Chronic myelomonocytic leukemia (CMML)

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CMML: a hybrid disease

Clonal hematologic "overlap"disease (MDS/MPN) characterized by myeloid dysplasia, proliferation, and absence of the molecular lesions BCR/ABL, PDGFRA, PDGFRB, and FGFR1.

There are currently no FDA or EMA approved therapies for any MDS/MPN subtypes, except CMML-dysplastic .

Reactive and Clonal Mimickers of CMML

Reactive:

- Subacute bacterial endocarditis/endo-myocarditis
- Tuberculosis
- Malaria infection
- EB virus infections
- Syphilis
- Typhoid fever
- Trypanosomiasis
- Drug-induced toxic reactions
- Corticosteroid therapy
- Treatment with GM-CSF
- Paraneoplastic (T cell lymphoma, Hodgkin disease, solid tumors)
- Chronic and acute autoimmune diseases
- Sarcoidosis
- Chronic hepatitis plus cirrhosis
- Collagen disease
- Asplenic state
- Pregnancy

Clonal:

- CMUS
- Low risk MDS with monocytosis
- High risk MDS with monocytosis
- Monoblastic AML
- MPN with monocytosis
- GATA2 deficiency with monocytosis
- RASopathies: CBL syndromes and others*
- JMML
- Histiocytosis

Valent P et al, Haematologica 2019

WHO 2016 classification

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

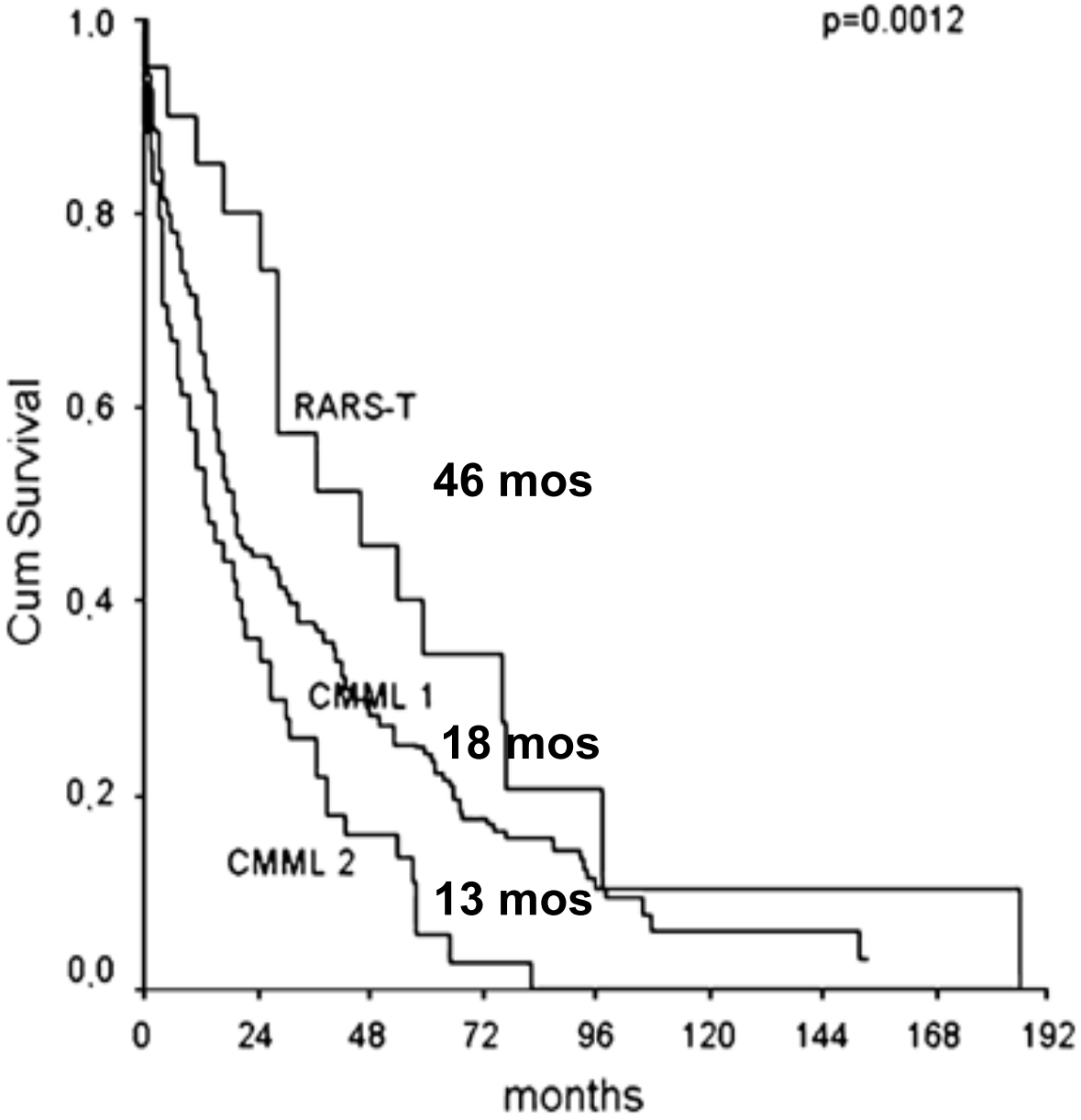
- Chronic myelomonocytic leukemia
- Atypical chronic myeloid leukemia, *BCR-ABL1*–negative
- Juvenile myelomonocytic leukemia
- Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable

