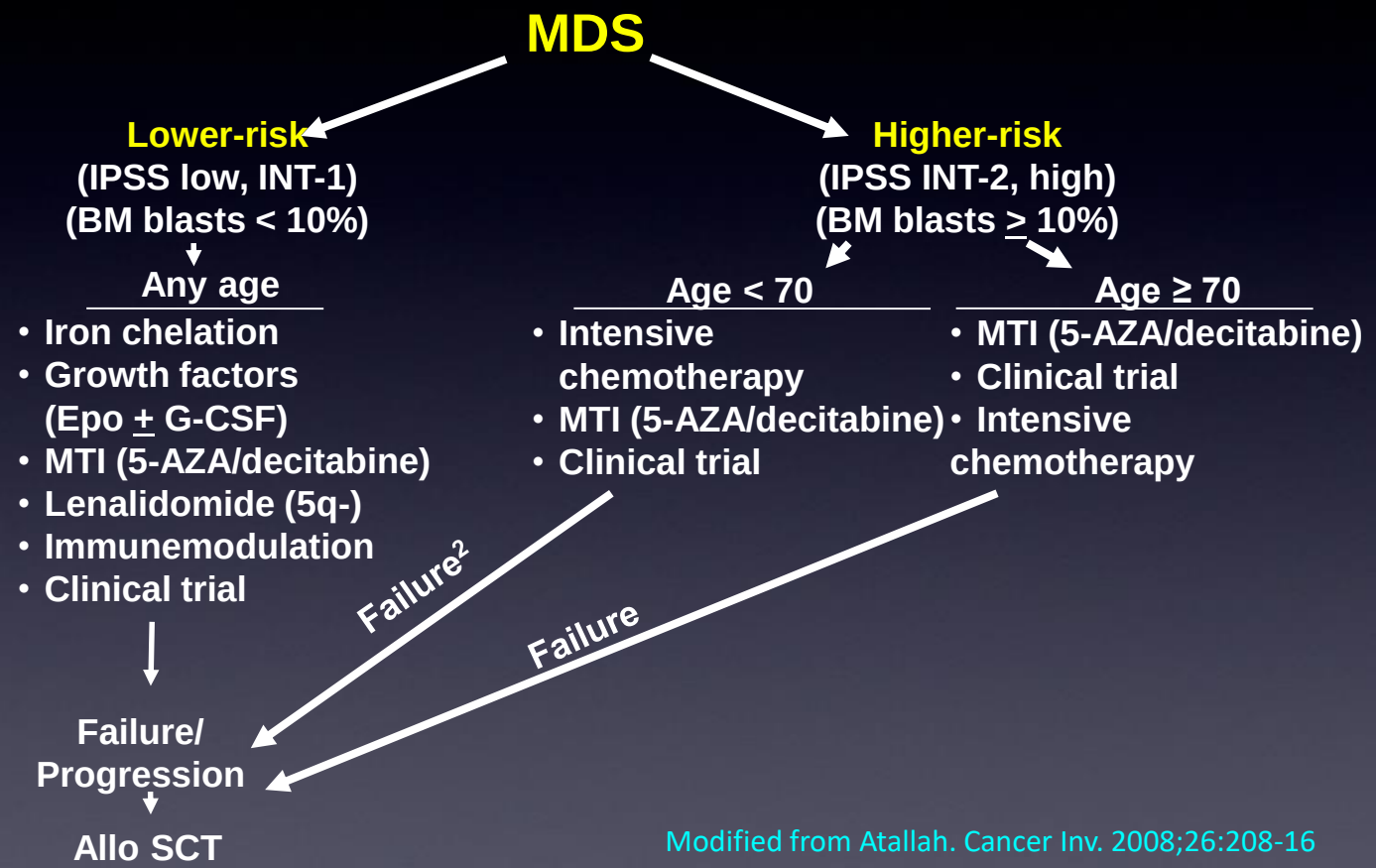
Bejar et al

Clonal Progression from Myelodysplastic Syndrome (MDS) to Secondary Acute Myeloid Leukemia (sAML).



Walter MJ et al. N Engl J Med 2012;366:1090-1098.

Proposed treatment algorithm for patients with MDS



Modified from Atallah. Cancer Inv. 2008;26:208-16

MDS 2019: Outline

- **Immediate impact:**
  - **Luspatercept**
  - **ASTX727 (oral decitabine)**
- **Coming 2020:**
  - **ABT-199**
  - **APR-246**
  - **IDH2, IDH1**
  - **Magrolimab**
- **Other agents: TIM-3, rigosertib, CB393, H3BIO**

Assessment of Longer-Term Efficacy and Safety in the Phase 3, Randomized, Double-Blind, Placebo-Controlled MEDALIST Trial of Luspatercept to Treat Anemia in IPSS-R Very Low-, Low-, or Int-Risk RBC Transfusion-Dependent MDS with Ring Sideroblasts (RS)

Pierre Fenaux[1,2], Ghulam J. Mufti[3], Rena Buckstein[4], Valeria Santini[5], María Díez-Campelo[6], Carlo Finelli[7], Mario Cazzola[8], Osman Ilhan[9], Mikkael A. Sekeres[10], Rami S. Komrokji[11], Alan F. List[11], Amer M. Zeidan[12], Amit Verma[13], Abderrahmane Laadem[14], Rodrigo Ito[14], Jennie Zhang[14], Anita Rampersad[14], Daniel Sinsimer[14], Peter G. Linde[15], Guillermo Garcia-Manero[16], Uwe Platzbecker[17]

[1]Service d'Hématologie Séniors, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, Paris, France; [2]Université Paris 7, Paris, France; [3]Department of Haemato-Oncology, King's College London, London, UK; [4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]MDS Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; [6]Hematology Department, Institute of Biomedical Research of Salamanca, University Hospital of Salamanca, Salamanca, Spain; [7]Department of Oncology and Hematology, S. Orsola-Malpighi University Hospital, Bologna, Italy; [8]Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [9]Department of Hematology, Ankara University School of Medicine, Ankara, Turkey; [10]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; [11]Moffitt Cancer Center, Tampa, FL, USA; [12]Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; [13]Department of Oncology, Albert Einstein College of Medicine, Bronx, NY, USA; [14]Bristol-Myers Squibb, Summit, NJ, USA; [15]Acceleron Pharma, Cambridge, MA, USA; [16]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [17]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Hematology and Cellular Therapy, Leipzig, Germany

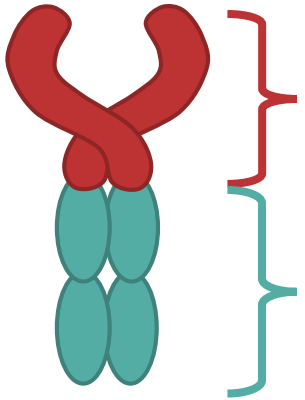
Abstract #841

LUSPATERCEPT: INTRODUCTION

- Luspatercept is a first-in-class erythroid maturation agent that binds several TGF-β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[1]
- Luspatercept is approved by the US FDA for the treatment of anemia in adult patients with β-thalassemia who require regular RBC transfusions[2]
- In the primary results of the MEDALIST trial[3] luspatercept met the following endpoints with statistical significance versus placebo:
  - Primary endpoint: RBC-TI ≥ 8 weeks (Weeks 1–24)
  - Key secondary endpoint: RBC-TI ≥ 12 weeks (Weeks 1–24, Weeks 1–48)
- Presented here is an updated analysis of longer-term clinical benefit and safety data from the MEDALIST trial

Luspatercept

ActRIIB / IgG1 Fc recombinant fusion protein



Modified extracellular domain of ActRIIB

Human IgG1 Fc domain

1. Suragani RN, et al. Nat Med. 2014;20:408-414.
2. Reblozyl [package insert]. Summit, NJ, USA: Celgene Corporation; 2019.
3. MEDALIST authors. Blood. 2018;132:abstract 1.

LUSPATERCEPT: STUDY DESIGN

Inclusion Criteria

- MDS with RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- Non-del(5q) MDS
- IPSS-R Very low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 U/8 weeks
- No prior treatment with disease-modifying agents (e.g. IMiD agents, HMAs)

Randomized 2:1

Luspatercept 1.0 mg/kg (s.c.) every 21 days
(n = 153)

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 3 weeks
(n = 76)

Disease and response assessment
Week 24 and every 6 months
Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria

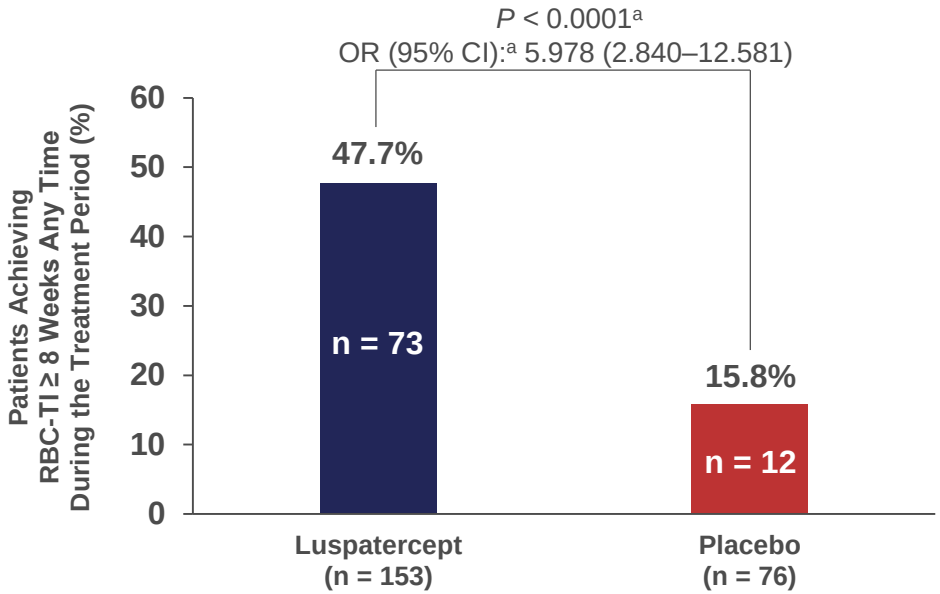
Patients followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment, and overall survival; crossover between groups was not allowed

Primary analysis data cutoff date May 8, 2018; current data cutoff date July 1, 2019.

Patients were randomized between March 2016 and June 2017 at 65 sites in Belgium, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, Turkey, UK, and USA.

AML, acute myeloid leukemia; EPO, erythropoietin; HMA, hypomethylating agent; IMiD, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; WHO, World Health Organization.

