How to Manage Myelodysplasia: Biomarkers and Novel Treatments

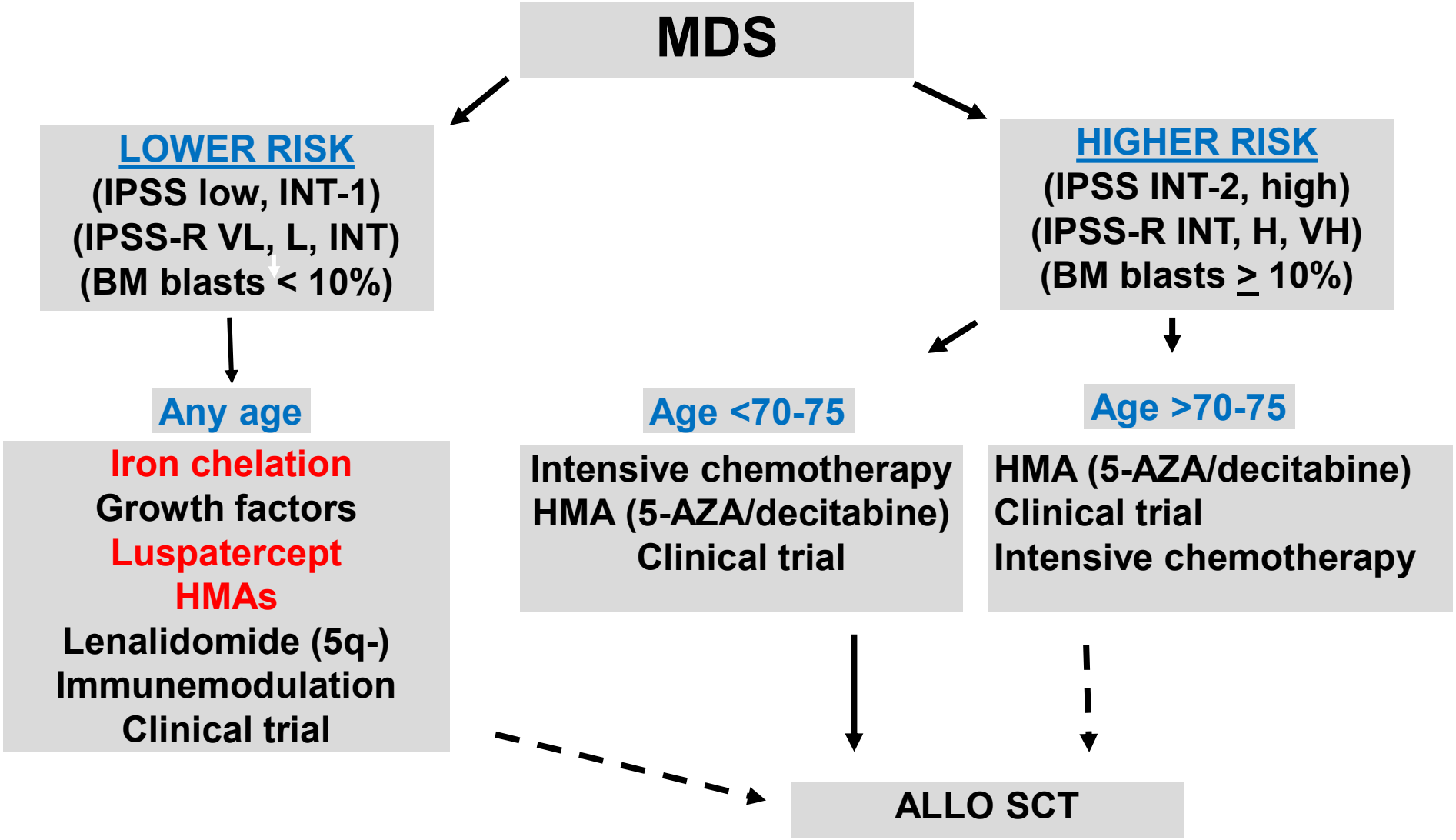
Guillermo Garcia-Manero MD
Professor of Medicine
Chief Section of MDS
Deputy Chair
Department of Leukemia
MD Anderson Cancer Center
University of Texas
Houston, TX

15th Annual New Orleans Summer Cancer Meeting

(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**
- **Approval of luspatercept 2020**
- **Approval oral decitabine 2020**

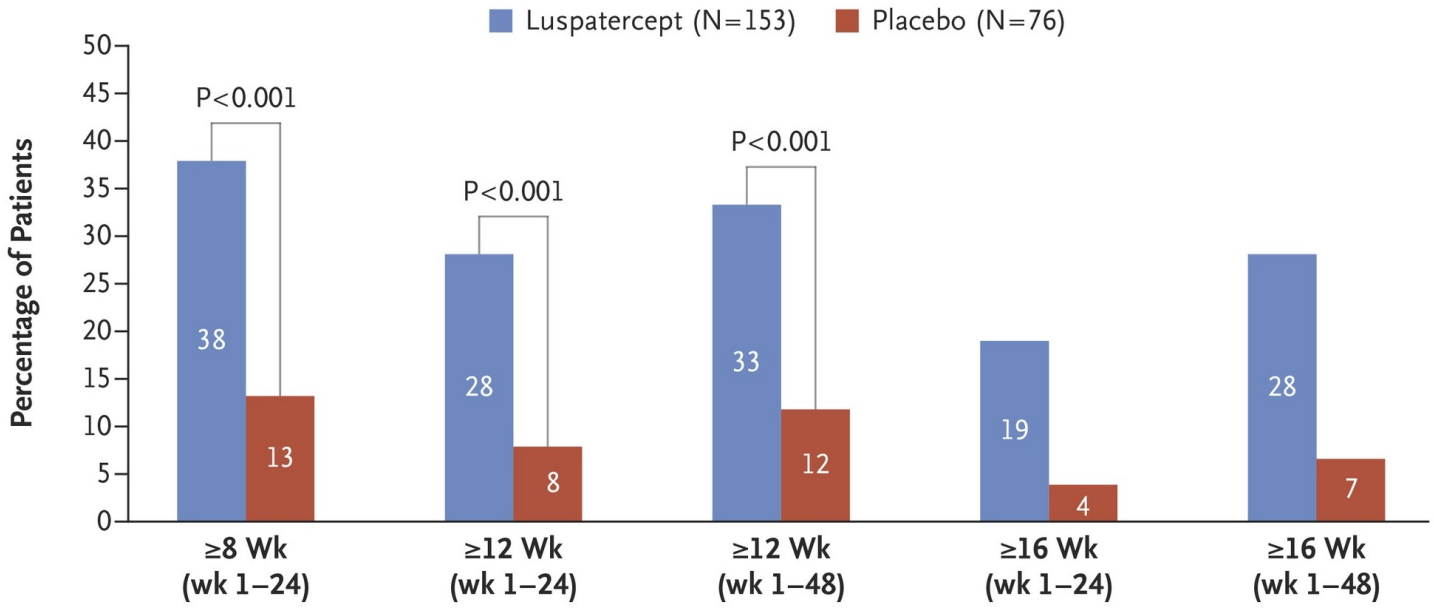
Proposed treatment algorithm for patients with MDS 2020



Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

MEDALIST Trial

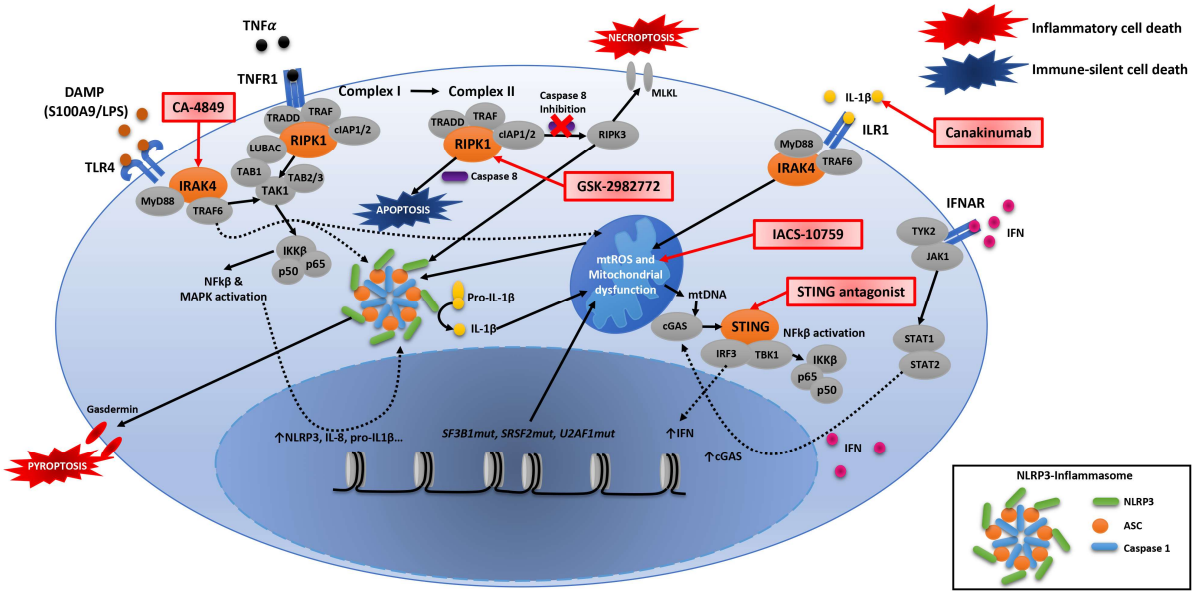
RBC-TI



No. of Patients with Response (% [95% CI])					
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

New approaches for anemia in MDS

- **COMMANDS: testing luspatercept in LR MDS against ESA**
- **Combinations of luspatercept with ESA, len, HMA in LR and HR-MDS**
- **New approaches:**
  - **Imetelstat**
  - **Roxadustat**



Courtesy G. Montalban-Bravo Wei et al Leukemia 2013, Wei et al Leukemia 2013, Zhang et al Nature 2015, Li et al Nat Immunol 2016

DAC vs. AZA in LR-MDS. Response (IWG)

Response	DAC (N=70) n (%)	AZA (N=39) n (%)	*P*
CR	26 (37)	14 (36)	0.90
mCR	6 (9)	2 (5)	
HI	17 (24)	3 (8)	
ORR	49 (70)	19 (49)	0.03
SD	18 (26)	17 (44)	
PD	3 (4)	3 (8)	

Median number of cycles: 9 (range: 1-41)

Jabbour et al. Blood 2017

Oral HMAs in MDS

- Two approaches to oral HMA development
- Combined with cytidine deaminase inhibitor
  - Cedazuridine (ASTX727, ASTX030)
  - Tetrahydrouridine
- Single agent uncombined (CC-486)
- Significant differences in PK profile

Garcia-Manero: Blood 2020; Molokie Plos Med 2017; Garcia-Manero JCO 2011

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

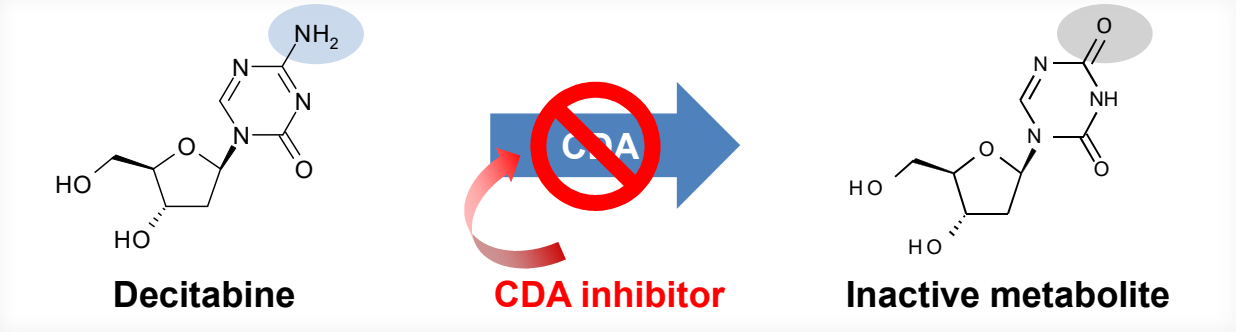
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]John Theurer Cancer Center, Hackensack Medical Center, NJ; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [5]Yale University and Yale Cancer Center, New Haven, 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



Decitabine **CDA inhibitor** **Inactive metabolite**

- 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)

CDA, cytidine deaminase.