Blood , April 2016

CMML: WHO2016 diagnostic criteria

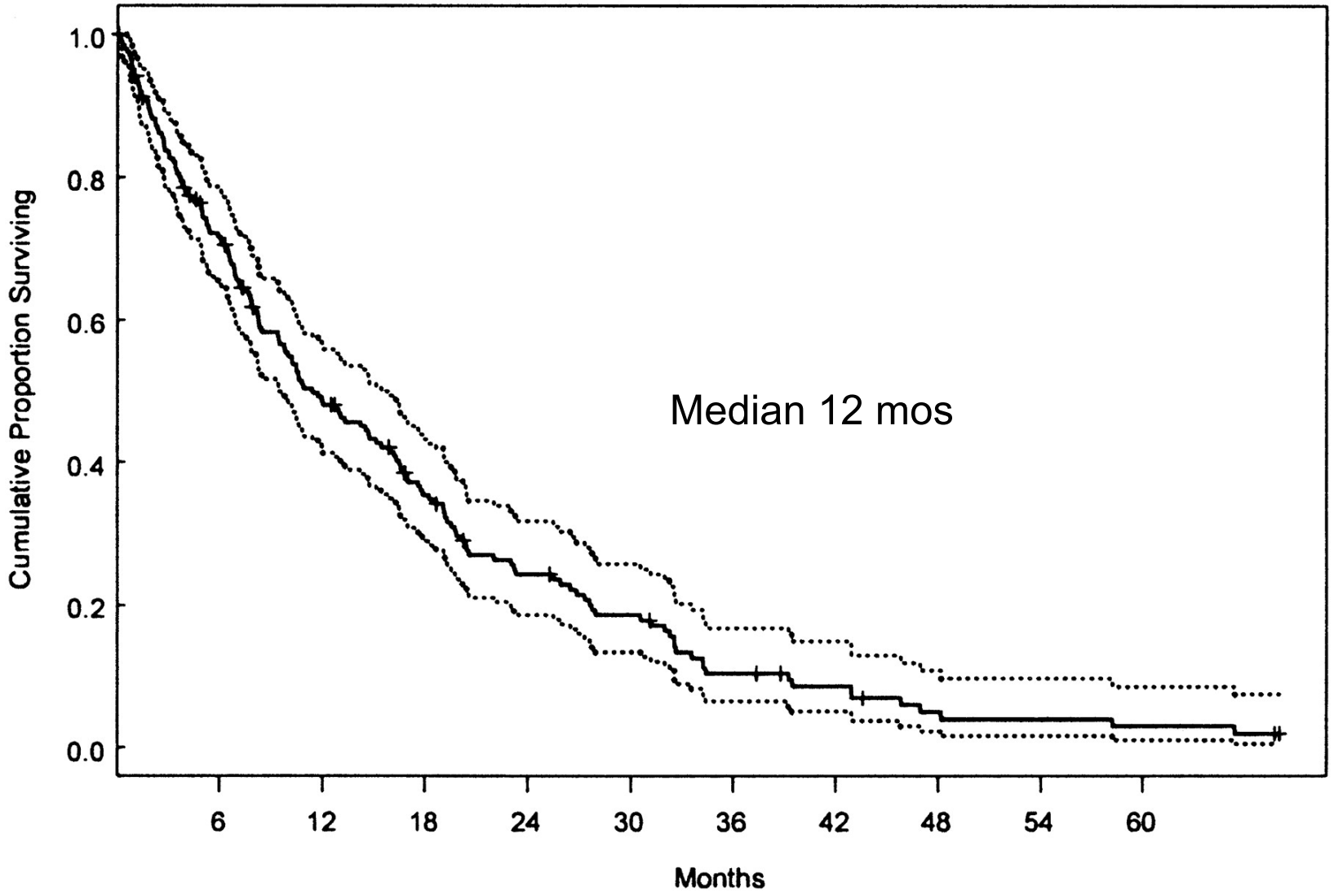
CMML diagnostic criteria
• Persistent PB monocytosis ≥1 × 10^9/L, with monocytes accounting for ≥10% of the WBC count
• Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PMF, PV, or ET*
• No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia)
• <20% blasts in the blood and BM†
• Dysplasia in 1 or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and
• An acquired clonal cytogenetic or molecular genetic abnormality is present in hemopoietic cells‡
or
• The monocytosis (as previously defined) has persisted for at least 3 mo and
• All other causes of monocytosis have been excluded

