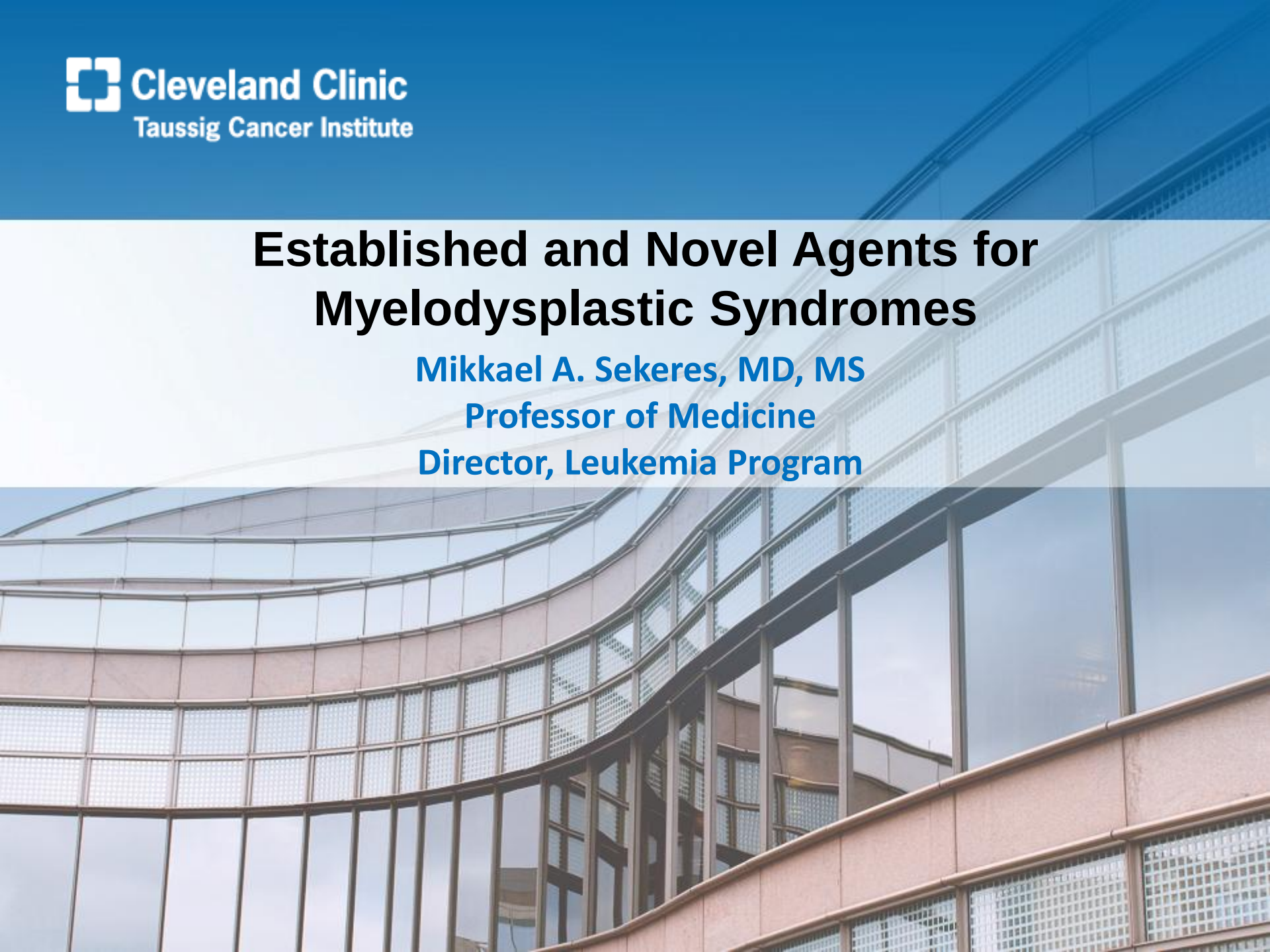
Cleveland Clinic
Taussig Cancer Institute

# Established and Novel Agents for Myelodysplastic Syndromes

Mikkael A. Sekeres, MD, MS
Professor of Medicine
Director, Leukemia Program



# HOA: MDS

- MDS Overview
- Disease Mechanisms
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease

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- **MDS Overview**
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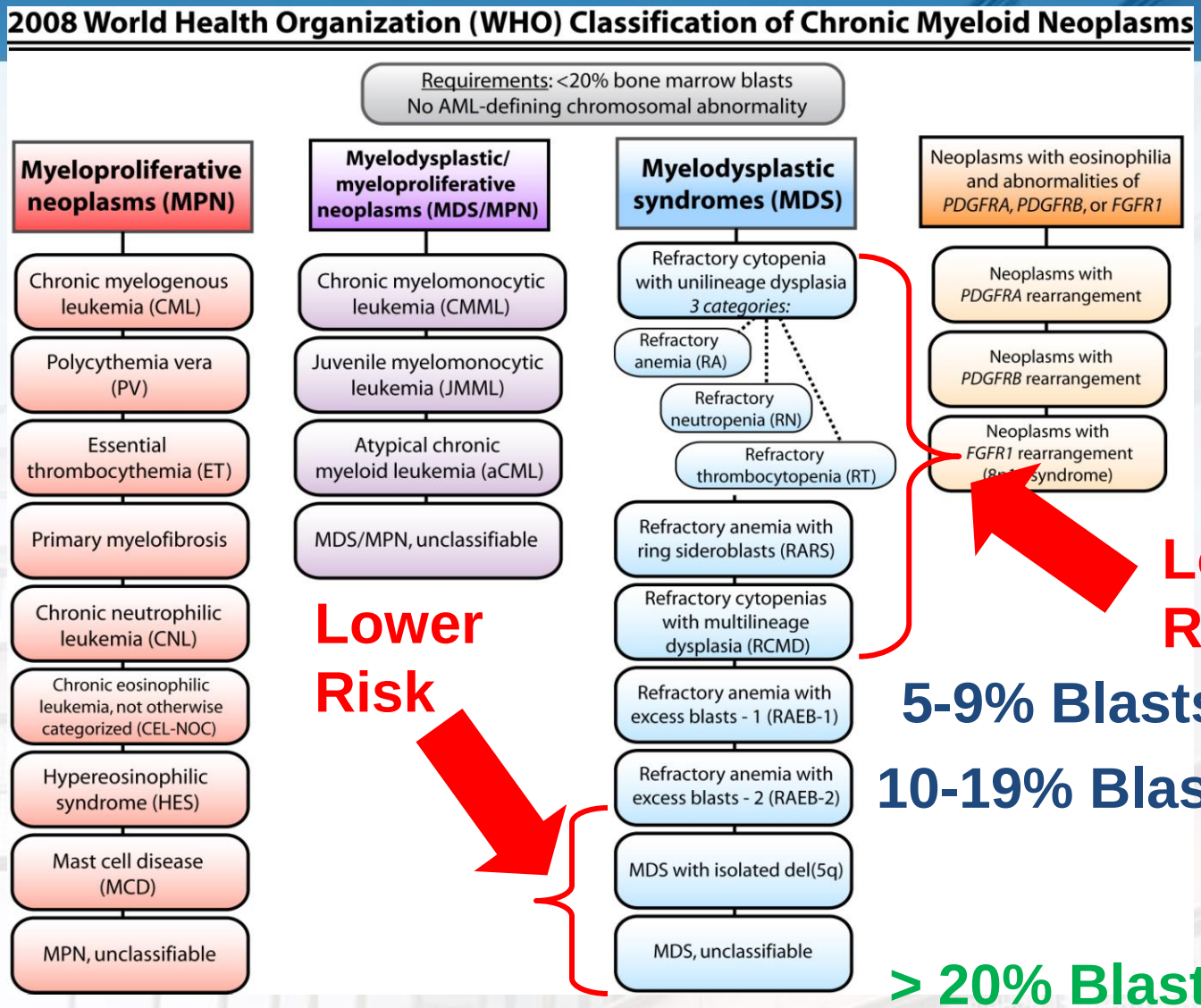
# MDS Overview: WHO Classification




Adapted from Vardiman et al. Blood 2009;114:937.

# MDS Overview: IPSS

## Calculation of prognostic score

| Score | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
|---|---|---|---|---|---|
| BM Blast % | < 5 | 5-10 | | 11-20 | 21-29 |
| Cytogenetics | Good | Intermediate | Poor | | |
| Cytopenias | 0/1 | 2/3 | | | |

## Estimation of prognosis

Lower Risk

| Overall Score | IPSS Subgroup | Median Survival (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 |

Greenberg P, et. al. *Blood* 1997:89:2079-88.

# MDS Overview:
## IPSS-R

| VARIABLE | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| Cytogenetics | V. Good | | Good | | Intermediate | Poor | V. Poor |
| BM Blast % | ≤2 | | >2-<5% | | 5-10% | >10% | |
| Hemoglobin | ≥10 | | 8-<10 | <8 | | | |
| Platelets | ≥100 | 50-<100 | <50 | | | | |
| ANC | ≥0.8 | <0.8 | | | | | |

**IPSS-R Prognostic Risk Categories/Scores**

| RISK GROUP | Risk Score | Median Survival (Yrs) |
|---|---|---|
| Very Low | ≤1.5 | 8.8 |
| Low | >1.5-3 | 5.3 |
| Intermediate | >3-4.5 | 3.0 |
| High | >4.5-6 | 1.6 |
| Very High | >6 | 0.8 |

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

# MDS Prognosis Made Easy!!!

- **Lower Risk**
  - RA, RARS
  - RCMD, RCUD
  - MDS-U, MDS del (5q)
  - IPSS Low, Int-1 (0-1.0); **IPSS-R V. Low, Low**

- **Higher Risk**
  - RAEB (-1, -2)
  - IPSS Int-2, High (≥ 1.5); **IPSS-R High, V. High**

# HOA: MDS

- MDS Overview
- **Disease Mechanisms**
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease

# 840

# Clonal Hematopoiesis with Somatic Mutations Is a Common, Age-Related Condition Associated with Adverse Outcomes

***Siddhartha Jaiswal, MD, PhD***, *Pierre Fontanillas, Jason Flannick, Alisa Manning, Peter Grauman, Brenton G. Mar, MD, PhD, R. Coleman Lindsley, MD, PhD, Craig Mermel, Noel Burtt, Alejandro Chavez, John M. Higgins, MD, Vladislav Moltchanov, Leena Kinnunen, Heikki Koistinen, Claes Ladenvall, Gad Getz, Ph.D., Adolfo Correa, Stacey Gabriel, PhD, Sekar Kathiresan, Heather Stringham, Michael Boehnke on behalf of GoT2D, Brian Henderson on behalf of SIGMA T2D, Mark McCarthy on behalf of T2D-GENES, Jaako Tuomilehto, Christopher A. Haiman, Sc.D., Leif Groop, Gil Atzmon, James Wilson, Donna S. Neuberg, ScD, David Altshuler and Benjamin L Ebert, MD, PhD*

# Age-related mutations associated with clonal hematopoietic expansion and malignancies

nature medicine

Mingchao Xie[1,2,7], Charles Lu[1,7], Jiayin Wang[1,2,7], Michael D McLellan[1], Kimberly J Johnson[3], Michael C Wendl[1,4,5], Joshua F McMichael[1], Heather K Schmidt[1], Venkata Yellapantula[1,2], Christopher A Miller[1], Bradley A Ozenberger[1,2], John S Welch[2,6], Daniel C Link[2,6], Matthew J Walter[2,6], Elaine R Mardis[1,2,4,6], John F Dipersio[2,6], Feng Chen[2,6], Richard K Wilson[1,2,4,6], Timothy J Ley[1,2,4,6] & Li Ding[1,2,4,6]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S., Johan Lindberg, Ph.D., Samuel A. Rose, B.S., Samuel F. Bakhoum, M.D., Ph.D., Kimberly Chambert, M.S., Eran Mick, B.S., Benjamin M. Neale, Ph.D., Menachem Fromer, Ph.D., Shaun M. Purcell, Ph.D., Oscar Svantesson, M.S., Mikael Landén, Ph.D., Martin Höglund, M.D., Ph.D., Sören Lehmann, M.D., Ph.D., Stacey B. Gabriel, Ph.D., Jennifer L. Moran, Ph.D., Eric S. Lander, Ph.D., Patrick F. Sullivan, M.D., Pamela Sklar, M.D., Ph.D., Henrik Grönberg, M.D., Ph.D., Christina M. Hultman, Ph.D., and Steven A. McCarroll, Ph.D.

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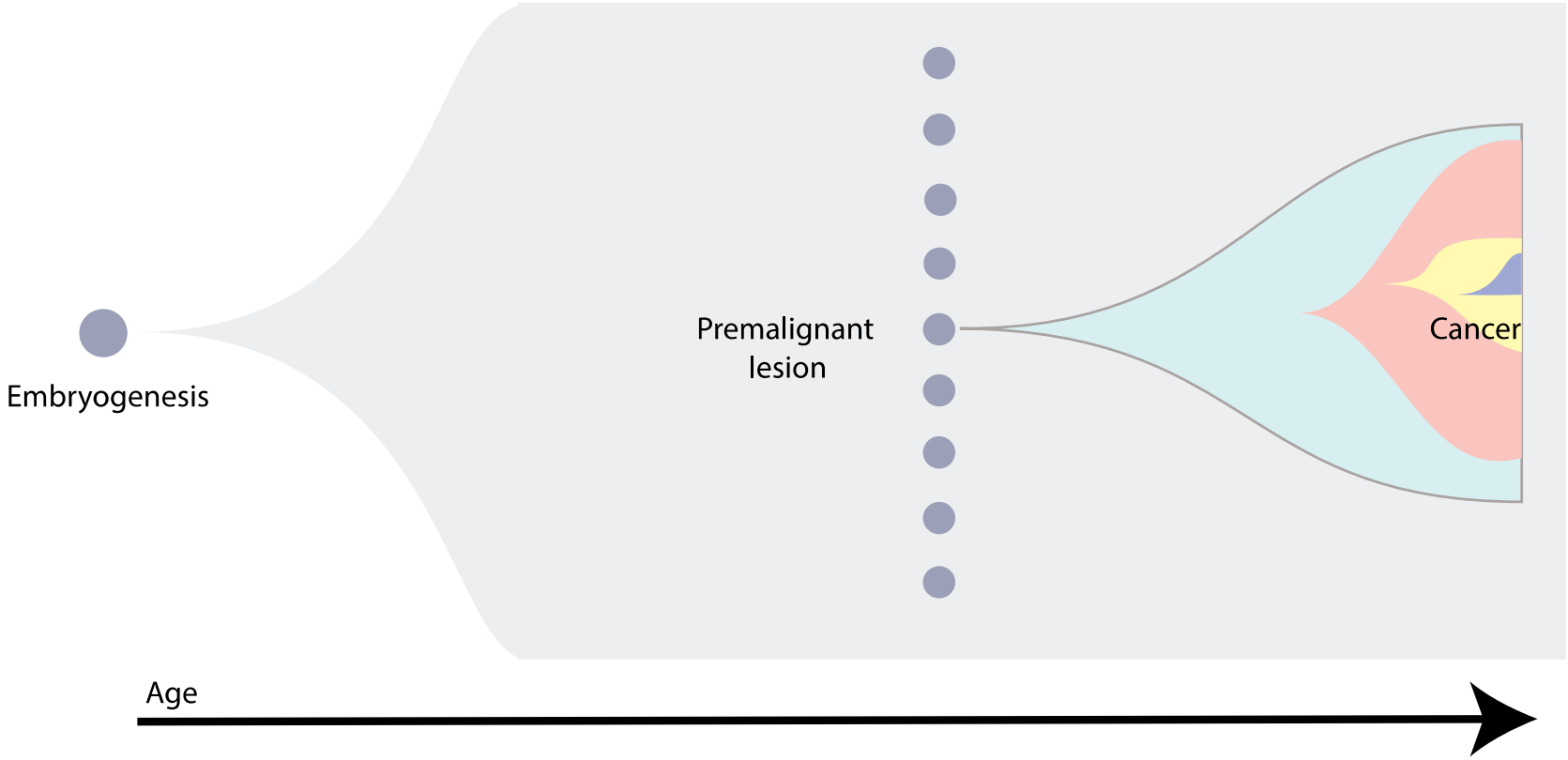
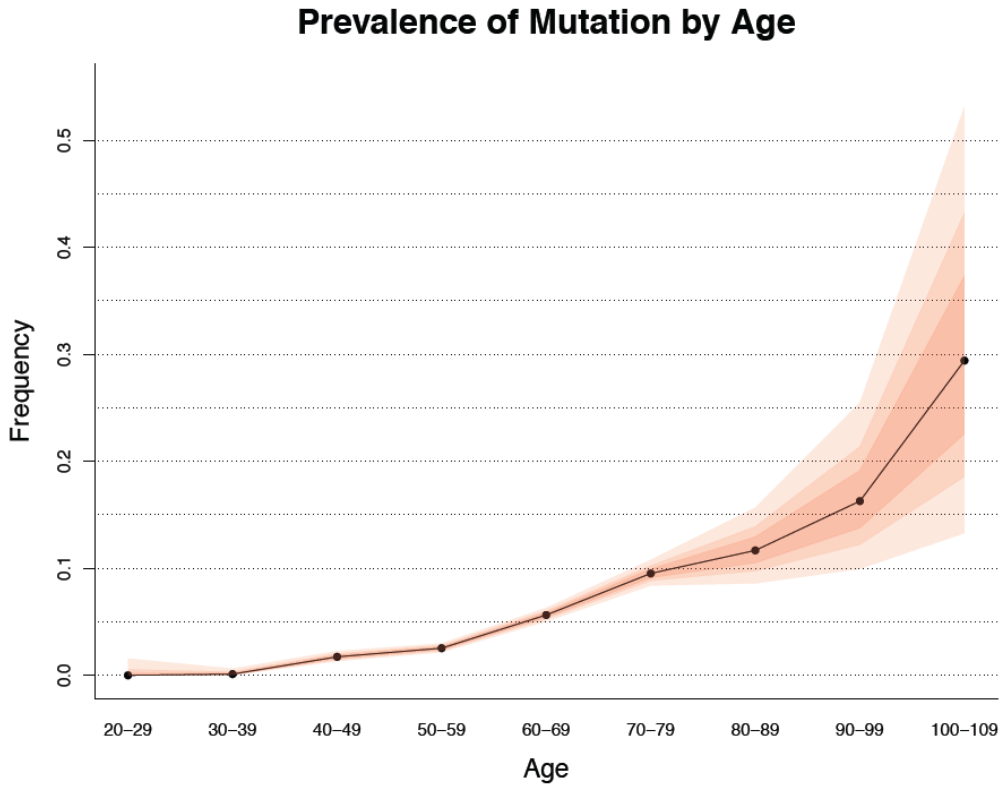
# Clonal evolution