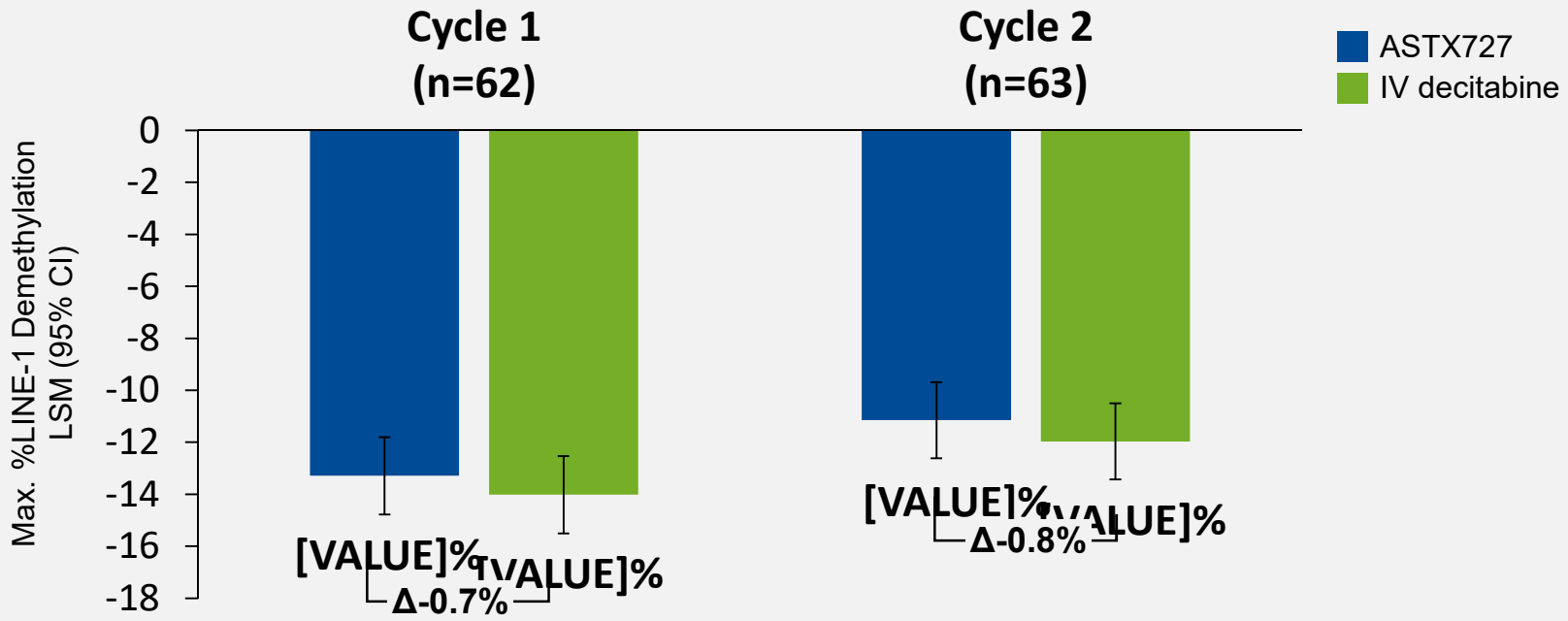
Primary Endpoint (5-day Decitabine AUC Equivalence)

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

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)

Efficacy: Preliminary Response in MDS/CMML
Central Review by Independent Review Committee (IRC)

	Evaluable Patients[1] N=101 n (%)
Complete response (CR)	12 (11.9%)
Partial response (PR)	0
Marrow CR (mCR)	46 (45.5%)
mCR with hematologic improvement	14 (13.9%)
Hematologic improvement (HI)	7 (5.3%)
HI-erythroid	2 (2.0%)
HI-neutrophils	1 (1.0%)
HI-platelet	6 (5.9%)
Overall response (CR + PR + mCR + HI)	65 (64.4%)
Stable disease	28 (27.7%)
Progressive disease	8 (7.9%)

[1] Due to short median follow up (~ 5 months) at data cutoff, 32 patients could not be evaluated for response by the Central IRC. Response was assessed by IWG 2006 criteria

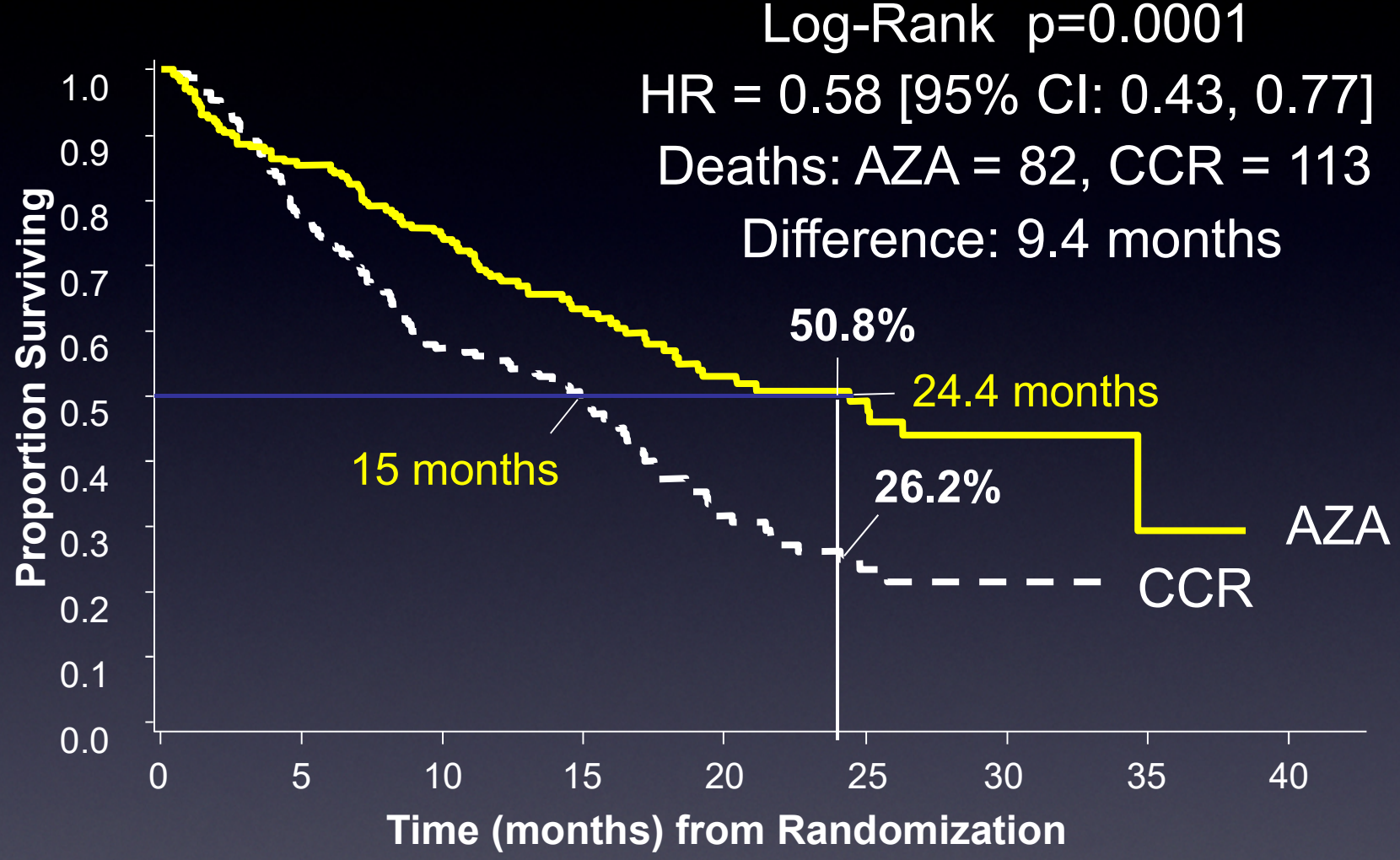
Longer term follow up response assessment and molecular/cytogenetic analyses are pending

Incorporation of oral HMAs in MDS

- **Expanded use in LR-MDS**
- **Replacing single agent azacitidine or decitabine (ASTX030, ASTX727, CC-486?)**
- **Multiple combinations: total oral therapy**
- **Role post alloSCT: total therapy in MDS**

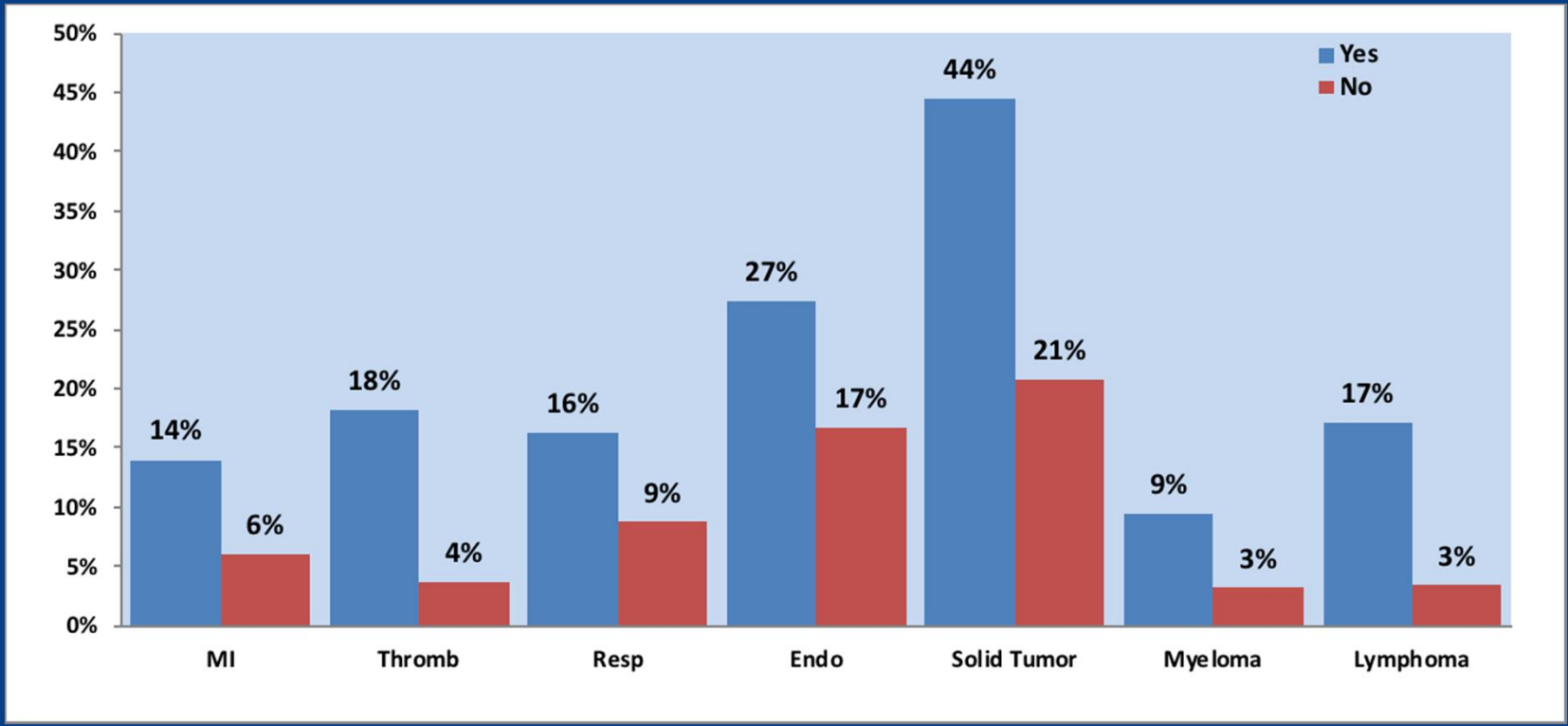
Courtesy G. Montalban-Bravo Wei et al Leukemia 2013, Wei et al Leukemia 2013, Zhang et al Nature 2015, Li et al Nat Immunol 2016

