# Myelodysplastic syndromes

# post ASH 2016

Dominik Selleslag

AZ Sint-Jan

Brugge

# Why did they put MDS at the end of the meeting ?

## Possible explanations

- Least fascinating disease without progress ?
- Poor speaker ?
- Allow people to be at home on time ?

- Most prevalent and interesting disease ?
- Good speaker ?
- Keep people in the room until the end ?

# views or


What are you talking about, you are lying. MDS is a great disease for our physicians
I think MDS is still a frustrating disease for our patients

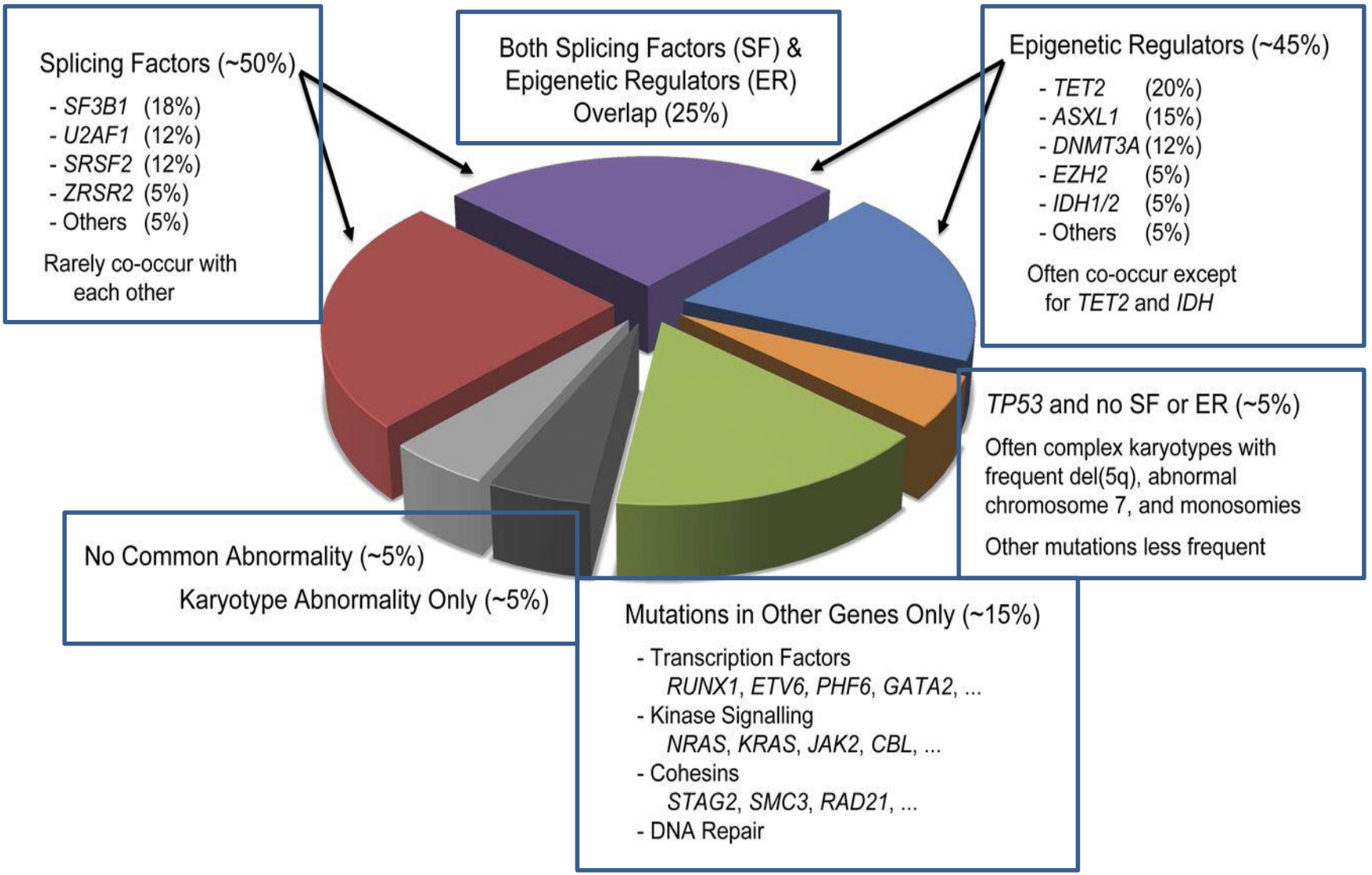
# Agenda

- Mutations in MDS
  - How to use for prognosis and diagnosis ?
  - What do they tell us about therapy related myeloid malignancies ?
- New treatment modalities
  - Low risk MDS
  - High risk MDS

# Molecular biology of MDS : "it's all in the genes"

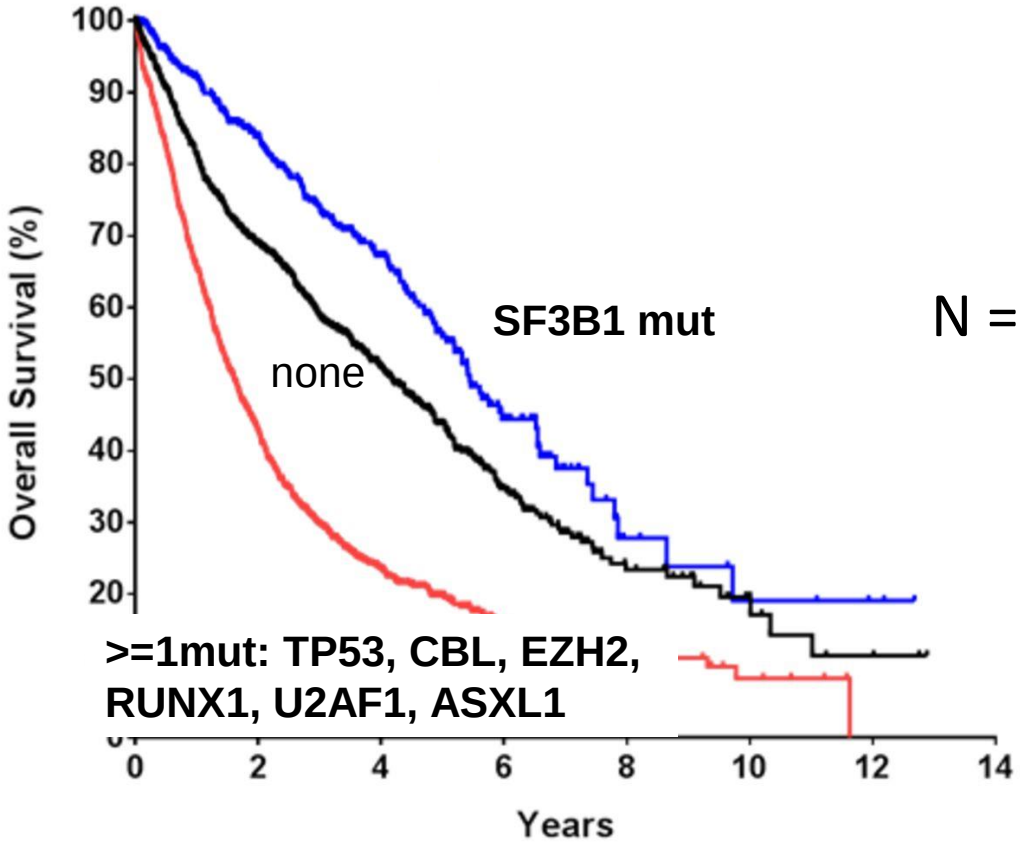
- Dramatical improvement of knowledge by NGS
- In MDS 40-50 genes are recurrently mutated
- 90 % of MDS pts have at least 1 mutation
- Median number of 3 mutations per pt
- Genes mutated in >= 10 % of pts :
  - TET2, SF3B1, ASXL1, SRSF2, DNMT3A, RUNX1, TP53

# Mutational landscape in MDS




Bejar R , and Steensma D P Blood 2014;124:2793-2803

# Somatic gene mutations in MDS have independent prognostic significance




N = 2504 pts

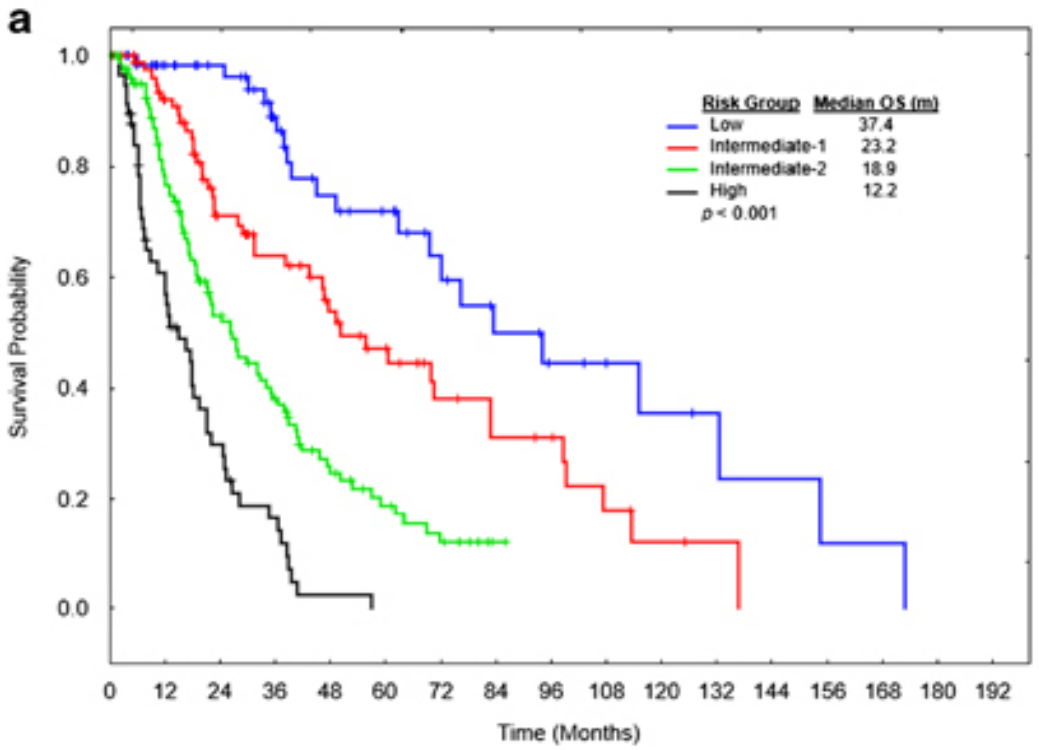
R.Bejar , ASH 2015, on behalf of International Working Group for Prognosis in MDS-Molecular Committee