RBC-TI ≥ 8 WEEKS ACHIEVED ANY TIME DURING TREATMENT PERIOD



- When assessed during the entire treatment period, a greater proportion of luspatercept-treated patients achieved RBC-TI ≥ 8 weeks compared with placebo than previously reported (37.9% of patients receiving luspatercept achieved RBC-TI ≥ 8 weeks during Weeks 1–24 of treatment vs 13.2% of placebo-treated patients; $P < 0.0001$)[1]

Abstract #841

RBC-TI ≥ 8 WEEKS ACHIEVED DURING THE ENTIRE TREATMENT PERIOD
RESPONSE BY BASELINE TRANSFUSION BURDEN

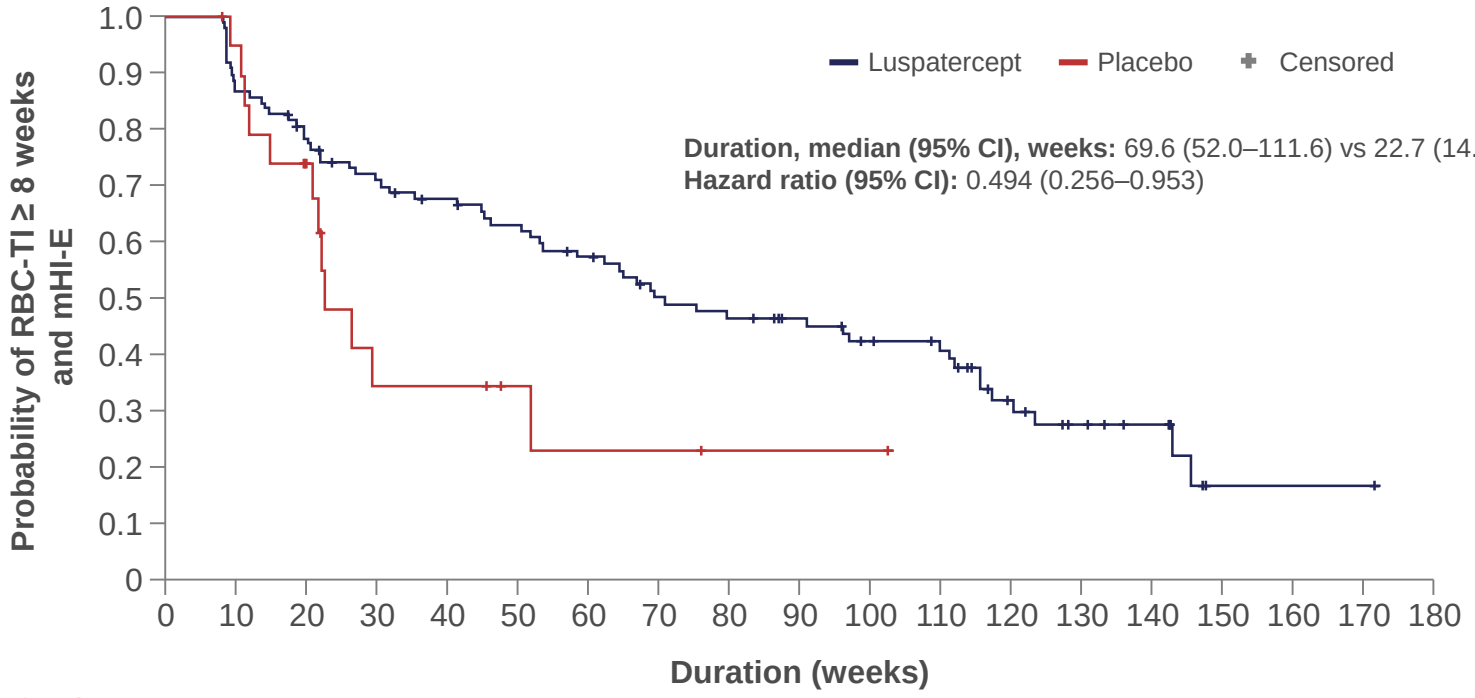
RBC-TI ≥ 8 Weeks Over the Entire Treatment Period	Luspatercept (n = 153)	Placebo (n = 76)	Luspatercept Minus Placebo	
			OR (95%CI)[a]	*P* Value[a]
Average baseline RBC transfusion requirement, n/N (%)				
≥ 6 U/8 weeks	14/66 (21.2)	2/33 (6.1)	4.17 (0.89–19.60)	0.0547
≥ 4 to < 6 U/8 weeks	20/41 (48.8)	2/23 (8.7)	10.00 (2.07–48.28)	0.0013
< 4 U/8 weeks	39/46 (84.8)	8/20 (40.0)	8.36 (2.51–27.83)	0.0002

[a] Determined using a Cochran-Mantel-Haenszel test.

- More luspatercept-treated patients achieved RBC-TI ≥ 8 weeks over the entire treatment period compared with those receiving placebo, regardless of baseline transfusion burden

Abstract #841

COMBINED DURATION OF RBC-TI ≥ 8 WEEKS AND mHI-E ACHIEVED DURING THE ENTIRE TREATMENT PHASE



Number of patients																	
Luspatercept	98	85	74	65	60	55	49	41	38	34	29	27	15	10	7	1	1	1
Placebo	20	18	13	5	5	3	2	2	1	1	1							

Abstract #841

Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (cedazuridine/decitabine) Compared to IV Decitabine

Guillermo Garcia-Manero[1], James McCloskey[2], Elizabeth Griffiths[3], Karen Yee[4], Amer Zeidan[5], Aref Al-Kali[6], Kim-Hien Dao[7], H Joachim Deeg[8], Prapti Patel[9], Mitchell Sabloff[10], Mary-Margaret Keating[11], Nancy Zhu[12*], Nashat Gabrail[13*], Salman Fazal[14], Joseph Maly[15], Olatoyosi Odenike[16], Aditi Shastri[17], Amy E DeZern[18], Casey O'Connell[19], Gail Roboz[20], Aram Oganesian[21*], Yong Hao[21*], Harold Keer[21], Mohammad Azab[21], Michael Savona[22]

On behalf of ASCERTAIN Investigators Team

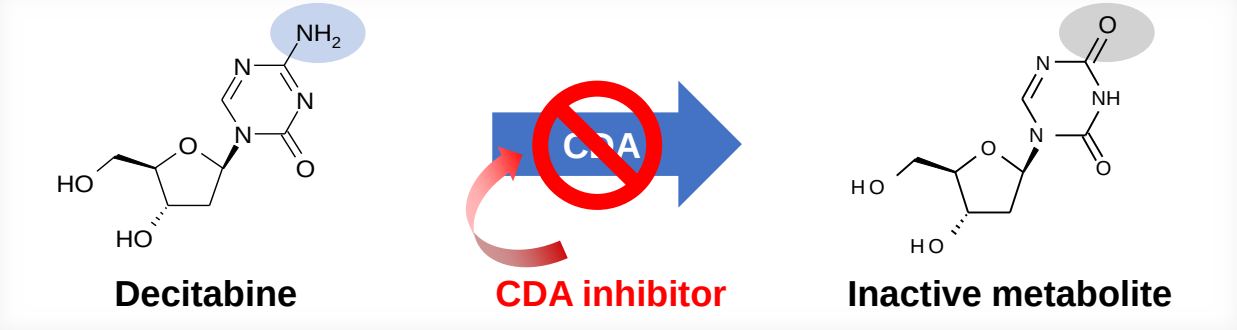
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]John Theurer Cancer Center, Hackensack Medical Center, NJ; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [5]Yale University and Yale Cancer Center, New Haven, CT; [6]Mayo Clinic, Rochester, MN; [7]Oregon Health & Science University, Portland, OR; [8]Fred Hutchinson Cancer Research Center, Seattle, WA; [9]University of Texas Southwestern Medical Center, Dallas, TX; [10]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada; [11]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; [12]University of Alberta, Edmonton, Alberta, Canada; [13]Gabrail Cancer Center, Canton, OH; [14]West Penn Hospital, Allegheny Health Network, Pittsburgh, PA; [15]Norton Cancer Institute, Louisville, KY; [16]University of Chicago, Chicago, IL; [17]Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY; [18]Johns Hopkins University Hospital, Baltimore, MD; [19]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [20]Weill Cornell Medicine, The New York Presbyterian Hospital, New York, NY; [21]Astex Pharmaceuticals, Inc., Pleasanton, CA; [22]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

61st ASH Annual Meeting, Orlando, FL. Dec 7-10, 2019. Abstract #846

Clinicaltrials.gov NCT03306264

ASTX727 (cedazuridine/decitabine): Background

- Current HMA treatment poses significant patient burden due to 5–7 days per month of parenteral administration in a clinic setting
- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver

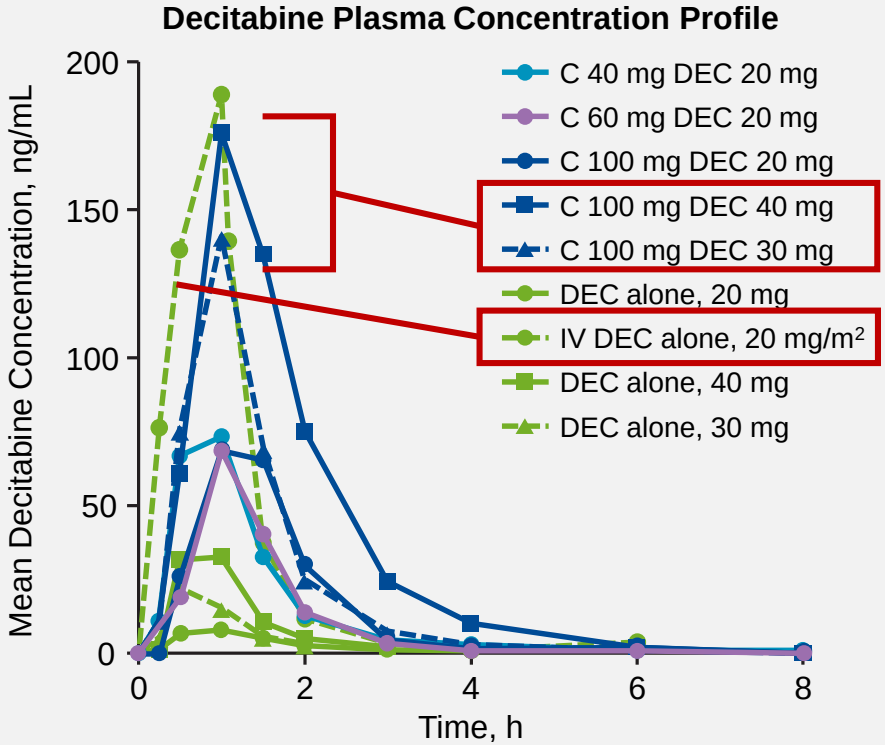


- Cedazuridine is a novel, potent, and safe CDA inhibitor
  - Large safety margin, with no adverse events at up to 200 mg/kg in monkeys (~2400 mg/m^2 human equivalent)

Abstract #846

CDA, cytidine deaminase.

ASTX727 (Cedazuridine/Decitabine) Phase 1 Dose Finding Study in MDS and CMML



- Oral ASTX727 (cedazuridine 100 mg / decitabine 30 to 40 mg) achieved decitabine AUC 5-day exposures oral/IV ratio between 81% and 128%
- Oral ASTX727 (cedazuridine 100 mg / decitabine 35 mg) selected for Phase 2

Savona MR, et al. Lancet Hematology 2019;6:PE194-E203.
AUC, area under concentration-time curve; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome.