Overall Survival: Azacitidine vs CCR
ITT Population



Fenaux et al. Lancet Oncology 2010

CHIP mutations and comorbidities in MDS. Comorbidities by mutations

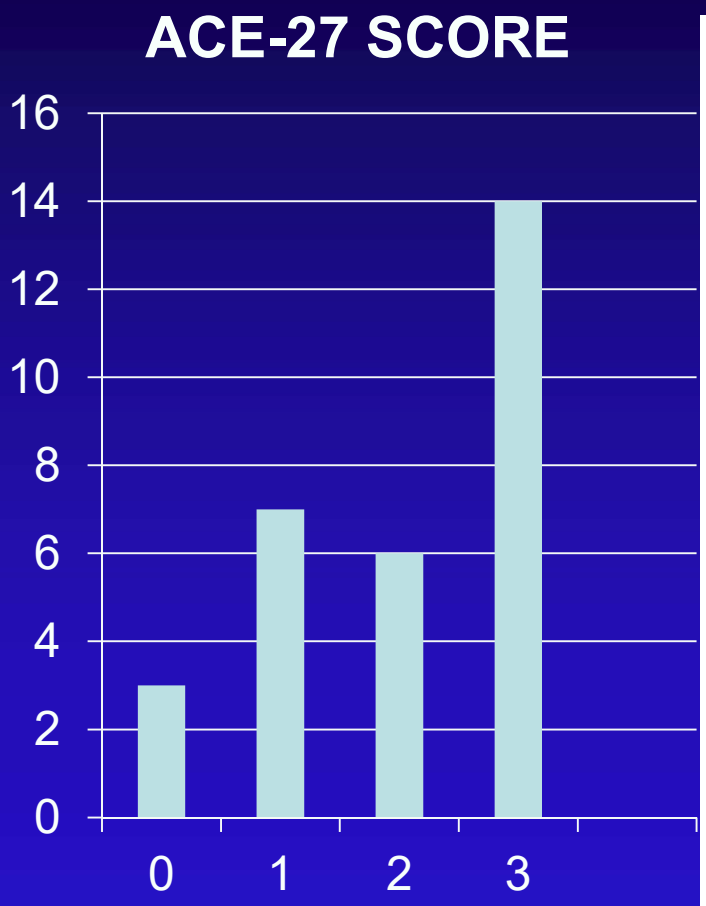


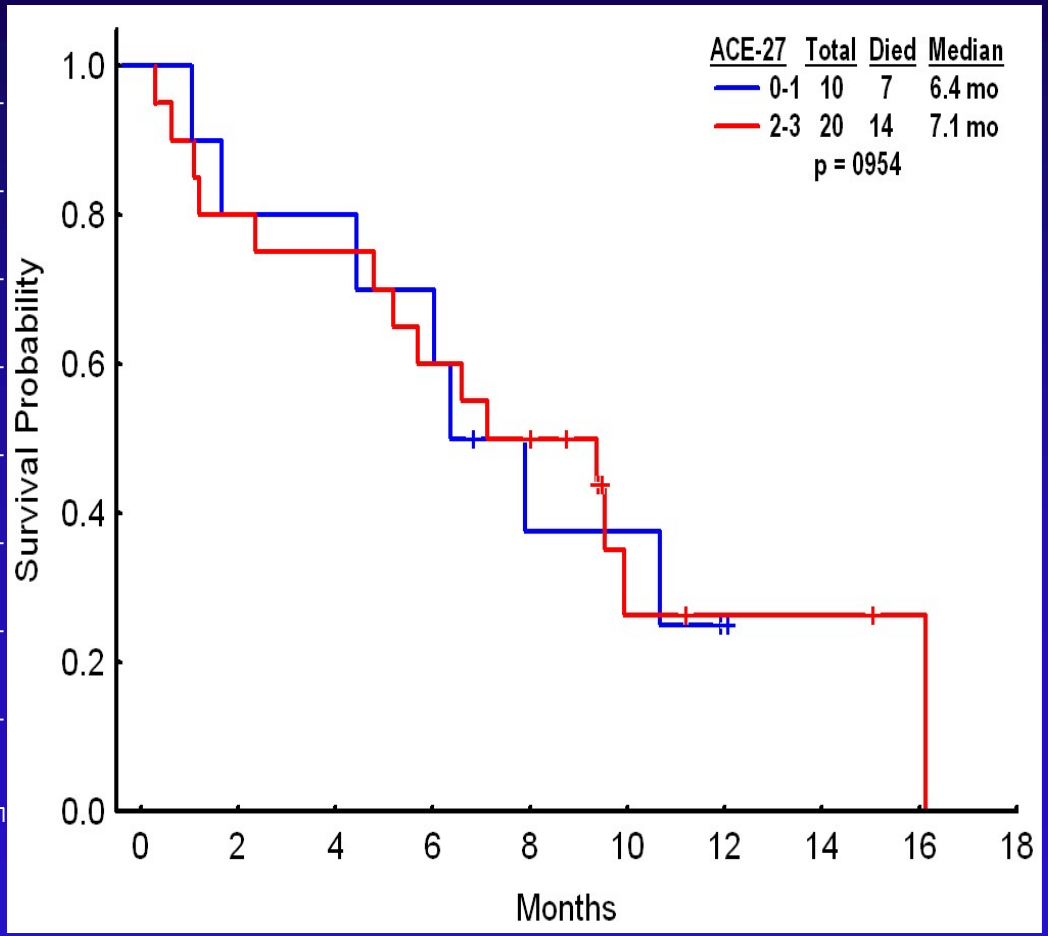
- ***DNMT3A*** **was associated with a higher frequency of prior history of myocardial infarction (MI) (OR= 2.62; 95% CI 1.095-6.246; p=0.03)**
- ***JAK2*** **was associated with a higher frequency of prior history of veno-occlusive disease (OR= 6.48; 95% CI 1.375-30.477; p=0.02)**
- ***TP53*** **mutation was highly associated with history of prior malignancy**

Naqvi et al. Cancer 2019

AZA+Vorinostat: Impact of Cormorbidity

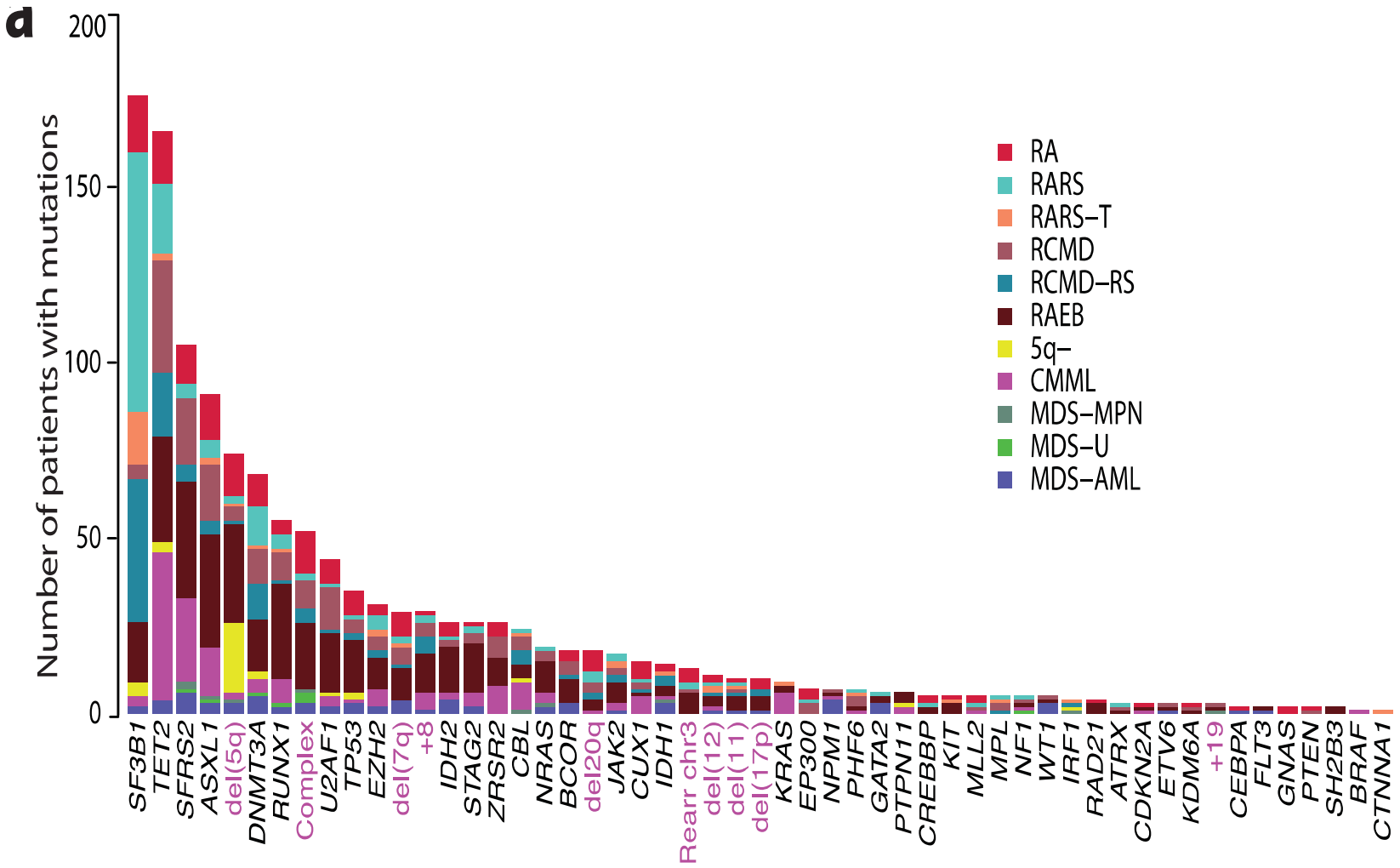
Median ACE-27 score in CR vs no-response: 2 vs 2.5





Montalban-Bravo; Leukemia 2017

Genomics of MDS

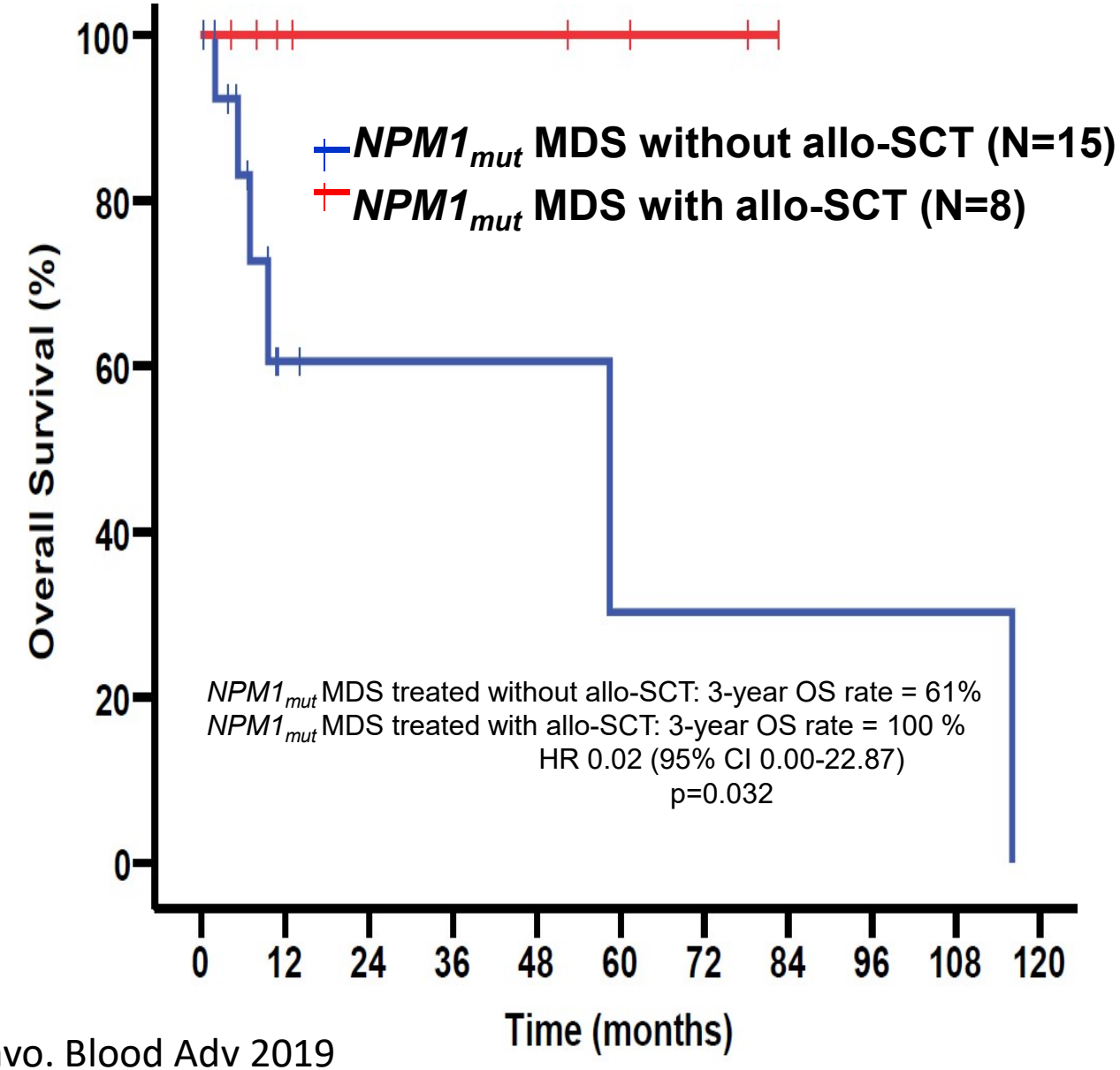


Papaemmanuil et al Blood 2013;122:3616-27

Targeted options in MDS

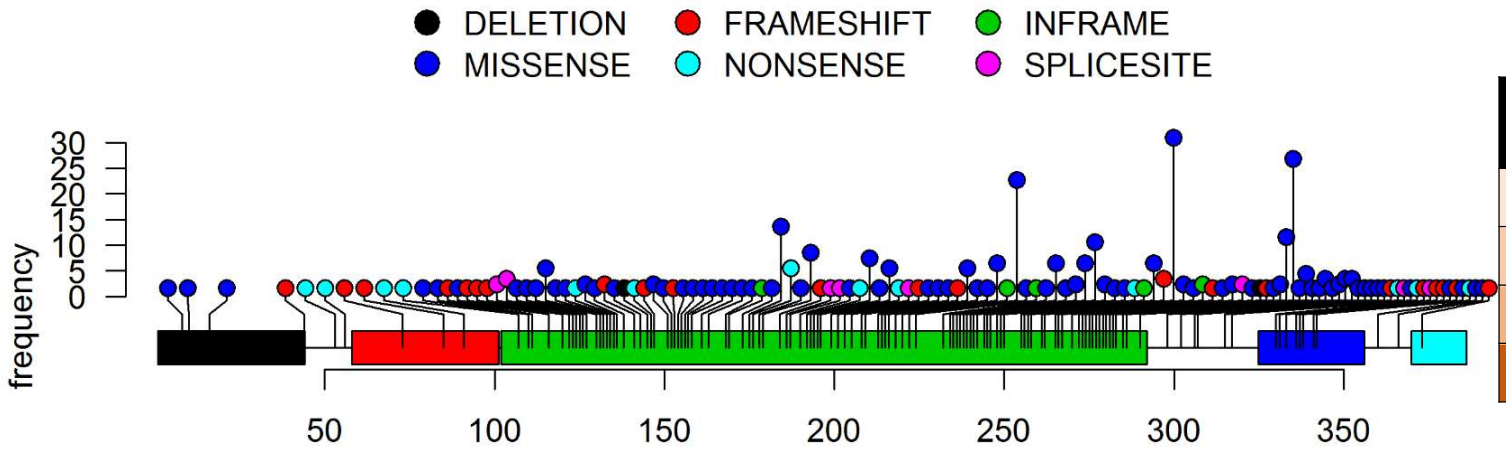
- IDH-2
- IDH-1
- Flt-3
- BCL-2
- CD47
- TP53
- NPM1
- NEDD8 (pevonidostat)
- ICPI/TIM-3 (sabatolimab)