# Use of mutations to improve prognostication

Best model still under development

# Integration of molecular data in IPSS-R in treated patients with MDS "Molecular IPSS-R"

**Nazha A et al , Leukemia 2016, 30,2214**




MDS, CMML, tMDS
N = 508

Better discriminative power than IPSS-R

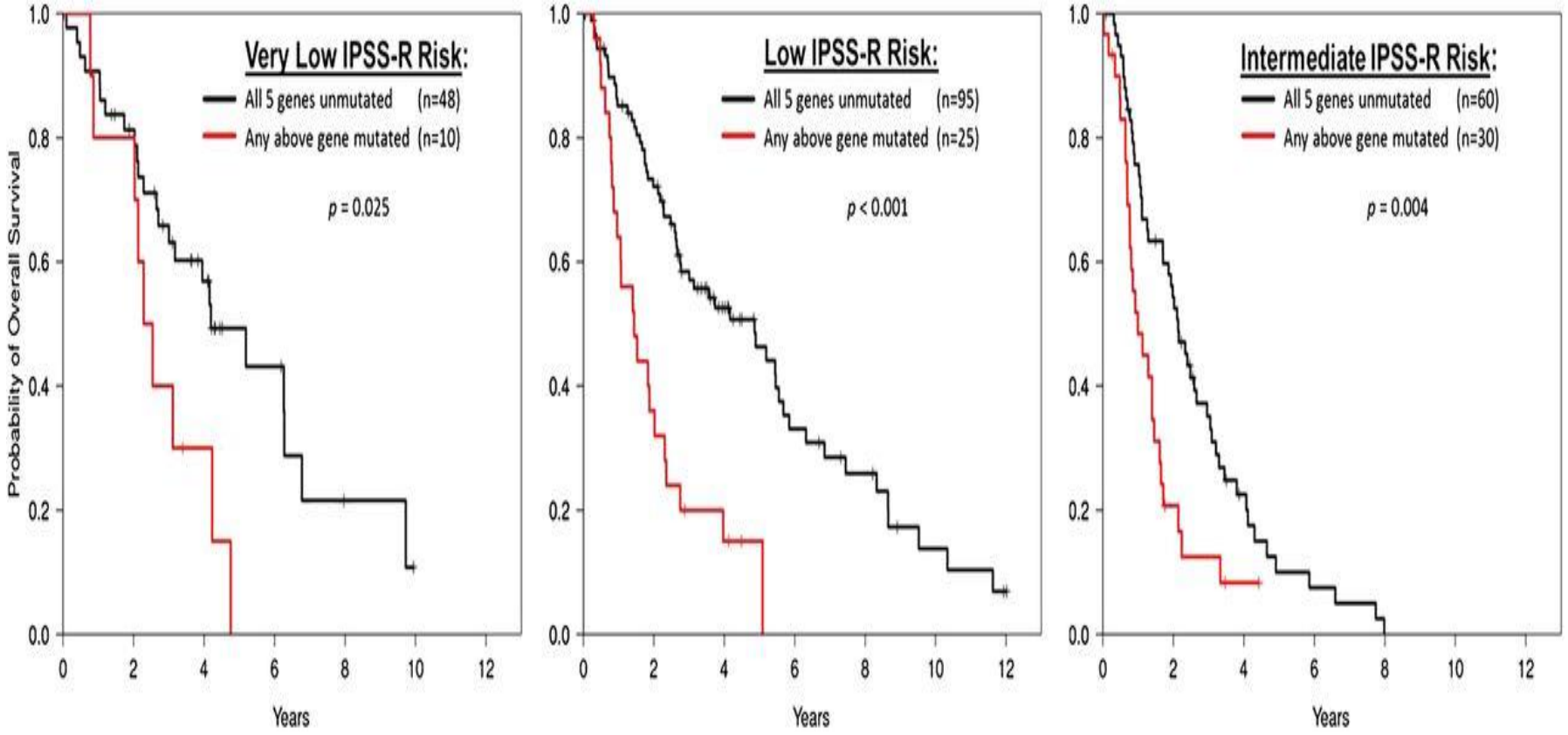
Applicable to treated patients

Dynamic : usable at all time points

**Age** x 0.04 + **R-IPSS** score x 0.3 + **EZH2** x 0.7 + **SF3B1** x 0.5 + **TP53** x 1

Low risk : score <= 3; Int-1: score 3.1-3.6; Int-2 :score 3.7-4.6; high score: >= 4.7

# Two step model :
# somatic mutation in any of the 5 genes (TP53, EZH2, RUNX1, ASLX1, or ETV6) can refine IPSS-R categories



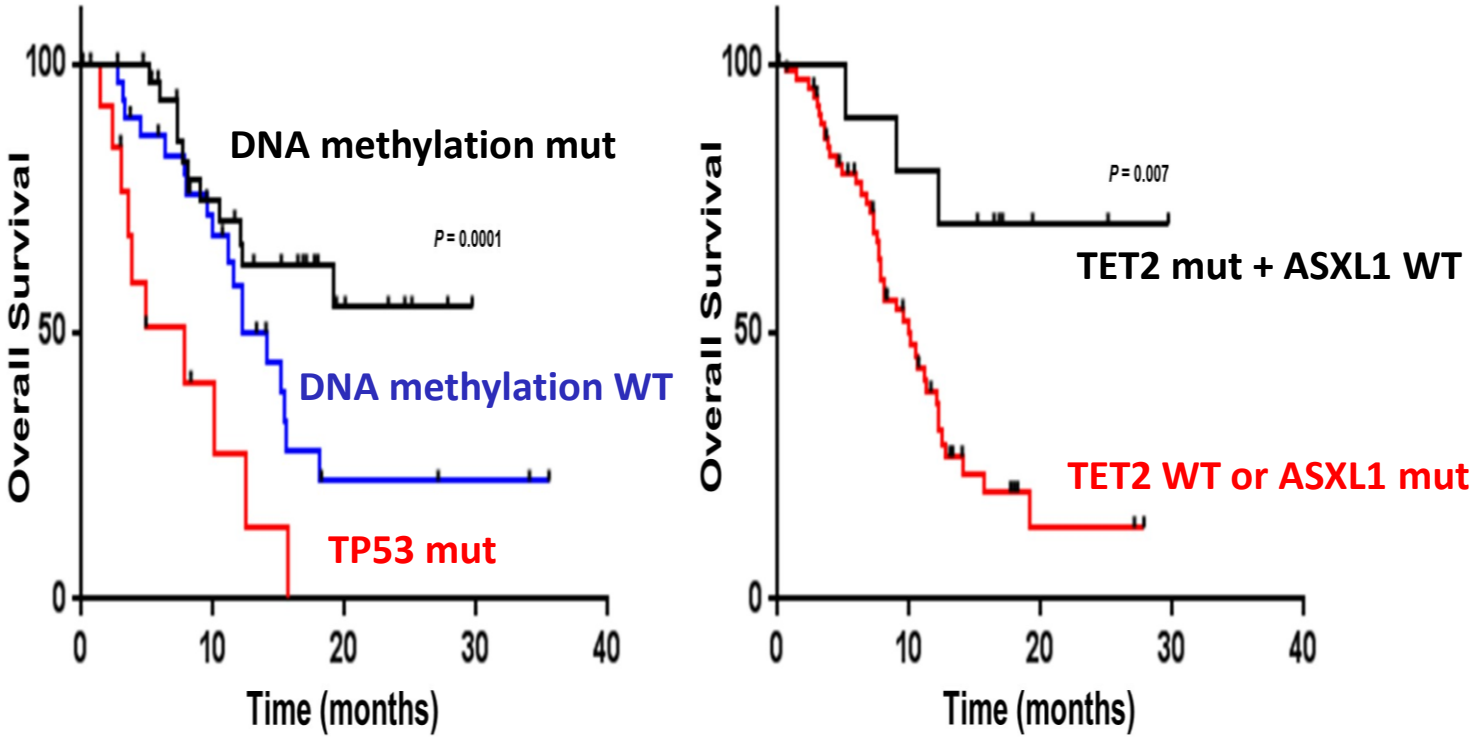

Rafael Bejar, and David P. Steensma Blood 2014;124:2793-2803

Use of mutations to predict response / survival with specific MDS therapies (ESA, LEN, AZA, allo SCT)

Patient selection ?

# Mutations in higher risk MDS treated with azacitidine

**David Sallman, Moffitt Cancer Center**

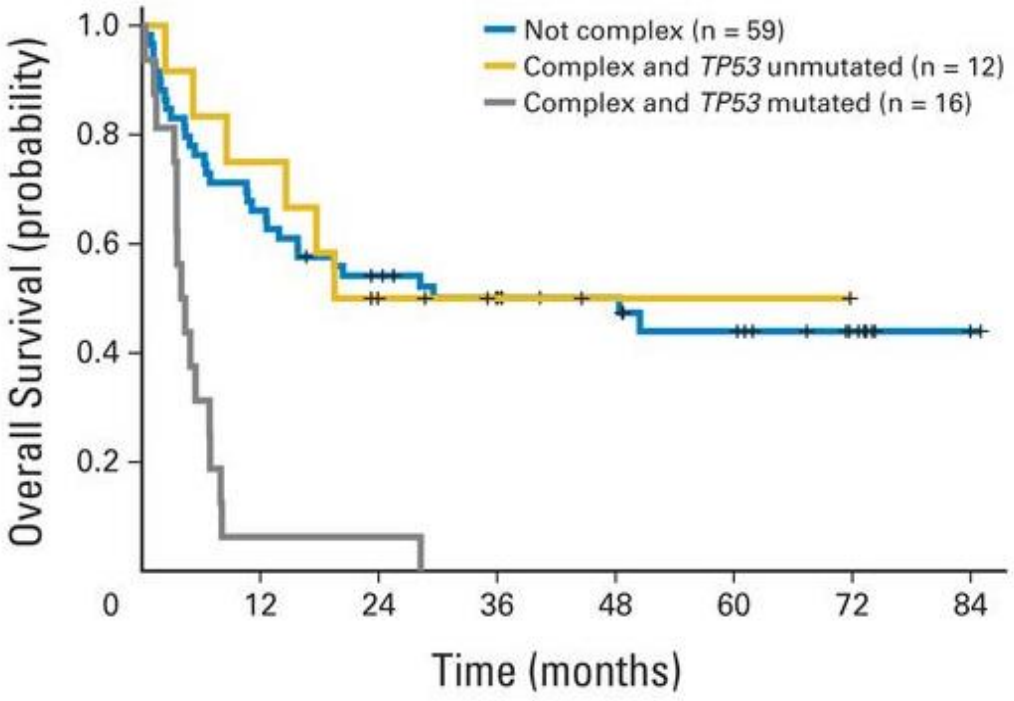



77 pts (MDS, CMML, AML < 30% blasts) treated with AZA

mutations associated with DNA methylation: *TET2*, *DNMT3A*, *IDH1*, *IDH2*, *WT1*