# Clonal hematopoiesis of indeterminate potential (CHIP)

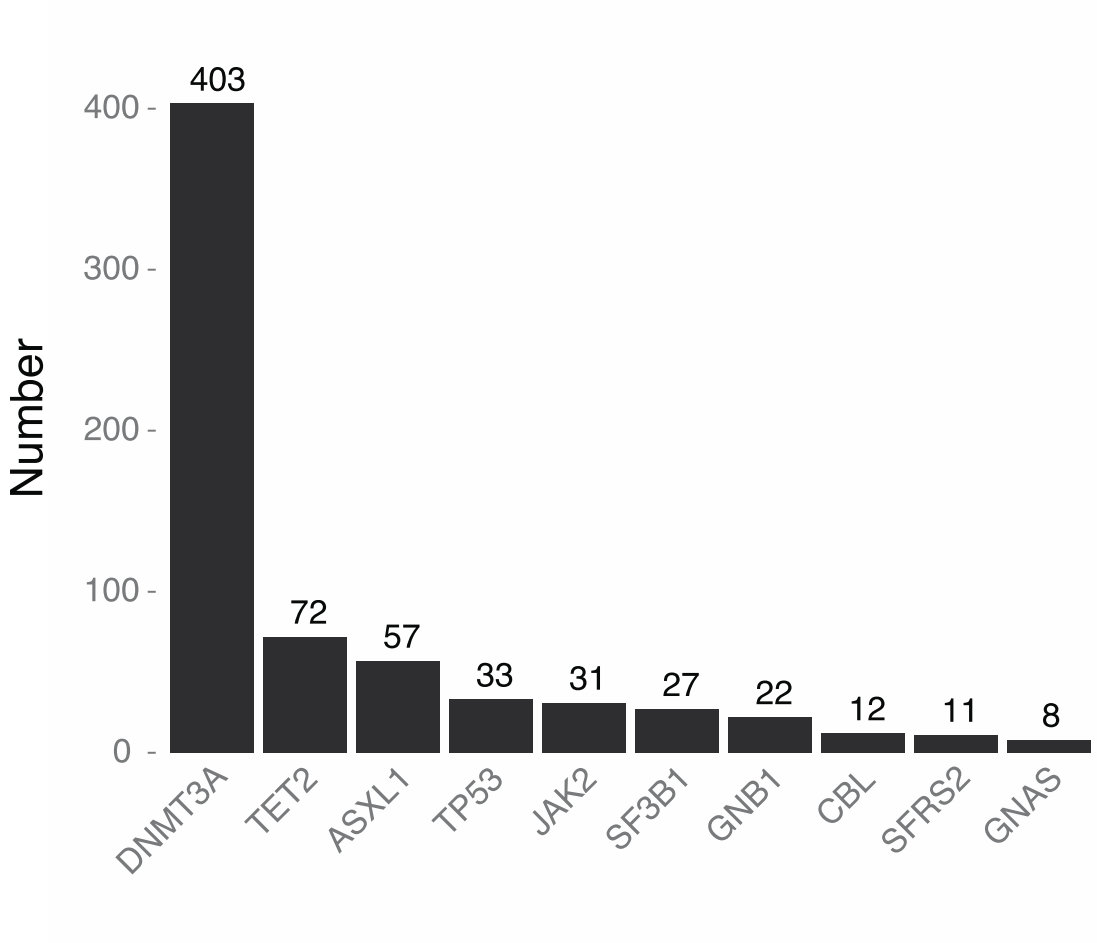



| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **No. with mutation** | 0 | 1 | 50 | 138 | 282 | 219 | 37 | 14 | 5 |
| **Total** | 240 | 885 | 2894 | 5441 | 5002 | 2300 | 317 | 86 | 17 |

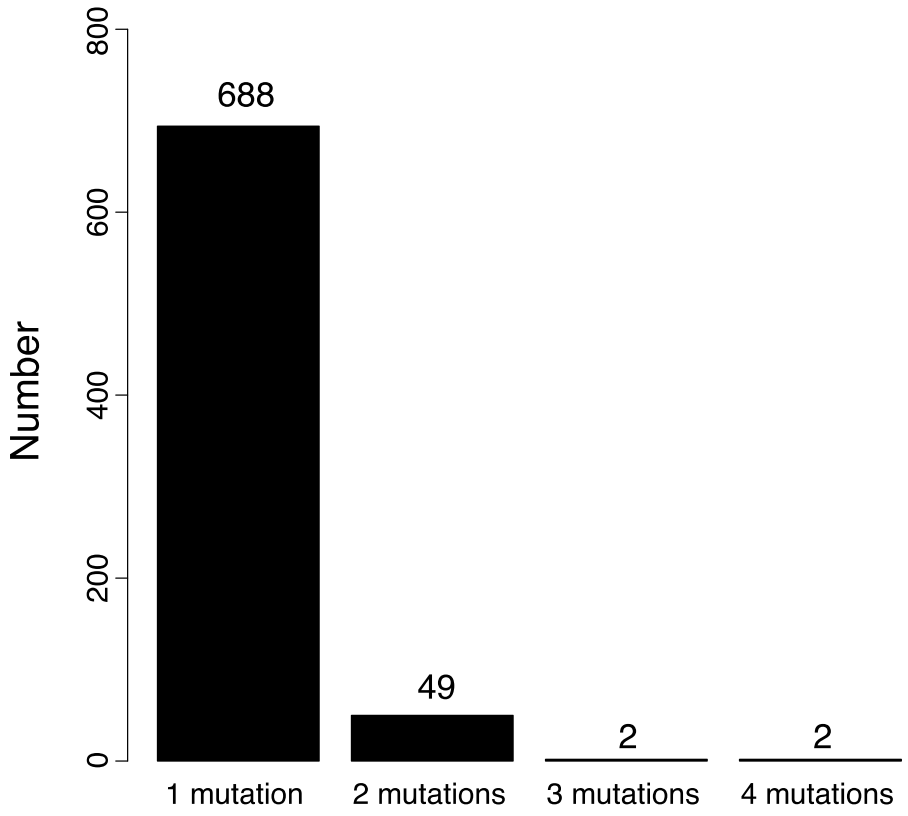
Exome sequencing of peripheral blood from > 17,000 individuals

Jaiswal et al., *NEJM* 2014

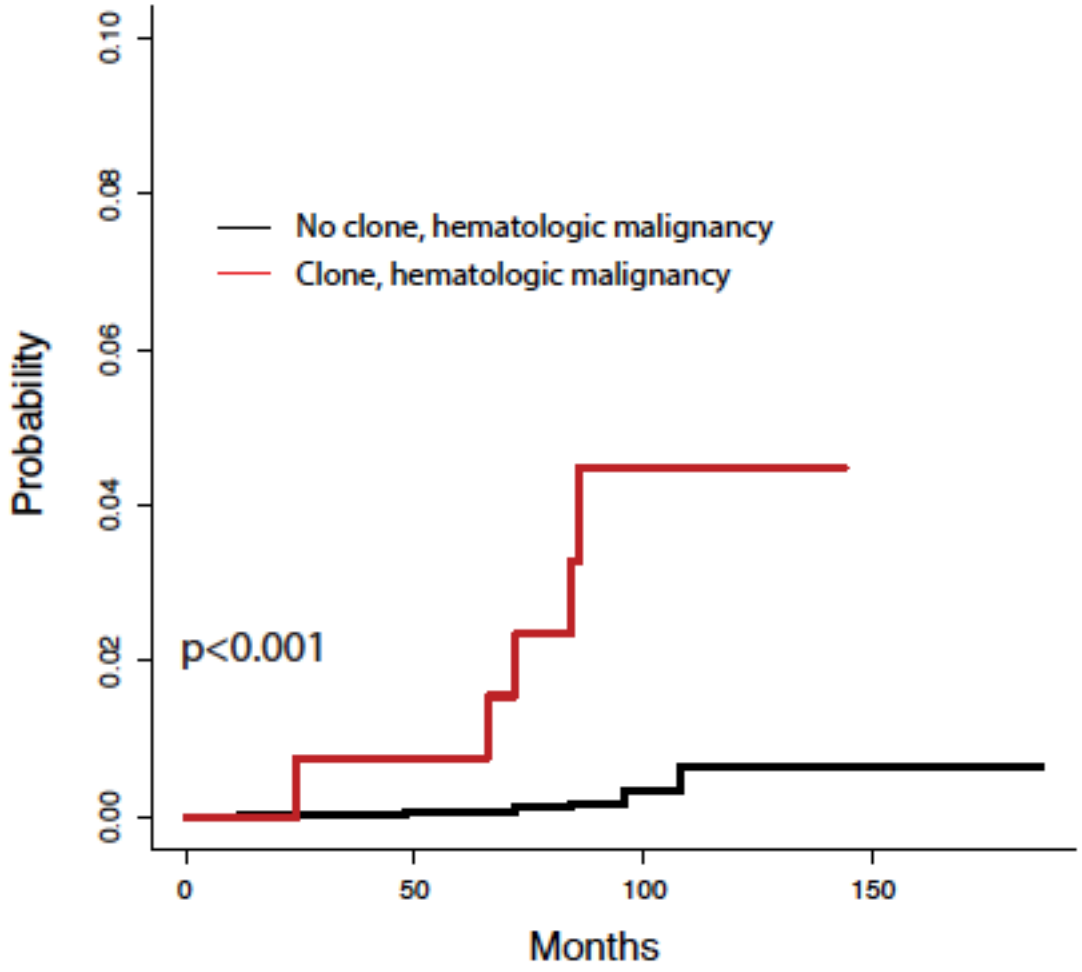
# *DNMT3A* is frequently mutated



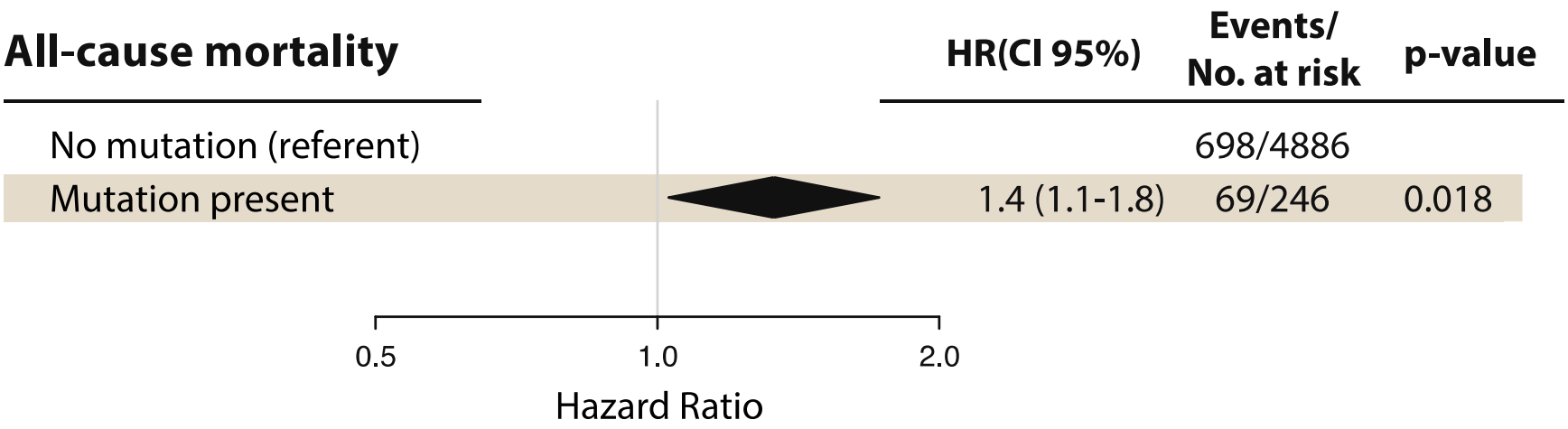
# Most subjects had only one mutation



# CHIP increases the risk of hematologic malignancy



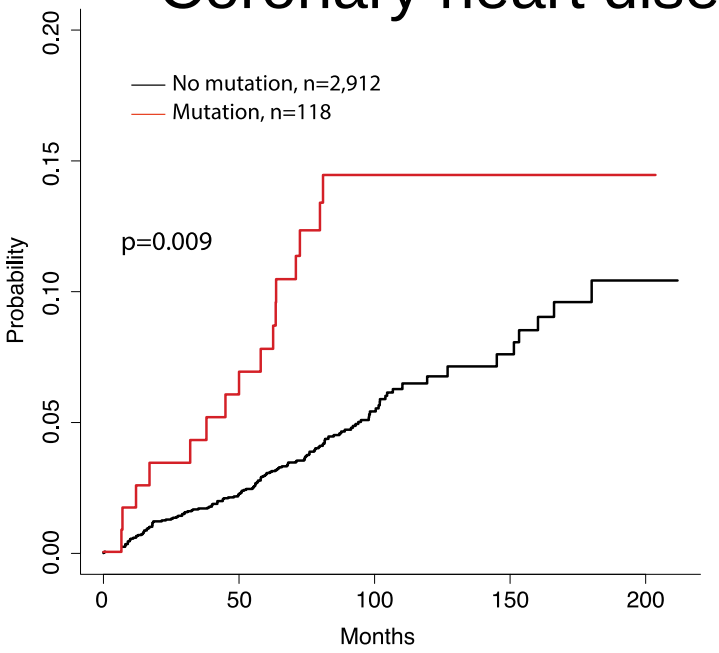
# Clonal hematopoiesis is associated with reduced overall survival