NPM1 in MDS: Survival Outcomes



Montalban-Bravo. Blood Adv 2019

Distribution of Mutations in patients with *TP53* mutated MDS



TP53 mut Number	Frequency N (%)
1	175 (67)
2	75 (29)
3	10 (4)
4	1 (0.4)

- **396 *TP53* mutations: 309 (78%) missense, 28 (7%) nonsense, 37 (9%) frameshift and 18 (5%) splice-site**
- **Median VAF 39% (range 1-94%)**
- **Most prevalent: R273H (n=18, 0.05%), Y220C (n=16, 0.04%), R248W (n=14, 0.04%), R175H (n=13, 0.03%)**

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Montalban-Bravo et al Blood Adv 2020

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]

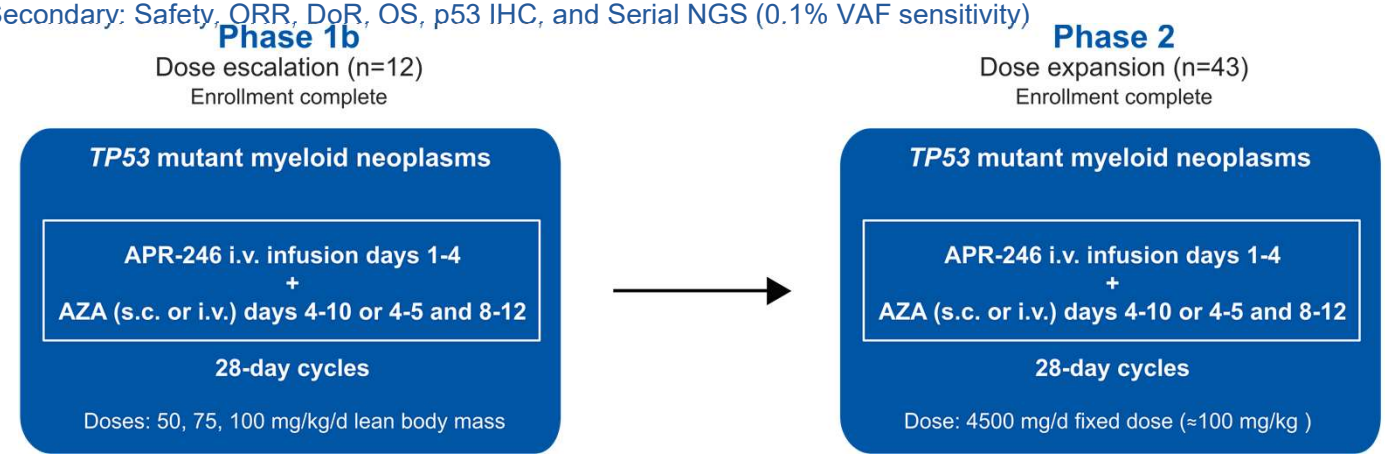
[1]Malignant Hematology Department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [3]Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Medical Oncology, 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

ASH 2019 Abstract #676

MOFFITT CANCER CENTER

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

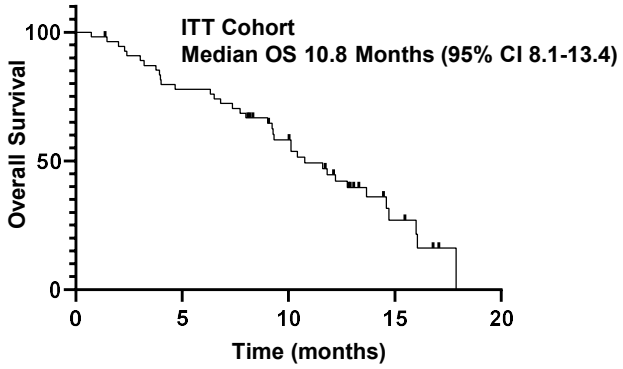
MOFFITT CANCER CENTER

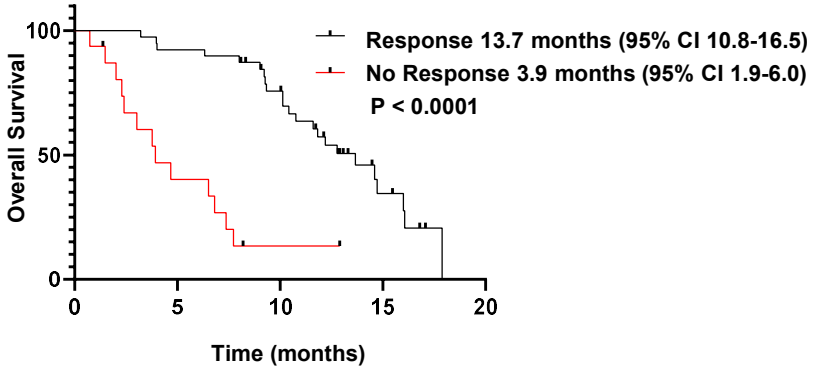
APR-426: Response to Treatment

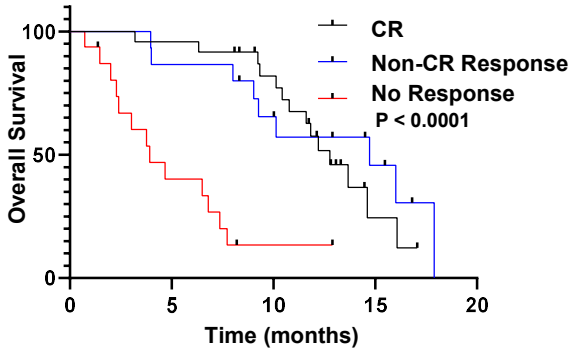
	All Patients (N=55)	Evaluable Patients (N=45)
ORR, n (%) [95% CI]	39 (71) [57 – 82]	39 (87) [73 – 95]
Time to first response in months, median (range)		2.1 (0.1 – 5.4)
Duration of response in months, median [95% CI]		8.0 [6.5 – 11.2]
Best response by IWG, n (%)		
CR	24 (44)	24 (53)
PR	0 (0)	0 (0)
mCR + 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)

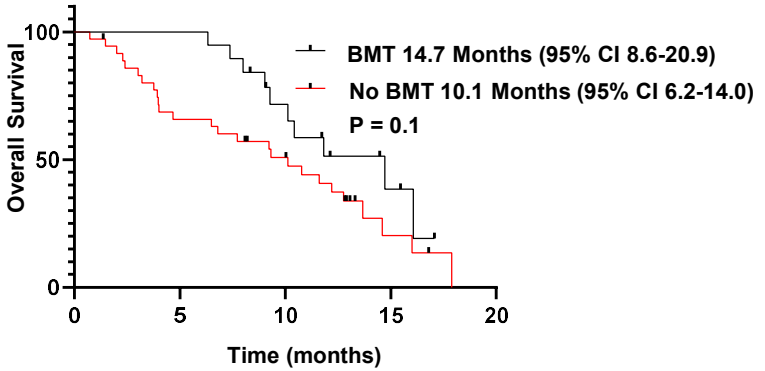
MOFFITT CANCER CENTER

APR-426: Overall Survival (ITT)



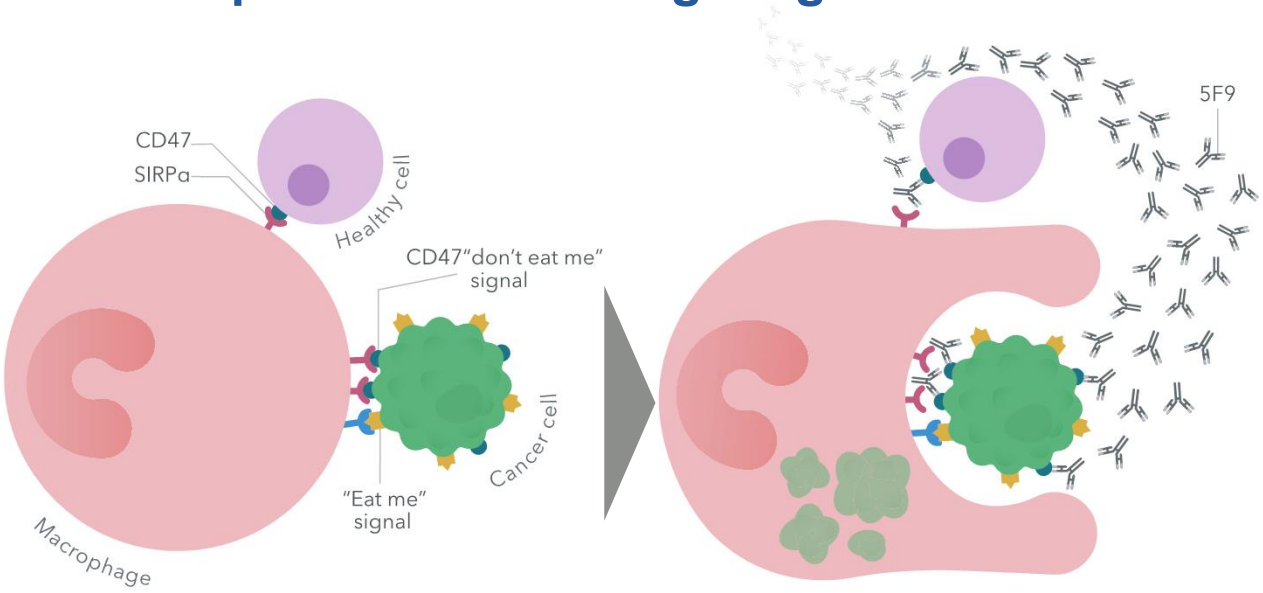




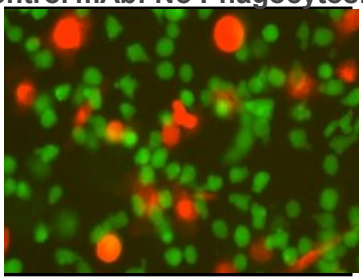


MOFFITT CANCER CENTER

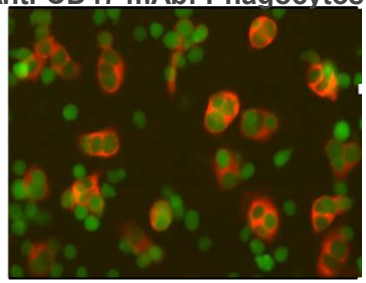
Magrolimab (Formerly 5F9) is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



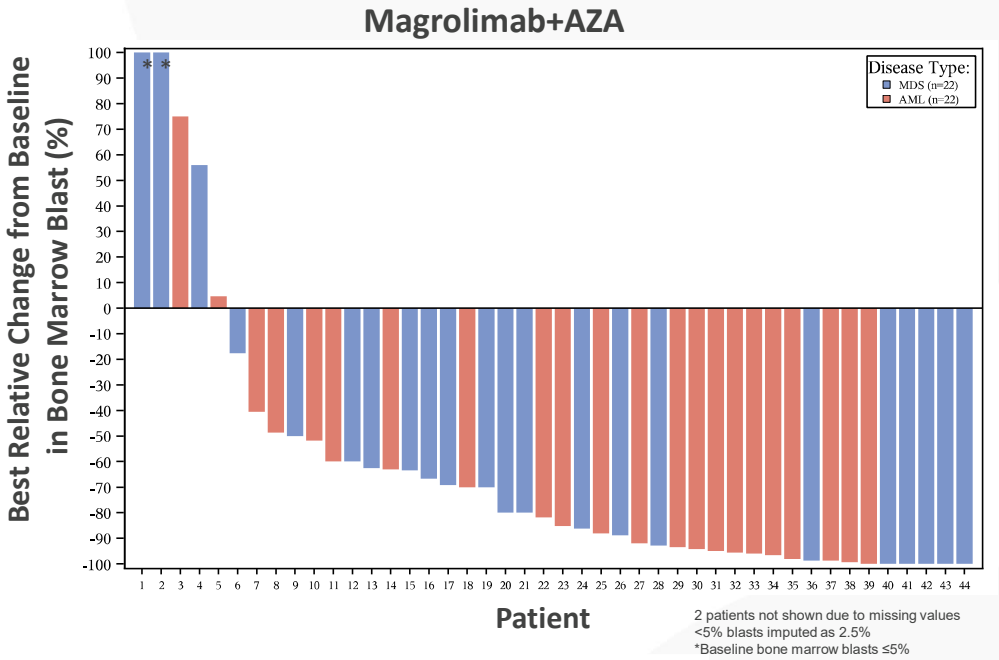
Macrophages Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody being investigated in multiple cancers
- Magrolimab was well tolerated in a UK Phase 1 trial in r/r AML with no MTD reached (Vyas et al., EHA abs 2018)