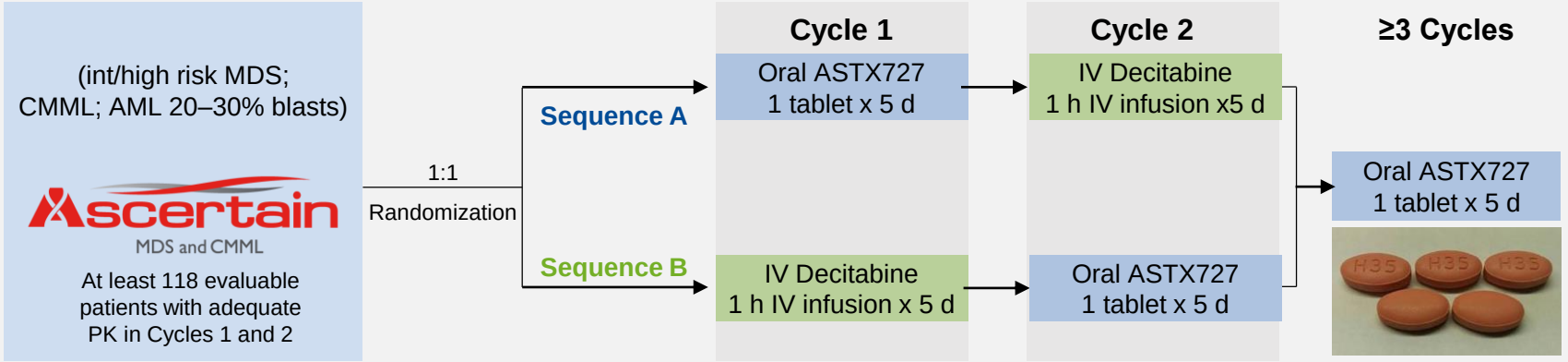
ASTX727 Phase 2: Durable Clinical Responses in MDS/CMML Patients

Best Response	N=80
Complete response (CR)	21.3%
Partial response (PR)	0
Marrow CR (mCR)	22.5%
mCR with hematologic improvement	7.5%
Hematologic improvement (HI)	16.3%
HI-erythroid	10%
HI-neutrophils	2.5%
HI-platelet	13.8%
Overall response (CR + PR + mCR + HI)	60%
RBCs transfusion independence (n=38)*	50%
Platelets transfusion independence (n=12)*	50%

Median FU: 24 months; median number of cycles: 7
CR median duration of response: 13.3 months
Median overall survival: 18.3 months

* No transfusion for at least 8 consecutive weeks in patients who were transfusion dependent at baseline.
Garcia-Manero 15th International MDS Symposium 2019.

ASTX727 Phase 3 Study (ASCERTAIN) in MDS/CMML
Trial Design: Randomized Cross-Over



Major entry criteria
- Candidates for IV decitabine
- ECOG PS 0–1
- Life expectancy of ≥3 months
- Adequate Organ Function
- One prior cycle of HMA is allowed

Primary endpoint
- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints
- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

ASTX727: Primary Endpoint (5-day Decitabine AUC Equivalence)

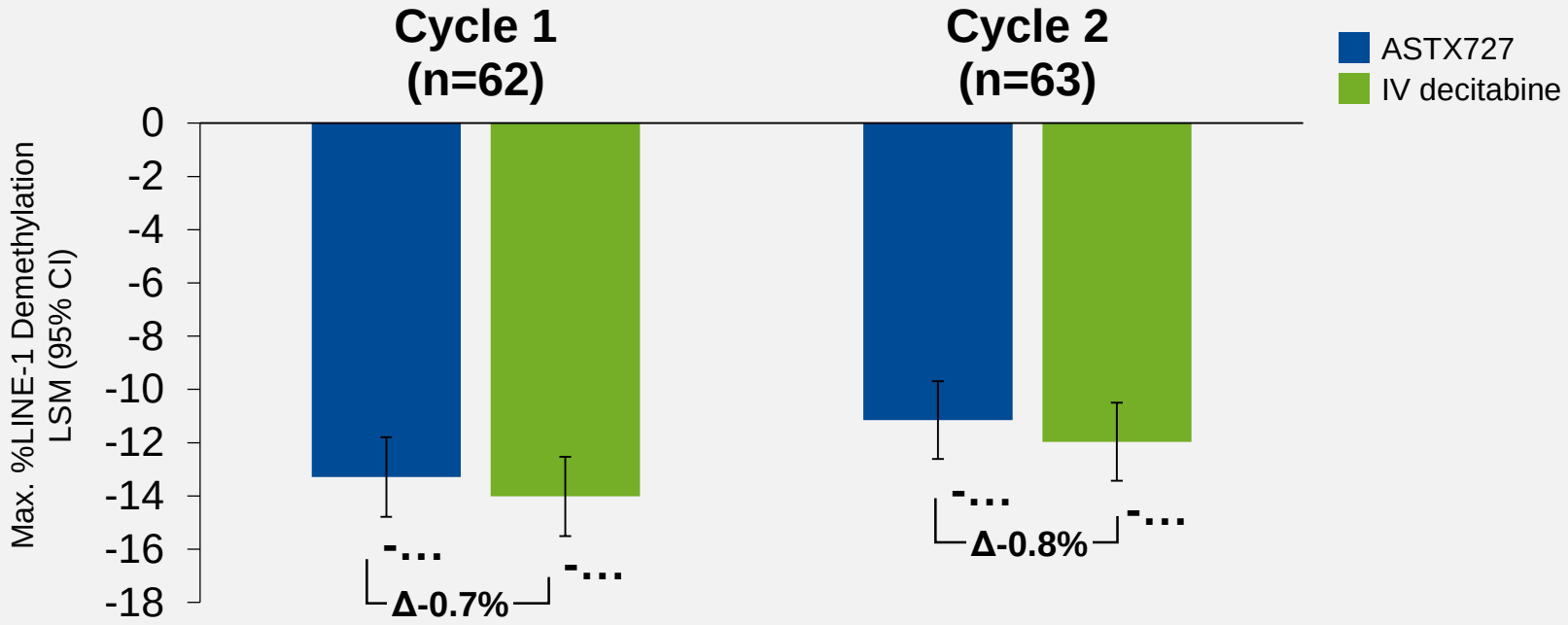
Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Abstract #846

Pharmacodynamics (*LINE-1* DNA Demethylation in Cycles 1 and 2)



- No significant difference in *% LINE-1* DNA demethylation between ASTX727 and IV decitabine (<1% difference in each cycle)

Abstract #846

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

568

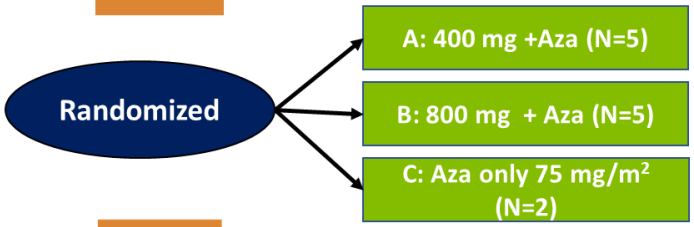
Andrew H Wei[1], Jacqueline S Garcia[2], Uma Borate[3], Chun Yew Fong[4], Maria R Baer[5], Florian Nolte[6], Pierre Peterlin[7], Joseph Jurcic[8], Guillermo Garcia-Manero[9], Wan-Jen Hong[10], Uwe Platzbecker[11], Olatoyosi Odenike[12], Ilona Cunningham[13], Martin Dunbar[14], Ying Zhou[14], Jason Harb[14],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

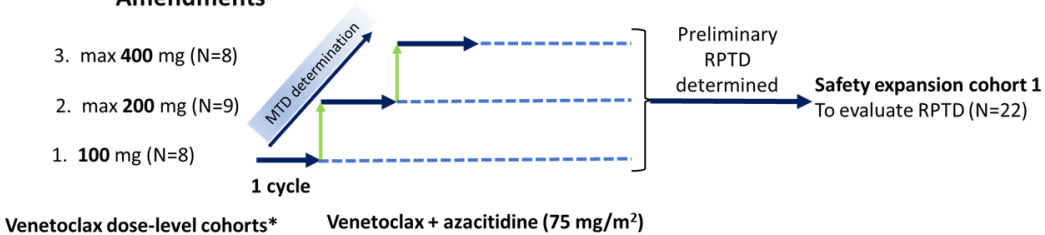
Venetoclax front line MDS

2017



2018

Protocol Amendments



2019

Option of a 2nd Safety expansion cohort (N=20)

R2PD: Recommended Phase 2 dose

NCT01682616

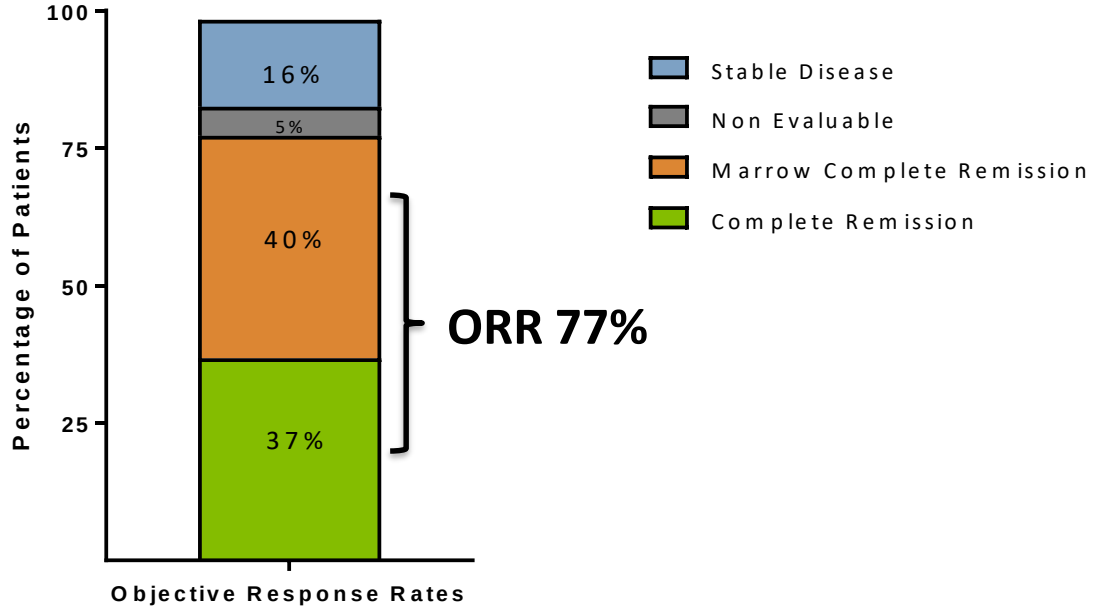
Venetoclax Dosing

Cohorts	mg/day	days	g/ cycle
A	400	28	11.2
B	800	28	22.4
C	0	0	0
1	100	14	1.4
2	200	14	2.8
3	400	14	5.6
SE1	400	14	5.6
SE 2	400	14	5.6

Abstract #568

Phase 1B, Open label, Multicenter Study (*Design developed over time*)
Venetoclax + Azacitidine combination for treatment naïve HR-MDS

Venetoclax: Response Rates (IWG 2006)