Cox proportional hazards models which included age, gender, and diabetes status as covariates, with results for cohorts analyzed as a fixed-effects meta-analysis

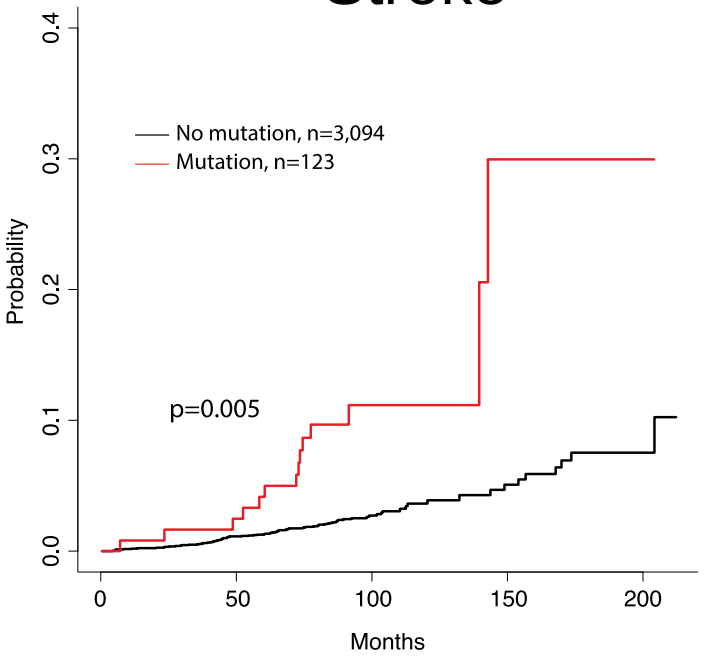
# Clonal hematopoiesis is associated with higher risk of heart attack and stroke

## Coronary heart disease




HR 2.0, 95% CI 1.2-3.4, p=0.018

## Stroke




HR 2.6, 95% CI 1.4 to 4.8, p=0.003

Regression models were adjusted for age, sex, BMI, lipids, blood pressure, and smoking

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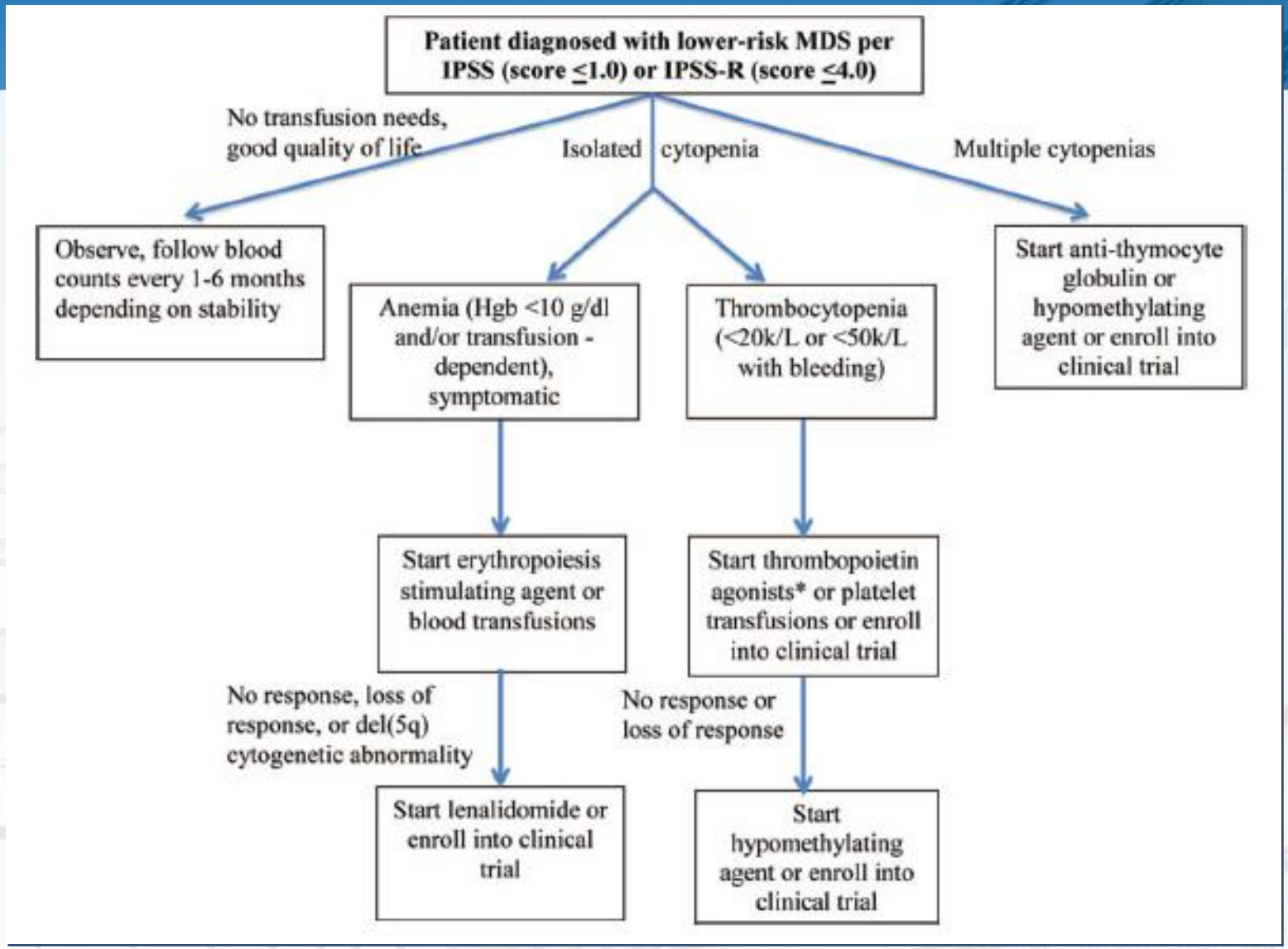
# MDS: Lower-risk, Treatment Algorithm




Sekeres and Gerds Hematology 2014.

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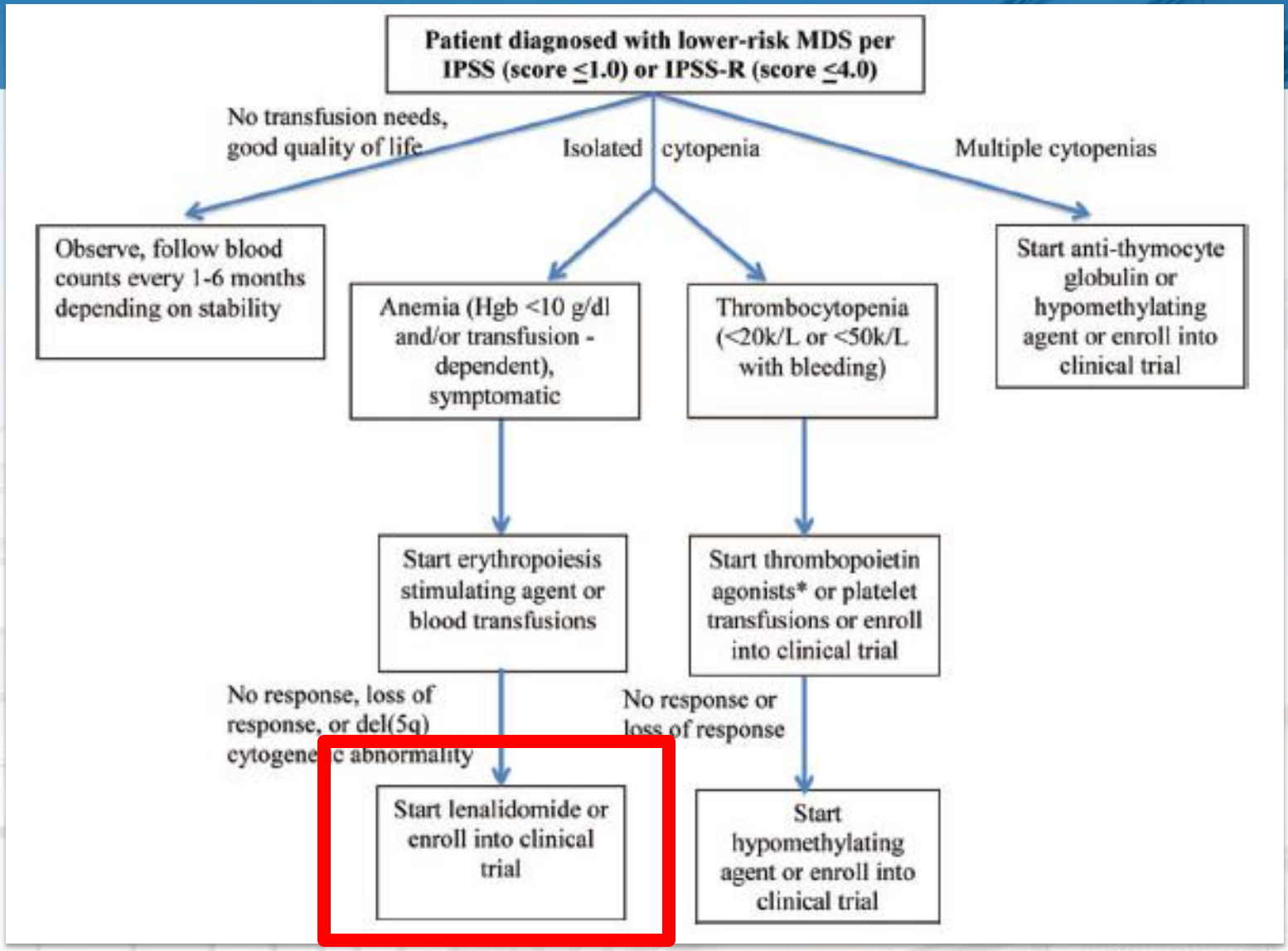
# MDS: Lower-risk, Treatment Algorithm



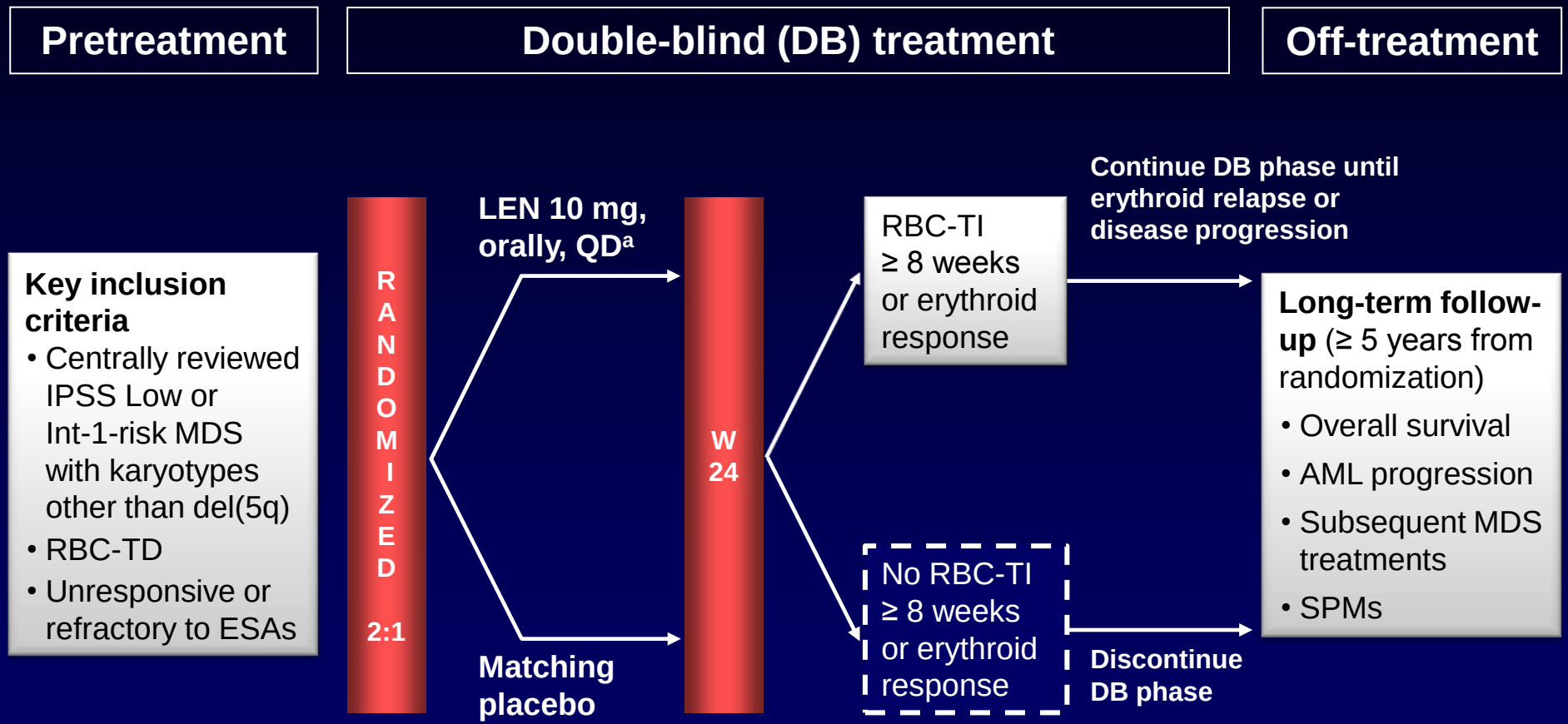

Sekeres and Gerds Hematology 2014.