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

ASH 2019 Abstract #569

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

ASH 2019 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)

ASH 2019 Abstract #678

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

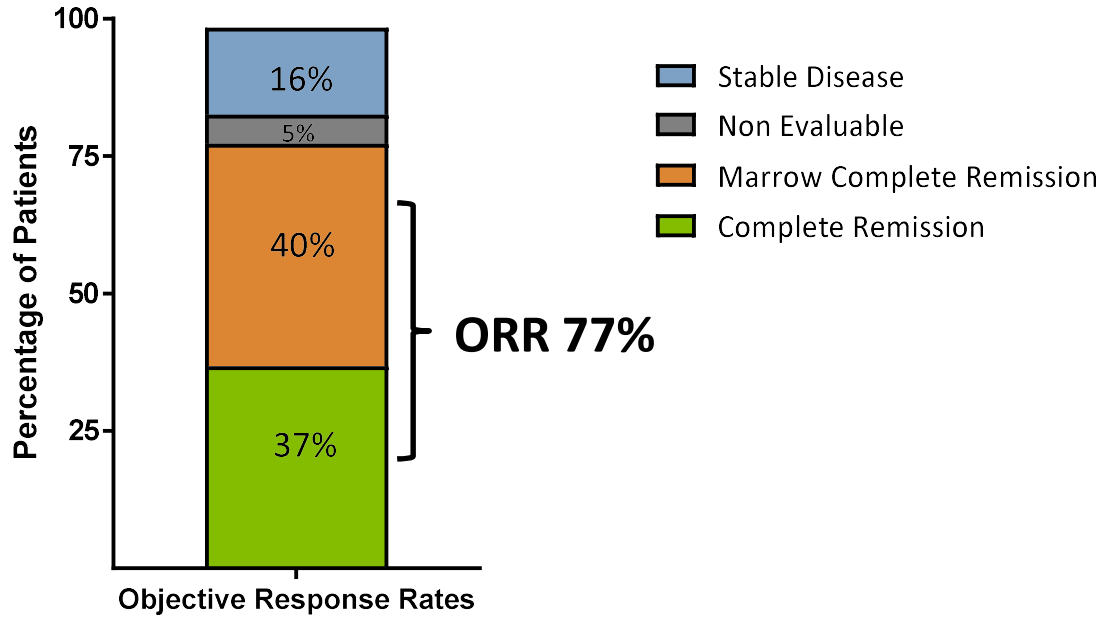
568

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, 2019

Venetoclax: Response Rates (IWG 2006)

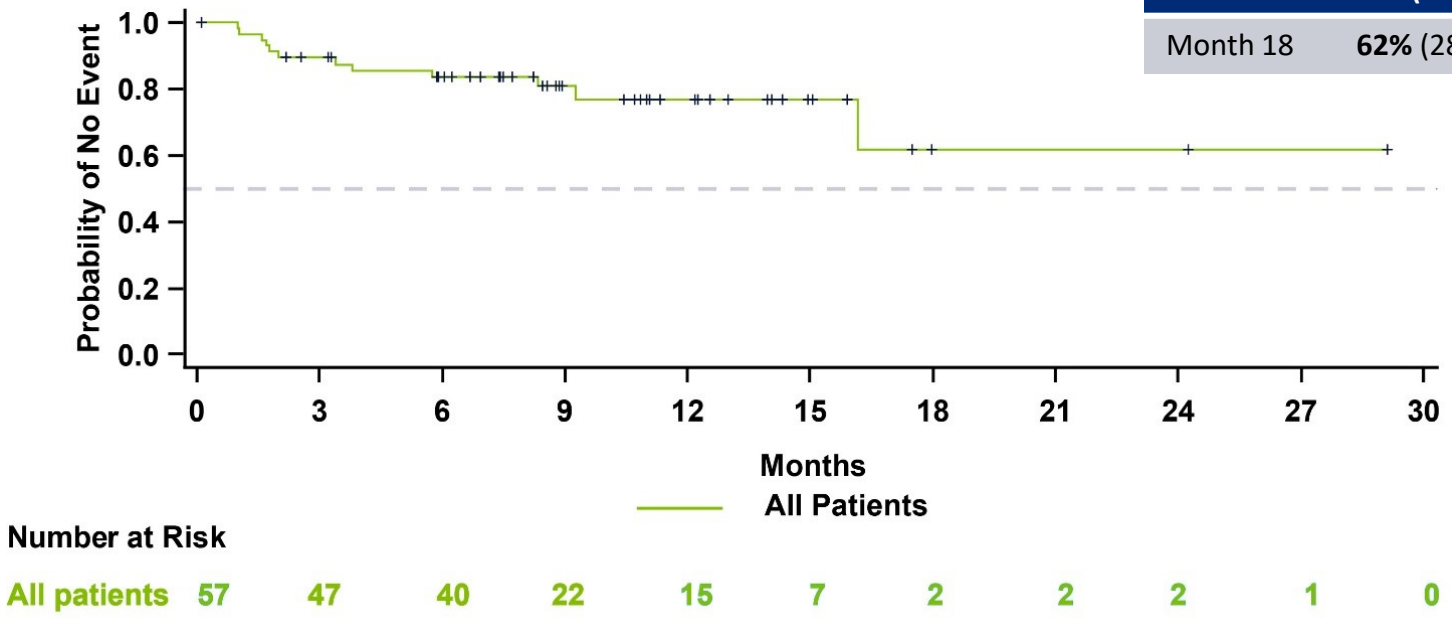


Proportion of patients with complete remission is 37% and marrow complete remission is 40%

Excludes patients of arm C (Aza only)

ASH 2019 Abstract #568

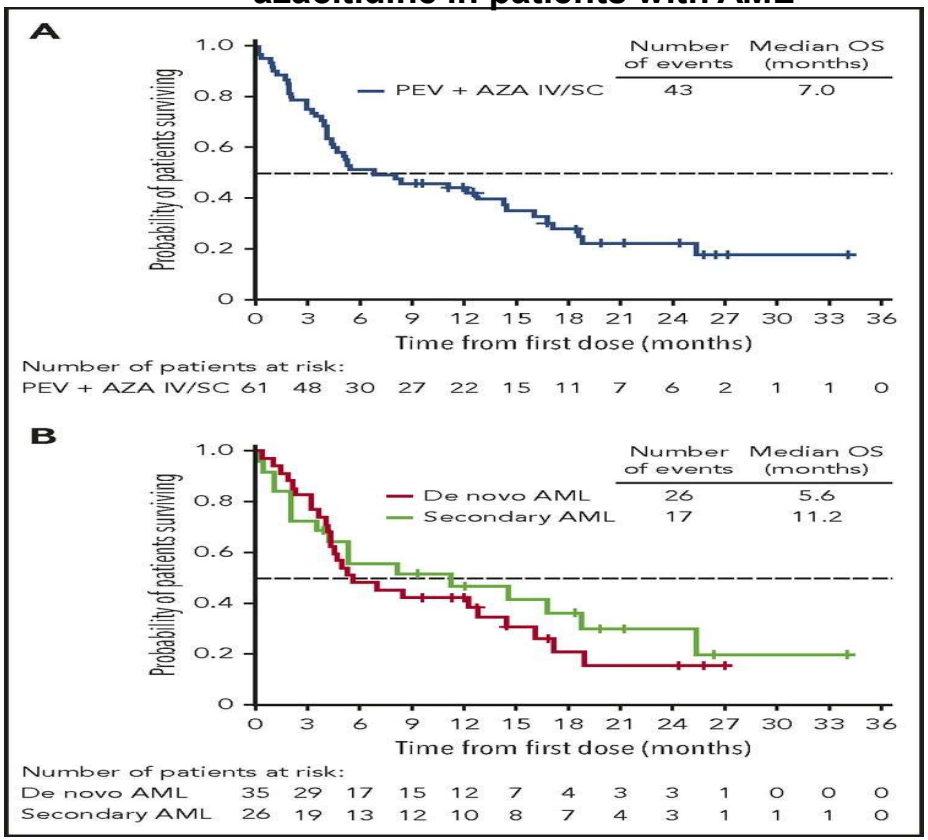
Venetoclax: Overall Survival



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

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

Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML



Swords et al. Blood 2018

Copyright © 2020 American Society of Hematology

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

PER® Physicians' Education Resource, LLC

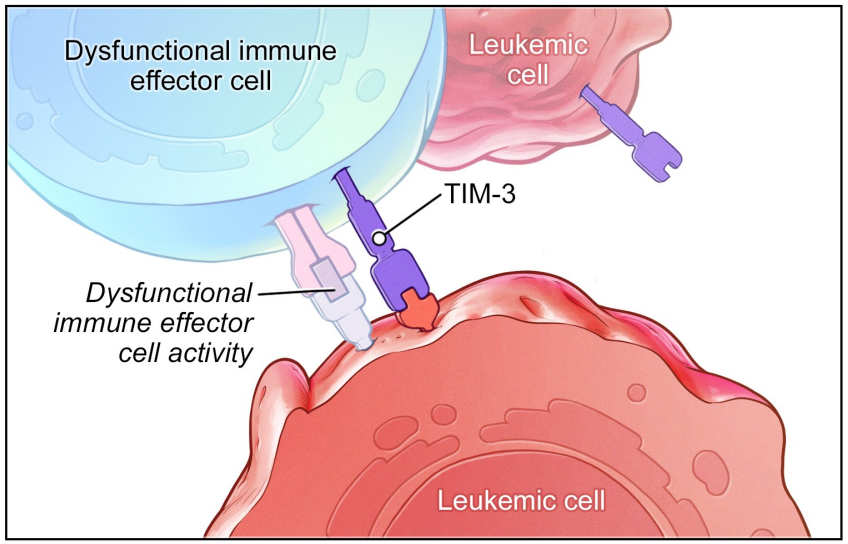
Phase Ib Study of the Anti–TIM-3 Antibody MBG453 in Combination With Decitabine in Patients With High-risk Myelodysplastic Syndrome and Acute Myeloid Leukemia

Uma Borate,[1] Jordi Esteve,[2] Kimmo Porkka,[3] Steve Knapper,[4] Norbert Vey,[5] Sebastian Scholl,[6] Guillermo García-Manero,[7] Martin Wermke,[8] Jeroen Janssen,[9] Elie Traer,[1] Chong Chyn Chua,[10] Rupa Narayan,[11] Natalia Tovar,[2] Mika Kontro,[3] Oliver Ottmann,[4] Haiying Sun,[12] Tyler Longmire,[13] Sebastian Szpakowski,[13] Serena Liao,[13] Anisa Mohammed,[12] Anuradha Patel,[12] Mikael Rinne,[13] Andrew Brunner,[11] Andrew H. Wei[10]

[1]Oregon Health & Science University, Portland, OR; [2]Hospital Clínic, Barcelona, Spain; [3]Helsinki University Hospital Cancer Center, Helsinki, Finland;
[4]Department of Haematology, Cardiff University, Cardiff, UK; [5]Institut Paoli-Calmettes, Marseille, France; [6]University Hospital Jena, Jena, Germany; [7]MD Anderson Cancer Center, Houston, TX; [8]University Hospital Dresden, Dresden, Germany; [9]Amsterdam University Medical Centers, loc. VUmc, Amsterdam, Netherlands; [10]The Alfred Hospital and Monash University, Melbourne, Australia; [11]Massachusetts General Hospital, Boston, MA; [12]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [13]Novartis Institutes for BioMedical Research, Cambridge, MA
Co-senior authors Andrew Brunner and Andrew H. Wei contributed equally to this work