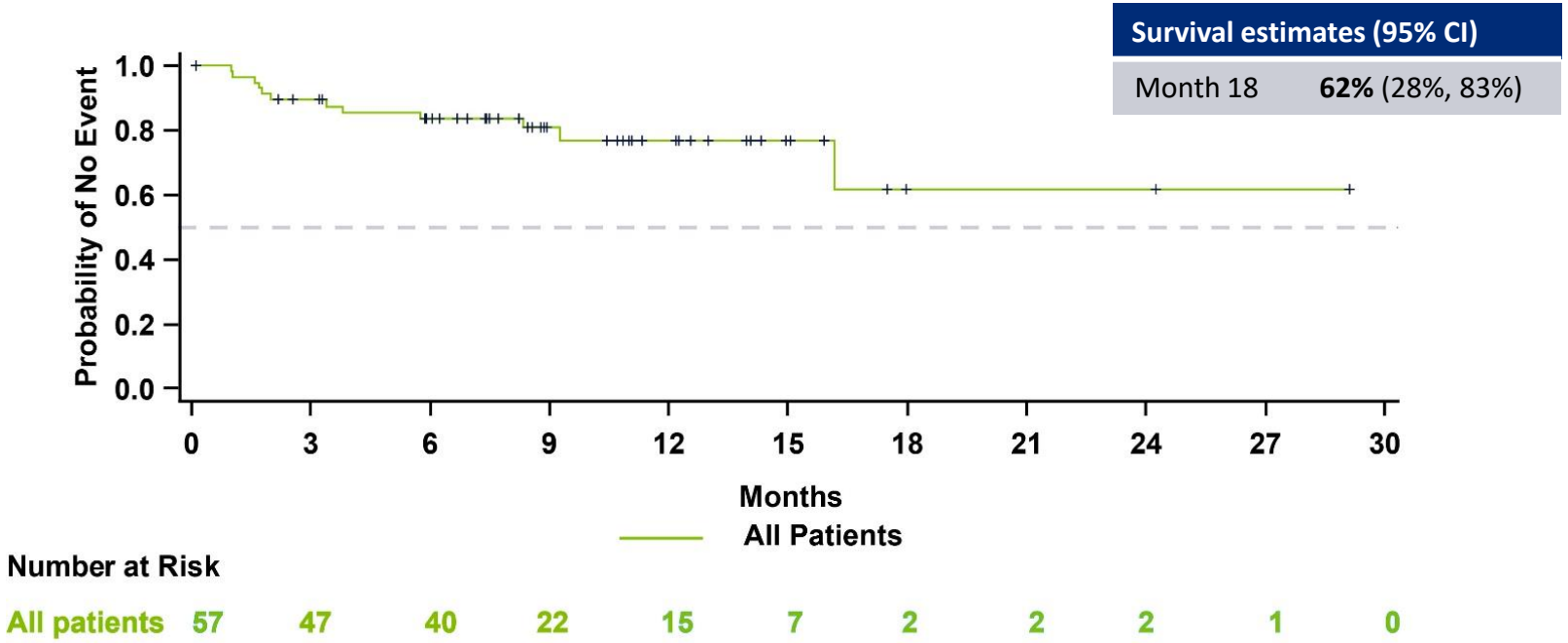


Proportion of patients with complete remission is 37% and marrow complete remission is 40%

Excludes patients of arm C (Aza only)

Abstract #568

Venetoclax: Overall Survival



Includes all patient that received Ven+Aza (excluding arm C) N=57

A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax as Monotherapy or in Combination with Azacitidine for the Treatment of Relapsed/Refractory Myelodysplastic Syndrome

565

Amer M. Zeidan[1], Daniel A Pollyea[2], Jacqueline S Garcia[3], Andrew M Brunner[4], Fernando Roncolato[5], Uma Borate[6], Olatoyosi Odenike[7], Ashish Bajel[8], Anne Marie Watson[9], Katharina Götze[10], Florian Nolte[11], Peter Tan[12], Haifa K Al-Ali[13], Wan-Jen Hong[14], Ying Zhou[15], Lori Gressick[15], William Ainsworth[15], Jason Harb[15], Ahmed H Salem[15], John Hayslip[15], Ronan Swords[15]

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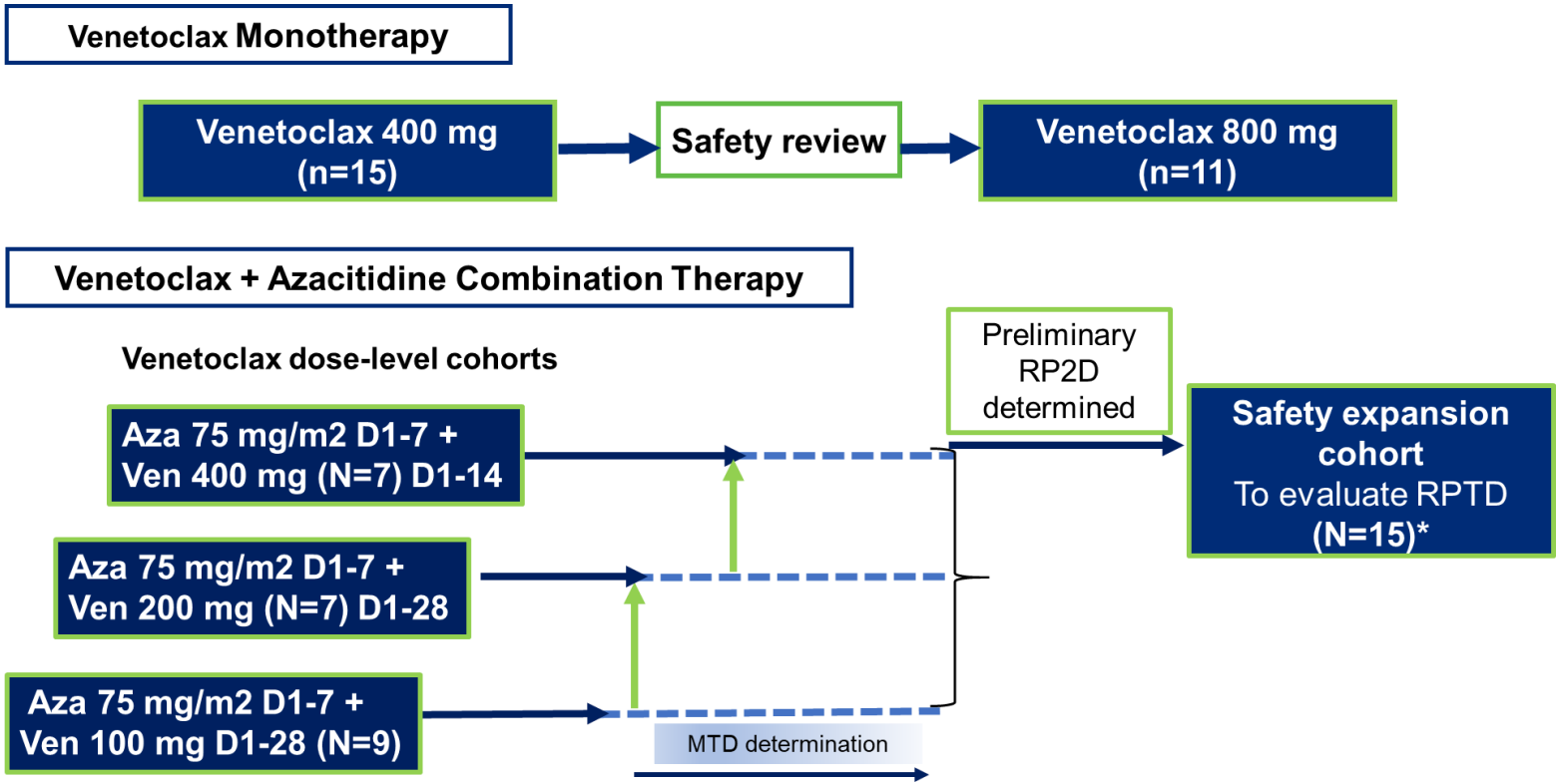
American Society of Hematology (ASH) – 61th Annual Meeting
Orlando, FL, USA ● December 9, 2019

Abstract #565

Venetoclax HMA failure: Study Design

NCT02966782

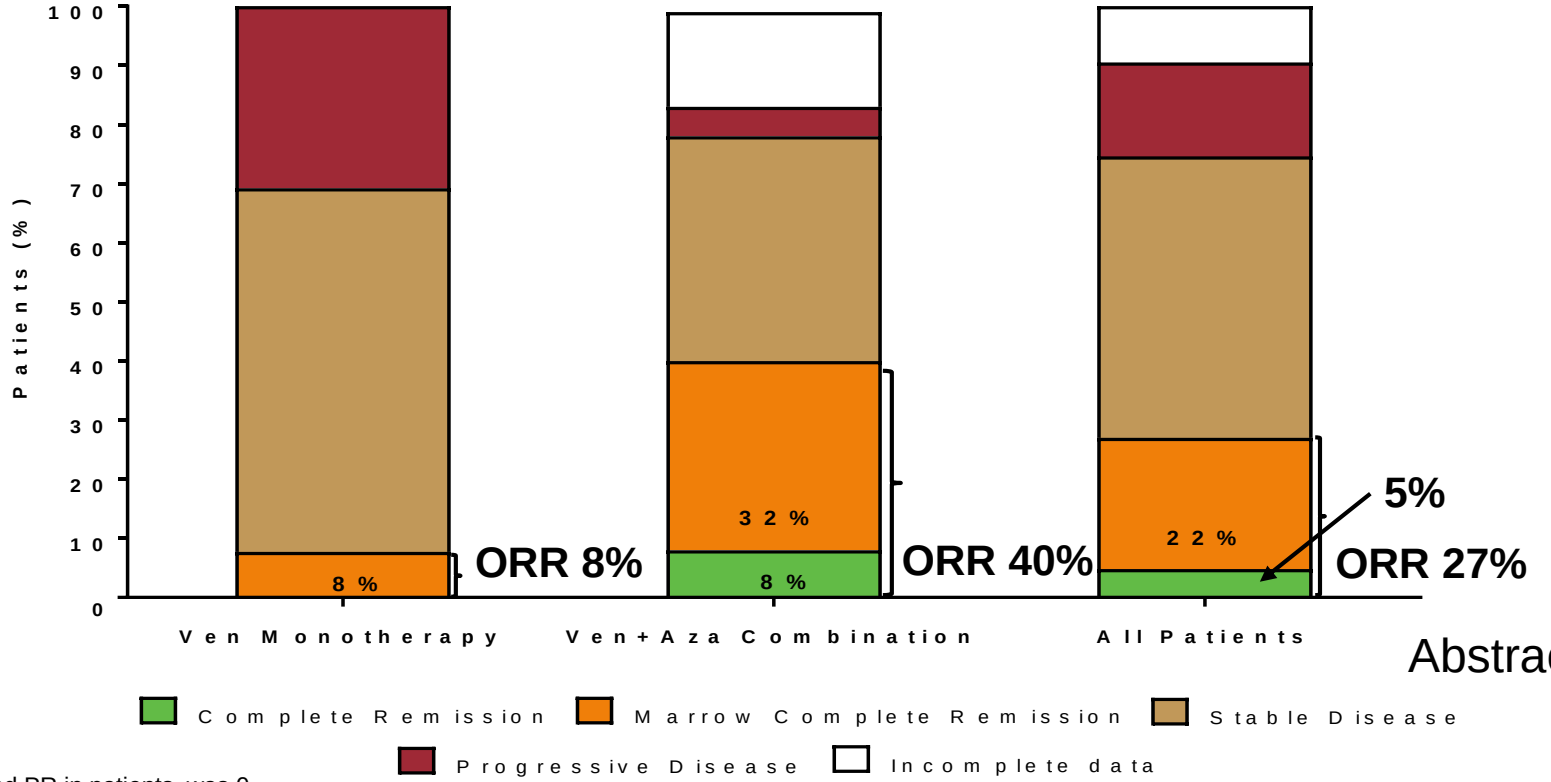


*Enrolled until data cut-off 30AUG2019; Aza: Azacitidine; RP2D: Recommended Phase 2 Dose; Ven: Venetoclax