# TP53 mutations and prognosis after allo SCT for MDS

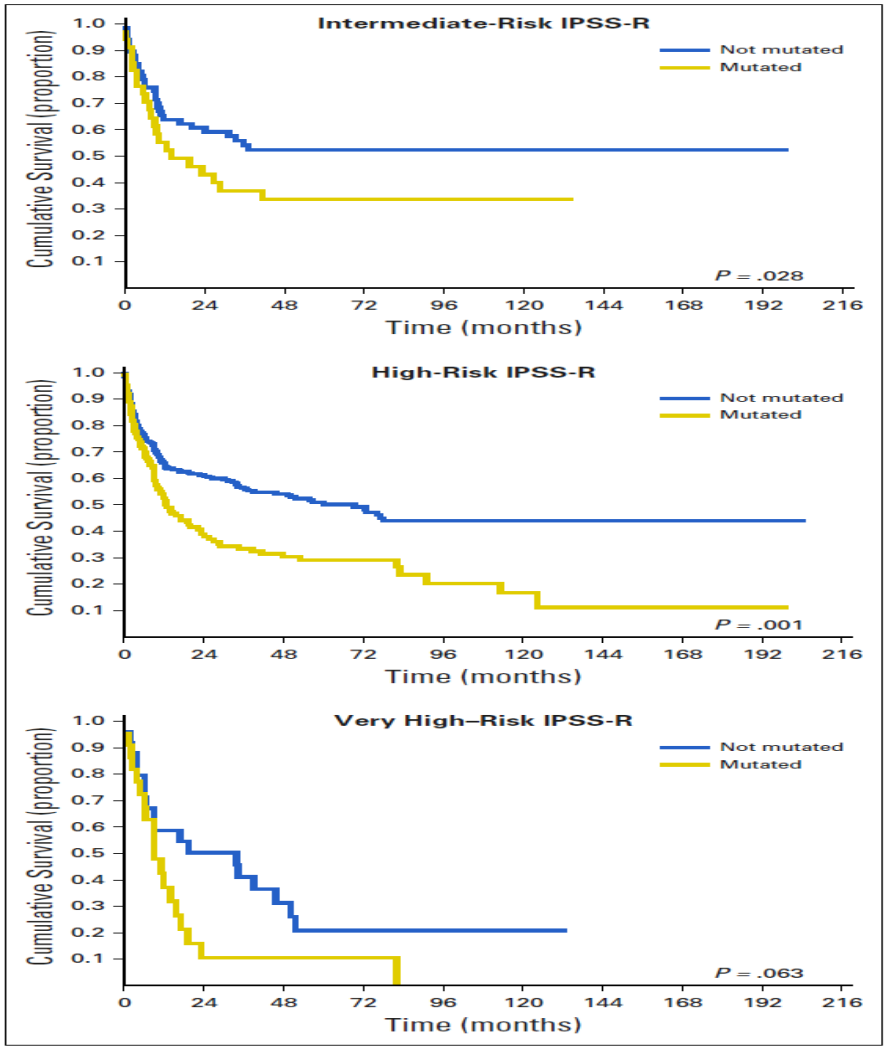
**Overall survival after allo-SCT**




Bejar et al, JCO , sept 2014

# Somatic mutations and outcome of allo SCT for MDS

**Della Porta et al, JCO, 2016,34,3627 (GITMO)**



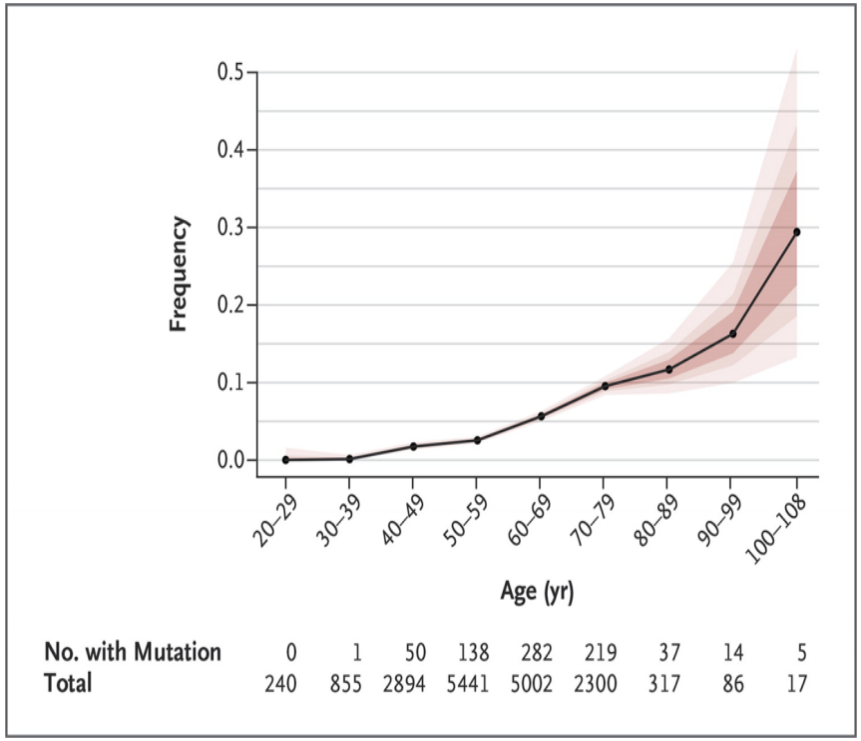

MDS and MDS/AML
N = 401
34 gene panel before SCT

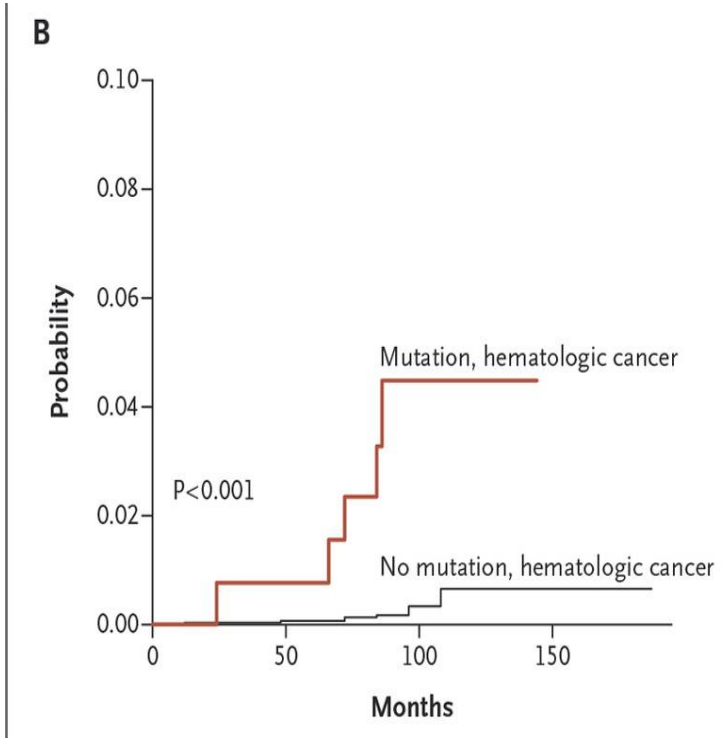
3 genes with significantly worse survival and relapse **independent of IPSS-R**

**Not only TP53,**
**but also ASXL1, RUNX1**

# Use of mutations for earlier diagnosis of MDS

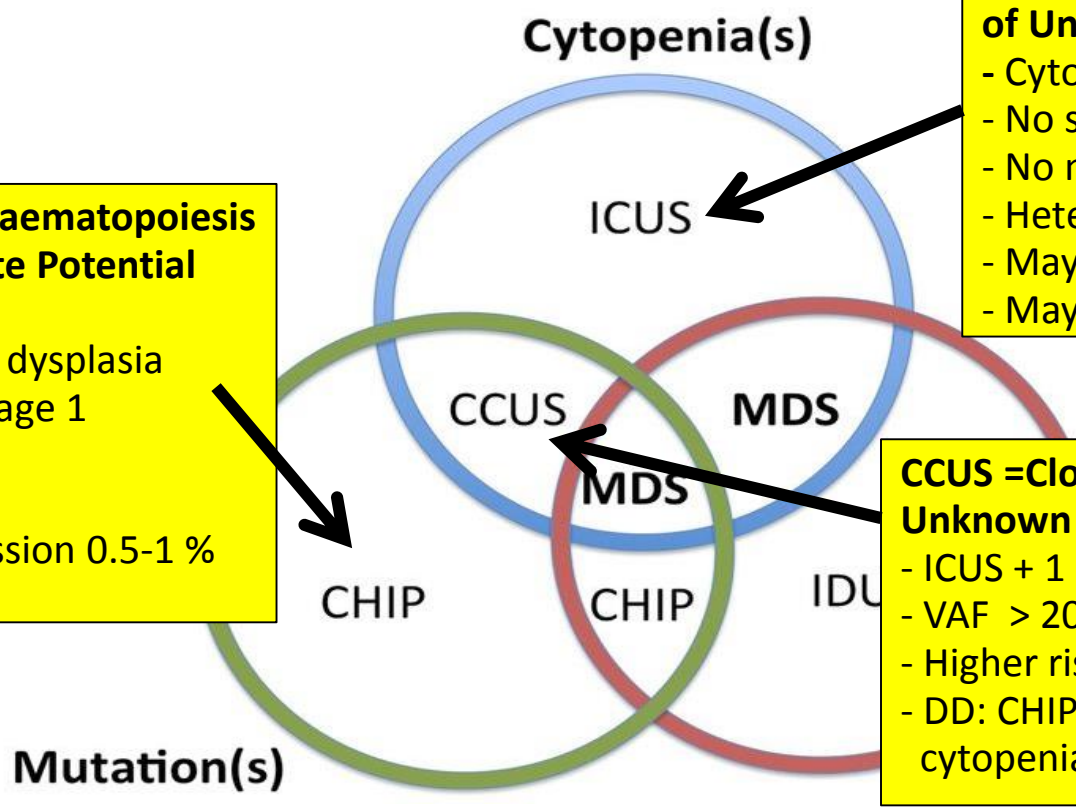
# 2014: Age related clonal haematopoiesis
# Clonal Haematopoiesis of Indeterminate Potential (CHIP)




- Mutations in DNMT3A, TET2 and ASXL1 are increasing with age
- Median number of mutations per patient  is only 1
- 10% of patients above age 65-70 yrs have mutations
- Risk of haematological cancer is 4 % at 10 yrs

# "The MDS Alphabet Soup"
# "The shadowlands of MDS"




**ICUS = Idiopathic Cytopenia of Unknown Significance**
- Cytopenia
- No significant dysplasia
- No mutations
- Heterogeneous causes
- May become MDS
- May disappear

**CHIP = Clonal Haematopoiesis of Indeterminate Potential**
- No cytopenia
- No or minimal dysplasia
- Mutation average 1
- VAF < 10 %
- Age related
- Risk of progression 0.5-1 % per year

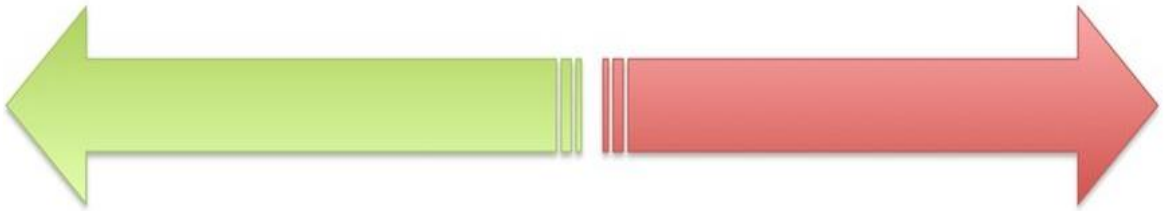
**CCUS =Clonal cytopenia of Unknown Significance**
- ICUS + 1 or more mutations
- VAF > 20 %
- Higher risk of progression to MDS
- DD: CHIP + non-MDS cause of cytopenia

David P. Steensma Hematology 2016;2016:67-73

# Interpretation of mutations in CCUS

- Single mutation
- Low variant allele frequency (<10%)
- Minimal or no cytopenia
- Mutation in common "CHIP"-associated genes (e.g. *TET2, DNMT3A)*

- Multiple mutations
- Higher variant allele frequency (>20%)
- Cytopenia, especially if progressive
- Mutation in genes more commonly associated with MDS (e.g. *U2AF1, TP53)*