ASH 2019

TIM-3: Cancer immunotherapy and leukemic stem cell target

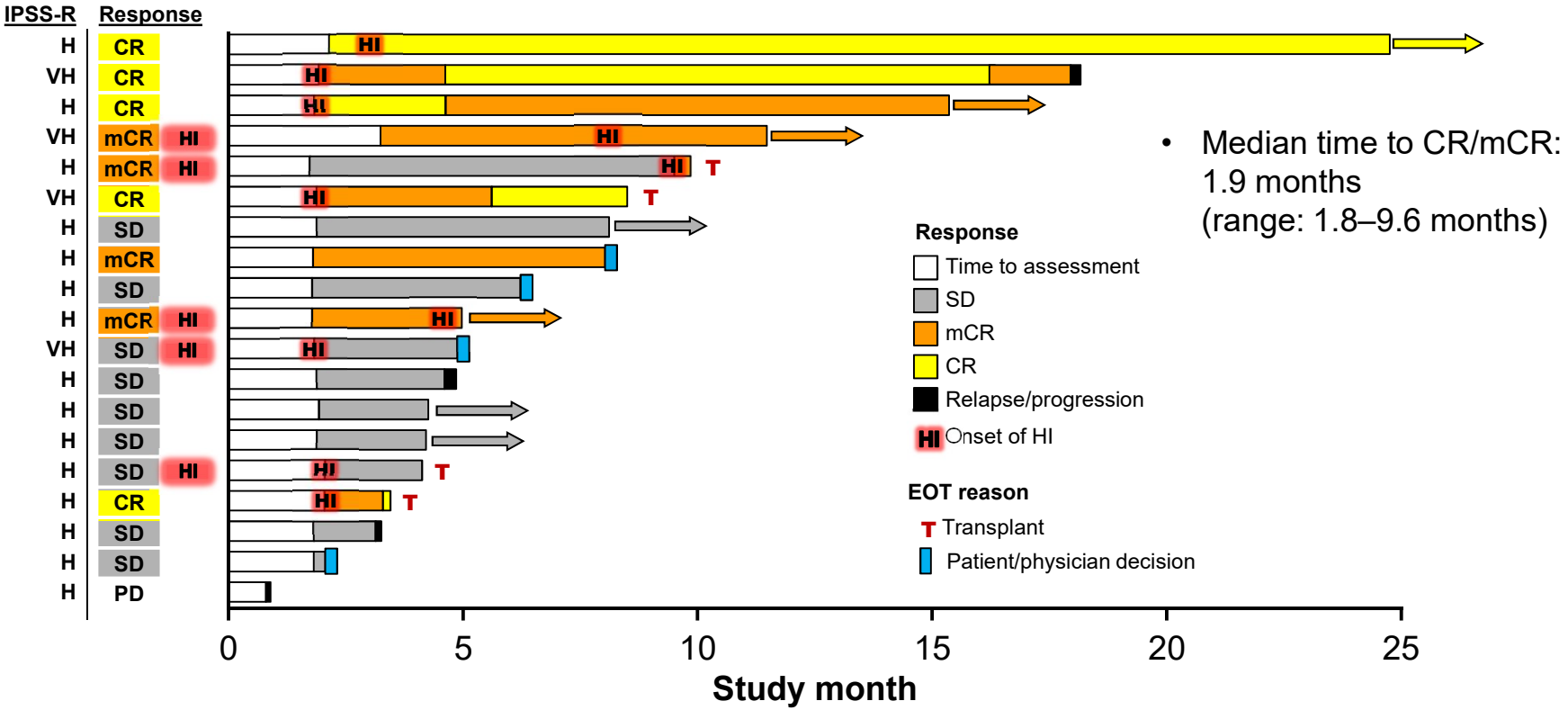


- TIM-3 is an inhibitory receptor on multiple immune cell types, with a key role in regulating adaptive and innate immune responses[1,2]
- TIM-3 is expressed on the majority of leukemic progenitors in AML, but not on normal HSCs[3,4]
  - TIM-3 expression is seen to correlate with the severity of MDS and progression to AML[5]
  - TIM-3 activation is involved in LSC self-renewal and activation,[6] as well as immune escape in AML[7]
- TIM-3 is a promising therapeutic target, providing an opportunity to both target leukemic stem cells and restore immune function[4,8,9]

AML, acute myeloid leukemia; HSC, hematopoietic stem cell; LSC, leukemic stem cell; MDS, myelodysplastic syndrome; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Pardoll DM. *Nat Rev Cancer* 2012;12:252–264; 2. Das M, *et al. Immunol Rev* 2017;276:97–111; 3. Kikushige Y and Miyamoto T. *Int J Hematol* 2013;98:627–633;
4. Kikushige Y, *et al. Cell Stem Cell* 2010;7:708–717; 5. Asayama T, *et al. Oncotarget* 2017;8:88904–88917; 6. Kikushige Y, *et al. Cell Stem Cell* 2015;17:341–352;
7. Gonçalves Silva I, *et al. EBioMedicine* 2017;22:44–57; 8. Ngiow SF. *Cancer Res* 2011;71:3540–3551; 9. Sakuishi K, *et al. Trends Immunol* 2011;32:345–349.

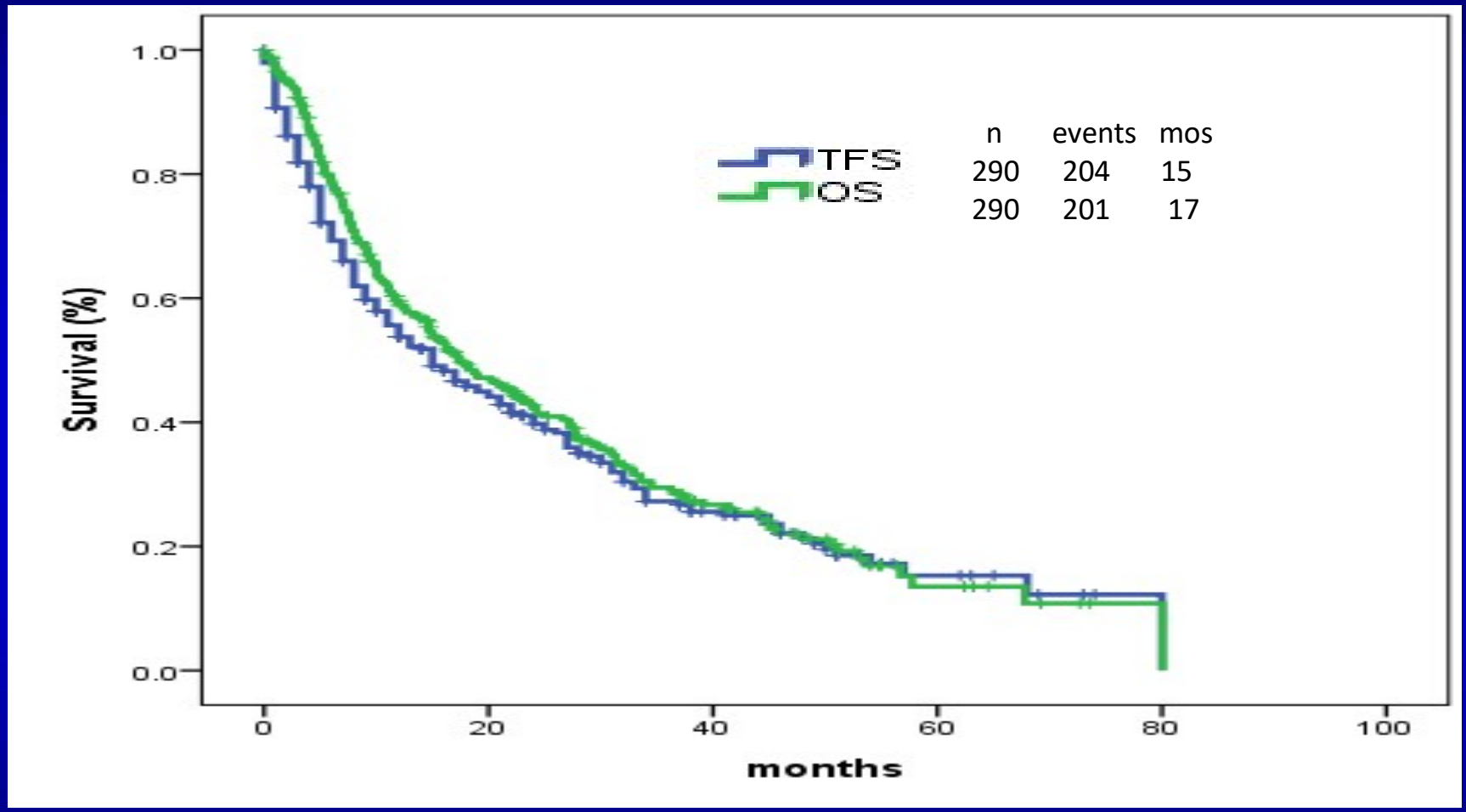
Early responses with encouraging durability in HR-MDS



- Median time to CR/mCR: 1.9 months (range: 1.8–9.6 months)

CR, complete remission; EOT, end of treatment; H, high; HI, hematologic improvement; HR-MDS, high-risk myelodysplastic syndrome; IPSS-R, Revised international Prognostic Scoring System; mCR, bone marrow CR; PD, progressive disease; SD, stable disease; VH, very high.

LR MDS post HMA Failure. Outcome



- Median follow-up: 16 (1-80) months
- Median TFS and OS: 15 and 17 months

Jabbour et al

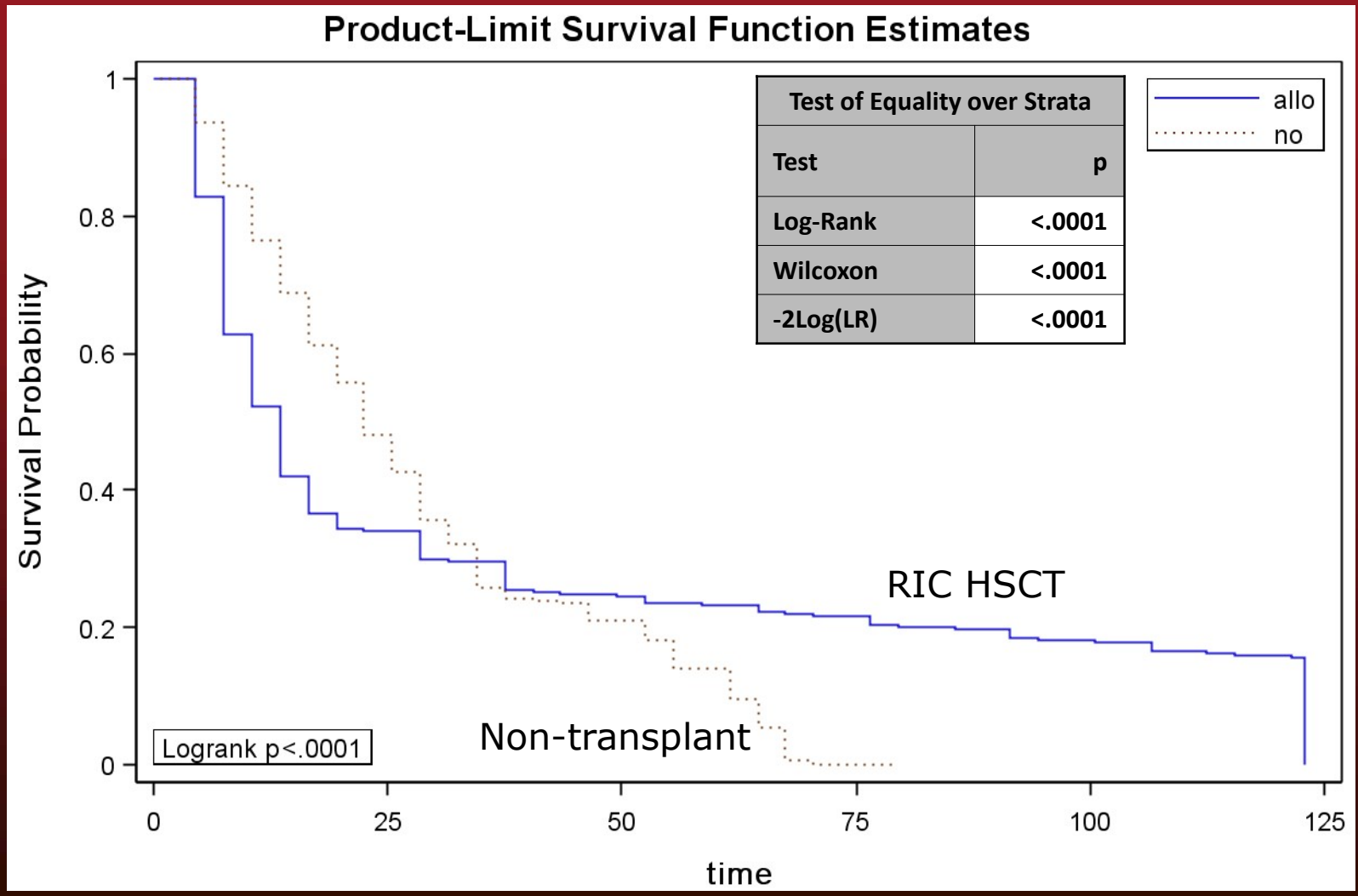
LR MDS post HMA Failure. Salvage Therapy

Salvage	N (%)	% Response
No therapy	90 (31)	NA
Conventional	83 (29)	18
Stem cell transplantation	26 (9)	62
Investigational	91 (31)	16