Note: Prophylactic antibiotics mandated

Abstract #565

Venetoclax HMA failure: Overall Response Rates



Abstract #565

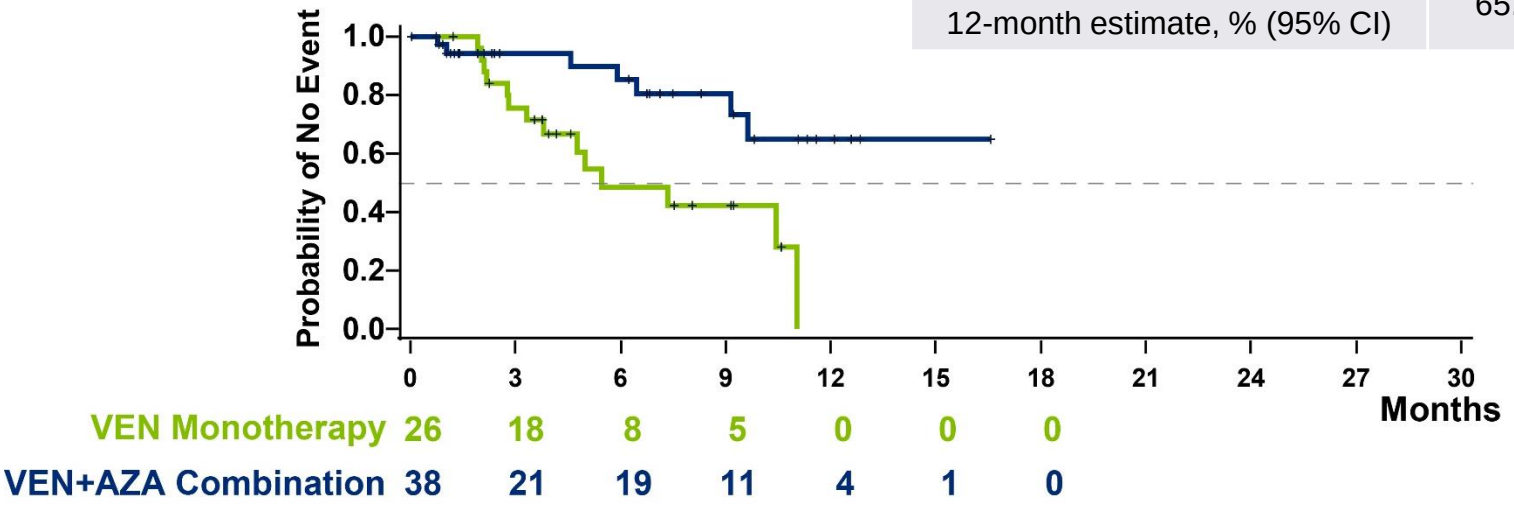
Note: Observed PR in patients was 0

Ven Monotherapy: Ven 400 mg or 800 mg; Ven+Aza Combination: Ven doses 100, 200, or 400 mg + Aza 75 mg/m^2

Data cutoff: 30 AUG 2019

Venetoclax HMA failure: Overall Survival

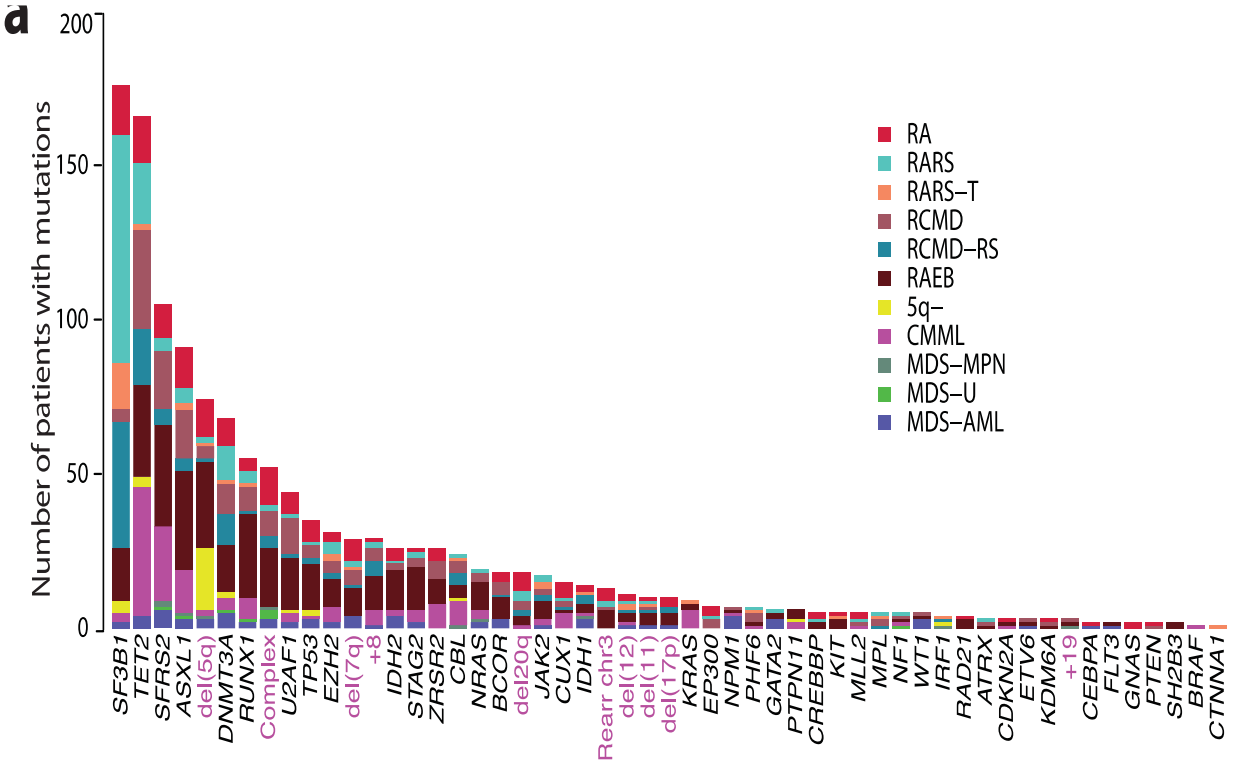
Overall survival	
Ven Monotherapy median, months (95% CI)	5.5 (3.3 – 11.1)
Ven+Aza Combination* 12-month estimate, % (95% CI)	65.0 (37.3 – 82.8)



*median OS not reached for Ven+Aza combination therapy
Ven Monotherapy: Ven 400 mg or 800 mg; Ven+Aza Combination: Ven doses 100, 200, or 400 mg+Aza 75 mg/m^2

Abstract #565

Genomics of MDS



Papaemmanuil et al Blood 2013;122:3616-27

Phase 1b/2 Combination Study of APR-246 and Azacitidine (AZA) in Patients with *TP53* Mutant Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

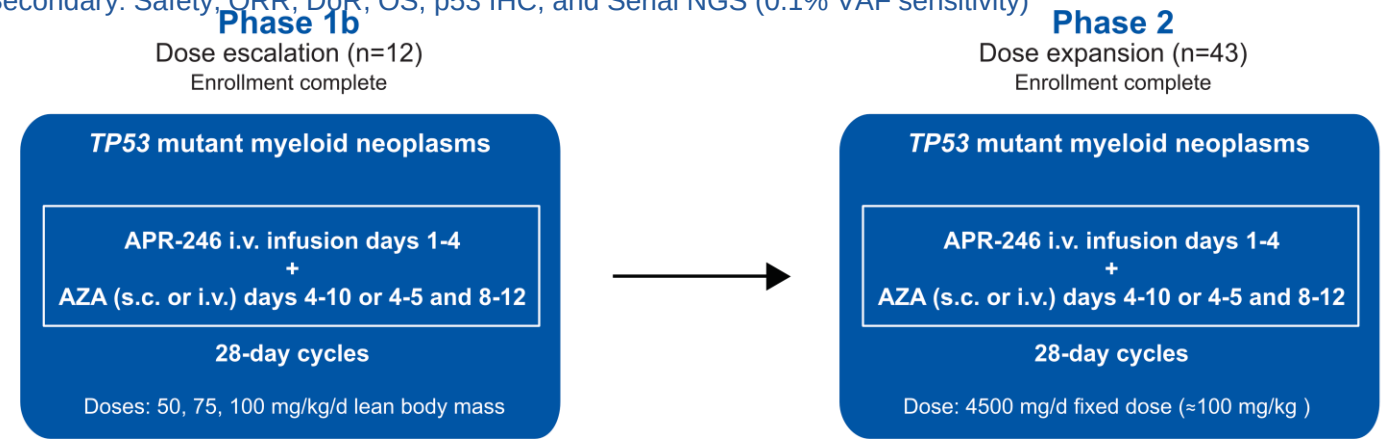
David A. Sallman[1], Amy E. Dezern[2], Guillermo Garcia-Manero[3], David P. Steensma[4], Gail J. Roboz[5], Mikkael A. Sekeres[6], Thomas Cluzeau[7], Kendra Sweet[1], Amy McLemore[1], Kathy McGraw[1], John Puskas[1], Ling Zhang[1], Jiqiang Yao[8], Qianxing Mo[8], Lisa Nardelli[1], Najla H Al Ali[1], Eric Padron[1], Greg Korbel[9], Eyal C. Attar[9], Hagop M. Kantarjian[3], Jeffrey E. Lancet[1], Pierre Fenaux[10], Alan F. List[1], and Rami S. Komrokji[1]

[1]Malignant Hematology Department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [3]Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [5]Weill Cornell Medical College, New York, NY, USA; [6]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; [7]Hematology Department, Cote D'azur University, Nice Sophia Antipolis University, Nice, France; [8]Department of Biostatistics & Bioinformatics, H. Lee Moffitt Cancer Center, Tampa, FL, USA; [9]Aprea Therapeutics, Boston, MA, USA, [10]Hospital St Louis, Paris 7 University, Paris, France

Abstract #676

APR-426: Frontline Combination Therapy with APR-246 + Azacitidine: Study Design and Objectives