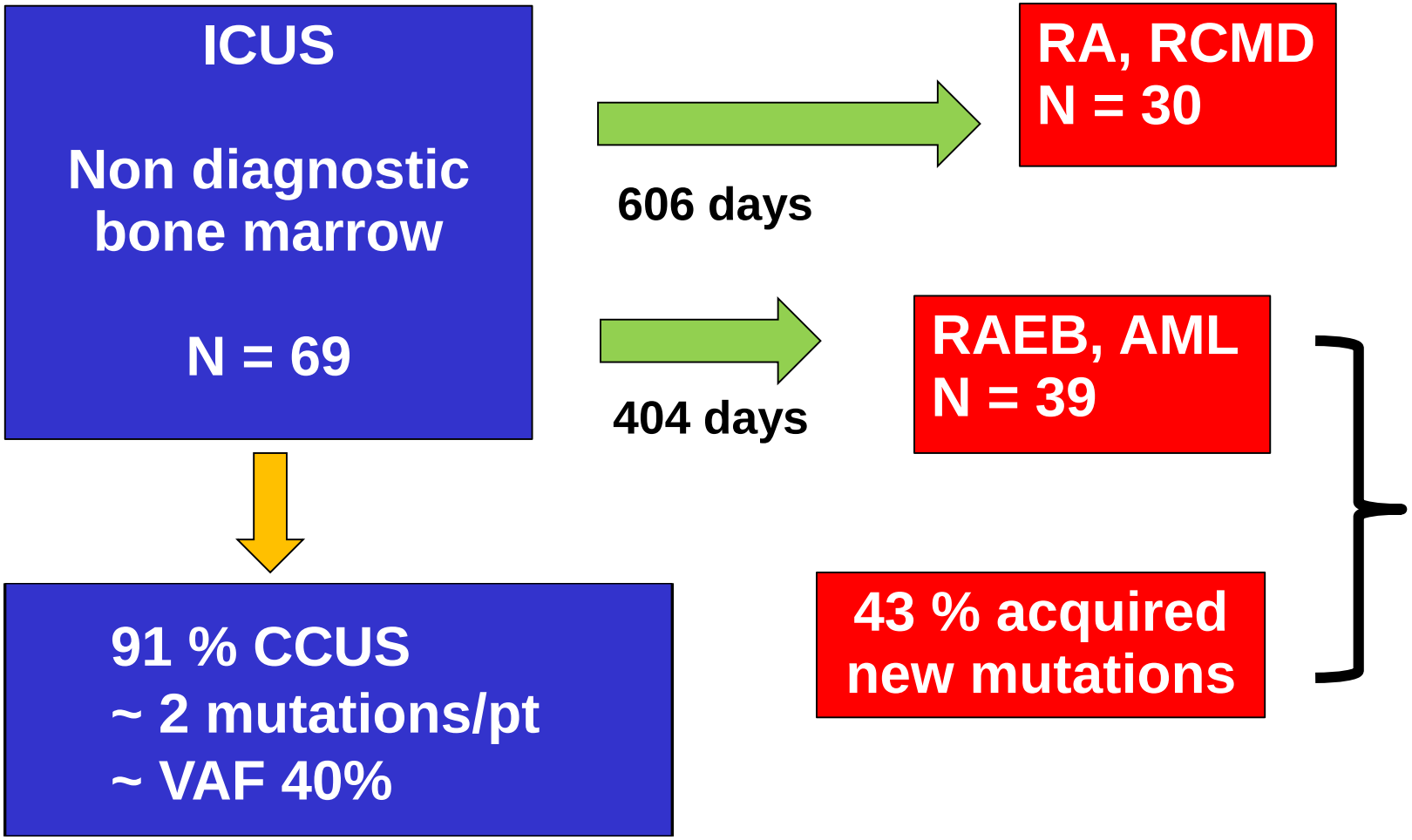
***Diagnostic threshold?***

**Favors CHIP** **Favors MDS**

David P. Steensma Hematology 2016;2016:67-73

# NGS can identify early MDS in ICUS

Cargo et al, Blood, 2015,126,2362




Limitations: retrospective study, no control group (non-progressors)

# Risk of MDS in patients with unexplained cytopenia

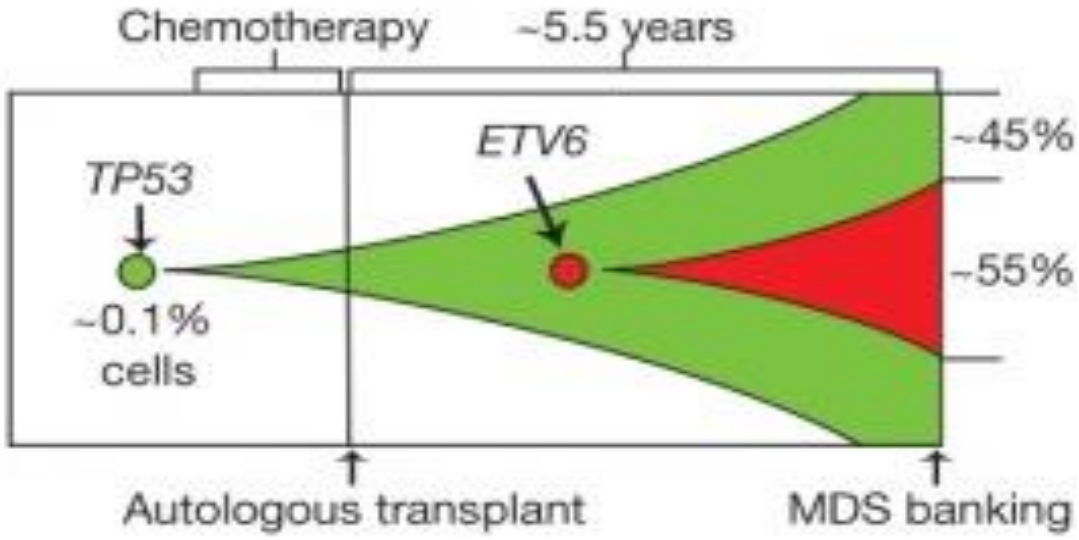
## Luca Malcovati (Pavia)

- 154 patients with ICUS
- NGS for 42 gene panel , on peripheral blood
- 37 % (57 of 154 ) carried one or more mutations **(CCUS).**
- **10 year probability to develop MDS**
  - ✓ **CCUS 96%**
  - ✓ **No clonality 15% (p< 0.001)**
- Highest risk for progression
  - ✓ Mutations in RNA splicing genes (SF3B1, SRSF2, U2AF1) irrespective of co-occurring mutations,
  - ✓ Mutations in “CHIP-genes” TET2, DNMT3A, ASXL1 + one or more co-mutated genes

What do mutations
tell us about
origin and risk of
therapy related myeloid
neoplasms ?

# Role of *TP53* mutations in the origin and evolution of therapy-related acute myeloid leukaemia

**TN Wong *et al.* Nature 2015, 518, 552**




Stem cell clones harbouring age-related *TP53* mutations are detected in patients before chemotherapy exposure. and expand after treatment due to chemotherapy resistance

nature

# Lancet Oncology 2017

## Preleukaemic clonal haemopoiesis and risk of therapy-related myeloid neoplasms: a case-control study

MDACC

Koichi Takahashi*, Feng Wang*, Hagop Kantarjian, Denaha Doss, Kanhav Khanna, Erika Thompson, Li Zhao, Keyur Patel, Sattva Neelapu, Curtis Gumbs, Carlos Bueso-Ramos, Courtney D DiNardo, Simona Colla, Farhad Ravandi, Jianhua Zhang, Xuelin Huang, Xifeng Wu, Felipe Samaniego, Guillermo Garcia-Manero, P Andrew Futreal

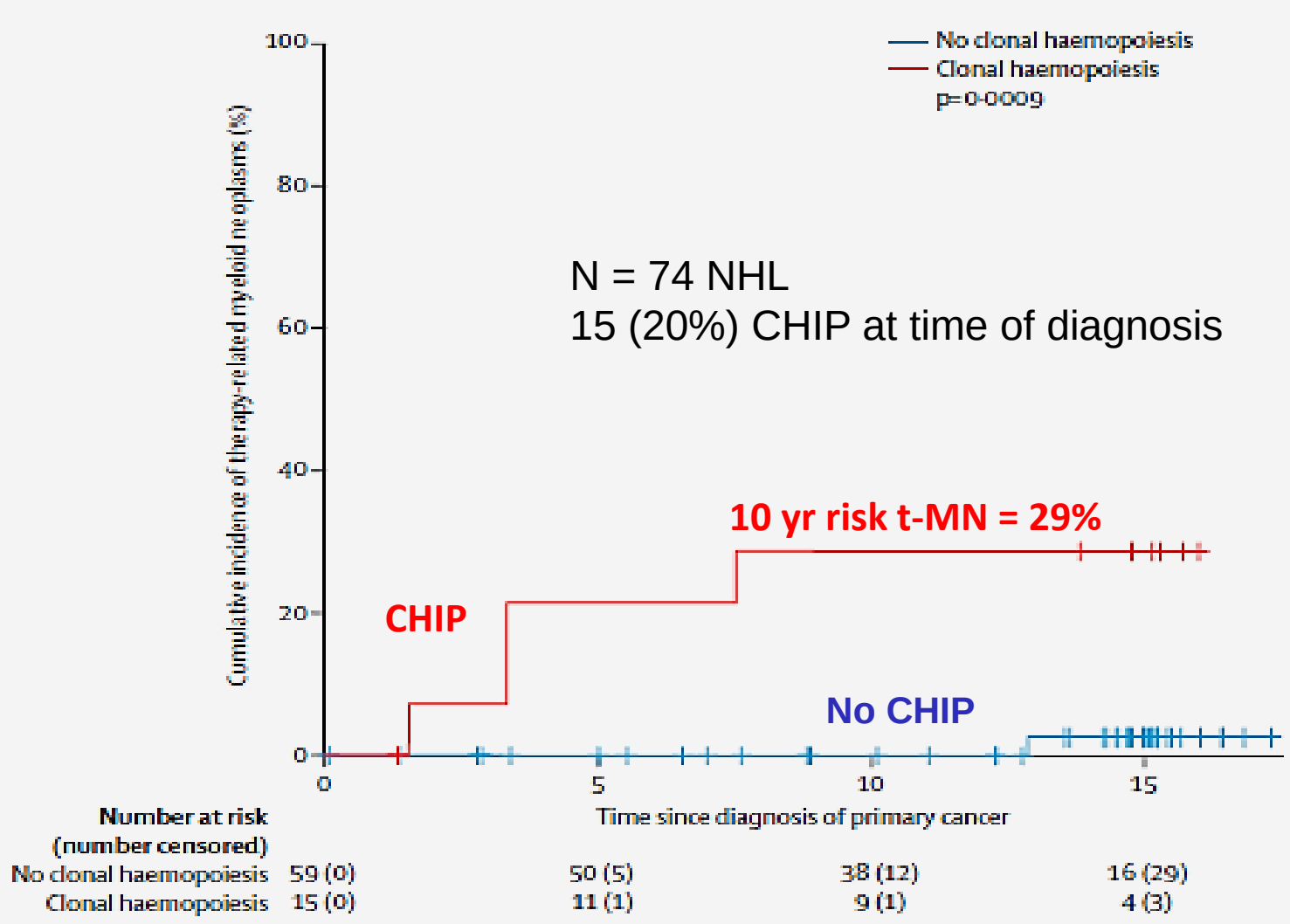
## Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: a proof-of-concept, case-control study

Lee Moffitt Cancer Center

Nancy K Gillis, Markus Ball, Qing Zhang, Zhenjun Ma, YuLong Zhao, Sean J Yoder, Maria E Balasis, Tania E Mesa, David A Sallman, Jeffrey E Lancet, Rami S Komrokji, Alan F List, Howard L McLeod, Melissa Alsina, Rachid Baz, Kenneth H Shain, Dana E Rollison, Eric Padron