Overall survival in MDS/MPN



Orazi and Germing, Leukemia **(2008) 22,**1308-1319

Overall survival in CMML



Onida F et al. Blood 2002;99:840-849

blood

CMML Classifications… the last one

Proposed Grading of Chronic Myelomonocytic Leukemia (CMML)*

Grading-based variants	Diagnostic features / criteria
CMML-0	<5% blasts in BM smears and <2% blasts in PB**
Dysplastic CMML-0	PB leukocytes $\leq 13x10^9/L$
Proliferative CMML-0	PB leukocytes $>13x10^9/L$
CMML-1	6-9% blasts in BM smears and 2-4% blasts in PB**
Dysplastic CMML-1	PB leukocytes $\leq 13x10^9/L$
Proliferative CMML-1	PB leukocytes $>13x10^9/L$
CMML-2***	10-19% blasts in BM smears and 5-19% in PB**
Dysplastic CMML-2	PB leukocytes $\leq 13x10^9/L$
Proliferative CMML-2	PB leukocytes $>13x10^9/L$***

Valent P et al, Haematologica 2019

CMML Classifications… the last one

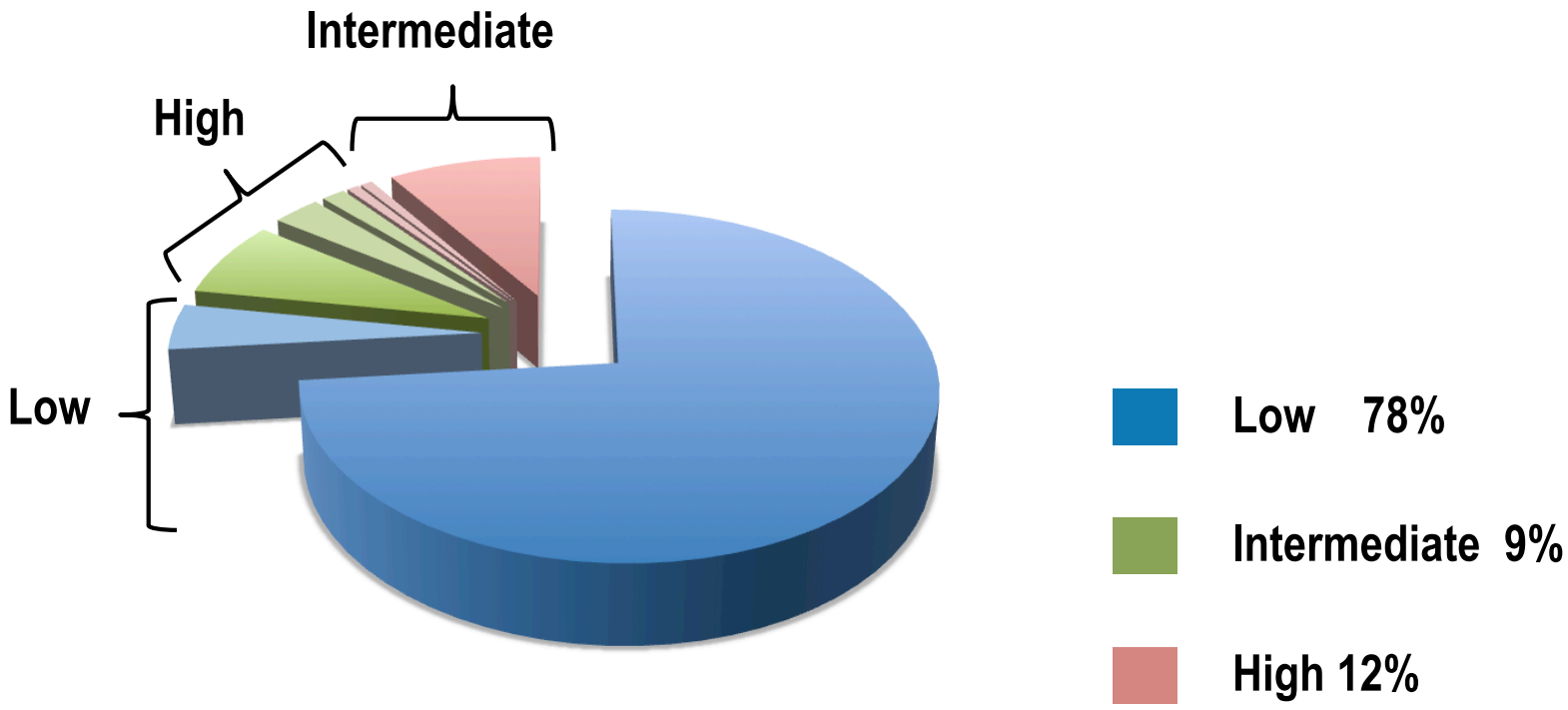
Phenotypic Classification of Monocytes and Distribution of Monocyte-Subsets in CMML and Controls*

Monocyte -Subset	Defining Phenotype	Typical Relative Frequency in*		
		CMML	MDS or MPN	Reactive BM
Classical (MO1)	$CD14^{bright}/CD16^{-}$	≥94%	70-97%	<94%
Intermediate (MO2)	$CD14^{bright}/CD16^{+}$	<20%	5-20%	5-15%
Non-classical (MO3)	$CD14^{dim}/CD16^{+}$	<5%	5-10%	5-20%

Valent P et al, Haematologica 2019

Cytogenetic classification

- **Low risk:** normal, -Y (unique alteration).
- **High risk :** +8, -7/del(7q) complex karyotype
- **Intermediate risk:** everything else



Such *et al.*, Haematologica 2011

CMML-specific prognostic scoring system (CPSS)

Training cohort: 558 pts (Spanish Group of Myelodysplastic Syndromes)