# Efficacy and Safety of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With IPSS Low or Intermediate-1-Risk Myelodysplastic Syndromes Without del(5q) and Unresponsive or Refractory to Erythropoiesis-Stimulating Agents: Results From a Randomized Phase 3 Study (CC-5013-MDS-005)

Valeria Santini[1], Antonio Almeida[2], Aristoteles Giagounidis[3], Stefanie Gröpper[3], Anna Jonasova[4], Norbert Vey[5], Ghulam J. Mufti[6], Rena Buckstein[7], Moshe Mittelman[8], Uwe Platzbecker[9], Ofer Shpilberg[10], Ron Ram[8], Consuelo del Canizo[11], Norbert Gattermann[12], Keiya Ozawa[13], Alberto Risueno[14], Kyle J. MacBeth[15], Jim Zhong[16], Francis Séguy[17], Albert Hoenekopp[17], C.L. Beach[16], Pierre Fenaux[18]

[1]AOU Careggi, University of Florence, Firenze, Italy; [2]Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [3]Marien Hospital Düsseldorf, Düsseldorf, Germany; [4]Charles University General Hospital 1st Department of Medicine, Prague, Czech Republic; [5]Institut Paoli-Calmettes Centre Régional de Lutte Contre le Cancer, Marseille, France; [6]King's College Hospital, London, UK; [7]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [8]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [9]Medical Clinic and Polyclinic I, University Hospital, Technical University Dresden, Dresden, Germany; [10]Assuta Medical Center, Tel Aviv, Israel; [11]Hospital Universitario de Salamanca, Salamanca, Spain; [12]Heinrich-Heine-Universität, Düsseldorf, Germany; [13]The Institute of Medical Science, The University of Tokyo, Tokyo, Japan; [14]Celgene Institute for Translational Research Europe (CITRE), Seville, Spain; [15]Celgene Corporation, San Francisco, CA, USA; [16]Celgene Corporation, Summit, NJ, USA; [17]Celgene International, Boudry, Switzerland; [18]Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France

# MDS-005: Study Design

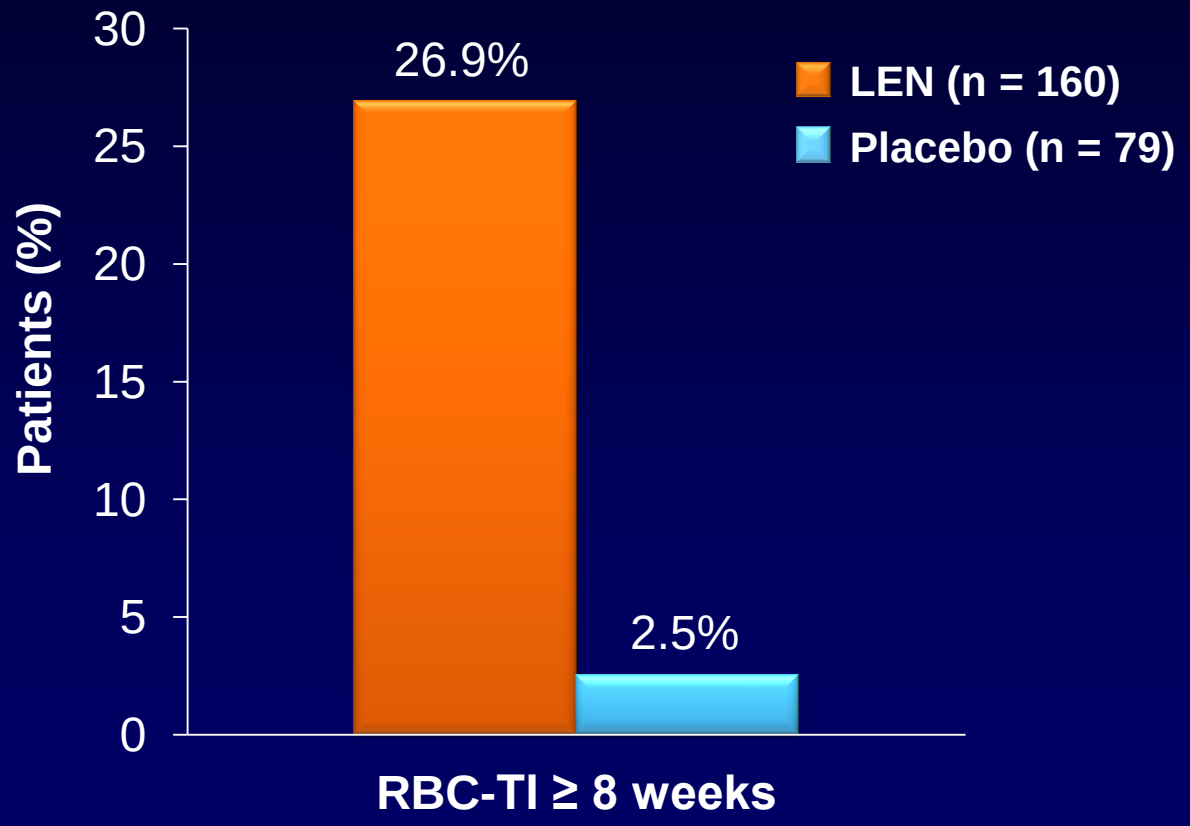



pRBC, packed red blood cell; SPM, secondary primary malignancy.

[a]LEN 5 mg for patients with creatinine clearance 40–60 mL/min.

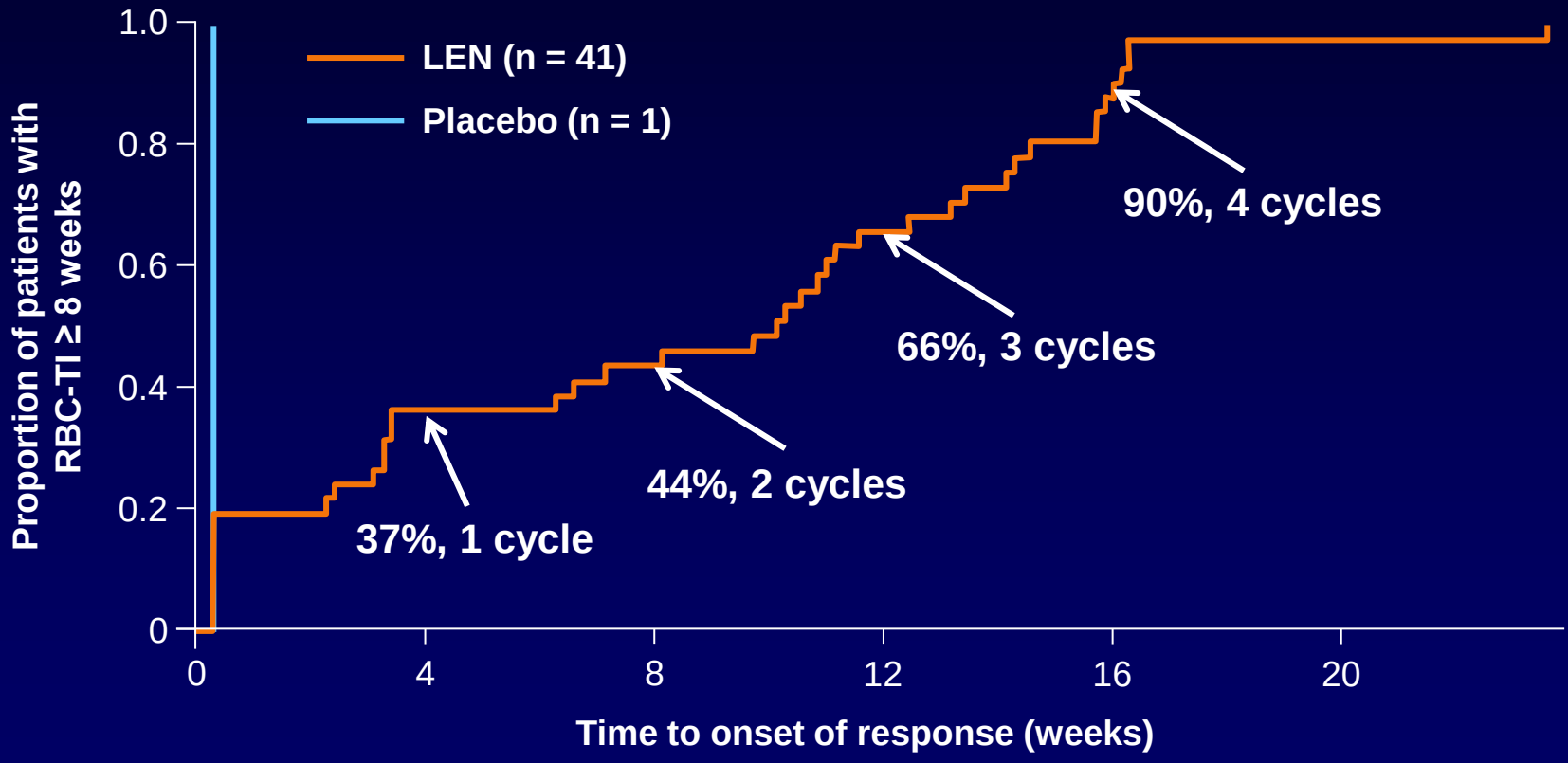
# MDS-005: RBC-TI ≥ 8 Weeks

**Significantly more LEN patients achieved RBC-TI ≥ 8 weeks versus placebo (*P* < 0.001)**



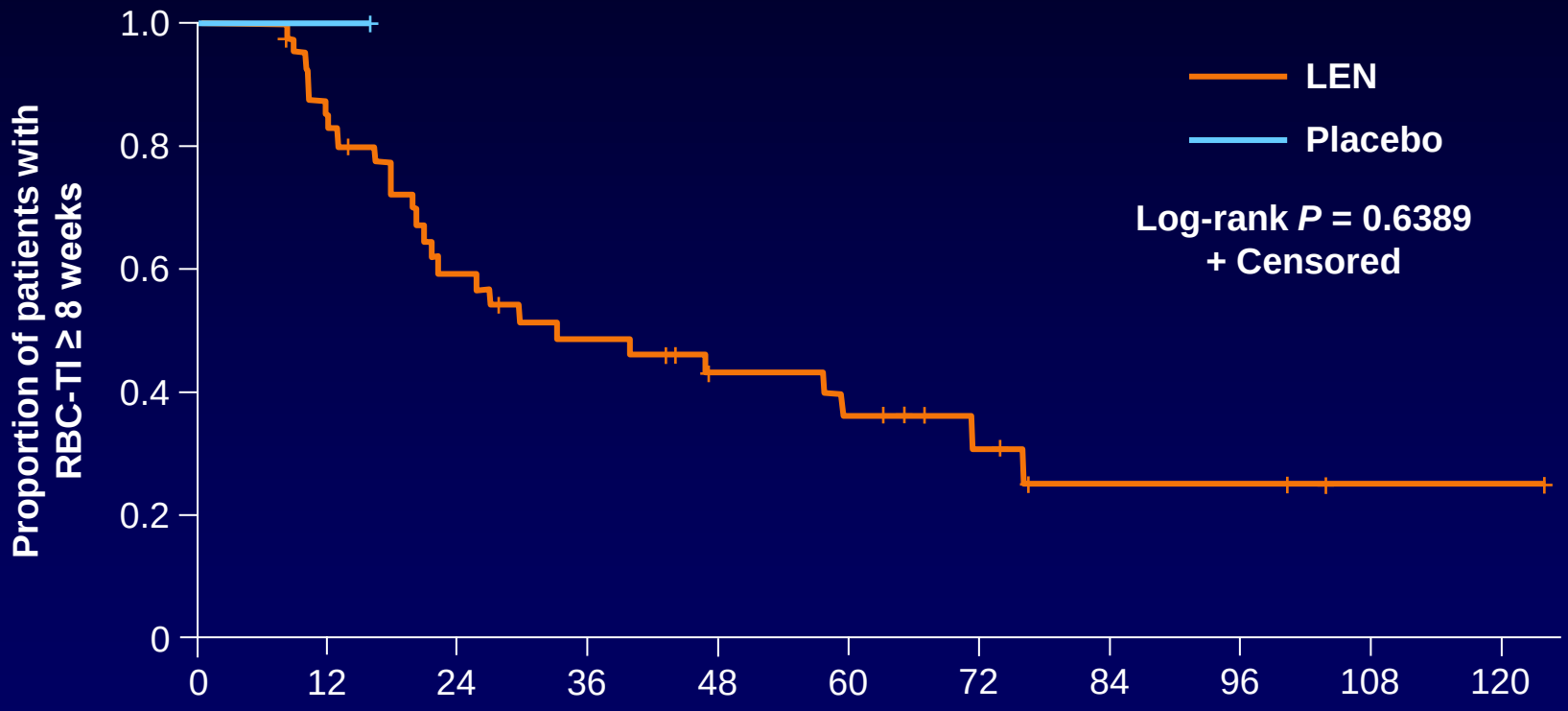
# MDS-005: Time to RBC-TI ≥ 8 Weeks

**90% of the patients with RBC-TI ≥ 8 weeks responded within 4 cycles of treatment**



# MDS-005: Duration of RBC-TI ≥ 8 Weeks

**The median duration of response was 32.9 weeks (95% CI 20.7–71.1) among RBC-TI ≥ 8 weeks responders with LEN**




No. of RBC-TI patients

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LEN | 41 | 34 | 23 | 18 | 13 | 11 | 6 | 3 | 3 | 1 | 1 |
| Placebo | 1 | 1 | 0 | | | | | | | | |

CI, confidence interval.

# Luspatercept (ACE-536) Increases Hemoglobin and Reduces Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Preliminary Results from a Phase 2 Study


Uwe Platzbecker, MD

U Platzbecker[1], U Germing[2], A Giagounidis[3], K Goetze[4], P Kiewe[5], K Mayer[6], O Ottman[7], M Radsak[8], T Wolff[9], D Haase[10], M Hankin[11], D Wilson[11], A Laadem[12], M Sherman[11] and K Attie[11]

[1]Universitätsklinikum Carl Gustav Carus, Dresden; [2]Universitätsklinikum Düsseldorf; [3]Marien Hospital Düsseldorf; [4]Technical University of Munich; [5]Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin; [6]Universitätsklinikum Bonn; [7]Klinikum der J.W. Goethe-Universität Frankfurt; [8]University Medical Center - Johannes Gutenberg-Universität, Mainz; [9]OncoResearch Lerchenfeld UG, Hamburg; [10]Department of Hematology and Medical Oncology, University Medicine of Göttingen, Germany; [11]Acceleron Pharma, Cambridge, MA; [12]Celgene Corporation, Summit, NJ, USA

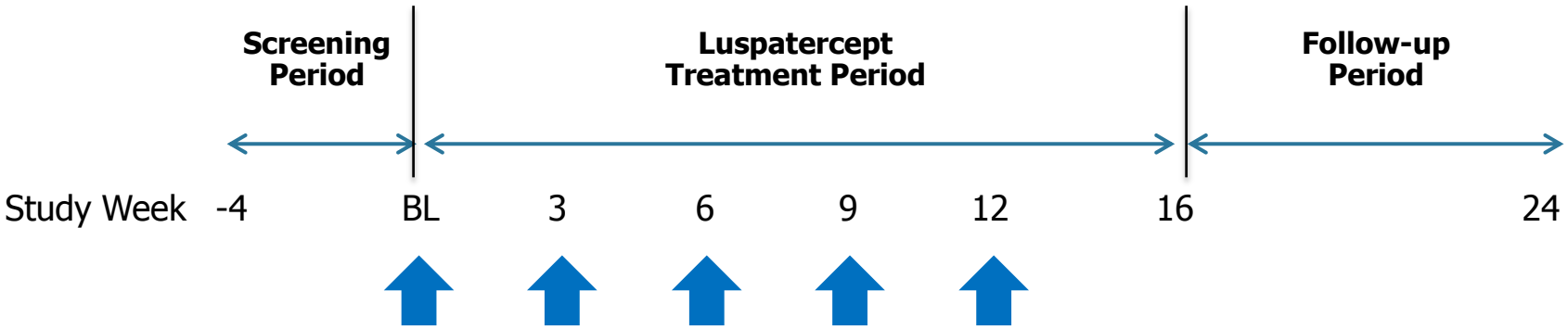


**Study supported by Acceleron and Celgene**


D·MDS
Deutsche MDS-Studiengruppe

# Luspatercept PACE-MDS Study Overview

- Phase 2, multicenter, open-label, dose-finding study in IPSS low/int-1 MDS
- **Eligibility criteria:** EPO >500 U/L or nonresponsive/refractory to ESA; no prior azacitidine or decitabine; no current lenalidomide, ESA, G-CSF
- **Primary efficacy endpoints**
  - Low Transfusion Burden (LTB, <4U RBC/8 weeks, Hgb <10 g/dL): Hemoglobin increase of ≥ 1.5 g/dL for ≥ 2 weeks
  - High Transfusion Burden (HTB, ≥4U RBC/8 weeks): Reduction of ≥4U or ≥50% units transfused over 8 weeks
- Luspatercept administered SC every 3 weeks for 3 months



# Baseline Characteristics

| All Patients | N = 26 |
|---|---|
| Age, yr, median (range) | 71 (27-88) |
| Sex, males (%) | 13 (50%) |
| Prior ESA treatment, n (%) | 14 (54%) |
| Prior lenalidomide treatment, n (%) | 5 (19%) |
| **Low Transfusion Burden (LTB)** | **N = 7 (27%)** |
| Hemoglobin, g/dL, median (range) | 9.1 (8.3-9.7) |
| Units RBC/8 weeks, median (range) | 0 (0-2) |
| **High Transfusion Burden (HTB)** | **N = 19 (73%)** |
| Units RBC/8 weeks, median (range) | 6 (4-13) |

Data as of 03 Oct 2014

# Efficacy Summary: HI-E Response Rate

| Patient Subgroup | 0.125-0.5 mg/kg (N=9) n (%) | 0.75-1.75 mg/kg (N=17) n (%) |
|---|---|---|
| LTB patients (N=7) | 0/2 (0%) | **2/5 (40%)** |
| HTB patients (N=19) | 2/7 (29%) | **5/12 (42%)** |
| All patients (N=26) | 2/9 (22%) | **7/17 (41%)** |