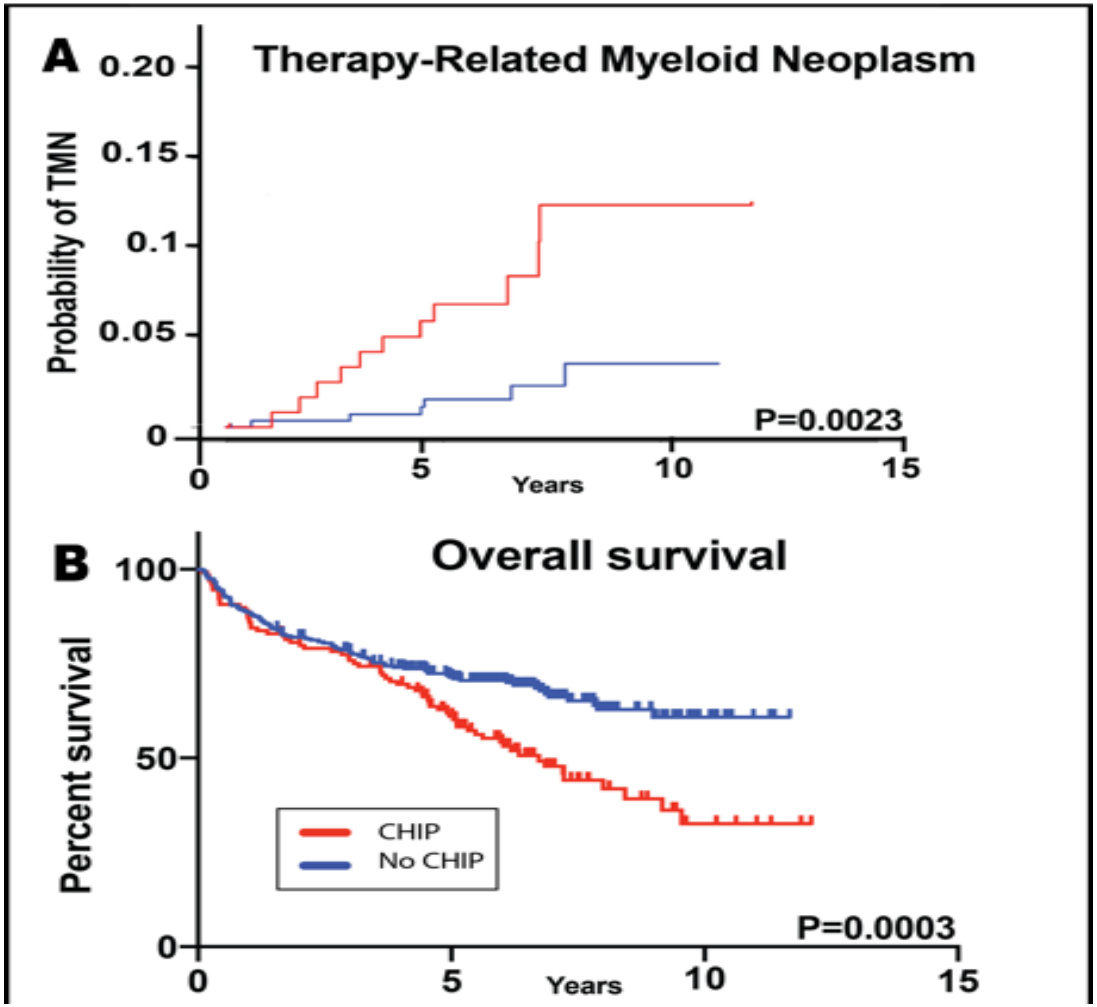
CHIP was present in biobanked samples at the time of diagnosis of primary cancer in 60-70% of pts who developed a therapy related myeloid malignancy *versus* in only 25-30 % of pts who received chemotherapy for primary cancer but did not develop a tMN

# Cumulative incidence of therapy related myeloid neoplasm




Takahashi et al, Lancet Oncology 2017

# Clonal hematopoiesis associated with adverse outcomes following autologous stem cell transplantation for NHL
## C. Gibson (DFCI)




N = 401 NHL

116 gene panel

banked mobilized peripheral blood

CHIP present in 30%

# What do these studies tell us ?

- Age-related CHIP is common in pts with tMN
  - ✓ at the time of primary cancer diagnosis
  - ✓ *before exposure to chemotherapy*
  - ✓ *at time of SC collection*
- Should CHIP be used as a predictive biomarker to identify the pts with cancer at risk for tMN ?
- Should autologous SCT candidates be offered other treatment if CHIP is present in the collection ?
- Mutation specific differences might exist in the risk for development of tMN

  TP53 more common in t-MN, TET2 in controls

**Donor CHIP causes donor-derived clonal hematopoiesis as complication of allogeneic stem cell transplantation**
**C. Gibson (DFCI)**

- Clonal haematopoieis was identified in the biobanked donor stem cells of 4 allografted pts who late after transplantation developed unexplained cytopenia or donor cell leukemia
- Engraftment and expansion of aberrant clone in the transplant recipient

**Challenge from this study**

- Should we prospectively identify CHIP in older stem cell donors (incidence 10% > 70 yrs) ?
- Should we modify donor selection strategy ?

# Low risk MDS

## New treatment modalities

# ESA : two registration studies (EHA 2016)

Inclusion: low/Int1-MDS,

Hgb <= 10 g/dl,

EPO <= 500,

low tranfusion burden (<= 4 PC/8 weeks)

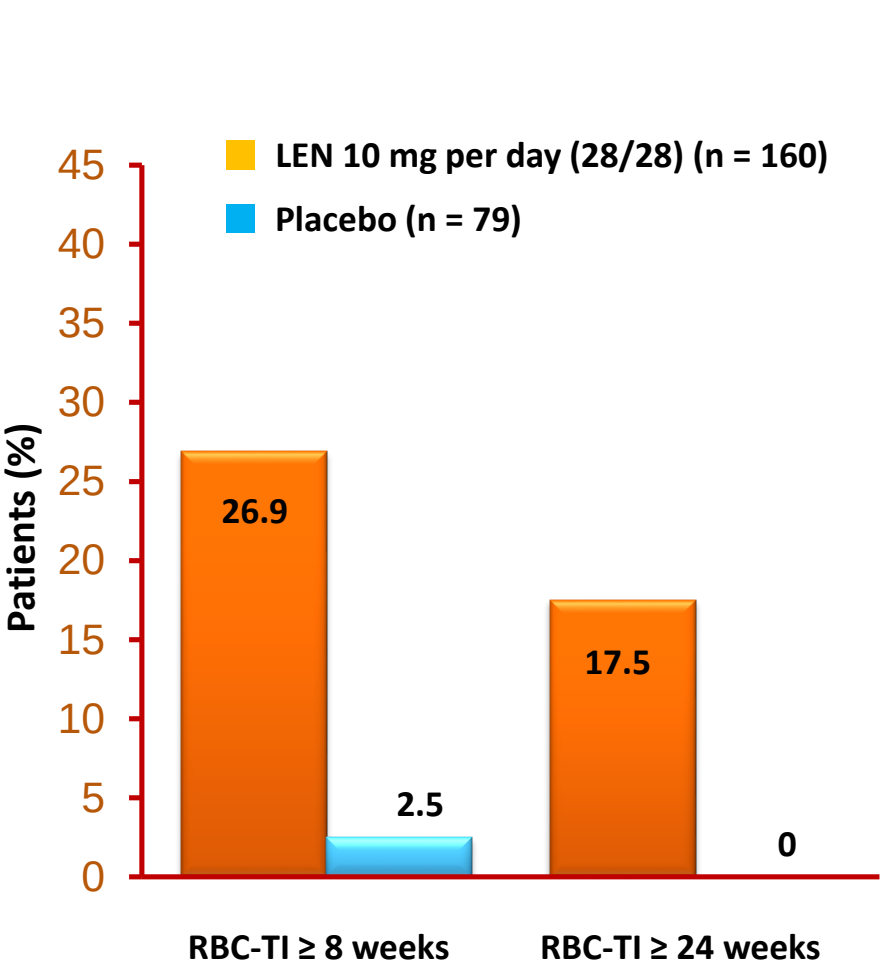
| | ARCADE Platzbecker | EPOANE 3021 Fenaux |
|---|---|---|
| Regimen | Darbepoietin vs Placebo 24 wks 2:1 | Epoietin Alfa (Eprex) vs Placebo 24 wks 2:1 |
| Dose of ESA | | 40.000 U) 1 x / week |
| HI-E (IWG 2006) at 24 weeks | 14.7 vs 0 % p = 0.016 | 31.8 vs 4.4 % p < 0.001 |
| Transfusion incidence week 5-24 | 36% vs 59 % p = 0.008 | 24 % vs 54 % |

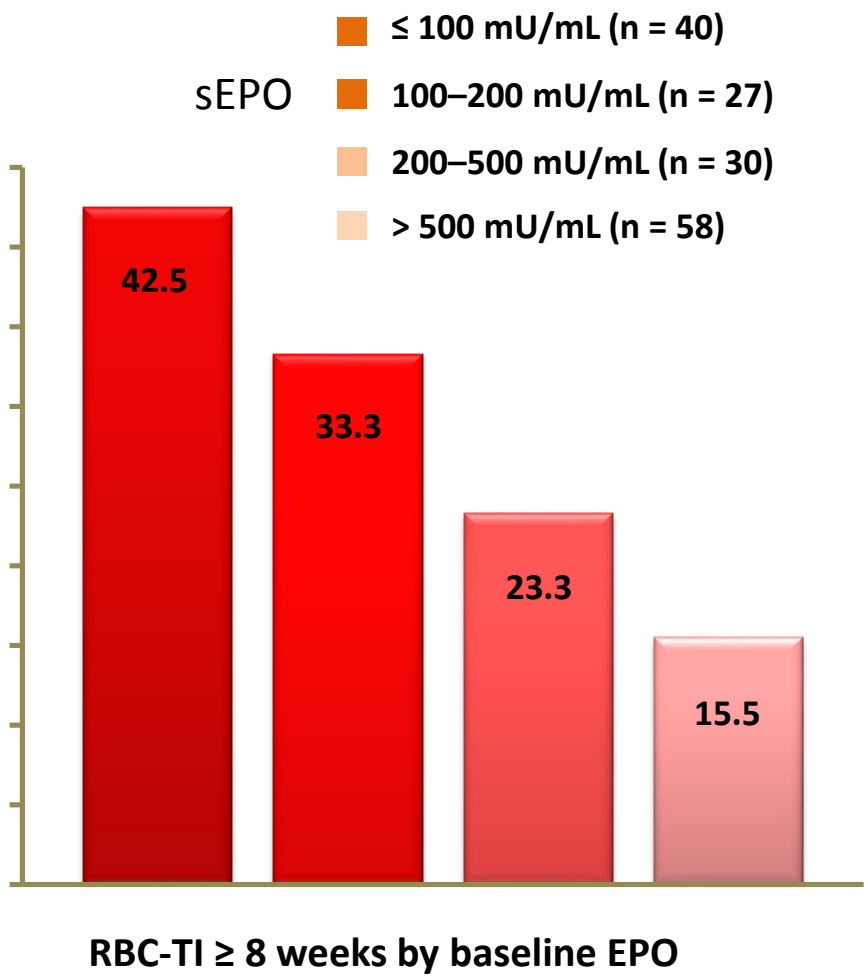
Results lower than expected due to stopping rules

# Treatment options in low risk non-del 5q MDS failing ESA

1. Lenalidomide
2. Len + ESA
3. Luspatercept
4. HMA

# MDS-005: Lenalidomide in ESA refractory non-del5q lower risk MDS induces RBC-TI




Santini V J Clin Oncol. 2016 Sep 1;34(25):2988-96.