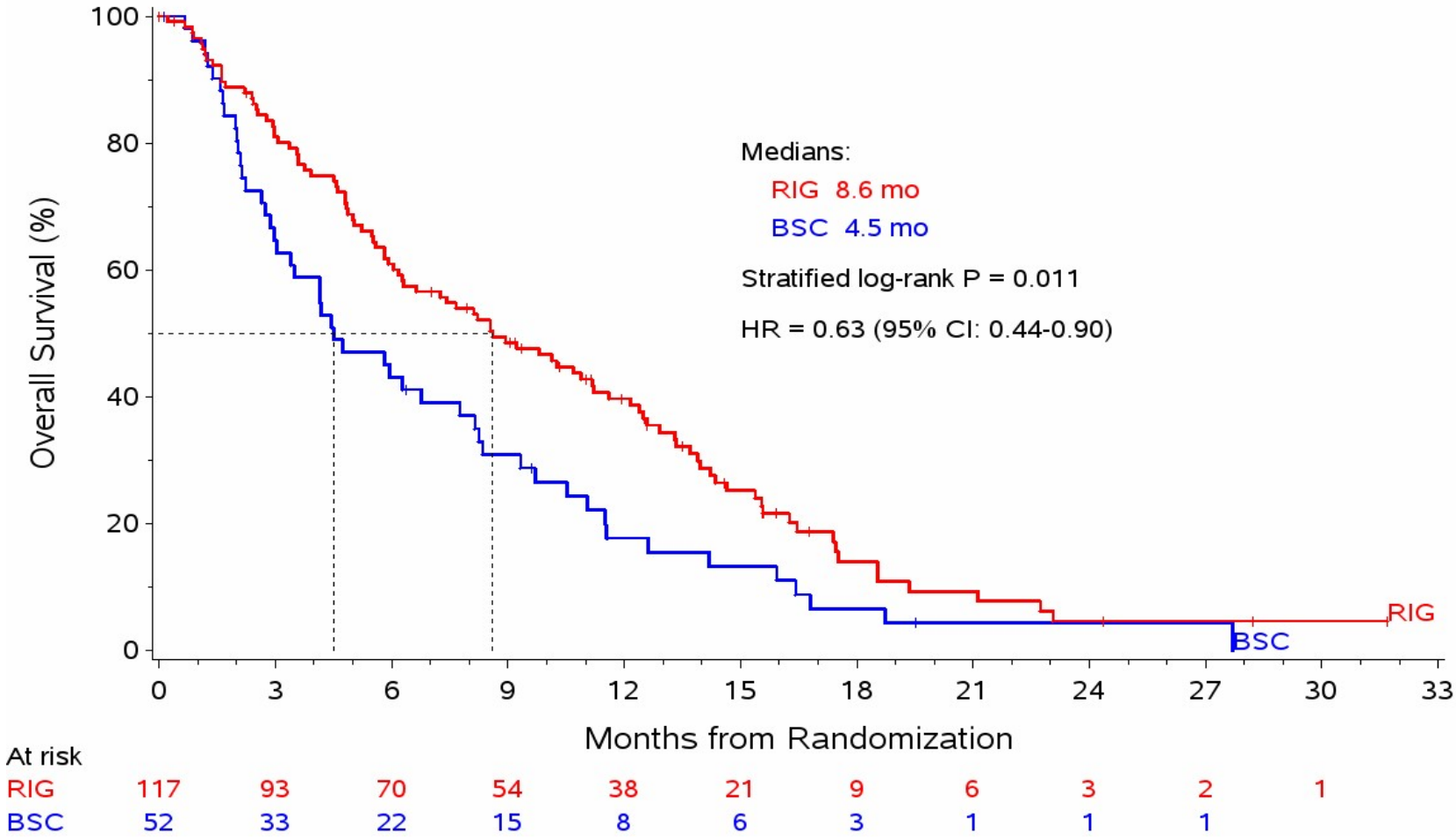
- Conventional therapies included cytarabine-based regimen and HMA

Jabbour et al

Monte Carlo – Int-2/High IPSS
Survival Estimates



ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure - Blinded, Centralized Assessment



Garcia-Manero. Lancet Oncology 2016

Clofarabine Plus Low-Dose Cytarabine For The Treatment Of Patients With higher-Risk Myelodysplastic Syndrome Who Have Relapsed Or Are Refractory To Hypomethylating Agent

Jabbour E, Sasaki K, Daver N, Pemmaraju N, Jain N, Kadia T, DiNardo C, Ravandi F, Miller D, Maduike R, Borthakur G, Konopleva M, Faderl S, O'Brien S, Cortes J, Kantarjian H, Garcia-Manero G

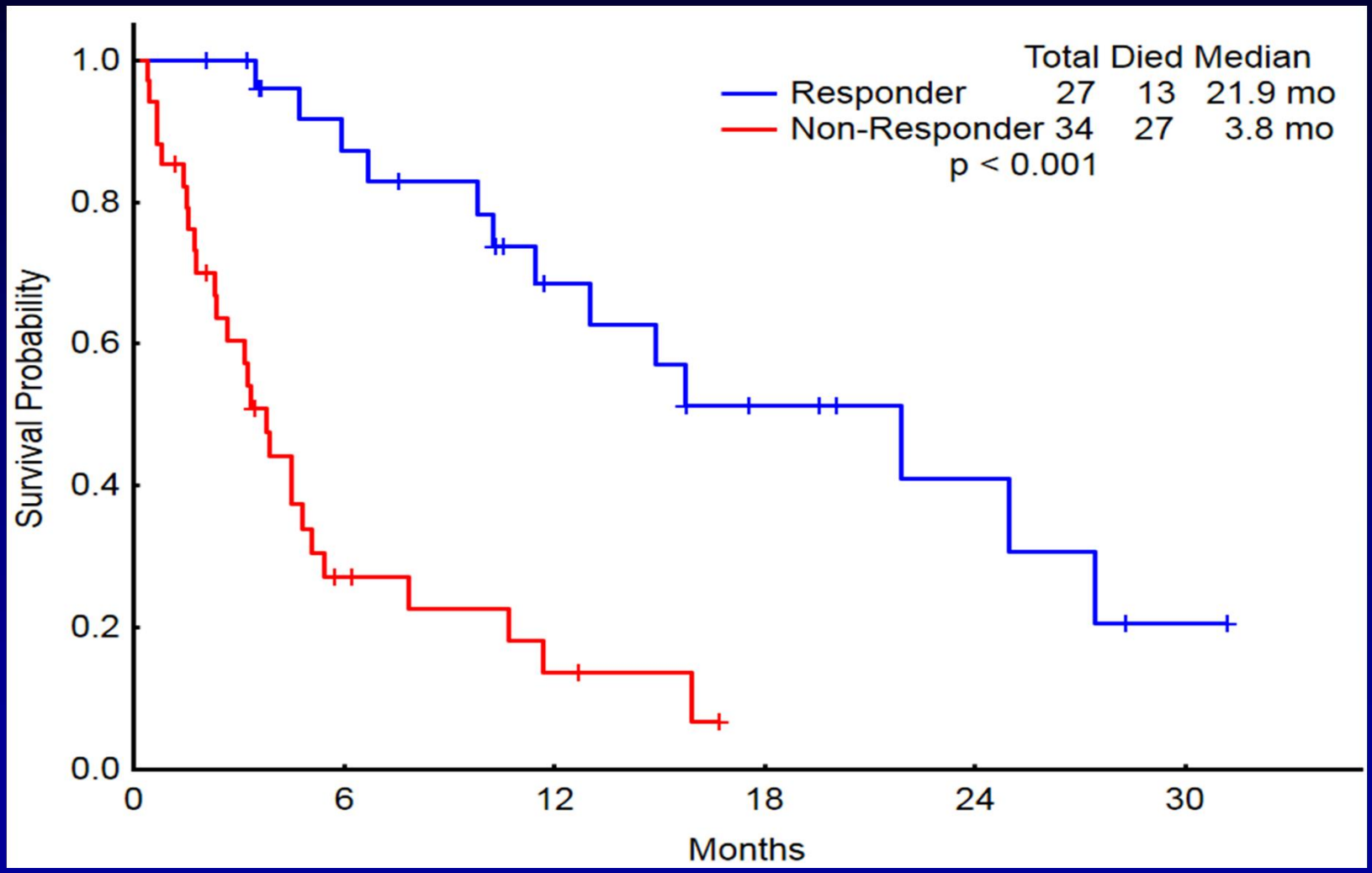
Cancer 2017

From the Department of Leukemia at MD Anderson Cancer Center
Houston, Texas

CLO and LDAC in HR MDS post HMA. MVA for Response and Survival

	Multivariate analysis			
	Response		Survival	
Parameter	OR	P	HR	P
Cyto Complex vs. Non	5.4	0.04	2.6	0.04
Plt ≤30 vs. >30	NA	NS	3.5	0.001
PS ≥2 vs. <2	NA	NS	5.5	<0.001
Response vs. Non-Response	NA	NS	7.1	<0.001
Prior response to HMA	NA	NS	NA	NS

CLO and LDAC in HR MDS post HMA. Survival by Response Status



Phase I Dose Escalation Study of CPX-351 for MDS and CMML

Study Design

MDS or CMML with Int-2 or High IPSS and >5% blasts

OR

MDS and CMML with 10-19% blasts

AND

Primary or secondary failure to any HMA

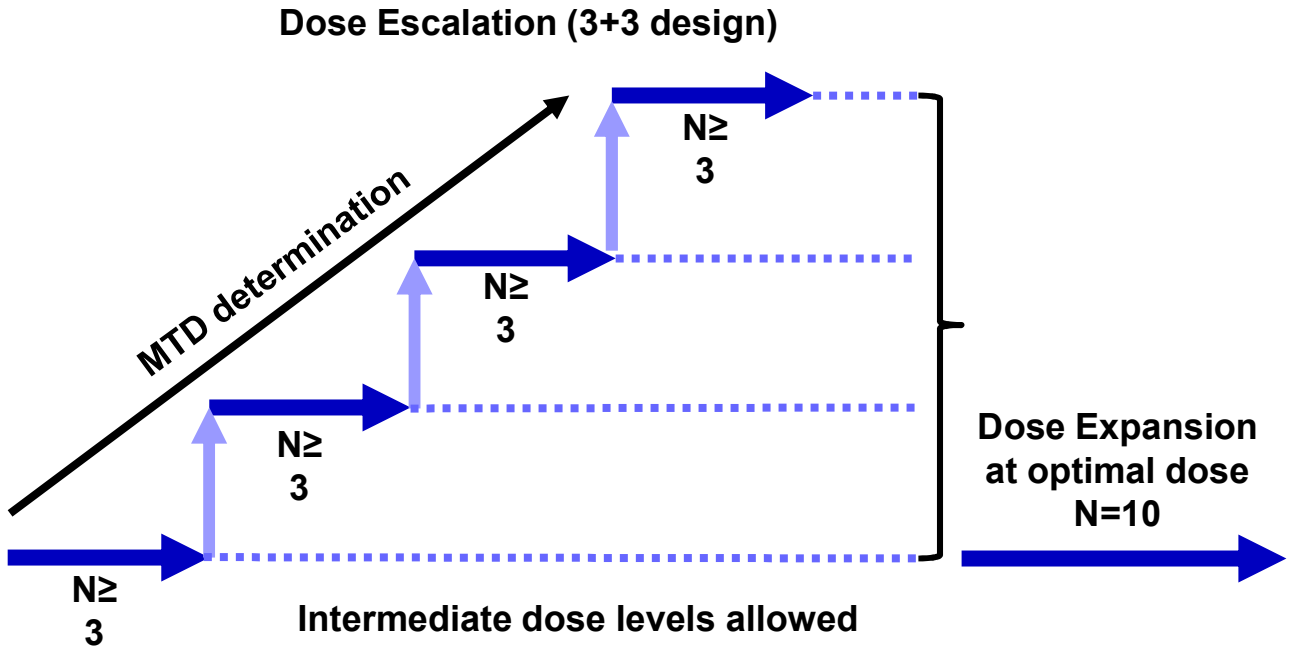
Dose levels

4
75units/m²
(33mg/m², 75mg/m²)

3
50units/m²
(22mg/m², 50mg/m²)

2
25units/m²
(11mg/m², 25mg/m²)

1
10units/m²
(4.4mg/m², 10mg/m²)