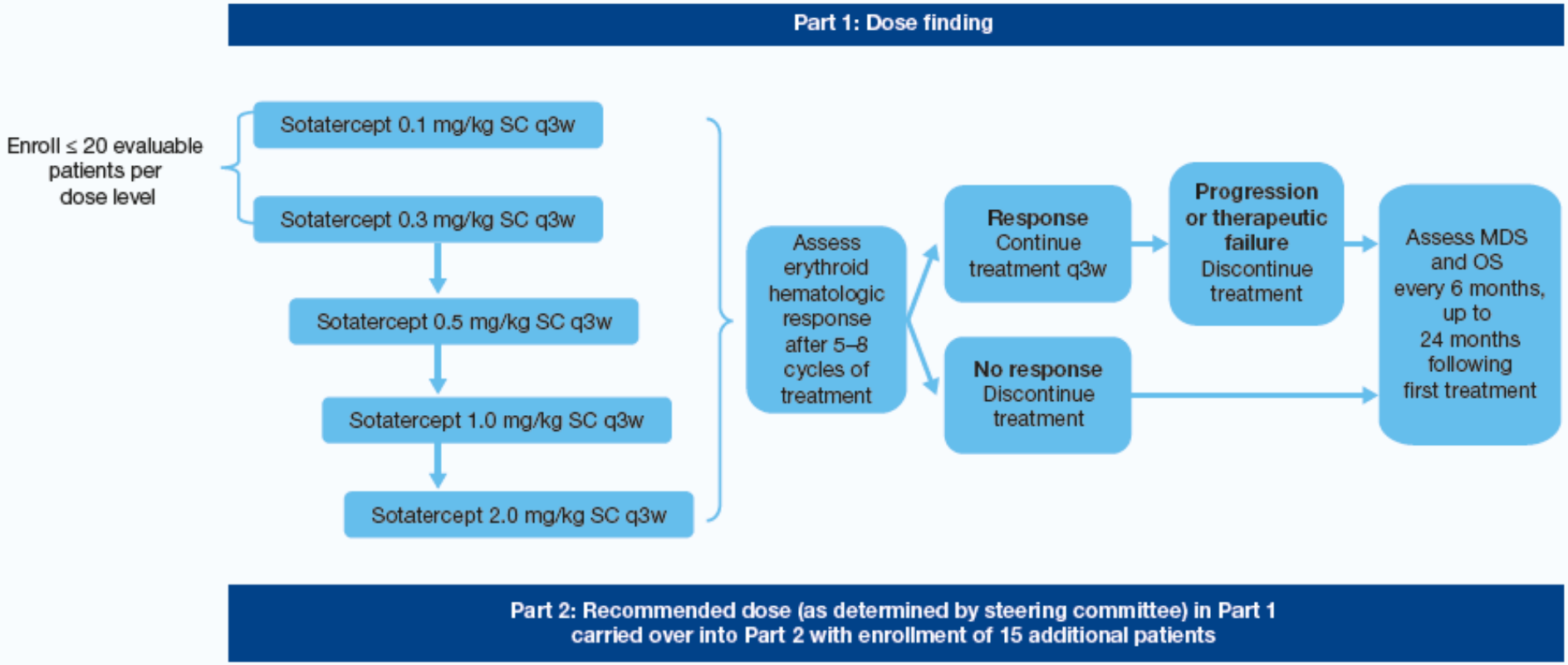
HI-E (IWG):
LTB: Hemoglobin increase ≥1.5 g/dL for ≥8 weeks
HTB: Reduction of ≥4 units RBCs transfused over 8 weeks

HI-E, hematologic improvement-erythroid
IWG, International Working Group
LTB, low transfusion burden; HTB, high transfusion burden

**Data as of 03 Oct 2014**

# An Open-Label, Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients With Low- or Intermediate (Int)-1-Risk Myelodysplastic Syndromes (MDS) or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML) and Anemia Requiring Transfusion

Rami Komrokji[1], Guillermo Garcia-Manero[2], Lionel Ades[3], Abderrahmane Laadem[4], Bond Vo[4], Thomas Prebet[5], Aspasia Stamatoullas[6], Thomas Boyd[7], Jacques Delaunay[8], David P. Steensma[9], Mikkael A. Sekeres[10], Odile Beyne-Rauzy[11], Jun Zou[4], Kenneth M. Attie[12], Matthew L. Sherman[12], Pierre Fenaux[13], Alan F. List[14]




Komrokji et al. 3251a

# An Open-Label, Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients With Low- or Intermediate (Int)-1-Risk Myelodysplastic Syndromes (MDS) or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML) and Anemia Requiring Transfusion

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**Table 2. Transfusion Response Among HTB Patients**

| | Sotatercept dose group | | | | Overall (N = 45) |
|---|---|---|---|---|---|
| | 0.1 mg/kg (n = 7) | 0.3 mg/kg (n = 6) | 0.5 mg/kg (n = 17) | 1.0 mg/kg (n = 15) | |
| Transfusion burden reduction ≥ 4 RBC units/56 days, n (%) | 0 | 4 (67) | 7 (41) | 8 (53) | 19 (42) |
| Duration of longest response, median (range), days | NA | 68 (62–144) | 150 (83–345+) | 88 (62–154+) | 106 (62–345+) |
| RBC-TI ≥ 56 days, n (%) | 0 | 1 (17) | 2 (12) | 2 (13) | 5 (11) |

HTB, high transfusion burden; NA, not applicable; RBC, red blood cell; RBC-TI, RBC transfusion independence.

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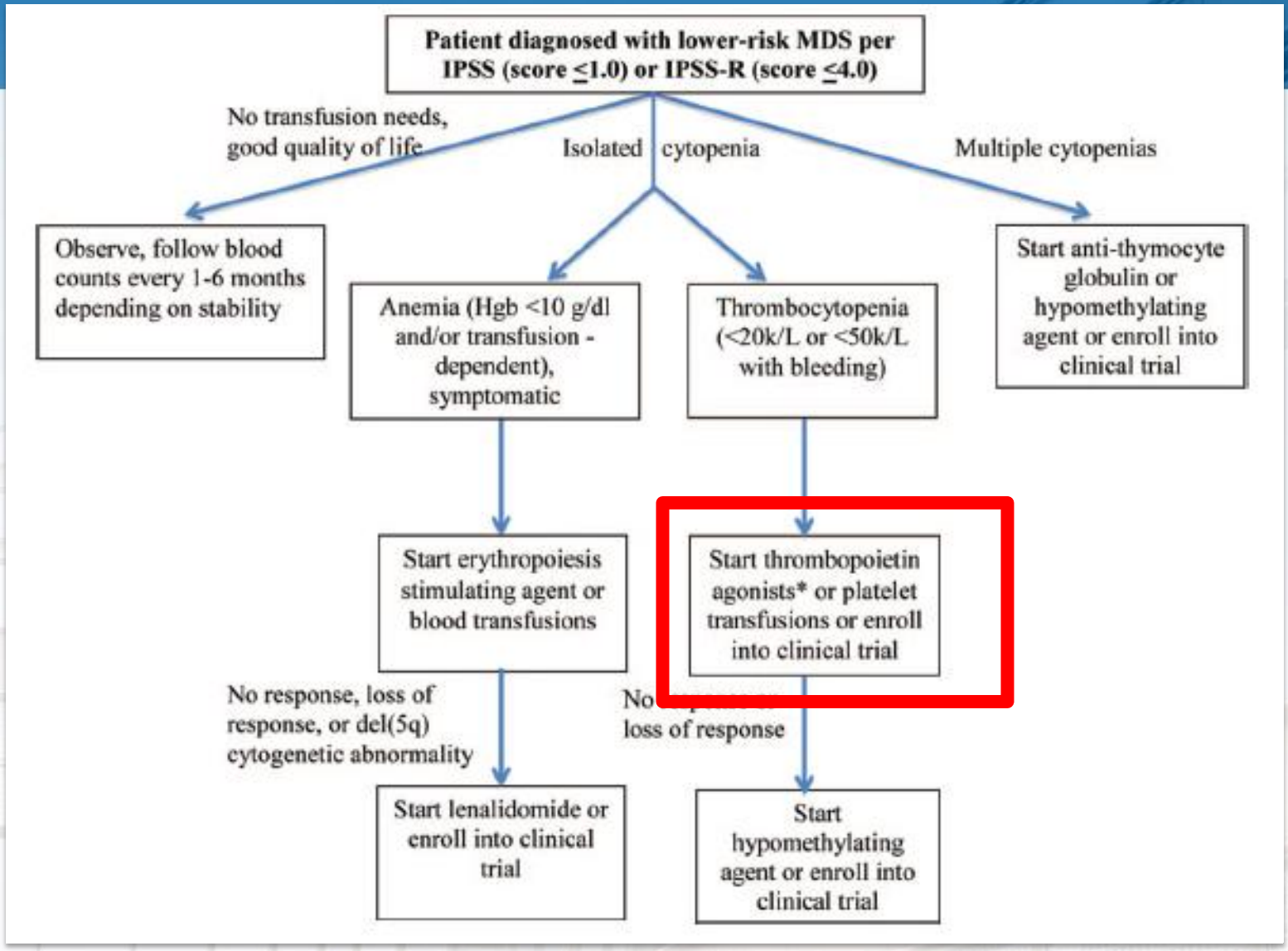
# MDS: Lower-risk, Treatment Algorithm




Sekeres and Gerds Hematology 2014.

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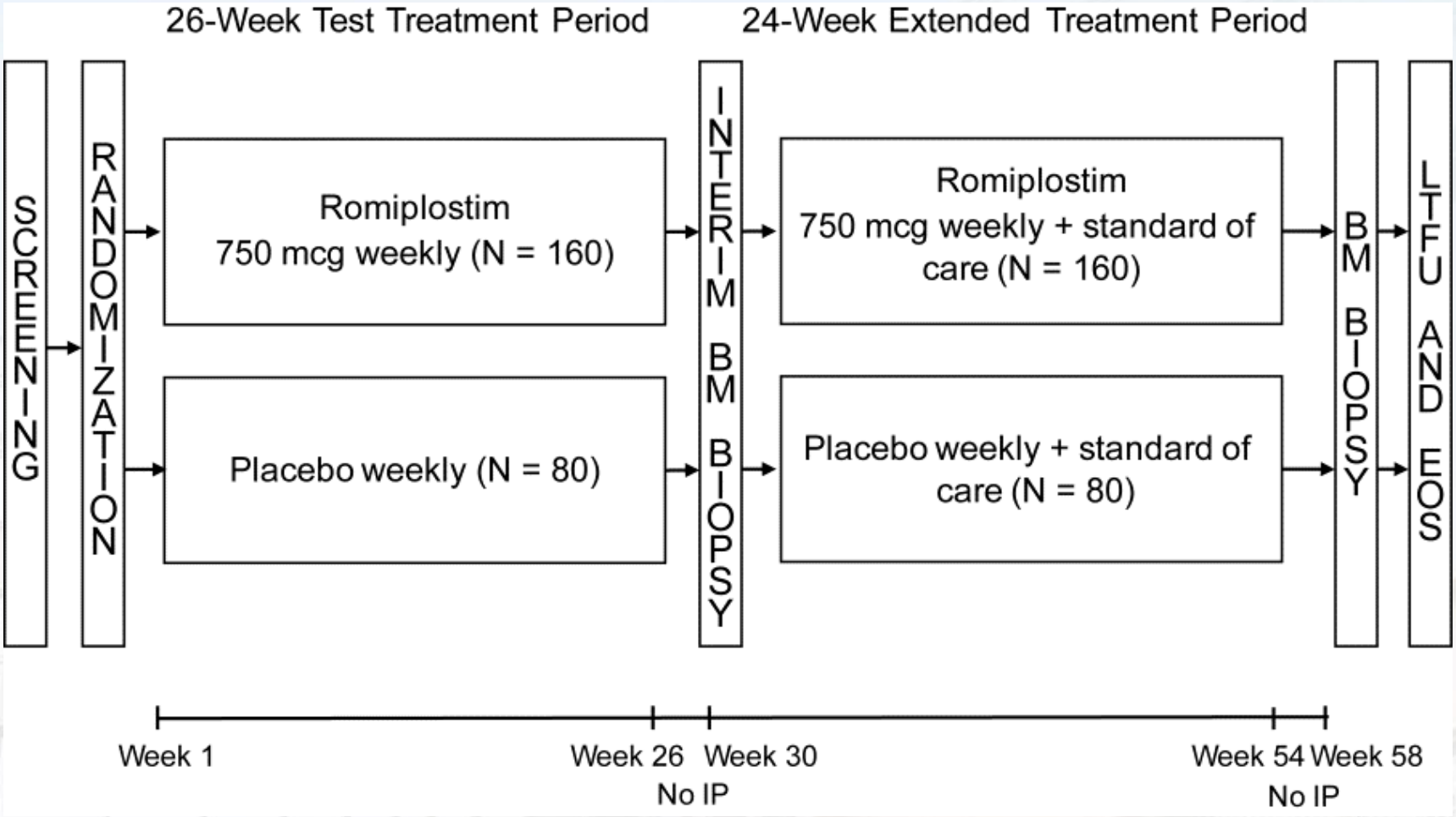
# Lower-risk MDS: TPO Agonists




Giagounides et al. Cancer 2014;120:1838.

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# Lower-risk MDS: TPO Agonists

| | Baseline platelets < $20x10^9$/L | | Baseline platelets ≥ $20x10^9$/L | |
|---|---|---|---|---|
| | Placebo (N = 43) | Romiplostim (N = 87) | Placebo (N = 40) | Romiplostim (N = 80) |
| CSBE (rate/100 pt-yr) | 501.2 | 514.9 | **226.4** | **79.5** |
| | RR = 1.03, p = 0.827 | | **RR = 0.35, p<0.0001** | |
| PTE (rate/100 pt-yr) | **1778.6** | **1250.5** | 179.8 | 251.8 |
| | **RR = 0.71, p<0.0001** | | RR = 1.38, p = 0.1479 | |

Giagounides et al. Cancer 2014;120:1838.

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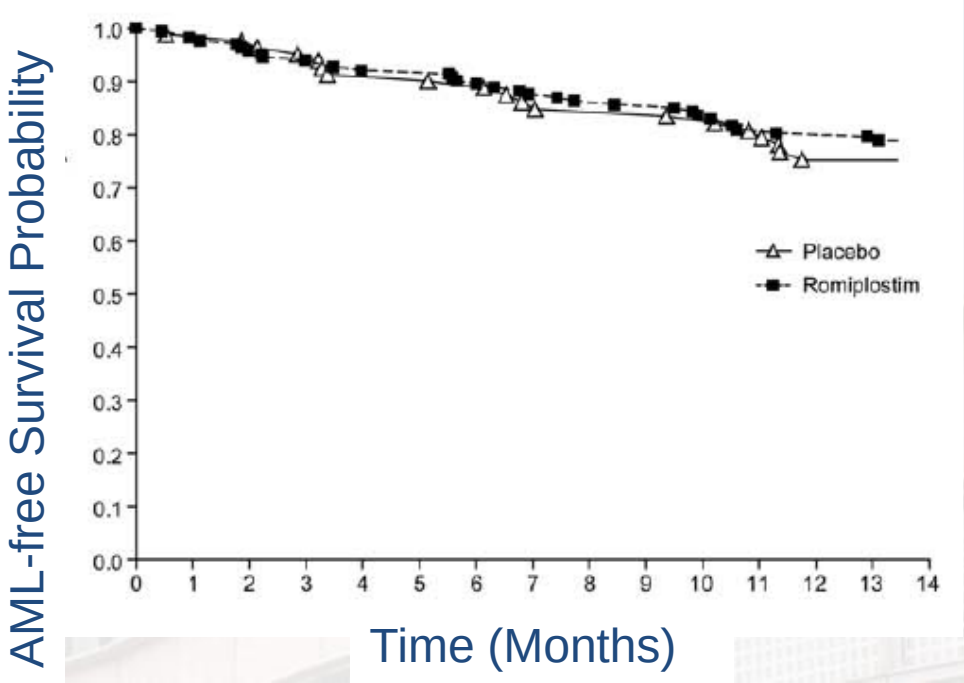
# Lower-risk MDS: TPO Agonists

## 58 weeks of follow-up

| | Romiplostim | Placebo | HR | 95% CI |
|---|---|---|---|---|
| Deaths | 17.9% (30) | 20.7% (17) | 0.86 | 0.47, 1.56 |
| AML | 6.0% (10) | 4.9% (4) | 1.20 | 0.38, 3.84 |
| AML-free survival | 19.6% (33) | 23.2% (19) | 0.85 | 0.48, 1.50 |




Giagounides et al.
Cancer 2014;120:1838.