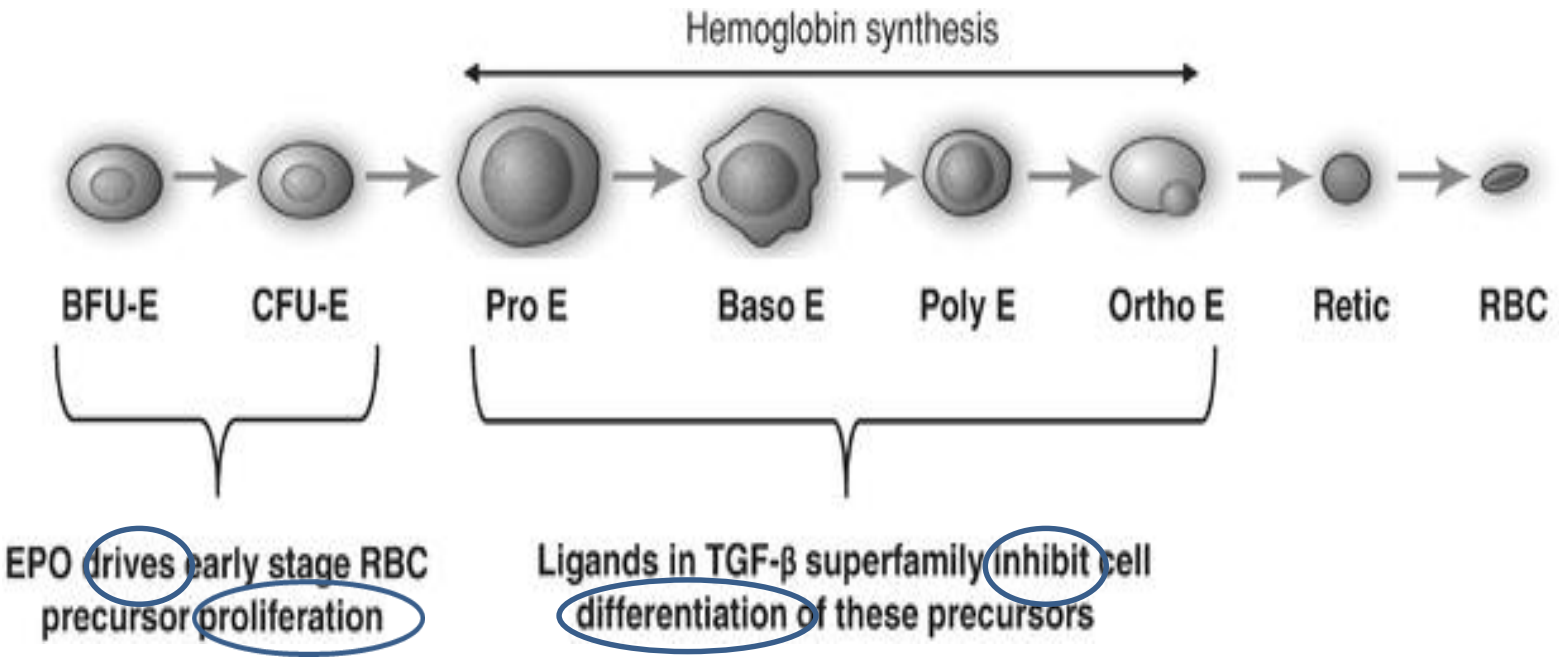
# MDS failing ESA: EPO +LEN

- In vitro: Lenalidomide improves EPO receptor signaling
- Inclusion: MDS low-Int 1, non del 5q, transfusion dependent
  **ESA failures** or EPO > 500

**LEN 10 mg (3/4 wks) + Epoeitin α/β 60.000 U/wk** **vs** **LEN 10 mg**

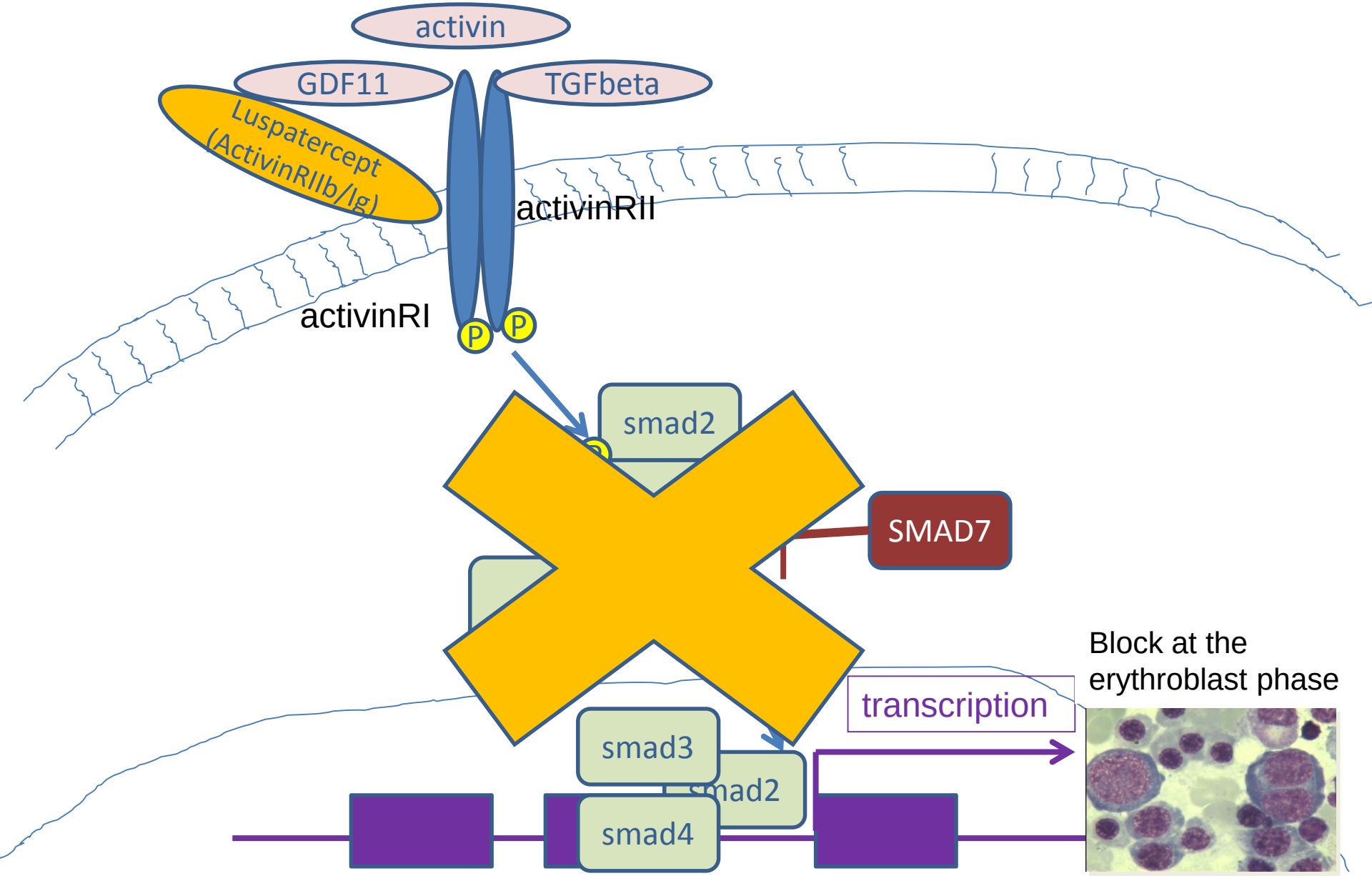
| | French MDS group Leukemia 2016 (Toma) | USA intergroup study ASH 2016 (List) |
|---|---|---|
| N | 131 | 195 |
| HI-E (IWG 2006) After 4 cycles | 39 vs 23 % P = 0.04 | 33 vs 14 % P = 0.018 |
| Transfusion independency | 24 vs 14 % P = 0.1 | NE |
| Response duration | 18 vs 15 months NS | NR vs 25 mths |
| Safety | No increase of tromboembolic events | |

# Erythropoiesis in MDS is blocked by TGFβ activation




**GDF11 increased in MDS**

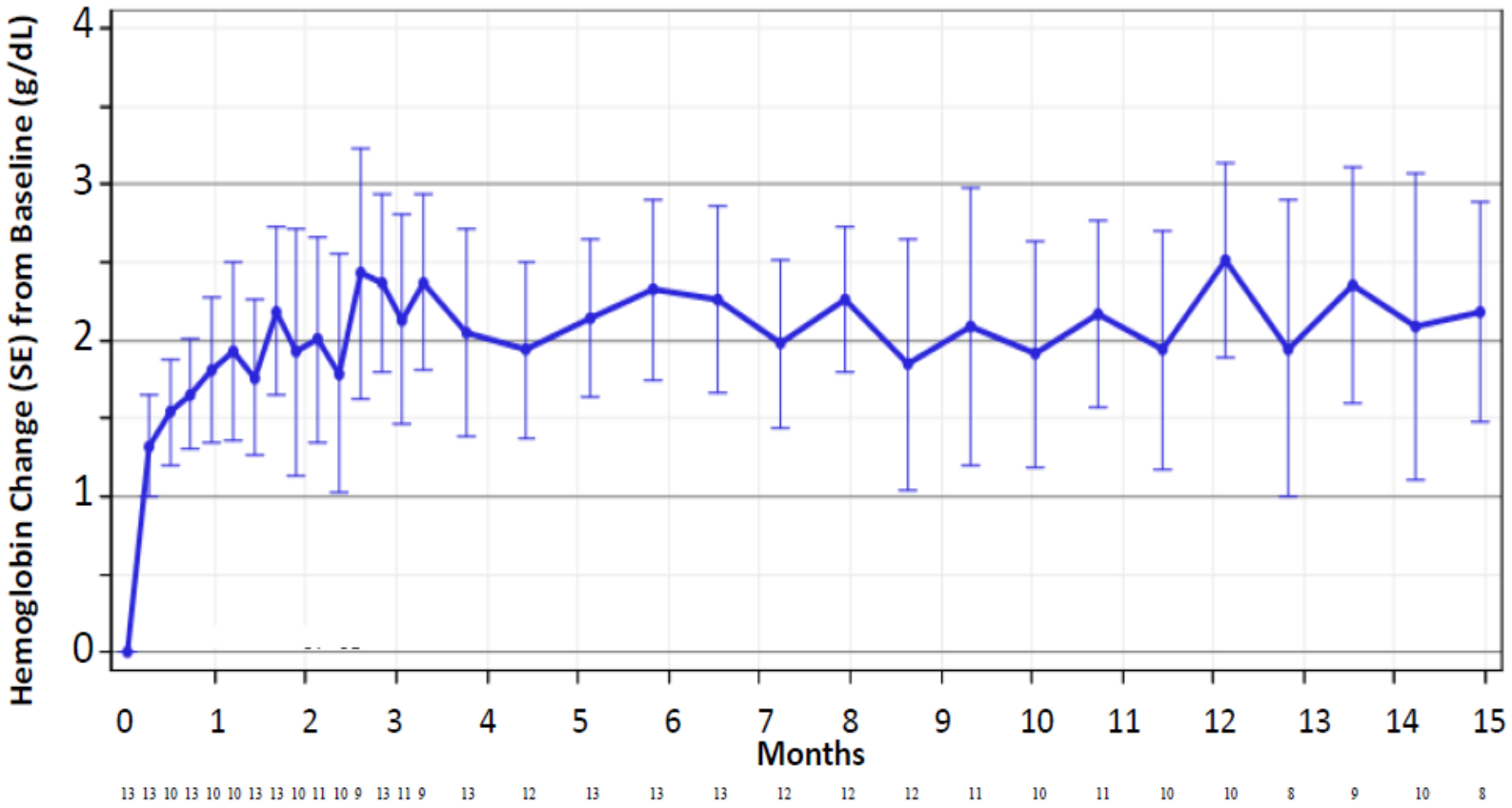
# Luspatercept is a soluble activin receptor and acts a ligand trap for TGFβ ligands