- IIT evaluating frontline APR-246 + azacitidine in *TP53* MT HMA-naïve MDS, oligoblastic AML (≤ 30% blasts) and MDS-MPN
- Phase 1b Results (Sallman D et al., ASH 2018)
  - RP2D of 4500mg/day days 1-4 (~100mg/kg LBM) + azacitidine (75mg/m^2)
  - Manageable G1/G2 nausea and transient neurological AEs (dizziness/altered sensation) to APR-246; No DLTs
  - Activation of p53-dependent pathways following monotherapy treatment (1 mCR+partial cytogenetic remission in lead-in phase)
- Phase 2
  - Primary: CR rate
  - Secondary: Safety, ORR, DoR, OS, p53 IHC, and Serial NGS (0.1% VAF sensitivity)

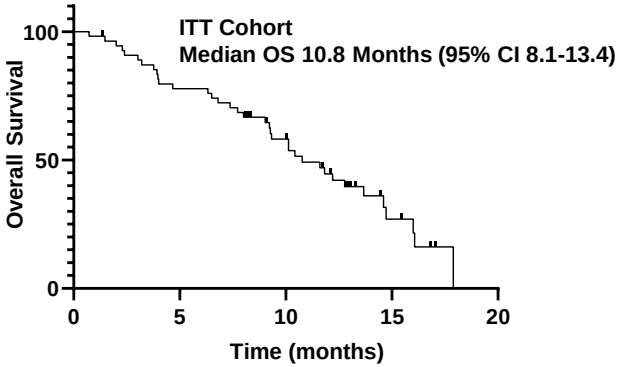


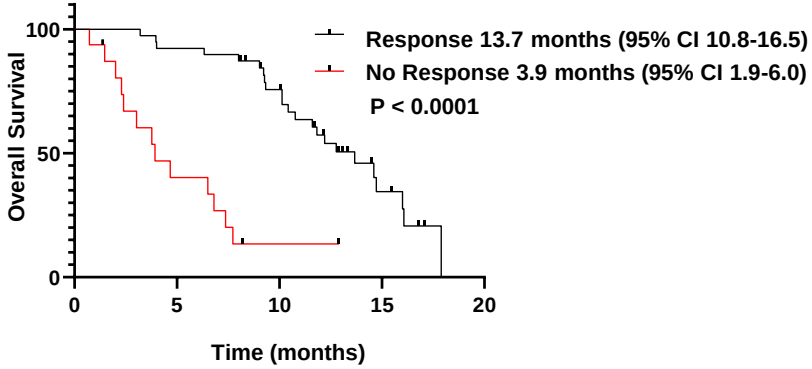
ClinicalTrials.gov NCT03072043; i.v., intravenous; s.c., subcutaneous; RP2D, recommended Phase 2 dose; CR, complete remission; DoR, duration of response; LBM, lean body mass

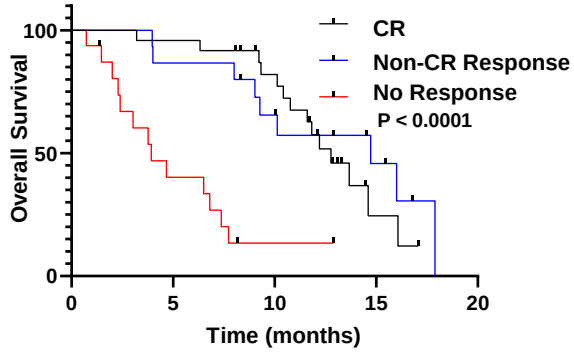
APR-426: Response to Treatment

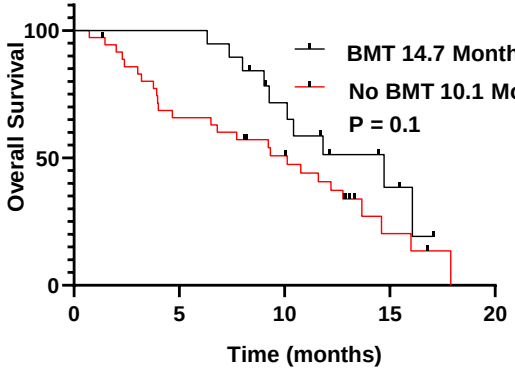
	All Patients (N=55)	Evaluable Patients (N=45)
ORR, n (%) [95% CI]	39 (71) [57 – 82]	39 (87) [73 – 95]
Time to first response in months, median (range)		2.1 (0.1 – 5.4)
Duration of response in months, median [95% CI]		8.0 [6.5 – 11.2]
Best response by IWG, n (%)		
CR	24 (44)	24 (53)
PR	0 (0)	0 (0)
mCR + HI	8 (15)	8 (18)
mCR / MLFS	4 (7)	4 (9)
HI	3 (5)	3 (7)
SD	4 (7)	4 (7)
NR	11 (20)	1 (2)
PD	1 (2)	1 (2)
CR, n (%) [95% CI]	24 (44) [30 – 58]	24 (53) [38 – 68]
Time to CR in months, median (range)		3.1 (2.5 – 6.1)
Duration of CR in months, median [95% CI]		7.3 [5.8 – N.E.]
Cytogenetic response, n (%) [95% CI]		26/44 (59) [43 – 74]
Partial		8/44 (18) [8 – 33]
Complete		18/44 (41) [26 – 57]
TP53		
NGS negative, n (%)		20 (44)
Serial IHC ≤ 5%		22 (49)

APR-426: Overall Survival (ITT)









FRENCH EXPERIENCE APR-426

Intention to treat	n=44		
Time of evaluation	*Best Response*	*After C3*	*After C6*
ORR	**55%**	**51%**	**51%**
CR	39%	25%	39%
mCR/MLFS	7%	12%	7%
PR	0%	7%	0%
SD with HI	9%	7%	5%

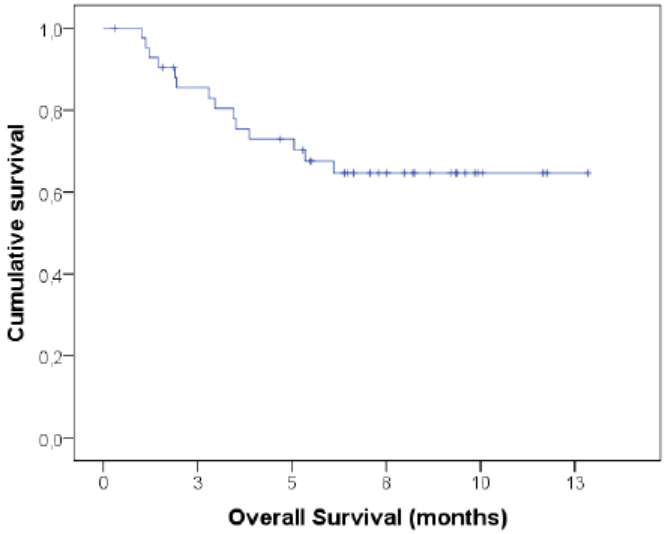
*Evaluable patients**	n=35		
Time of evaluation	*Best response*	*After C3*	*After C6*
ORR	**66%**	**64%**	**64%**
CR	49%	31%	49%
mCR/MLFS	9%	15%	9%
PR	0%	9%	0%
SD with HI	9%	9%	6%

** ie patients who received at least 3 cycles and had a marrow evaluation after 3 cycles*

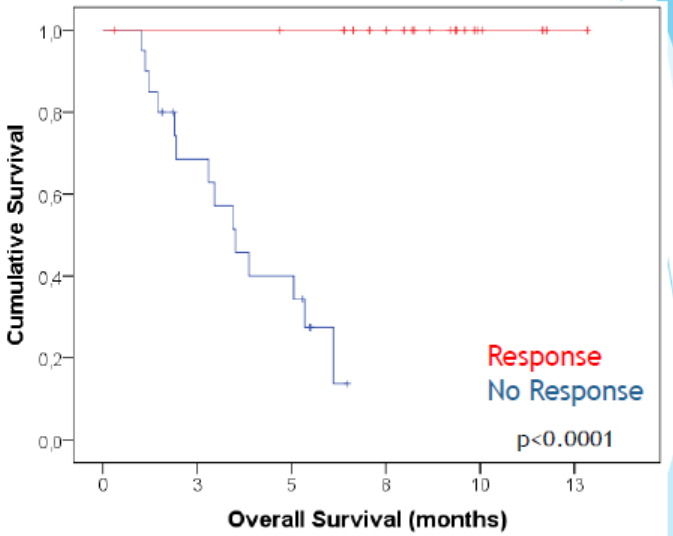
3 patients underwent Allogeneic SCT, one of them had started maintenance treatment post transplant

Abstract #677

FRENCH EXPERIENCE APR-426



Median FU: 6.4 months
Median OS: NR

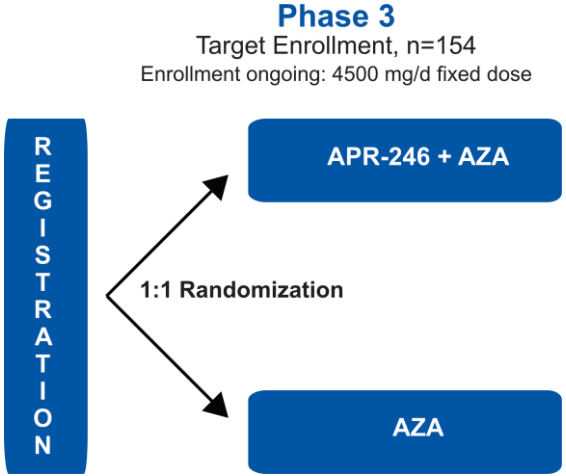


Median FU: 6.4 months
Median OS in responders: NR
Median OS in non responders: 3 months

Abstract #677

Pivotal Phase 3 MDS Trial in *TP53* Mutant MDS

- Randomized study of frontline azacitidine ± APR-246 in *TP53* mutant MDS



- Intermediate/High/Very High Risk *TP53* mutant MDS
- Primary endpoint: CR rate
- Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

- Status
  - Enrollment commenced in January 2019
  - Currently targeting full enrollment in first quarter 2020
  - Fast Track Designation for MDS: granted by FDA in April 2019
  - Orphan Drug Designations for MDS: granted by FDA in April 2019 and EMA in July 2019

ClinicalTrials.gov
NCT03745716

Preliminary Results from the Phase II Study of the IDH2-Inhibitor Enasidenib (AG-221) in Patients with High-Risk *IDH2*-Mutated Myelodysplastic Syndromes (MDS)

Guillaume Richard-Carpentier, Amy DeZern, Koichi Takahashi, Marina Konopleva, Sanam Loghavi, Lucia Masarova, Yesid Alvarado, Farhad Ravandi, Christopher Benton, Guillermo Montalban-Bravo, Kiran Naqvi, Koji Sasaki, Ricardo Delumpa, Mikkael A. Sekeres, Gail Roboz, Hagop M. Kantarjian, Guillermo Garcia-Manero and Courtney D. DiNardo

Abstract number 678
American Society of Hematology Annual Meeting
Orlanda, December 9th 2019

Abstract #678

Study Design

- Phase II, muticenter, 2-arm, open-label clinical trial

Arm A (Untreated)