# HOA: MDS

- MDS Overview
- Disease Mechanisms
- Treatment of Lower-risk Disease
- **Treatment of Higher-risk Disease**

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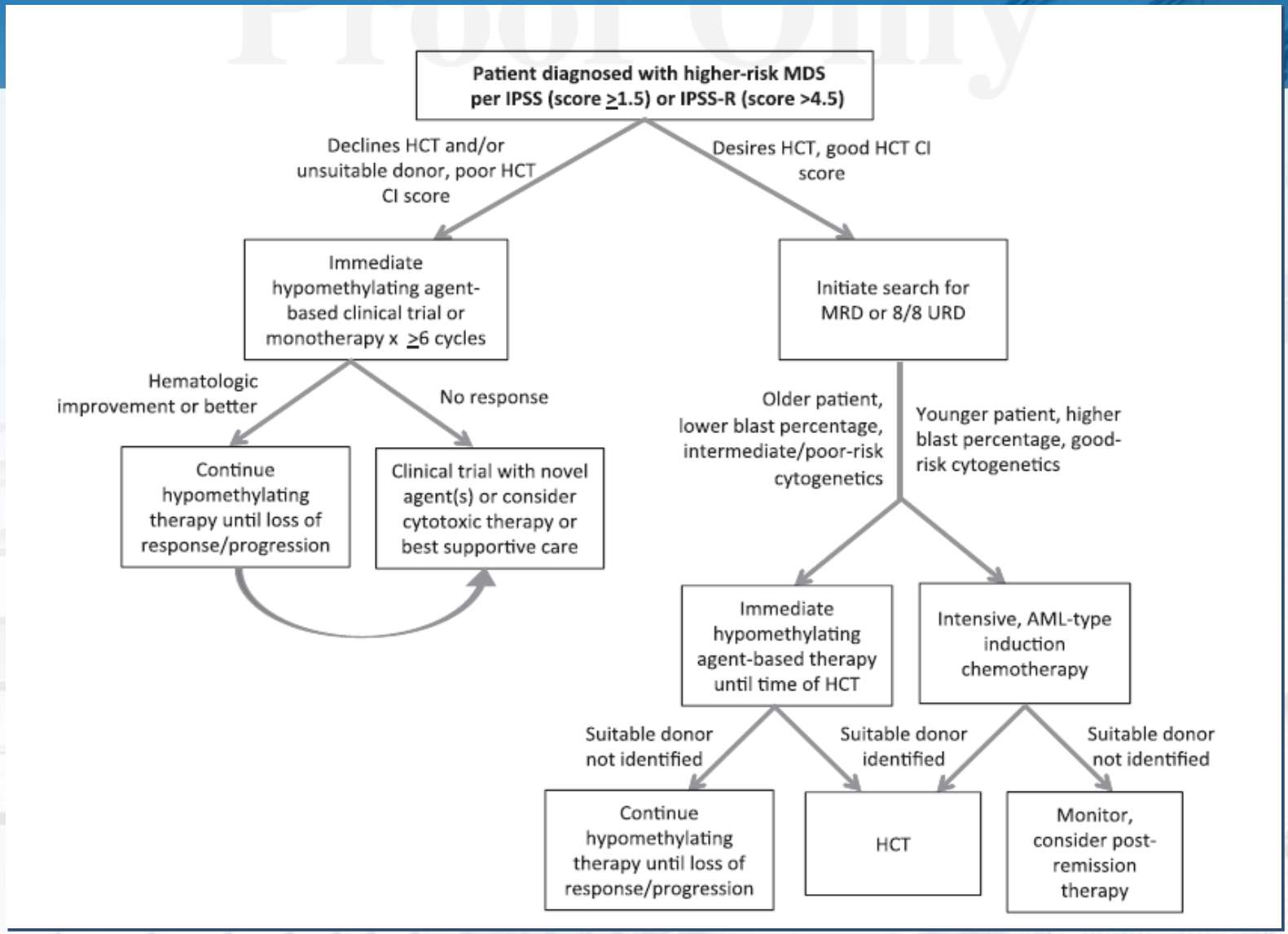
# MDS: Higher-risk, Treatment Algorithm




Sekeres and Cutler Blood 2014;123:829.

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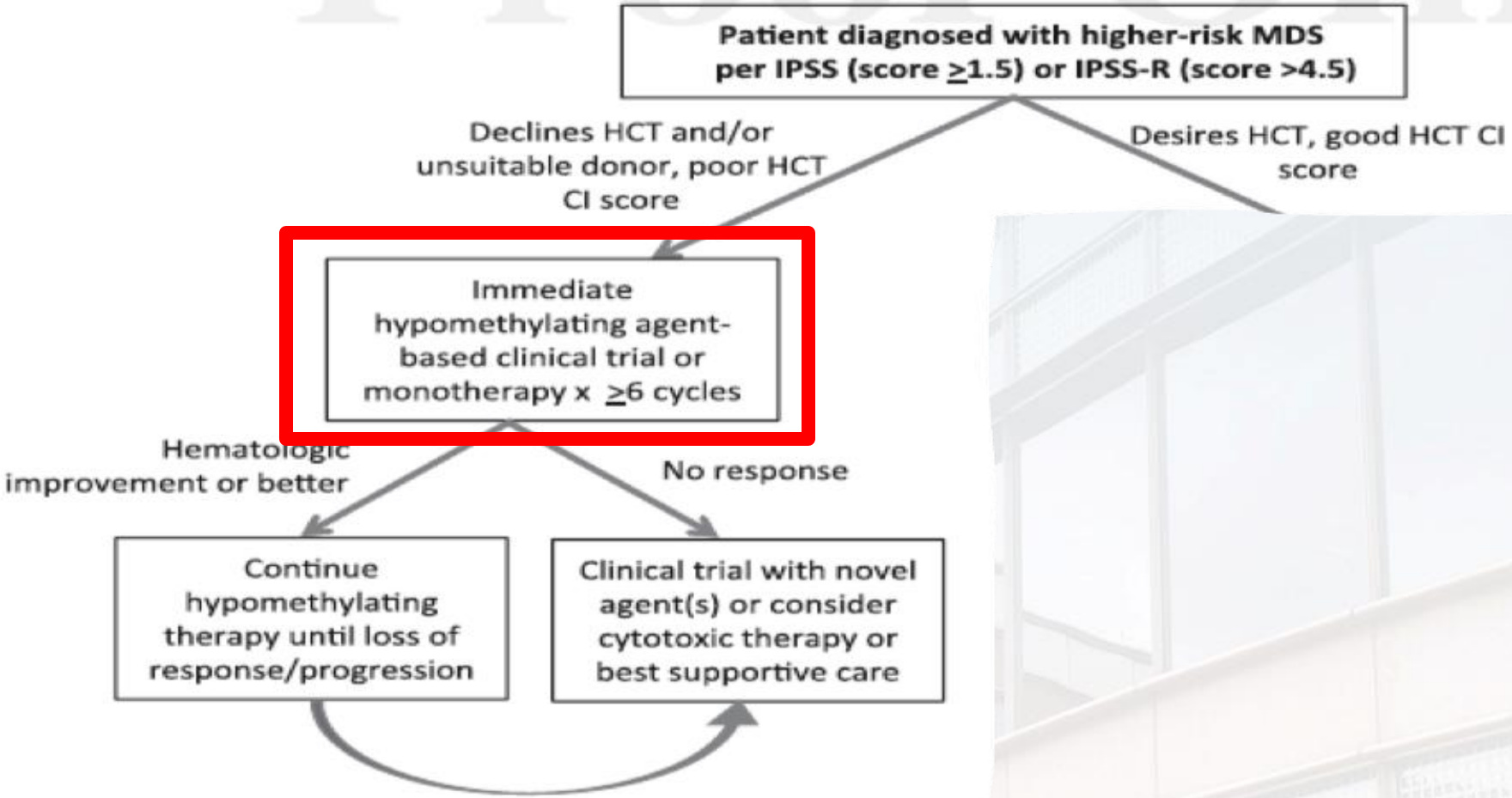
# MDS: Higher-risk, Treatment Algorithm




Sekeres and Cutler Blood 2014;123:829.

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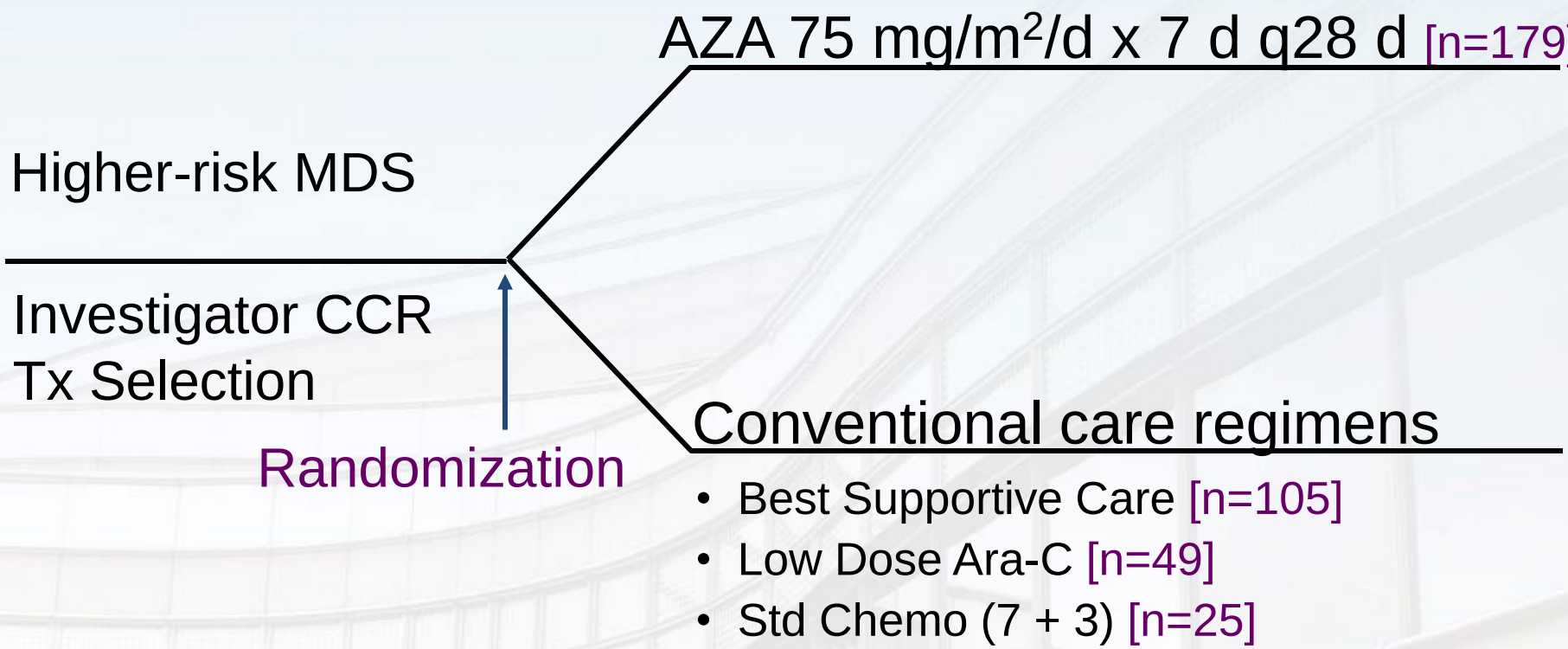
# Higher-risk MDS: AZA




Fenaux P, et al. Lancet Oncology 2009;10:223-232.

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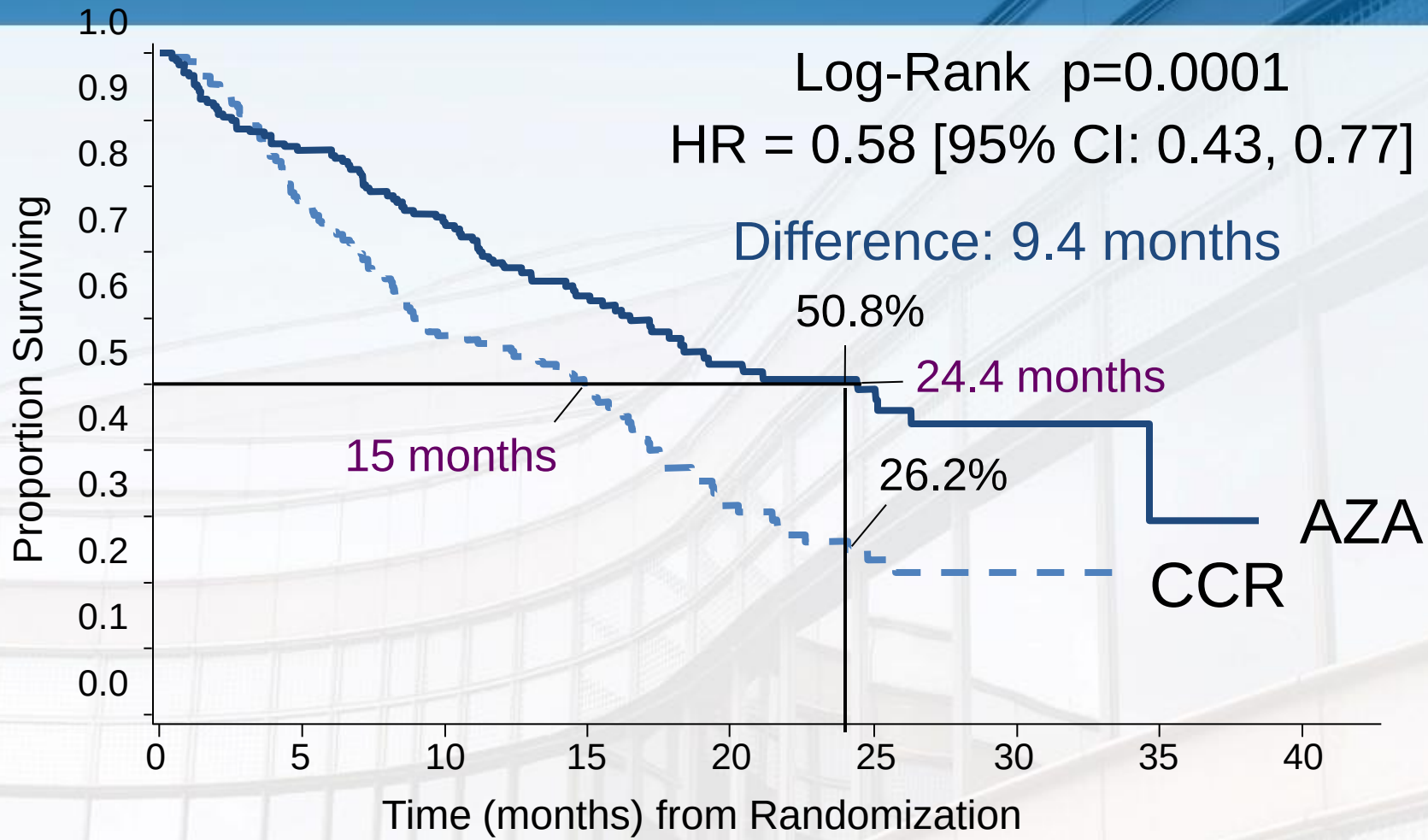
# Higher-risk MDS: AZA




Fenaux P, et al. Lancet Oncology 2009;10:223-232.