# Long-term results from phase II PACE-MDS study Platzbecker

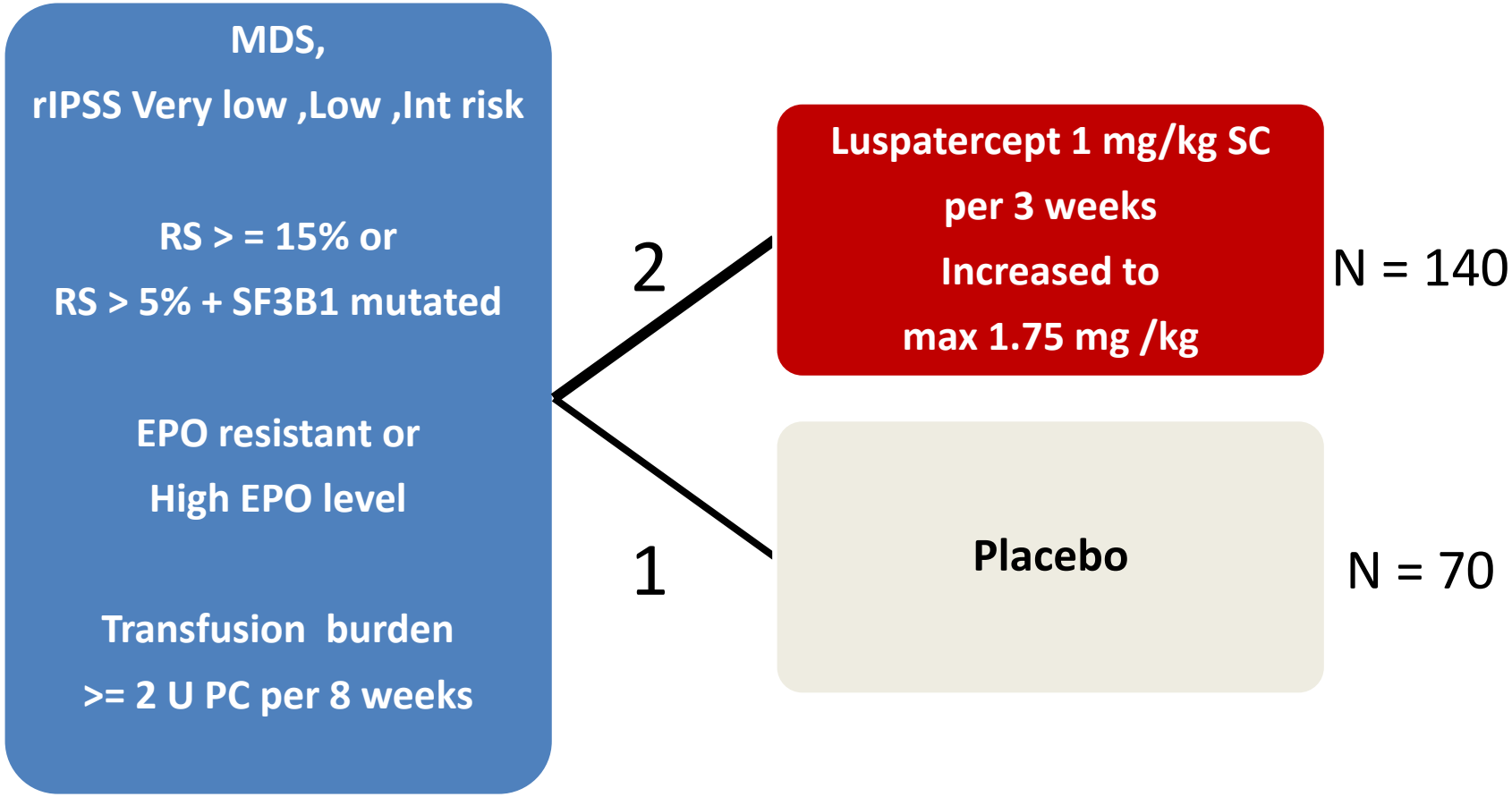
- **Inclusion:**
  - low-intermediate 1 risk MDS
  - Hgb < 10 g/dL or transfusion need ≥ 4U RBC/8 weeks
  - ESA refractory/intolerant or Epo level > 500 U/L
- 32 extension study patients (received luspatercept for > 3 mths)
- 91% RS+ (≥ 15% ring sideroblasts in BM); 71% SF3B1 +
- Luspatercept SC every 3 wks at a dose of 1 -1.75 mg/kg
- **Results:**
  - IWG HI-E : **85% of low transfusion burden patients**
  - **79% of high transfusion burden patients**
  - Median time to response was 6 weeks
  - **50 % achieved RBC transfusion independence** for at least 8 weeks
  - duration of transfusion independence was 9 to 80+ weeks
  - well tolerated