1) HMA naïve

AND

1) IPSS-R High or Very High OR
2) High-risk mutation (*TP53*, *ASXL1*, *EZH2* and/or *RUNX1*)

→ **Azacitidine (AZA) 75 mg/m^2/day IV or SC on days 1-7 in each 28-day cycle**

Enasidenib (ENA) 100 mg PO daily continuously 28-day cycle

Arm B (HMA-failure)

1) Relapsed/Refractory after HMA

No response after ≥ 6 cycles OR
Relapse/Progression

→ **Enasidenib (ENA)100 mg PO daily continuously 28-day cycle**

Abstract #678

Response rates

	Total (N = 31)	Arm A (Untreated) AZA + ENA (N = 13)	Arm B (HMA-failure) ENA (N = 18)
Overall response rate (ORR), n (%)	**21 (68)**	**11 (85)**	**10 (56)**
Complete remission (CR)	8 (26)	3 (23)	5 (28)
Partial remission (PR)	1 (3)	0 (0)	1 (6)
Marrow CR (mCR)	9 (29)	7 (54)	2 (11)
Hematological improvement (HI) only	3 (10)	1 (8)	2 (11)
No response (NR), n (%)	**10 (32)**	**2 (15)**	**8 (44)**
Stable disease (SD)	9 (29)	2 (15)	7 (39)
Progressive disease (PD)	1 (3)	0 (0)	1 (6)

Abstract #678

Olutasidenib (FT-2102) Induces Rapid Remissions in Patients with IDH1-Mutant Myelodysplastic Syndrome: Results of Phase 1/2 Single-Agent Treatment and Combination with Azacitidine

Jorge E. Cortes[1], Eunice S. Wang[2], Justin M. Watts[3], Sangmin Lee[4], Maria R. Baer[5], Kim-Hein Dao[6], Shira N. Dinner[7], Jay Yang[8], William B. Donnellan[9], Anthony Schwarer[10], Christian Recher[11], Patrick Kelly[12], Jennifer Sweeney[12], Julie Brevard[12], Patrick Henrick[12], Sanjeev Forsyth[12], Sylvie Guichard[12], Hesham Mohamed[12], Andrew H. Wei[13]

[1]Georgia Cancer Center, Augusta, GA; [2]Roswell Park Comprehensive Cancer Institute, Buffalo, NY; [3]Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL; [4]Weill Cornell Medicine, New York, NY; [5]University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD; [6]Oregon Health Sciences University, Portland, OR; [7]Northwestern University, Chicago, IL; [8]Karmanos Cancer Center, Detroit, MI; [9]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [10]Box Hill Hospital, Box Hill, VIC, Australia; [11]Institut Universitaire du Cancer de Toulouse Oncopole, CHU de Toulouse and Université de Toulouse III, Toulouse, France; [12]FORMA Therapeutics, Inc., Watertown, MA; [13]The Alfred Hospital and Monash University, Melbourne, VIC, Australia

Abstract #674

FT-2102 in MDS: Clinical Activity

Investigator-Assessed Response, n (%)	Olutasidenib (N = 6)	Olutasidenib + AZA (N = 16)[a]
ORR[b] [95% CI]	**3 (50) [11.8-88.2]**	**9 (56) [29.9-80.2]**
CR	2 (33)	4 (25)
Marrow CR	1 (17)	5 (31)
Clinical benefit (CB = SD ≥8 weeks)	1 (17)	5 (31)
PD	1 (17)	1 (6)
NE	1 (17)	1 (6)
Time to first response, median (range), months	**8.3 (<1-9.7)**	**2.8 (<1-5.1)**
Duration of overall response, median (range), months	**NR (6.7-NR)**	**12.9 (<1-NR)**

[a] Efficacy evaluable population. One patient was excluded from efficacy analysis due to lack of R132X mutation.
[b] ORR = CR + marrow CR + PR. NR, not reached

Abstract #674

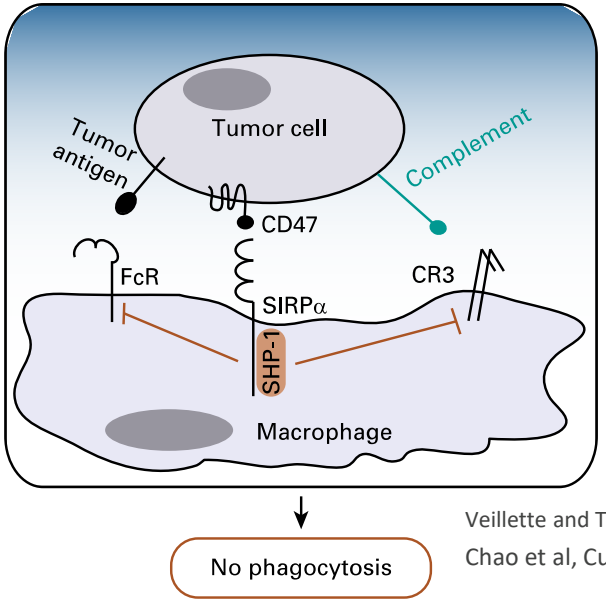
The First-in-Class Anti-CD47 Antibody Magrolimab in Combination with Azacitidine is Effective in MDS and AML Patients: Updated Ongoing 1b Results

David A Sallman[1], Adam Asch[2], Monzr Al-Malki[3], Daniel Lee[4], Guillermo Garcia-Manero[5], William Donnellan[6], Daniel Pollyea[7], Suman Kambhampati[8], Guido Marcucci[3], Rami Komrokji[1], Joanna Van Elk[9], Ming Lin[9], Jens-Peter Volkmer[9], Roy Maute[9], Chris Takimoto[9], Mark Chao[9], Paresh Vyas[10], Naval Daver[5]

[1]Moffitt Cancer Center, Tampa, FL; [2]University of Oklahoma, Oklahoma City, OK; [3]City of Hope, Duarte, CA; [4]Columbia University, New York, NY; [5]MD Anderson Cancer Center, Houston, TX; [6]Sarah Cannon Research Institute, Nashville, TN; [7]University of Colorado, Denver, CO; [8]Healthcare Midwest, Kansas City, MO; [9]Forty Seven, Inc., Menlo Park, CA; [10]University of Oxford, Oxford, UK

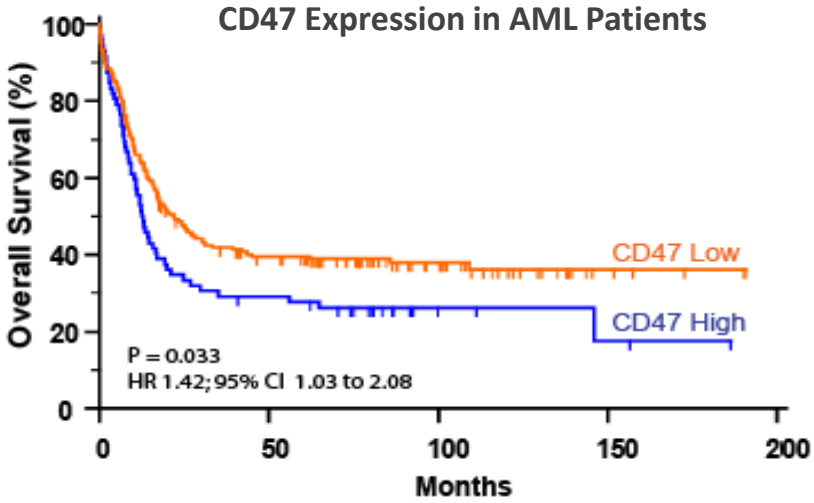
Abstract #569

CD47 is a Major Macrophage Immune Checkpoint and "Do Not Eat Me" Signal in Myeloid Malignancies including MDS and AML



Veillette and Tang, JCO 2019

Chao et al, Current Opin Immunol 2012

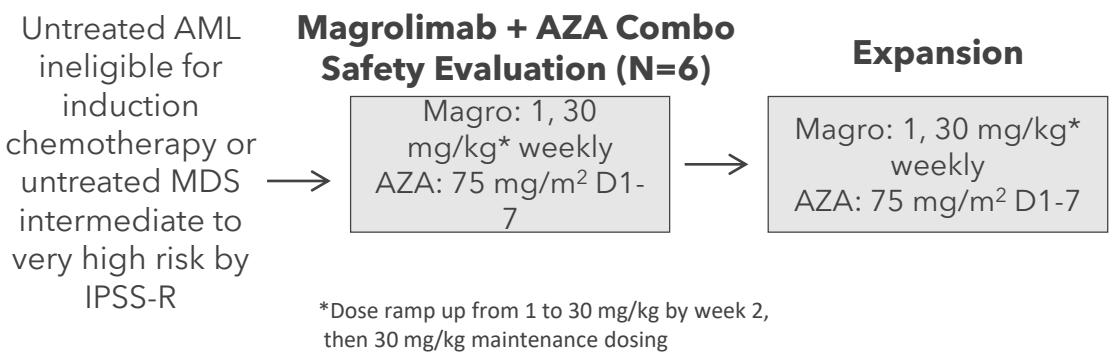


Majeti, Chao et al., Cell 2009

- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients

Abstract #569

5F9005 Study Design: Magrolimab in Combination with Azacitidine in MDS and AML



Primary objectives

1) Safety of magrolimab alone or with AZA
2) Efficacy of magrolimab + AZA in untreated AML/MDS

Secondary objectives

1) PK, PD and immunogenicity of 5F9
2) Additional measures of efficacy (DOR, PFS, OS)