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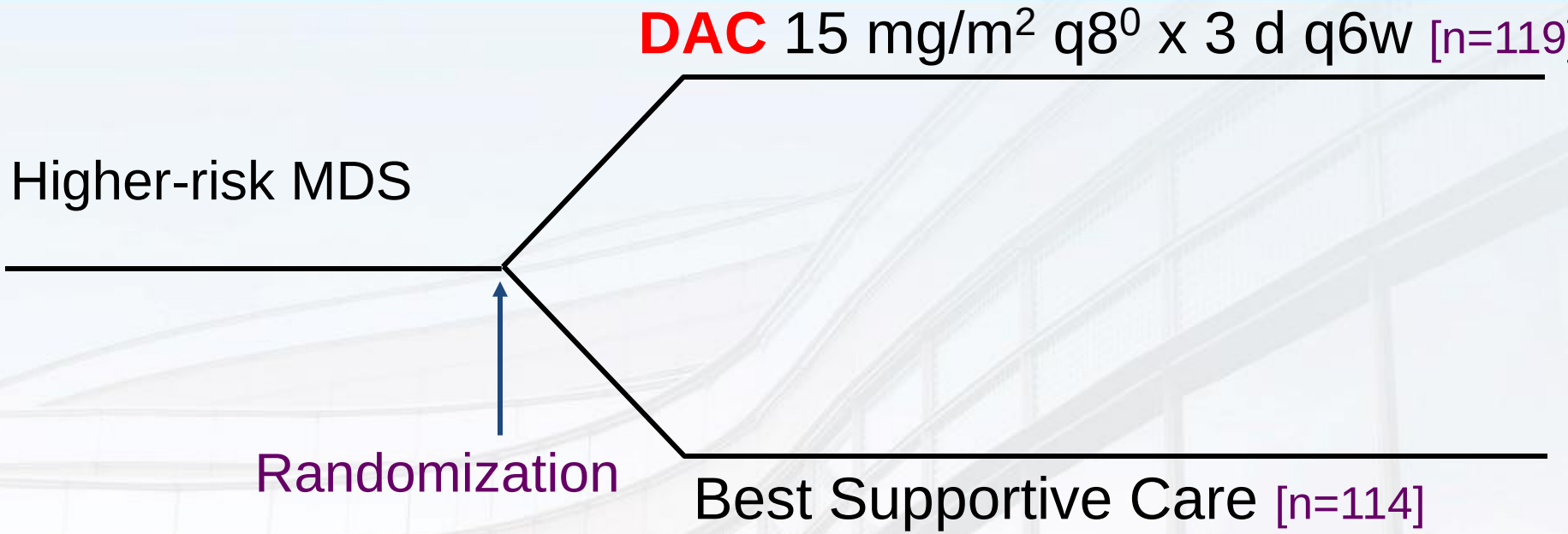
# Higher-risk MDS: DAC




Lubbert et al. JCO 2011;29:1987.

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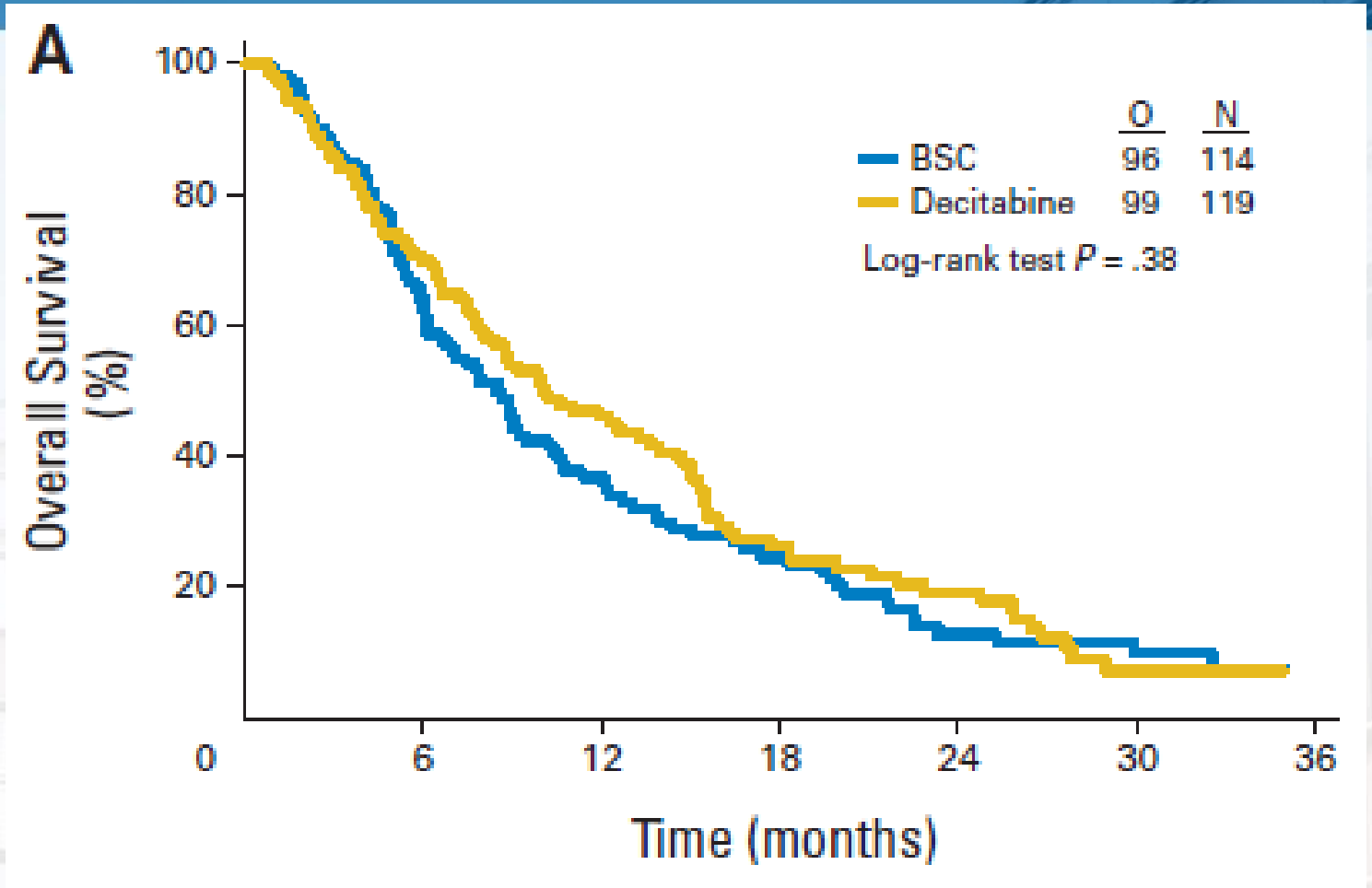
# Higher-risk MDS: DAC




Median OS 10.1 vs. 8.5 months

Lubbert et al. JCO 2011;29:1987.

# First clinical results of a randomized phase 2 study of SGI-110, a novel subcutaneous hypomethylating agent, in 102 patients with Intermediate or High Risk MDS or CMML

**On Behalf of the SGI-110 Investigative Team**

**Guillermo Garcia Manero[1], Ellen Ritchie[2], Katherine Walsh[3] ,Michael Savona[4] , Patricia Kropf [5] , Casey O'Connell[6] , Raoul Tibes[7] , Naval Daver[1] , Elias Jabbour[1], Scott Lunin[8], Todd Rosenblat[9] , Karen Yee[10], Wendy Stock[11], Elizabeth Griffiths[12], Joseph Mace[13], Nikola Podoltsev[14], Jesus Berdeja[4] , Jean-Pierre Issa[15] , Woonbok Chung[15], Sue Naim[16], Pietro Taverna[16], Yong Hao[16], Mohammad Azab[16],Hagop Kantarjian[1], Gail Roboz[2]**

[1] MD Anderson Cancer Center, Houston, TX, [2]Weill Cornell Medical College, New York, NY , [3]The Ohio State University, Columbus, OH , [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN , [5] Fox Chase Cancer Center, Philadelphia, PA , [6]USC Keck School of Medicine, University of Southern California, Los Angeles, CA, [7]Mayo Clinic Arizona, Scottsdale, AZ, [8] Florida Cancer Specialist, Englewood , FL , [9]New York Presbyterian/Columbia University Medical Center, New York, NY , [10] Princess Margaret Cancer Center, Toronto, Canada, [11]University of Chicago Medical Center, Chicago, IL , [12]Roswell Park Cancer Institute, Buffalo, NY, [13]Florida Cancer Specialists, St Petersburg, FL, [14]Yale University School of Medicine, New Haven, CT, [15]Fels Institute, Temple University, Philadelphia, PA,[16]Astex Pharmaceuticals Inc., Dublin, CA.

# Randomized Phase 2 Study of SGI-110 in MDS/CMML[1]

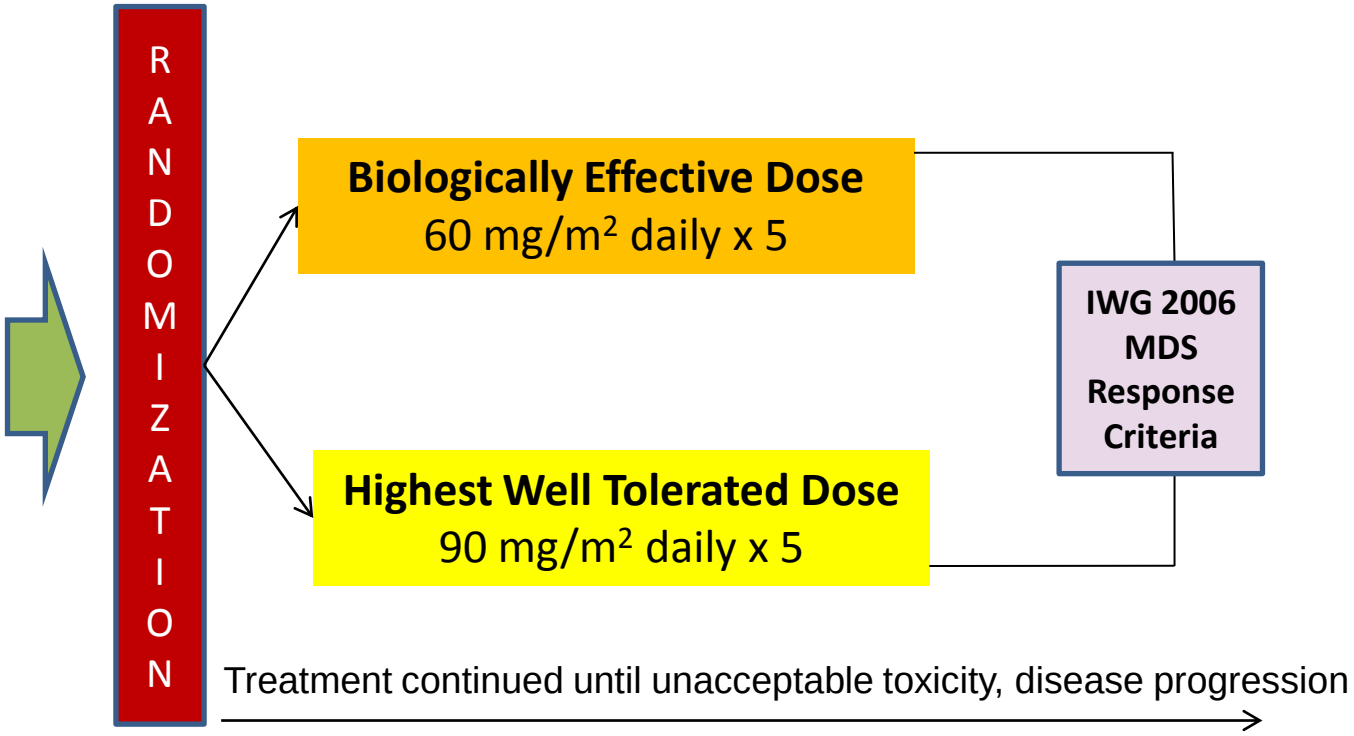
**Major Eligibility**

**Previously Treated MDS/CMML**

**or**

**Treatment Naïve MDS/CMML**

- IPSS Int-1,2 and HR
- ECOG PS 0-2
- Adequate hepato-renal function




- **Primary Endpoint: Overall Response Rate (CR, PR, mCR, HI)**
- **Secondary Endpoints: Transfusion independence, LINE-1 demethylation time to AML, overall survival**

[1] Data presented with data cutoff end of July 2014

# SGI-110: Patients Characteristics By MDS Status

| Patient Characteristics | Prev. Treated (n=53) | Tx Naïve (n=49) |
|---|---|---|
| Median Age, (range) | 72.5 (52-89) | 71.7 (18-85) |
| Gender, M n (%) | 32 (60) | 35 (71) |
| ECOG PS %: 0/1/2 | 21/58/21 | 27/67/6 |
| Disease Category (IPSS) n (%)<br>Int-1<br>Int-2<br>High Risk<br>CMML | <br>4 (8)<br>13(25)<br>24 (45)<br>10 (19) | <br>23 (47)<br>5 (10)<br>9 (18)<br>12 (24) |
| Median BM Blast % (range) | 8 (0-19) | 3 (0-14) |
| Median Neutrophils ($10^9$/L) | 0.81 | 1.64 |
| Median Platelets ($10^9$/L) | 37 | 62.5 |
| Median Hb (g/dL) | 9.30 | 9.10 |
| Prior decitabine or azacitidine n(%) | 51 (96) | 1 (2) [1] |
| Randomized Dose (n)<br>60 mg/m2<br>90 mg/m2 | <br>26<br>27 | <br>27<br>22 |

[1]Patient received only 1 prior cycle of HMA

# SGI-110: Best Response[1] By MDS Status

| Response Category[1] | Prev Treated (n=53) | Tx Naïve (n=49) |
|---|---|---|
| | **Response rate n (%)** | **Response rate n (%)** |
| CR | 2 (3.8) | 7 (14.3) |
| mCR | 9 (17.0) | 3 (6.1) |
| HI | 1 (1.9) | 9 (18.4) |
| CR+mCR | 11 (20.8) | 10 (20.4) |
| Overall Response Rate | 12 (22.7) | 19 (38.8) |

[1]International Working Group 2006 MDS Response Criteria

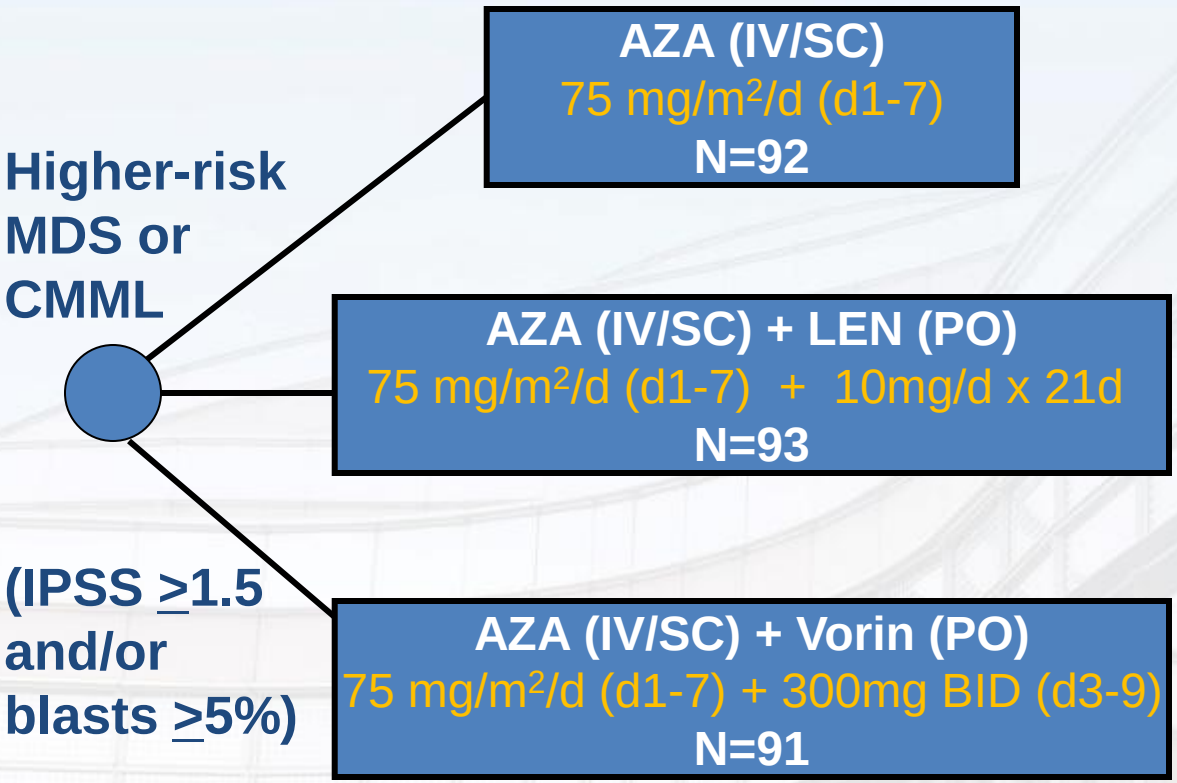
# What happens when we add drugs together?