# Increase in Mean Hemoglobin in LTB Patients with > 3 Months of Treatment (Extension Study)




- 11/13 (85%) HI-E responders; median time to response: 6 weeks

# MEDALIST trial

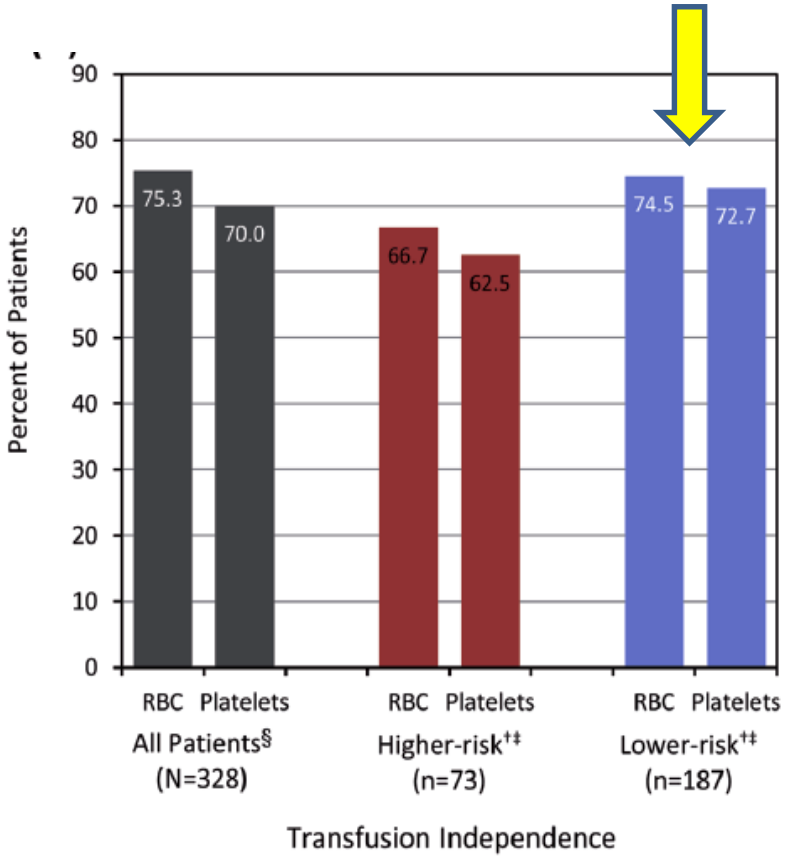



Primary endpoint : transfusion independency for > 8 weeks

Assessment every 6 mths

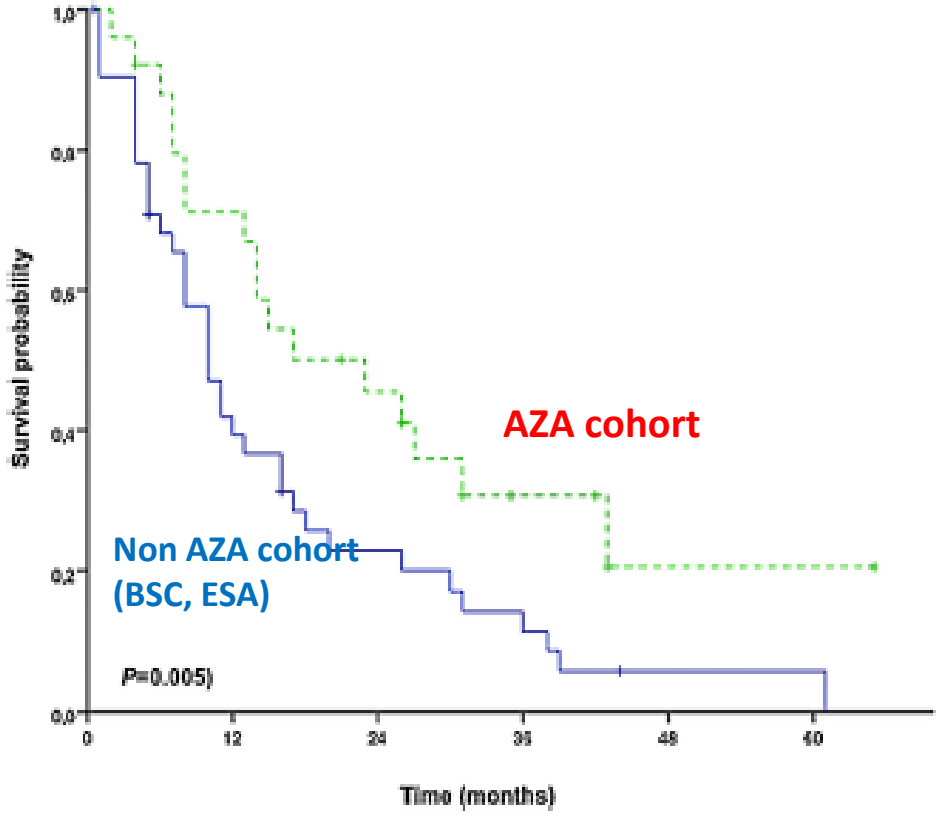
No cross over

# Low risk MDS may benefit from HMA




Grinblatt, Leukemia & Lymphoma 2015

AVIDA registry for AZA treated MDS



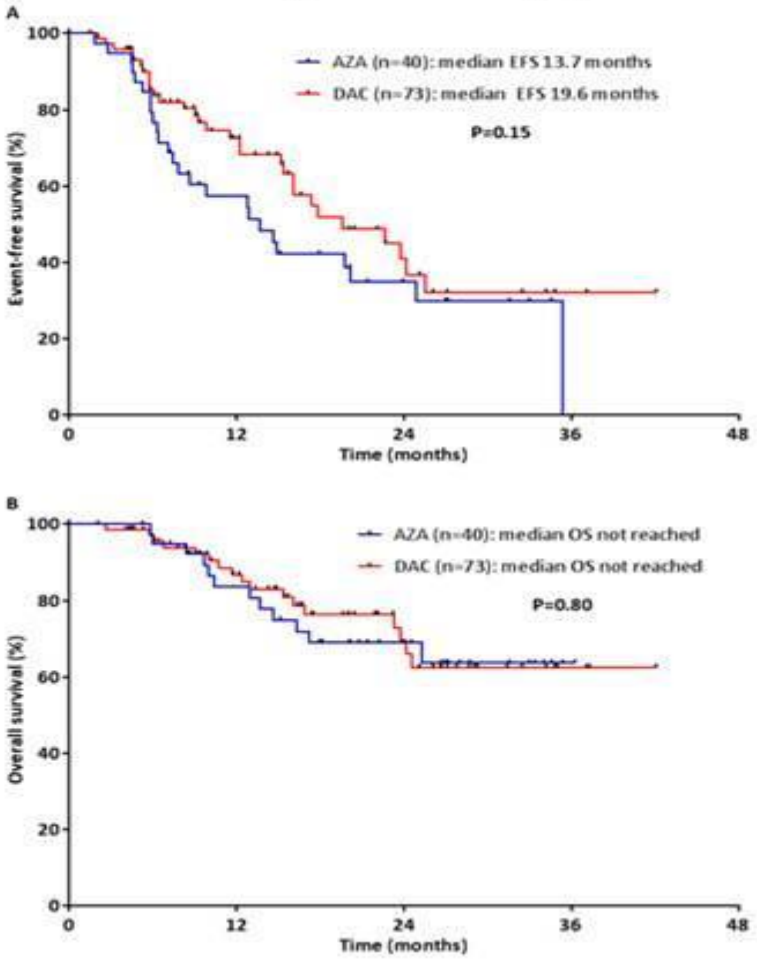

Falantes, Leukemia Research 2014

Retrospective comparison
LR-MDS with adverse features

# A randomized phase II study of low-dose decitabine versus azacitidine in patients with low- or intermediate-1-risk myelodysplastic syndromes: a report on behalf of the MDS Clinical Research Consortium

E. Jabbour (MDACC)

**Figure 1.** Event-free survival (A) and overall survival (B) by treatment arm.




113 pts
LR-INT1 MDS, tMDS,CMML

| | AZA | DAC |
|---|---|---|
| | 75 mg/m2<br>3 days | 20 mg/m2<br>3 days |
| ORR<br>= CR + mCR + HI | 51 % | 51 % |
| Cytogenetic response | 24 % | 63 % |
| Transfusion independence | 17 % | 32 % |

# High risk MDS
# novel treatment options

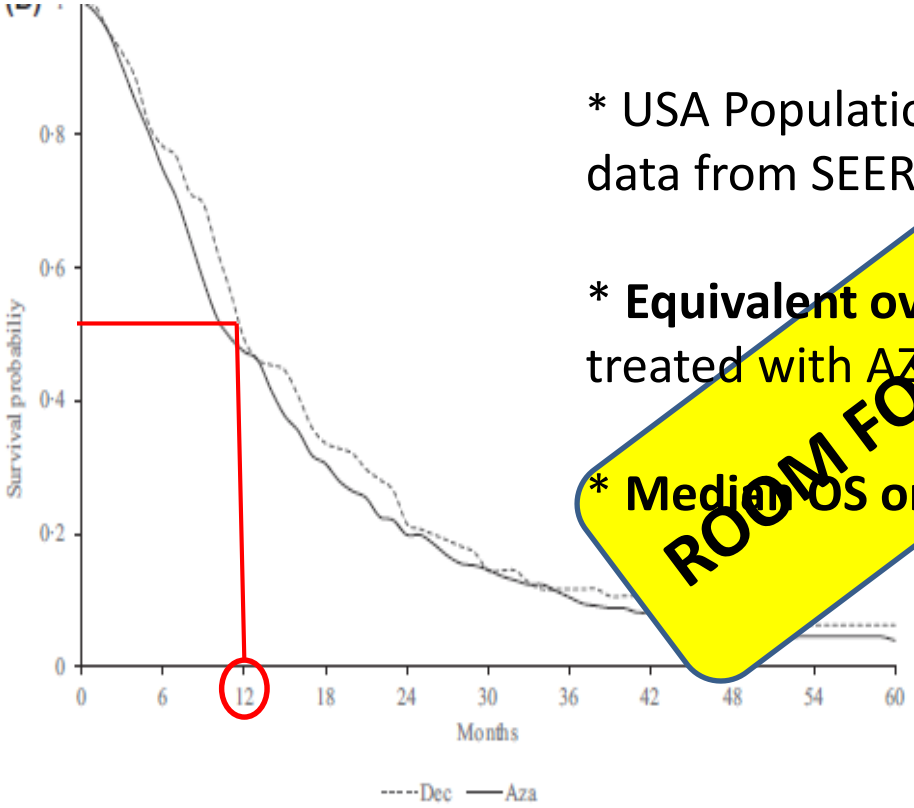
Guadecitabine

ASTX 727

SUPPORT study

# AZA vs Decitabine in higher risk MDS

**Zeidan et al , BJHaem, 2016,175, 829**




* USA Population based study with data from SEER and Medicare

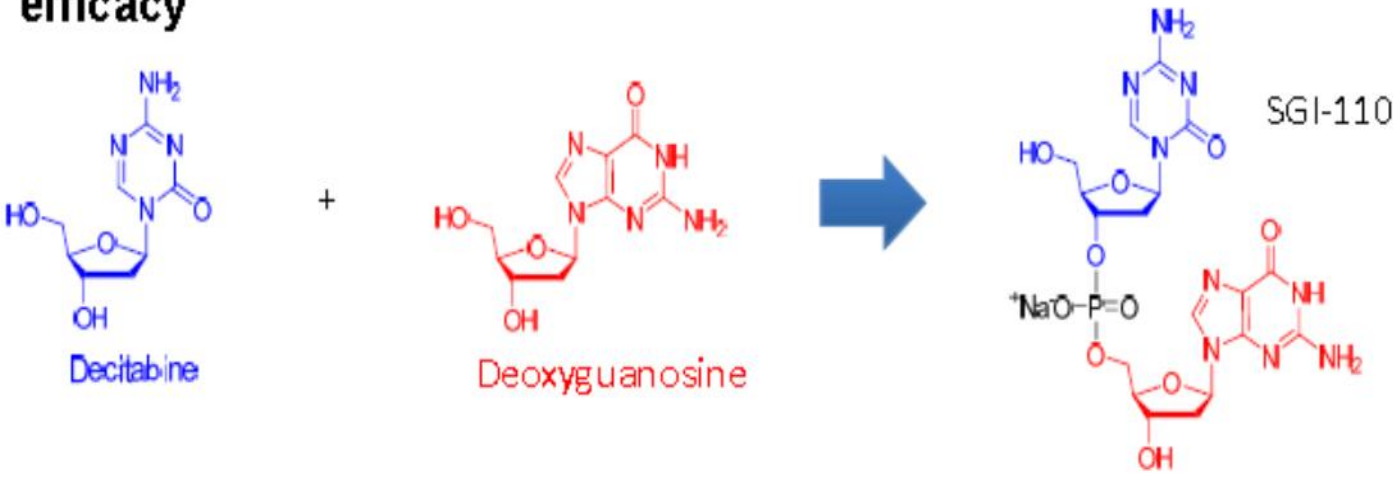
* **Equivalent overall survival** in 523 RAEB patients treated with AZA or DAC

* **Median OS only 12 mths** versus 24.5 mths in AZA-001

**ROOM FOR IMPROVEMENT**

# SGI-110 = Guadecitabine (Astex)
# 2nd generation hypomethylating agent

- **SGI-110 is a Dinucleotide of Decitabine and Deoxyguanosine that prolongs the *in vivo exposure* of decitabine by protecting it from deamination**
- **Prolonged decitabine *in vivo* exposure may translate to better efficacy**




**Other advantages:**

- **Low injection volume**
- **Prolonged stability (1 month) after reconstitution**

# Phase II study of guadecitabine in previously untreated INT-2 or high risk MDS or CMML

**G. Montalban-Bravo (MDACC)**

- Dose 60mg/m2 SC daily for 5 days every 28 days
- N = 50 (43 MDS, 7 CMML)
- Very high risk:
  - complex karyotype 45%, tMDS 38%, TP53 mutation 35%
- Overall response 71% **(AZA-001 78 %)**
  - Complete remission 32 % **(AZA-001 19%)**
  - Marrow CR 32 %
  - HI 7%
- Time to response 3 cycles (1-6)
- Response duration 4 cycles (0-14)
- Overall survival 14 months **(AZA-001 24 mths)**
- Mortality at 8 weeks 6%

- **Superior to first generation HMA ?**

# ASTX 727 , a new oral HMA (Astex Ph)

## G.Garcia-Manero

- Decitabine /AZA : low oral bioavailability due to rapid clearance by cytidine deaminase present in the gut and liver

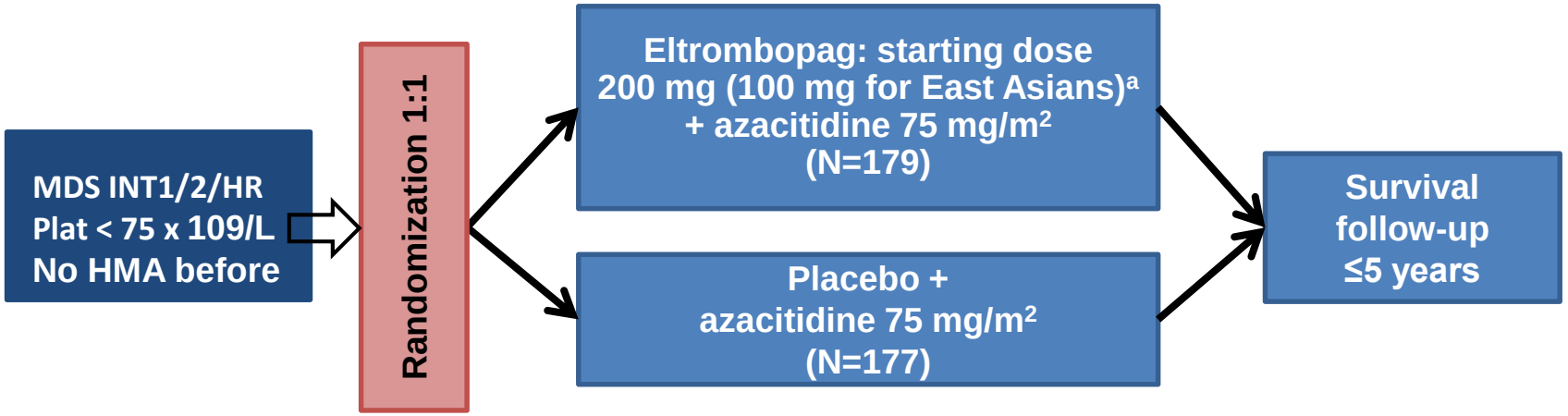
- ASTX 727 = oral combination of Decitabine
  + E7727, a Cytidine Deaminase inhibitor

- PK studies : Decitabine 35 mg + E7727 100 mg orally for 5 days
  = Decitabine 20 mg/m2 IV for 5 days

- Clinical responses similar to Decitabine IV

- Randomized Phase II just started

# SUPPORT: Phase III study
# M. Dickinson




| | AZA + eltrombopag N 179 | AZA + placebo N 177 |
|---|---|---|
| Platelet transfusion independence in first 4 cycles | 16 % | 31 % |
| Progression to AML | 12% | 6% |

“A room with a view” : Mission Bay , San Diego


I ♥ Hematology
58th ASH® Annual Meeting and Exposition
I ♥ ASH
I ♥ ASH