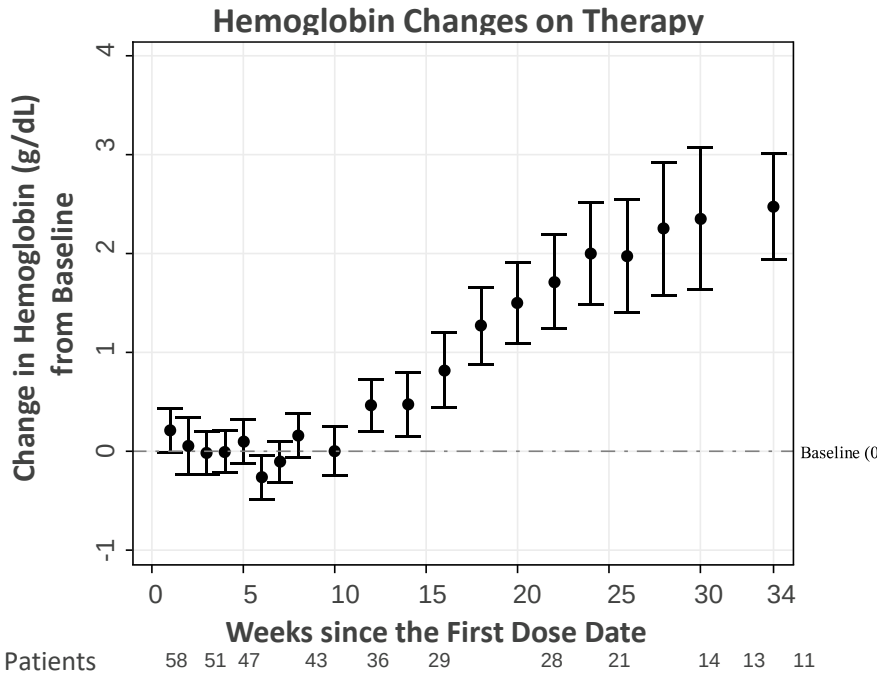
Exploratory objectives

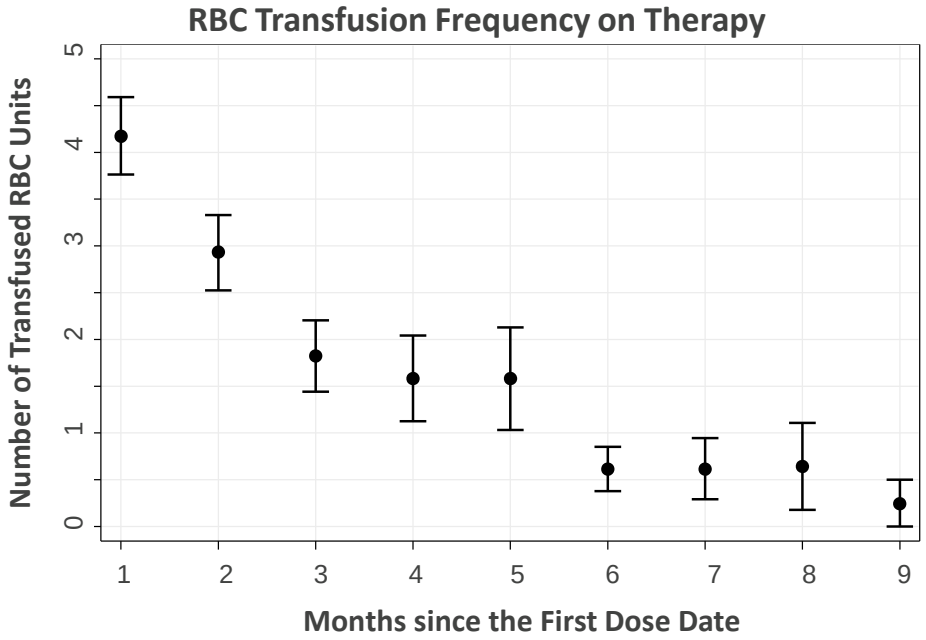
1) To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

- A magrolimab priming dose (1 mg/kg) and dose ramp up was utilized to mitigate on target anemia
- Data from the Expansion Cohort is presented

Abstract #569

On Target Anemia is a Pharmacodynamic Effect and is Mitigated with a Magrolimab Priming and Maintenance Dosing Regimen





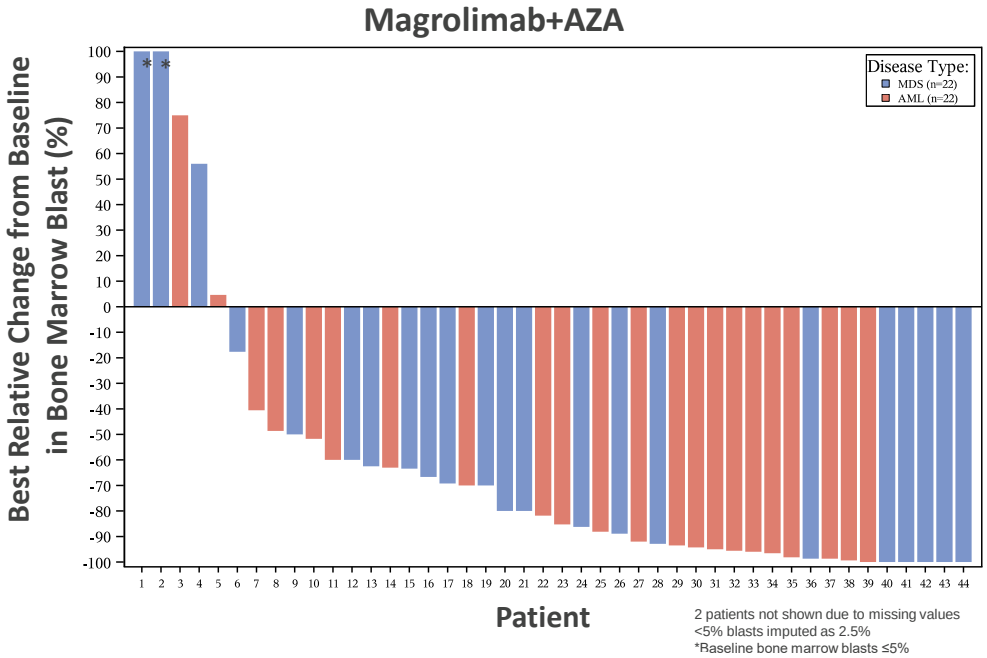
- An initial priming dose mitigates on target anemia by CD47 blockade, resulting in a transient mild hemoglobin drop on the first dose (mean of 0.4 g/dL) , which returns to baseline
- **The majority of patients have had significant hemoglobin improvement and decrease in transfusion frequency with therapy**

Abstract #569

Anti-Leukemic Activity is Observed with Magrolimab + AZA in MDS and AML

Best Overall Response	1L MDS N=24	1L AML N=22
ORR	22 (92%)	14 (64%)
CR	12 (50%)	9 (41%)
CRi	-	3 (14%)
PR	0	1 (5%)
MLFS/ marrow CR	8 (33%) 4 with marrow CR + HI	1 (5%)
Hematologic improvement (HI)	2 (8%)	-
SD	2 (8%)	7 (32%)
PD	0	1 (5%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria; Patients with at least one post-treatment response assessment are shown, all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML (1 AE, 2 early withdrawal)
"-" not applicable



- Magrolimab + AZA induces a 92% ORR (50% CR) in MDS and 64% ORR (55% CR/CRi) in AML
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy

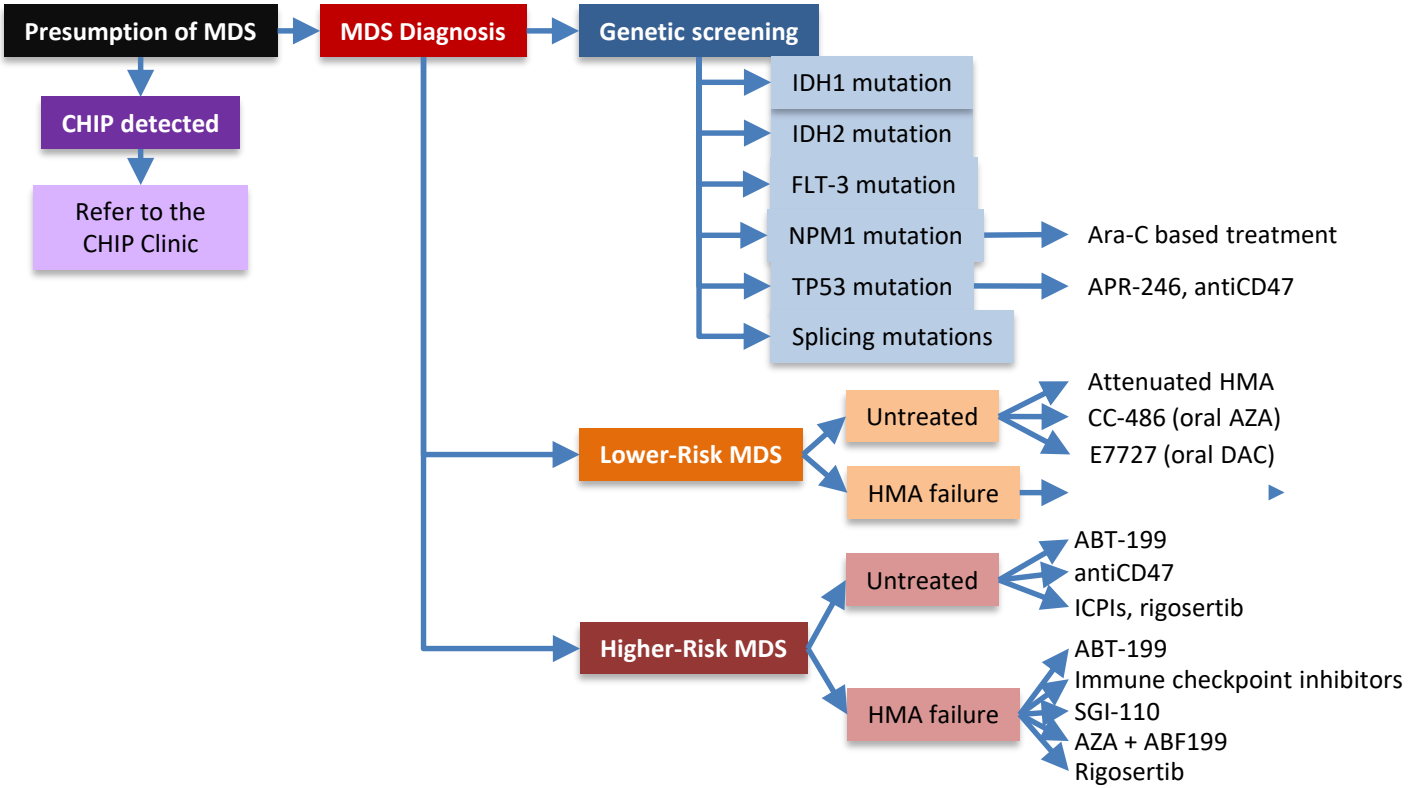
Abstract #569

Conclusion #1

- **Immediate impact:**
  - **Luspatercept: approved by FDA. Need to define role/position**
  - **ASTX727 (oral decitabine). Met all endpoints. Role?**
- **Coming:**
  - **APR-246: study to complete in 2020**
  - **Magrolimab: the same**
  - **ABT-199: starting large randomized trials**
  - **IDH2, IDH1: expanding single arm experience**
- **Others: TIM-3, rigosertib, CB393, H3BIO**

Conclusion #2

- Multiple areas of opportunity (challenge)
- Increased role of genomic annotation in MDS
- Multiple new targets: Bcl-2, TGF-b, TLR, SF3B1, IDH, Flt-3, NPM1, CD33, CD123
- New ways to deliver HMA: attenuated schedules, CC-486, ASTX727, SGI-110
- Potential for multiple oral combinations
- 3 ongoing Phase III trials: Rigosertib, ACE-536, SGI-110 for failures


Presumption of MDS
MDS Diagnosis
Genetic screening
CHIP detected
Refer to the CHIP Clinic
IDH1 mutation
IDH2 mutation
FLT-3 mutation
NPM1 mutation
TP53 mutation
Splicing mutations
Ara-C based treatment
APR-246, antiCD47
Lower-Risk MDS
Untreated
HMA failure
Attenuated HMA
CC-486 (oral AZA)
E7727 (oral DAC)
Higher-Risk MDS
Untreated
HMA failure
ABT-199
antiCD47
ICPIs, rigosertib
ABT-199
Immune checkpoint inhibitors
SGI-110
AZA + ABF199
Rigosertib

Guillermo Garcia-Manero
ggarciam@mdanderson.org