# A Randomized Phase II Study of Azacitidine Combined with Lenalidomide or with Vorinostat vs. Azacitidine Monotherapy in Higher-Risk Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML): North American Intergroup Study SWOG S1117 [LBA – 5]

Mikkael A. Sekeres, MD, MS, Megan Othus, PhD, Alan F. List, MD, Olatoyosi Odenike, MD, Richard M. Stone, MD., Steven D. Gore, MD, Mark R. Litzow, MD, Rena Buckstein, MD, Mario R. Velasco, MD, Rakesh Gaur, MD, MPH, Ehab Atallah, MD, Eyal C. Attar, MD, Frederick R. Appelbaum, MD, Harry P. Erba, MD, PhD

SWOG Alliance ECOG NCIC

# North American Intergroup Randomized Phase 2 MDS Study S1117: Study Design




**Groups: SWOG, ECOG, Alliance, NCIC**

**Total Sample Size: 276**

**Primary Objective: 20% improvement of ORR (CR/PR/HI) based on 2006 IWG Criteria**

**Secondary Objectives: OS, RFS, LFS**

**Power 81%, alpha 0.05 for each combo arm vs. AZA**

**03/2012 – 06/2014**

Sekeres et al. ASH 2014: LBA - 5

# North American Intergroup Randomized Phase 2 MDS Study S1117: Grade ≥3 Toxicities

| Toxicity Variable | AZA | AZA+LEN (P-value vs. AZA) | AZA+VOR (P-value vs. AZA) | Total n=260 |
|---|---|---|---|---|
| Febrile neutropenia (n) | 10 | 13 (0.66) | 13 (0.51) | 36 |
| GI (n) | 4 | 11 (0.10) | **23 (<0.001)** | 38 |
| Rash (n) | 2 | **12 (0.01)** | 1 (1) | 15 |
| Off Tx due to Toxicity/Side Effect/Complication | 9% | **23% (.04)** | **24% (.03)** | 19% |
| Non-protocol defined dose modifications | 23% | **41% (.01)** | **36% (.05)** | 33% |

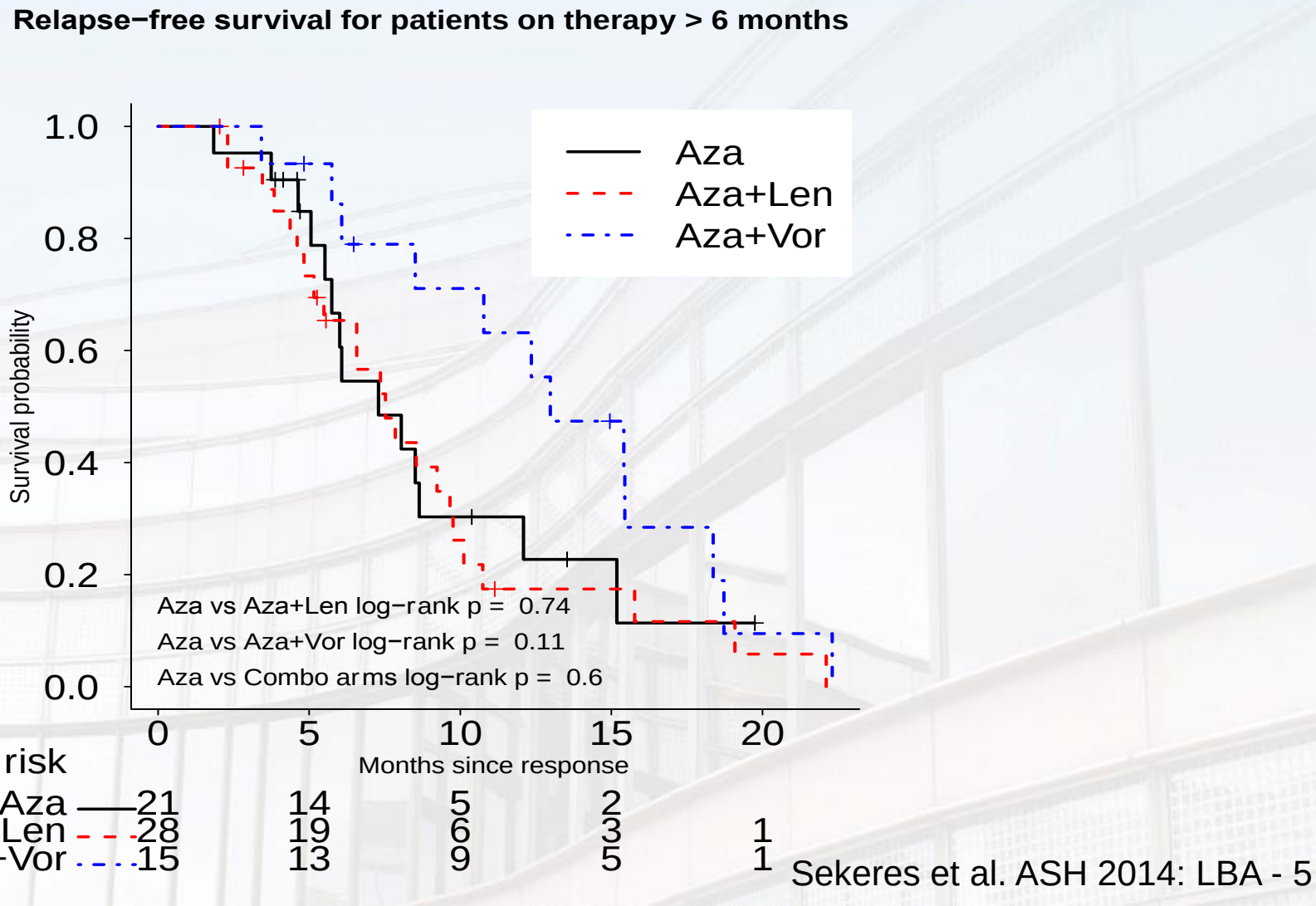
Sekeres et al. ASH 2014: LBA - 5

# North American Intergroup Randomized Phase 2 MDS Study S1117: Response

| Response Variable | AZA | AZA+LEN (P-value vs. AZA) | AZA+VOR (P-value vs. AZA) | Total n=260 |
|---|---|---|---|---|
| Median Tx Duration (Wks) | 25 | 24 | 20 | 23 |
| Overall Response Rate (%) | 37 | 39 (1.0) | 24 (.07) | 33 |
| CR/PR/HI (%) | 24/0/13 | 18/1/19 (.66) | 15/1/7 (.12) | 19/1/13 |
| CMML ORR (%) | 33 (n=15) | 59 (.15) (n=19) | 13 (.41) (n=16) | 34 |
| Relapse-free Survival (median) | 7 months | 8 months (.45) | 11 months (.29) | 7 months |
| Relapse-free survival, on Tx >6 months (median) | 7 months | 7.5 months (.74) | 13 months (.11) | 8.5 months |

Sekeres et al. ASH 2014: LBA - 5

# North American Intergroup Randomized Phase 2 MDS Study S1117: Relapse-free Survival (II) All Responders on Tx >6 Months




Sekeres et al. ASH 2014: LBA - 5

# North American Intergroup Randomized Phase 2 MDS Study S1117: Conclusions (I)

**No differences in ORR comparing AZA + LEN or AZA + VOR to AZA monotherapy.**

**Some subgroups may have benefitted from AZA-based combinations.**

**Signal of RFS improvement with AZA + VOR; EFS/OS data maturing and analyses by cytogenetic subgroups pending.**

Sekeres et al. ASH 2014: LBA - 5

# Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib vs Best Supportive Care in Patients with Higher-risk Myelodysplastic Syndrome After Failure of Hypomethylating Agents (ONTIME Trial of ON 01910)

G. Garcia-Manero, P. Fenaux, A. Al-Kali, M. R. Baer, M. Sekeres, G. Roboz, G. Gaidano, B. Scott, P. Greenberg, U. Platzbecker, D. P. Steensma, S. Kambhampati, L. Godley, R. Collins, E. Atallah, F. Wilhelm, I. Darnis-Wilhelm, N. Azarnia, M. Maniar, L. R. Silverman, for the ONTIME Investigators

# ONTIME Trial: Study Design

- **Phase III, randomized, controlled, safety & efficacy study comparing rigosertib + BSC* vs BSC* alone (2:1)**
  - **Adult pts who had relapsed after, failed to respond to, or progressed during HMA therapy**
  - **299 pts enrolled at 87 sites in US and Europe**
  - **Rigosertib administered as 1800 mg/24 hr for 72 hrs as a continuous IV ambulatory infusion**
- **Pts stratified by bone marrow blast count (5-19% vs 20-30%)**
  - **Additional information on the relationship between OS and BMBL is available in Poster #3259**
- **Primary endpoint = overall survival**
- **Analysis based on 242 events (deaths; ≥ 80% maturity)**
- **Median follow-up of >18 months**

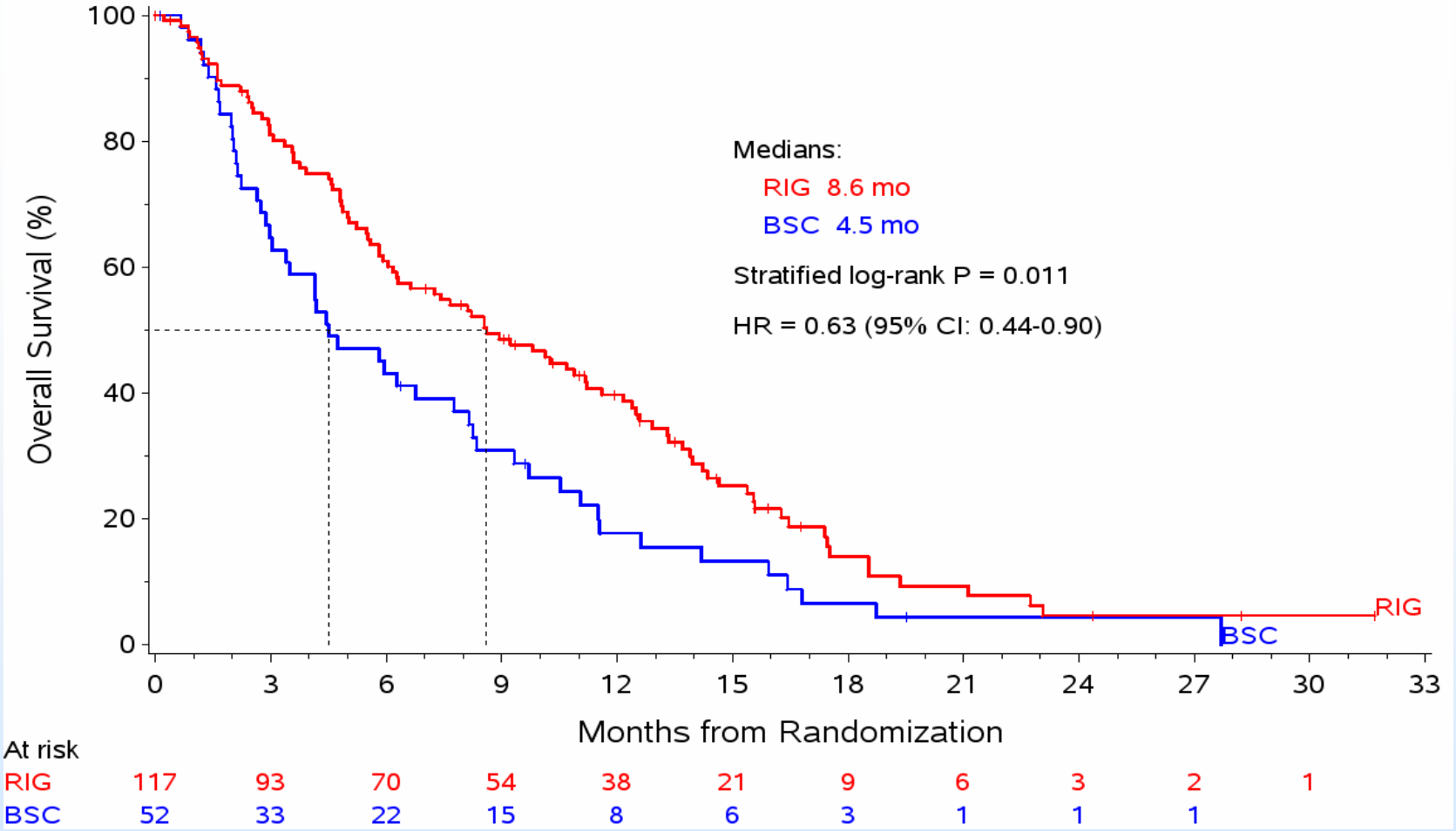
*BSC=Best supportive care: RBC & platelets; growth factors; hydroxyurea to manage blastic crises when pts transition to leukemia; pts on the BSC arm also allowed low-dose cytarabine, as medically justified.

# ONTIME Trial: Primary Efficacy Results - ITT

| | Rigosertib N = 199 | BSC N = 100 |
|---|---|---|
| Number (%) of deaths | 161 (81%) | 81 (81%) |
| Median follow-up (months) | 17.6 | 19.5 |
| Median survival (months) | 8.2 | 5.9 |
| 95% CI | 6.0 - 10.1 | 4.1 - 9.3 |
| Stratified HR (rigosertib/BSC) | 0.87 | |
| 95% CI | 0.67 - 1.14 | |
| Stratified log-rank p-value* | 0.33 | |

* Stratification factor: bone marrow blast at randomization (5-19% versus 20-30%)

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




**Per Prebet 2011, "Primary HMA Failure" was defined as either no response to or progression during HMA therapy**

# ONTIME Trial: Conclusions

- **Primary endpoint of OS did not reach statistical significance in the ITT population**
  - **2.3-month improvement in median OS in the ITT population**
- **Rigosertib treatment-related improvement in OS was noted in the following well-balanced subgroups:**
  - **Primary HMA failure (64% of pts: HR = 0.69; p = 0.04)**
  - **IPSS-R Very High Risk (45% of pts: HR = 0.56; p = 0.005)**
  - **Cytogenetic criteria also important prognostic factors**
    - **Monosomy 7 (HR = 0.24; p = 0.003)**
    - **Trisomy 8 (HR = 0.34; p = 0.035)**
- **Continuous IV infusion with rigosertib had a favorable safety profile in this population of elderly pts with HR MDS**

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# MDS: Conclusions

- The molecular landscape of MDS is becoming much more complex, and is being folded into clinical prognostic schemes.
- Therapy for lower-risk disease addresses specific cytopenias, particularly anemia.
- Standard therapy for higher-risk disease is HMA monotherapy; more data coming with combos.
- The next regulatory frontier is in the relapsed/refractory setting for lower- and higher-risk disease.

# Thanks!

## Cleveland Clinic Leukemia/MDS Program

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**And Our Patients!!!**