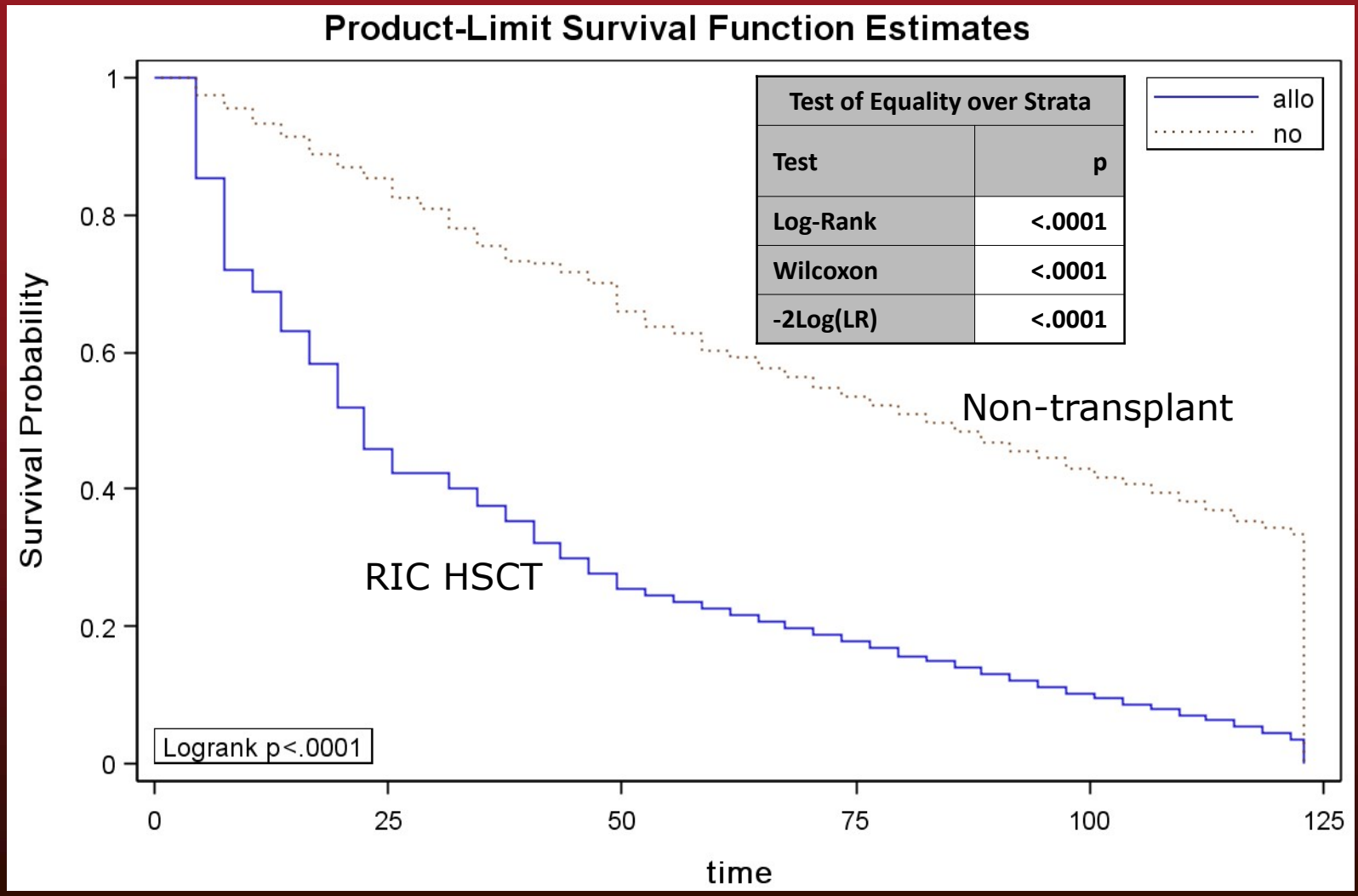
Daunorubicin/Cytarabine

Primary Objective: Safety, tolerability and determination of MTD

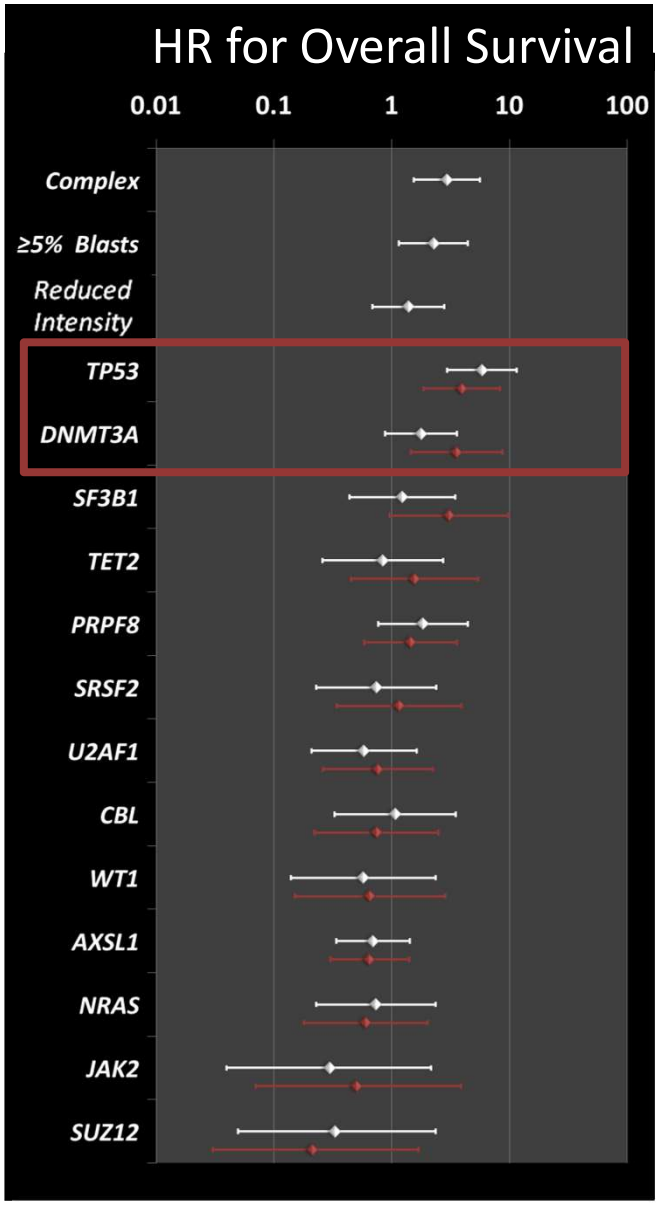
Secondary objectives: overall response, overall survival, duration of response

Dr Montalban-Bravo MDACC

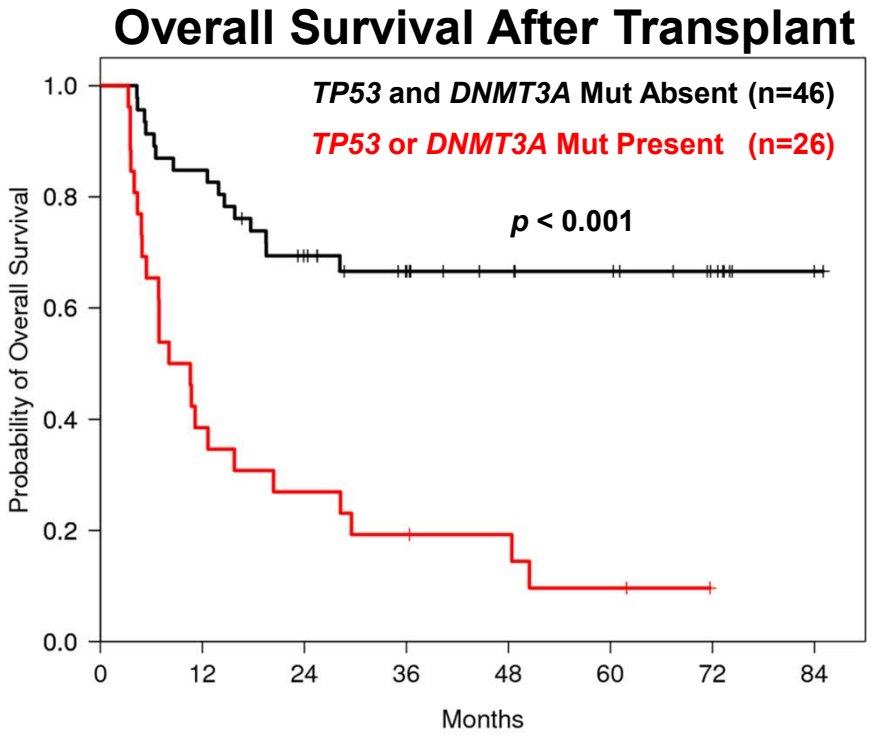
Monte Carlo – Low/int-1 IPSS Survival Estimates



SCT Cohort – Treatment Outcomes

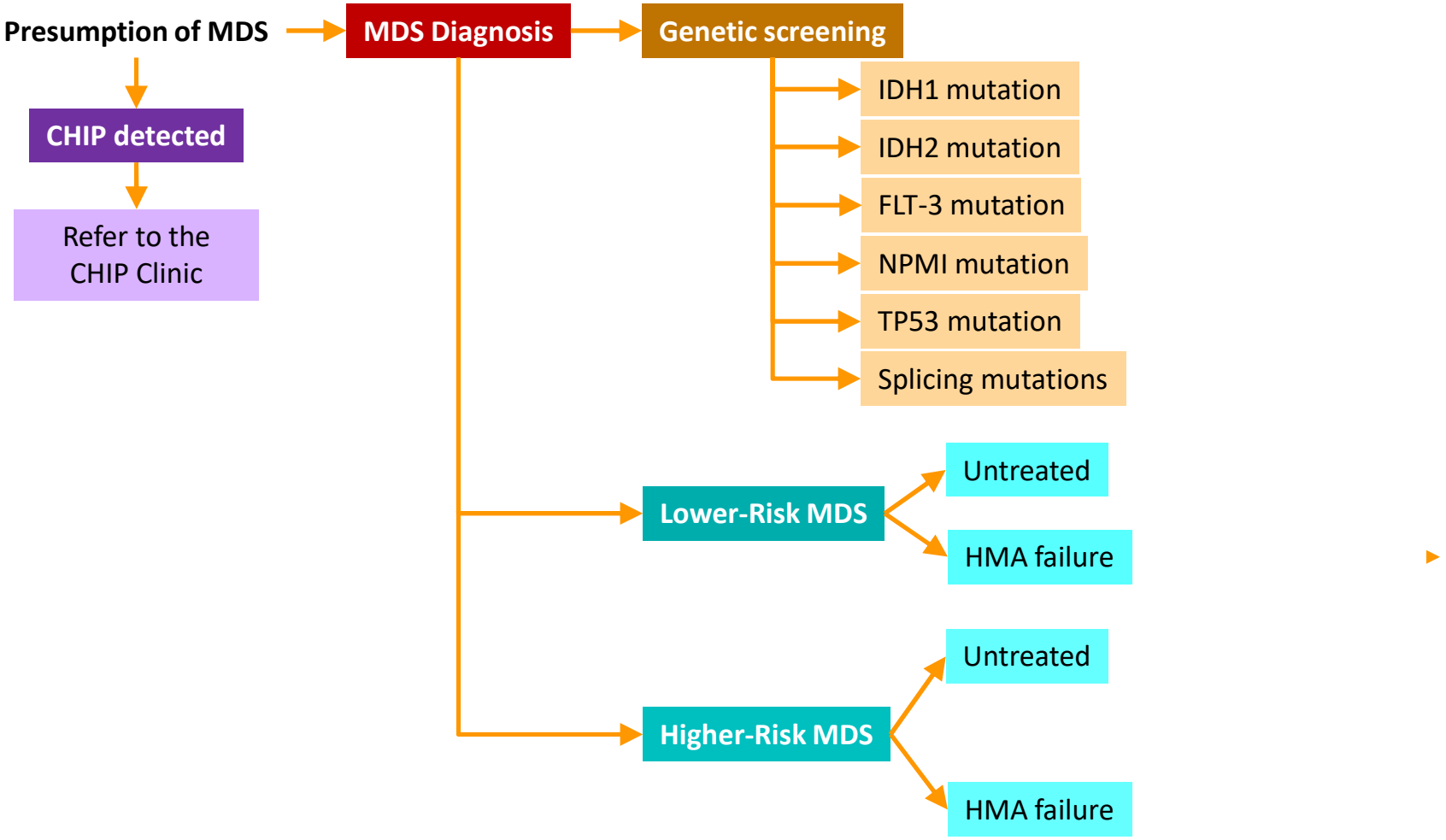


Gene	Adjusted HR (95% CI)	p-value
TP53 (n = 14)	**3.90** (1.85, 8.22)	<0.001
DNMT3A (n = 14)	**3.54** (1.45, 8.64)	0.005



Kristen Stevenson and Donna Neub

Treatment approach to MDS at MDACC



alloSCT at time of best response
Close monitoring post alloSCT, consideration of post SCT therapy

Conclusion #1

- **Immediate impact:**
  - **Luspatercept: approved by FDA. Need to define role/position**
  - **ASTX727 (oral decitabine). Met all endpoints. Role?**
- **Potential:**
  - **APR-246: study to complete in 2020/21**
  - **Magrolimab: 2020/2021**
  - **Pevonidostat: 2020/2021**
  - **ABT-199: starting large randomized trials**
  - **IDH2, IDH1: expanding single arm experience**
- **Others: TIM-3 (sabatolimab)**

Conclusion #2

- Increased role of genomic annotation in MDS
- Multiple new targets: Bcl-2, TGF-b, TLR, SF3B1, IDH, Flt-3, NPM1, CD33, CD123, IL-1
- New ways to deliver HMA: attenuated schedules, CC-486, ASTX727, SGI-110
- Potential for multiple oral combinations
- Multiple registration trials: Commands (luspatercept), Verona (ABT-199), APR-246, magrolimab, pevonidostat, MBG453 (TIM-3)

Thank you!

Any questions?

Guillermo Garcia-Manero

ggarciam@mdanderson.org

cell 281 380 7813