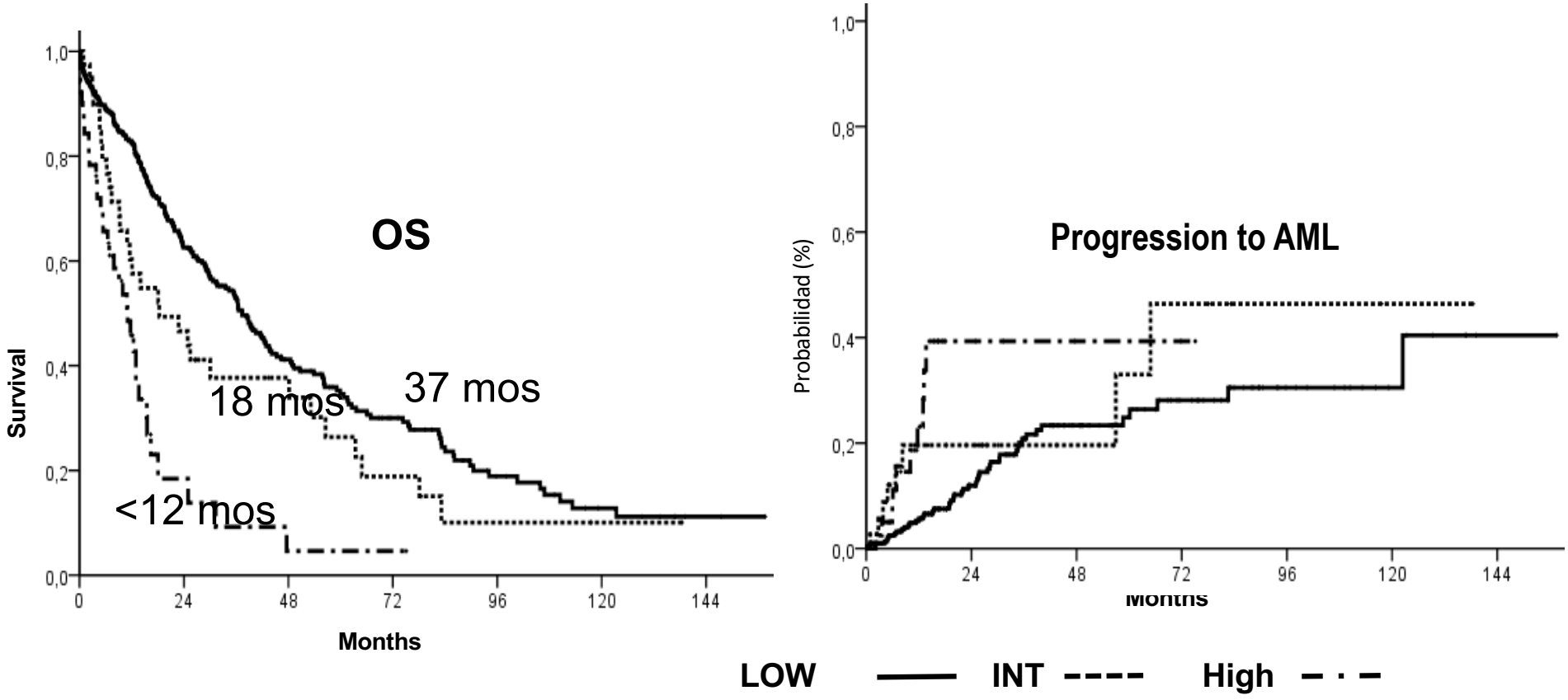
Validation cohort: 274 pts (Düsseldorf, Pavia)

	Variable scores		
Variable	**0**	**1**	**2**
WHO subtype	CMML-1 blasts (including promonocytes) <5% in the PB and <10% in the BM	CMML-2 blasts (including promonocytes) from 5% to 19% in the PB and from 10% to 19% in the BM, or when Auer rods are present irrespective of blast count	—
FAB subtype	CMML-MD (WBC count $<13 \times 10^9$/L)	CMML-MP (WBC count $\geq 13 \times 10^9$/L)	—
CMML-specific cytogenetic risk classification*	Low	Intermediate	High
RBC transfusion dependency†	No	Yes	—

Risk group	Overall score
Low	0
Intermediate-1	1
Intermediate-2	2-3
High	4-5

Such *et al.*, Haematologica 2011

Outcome of CMML pts according to cytogenetic risk



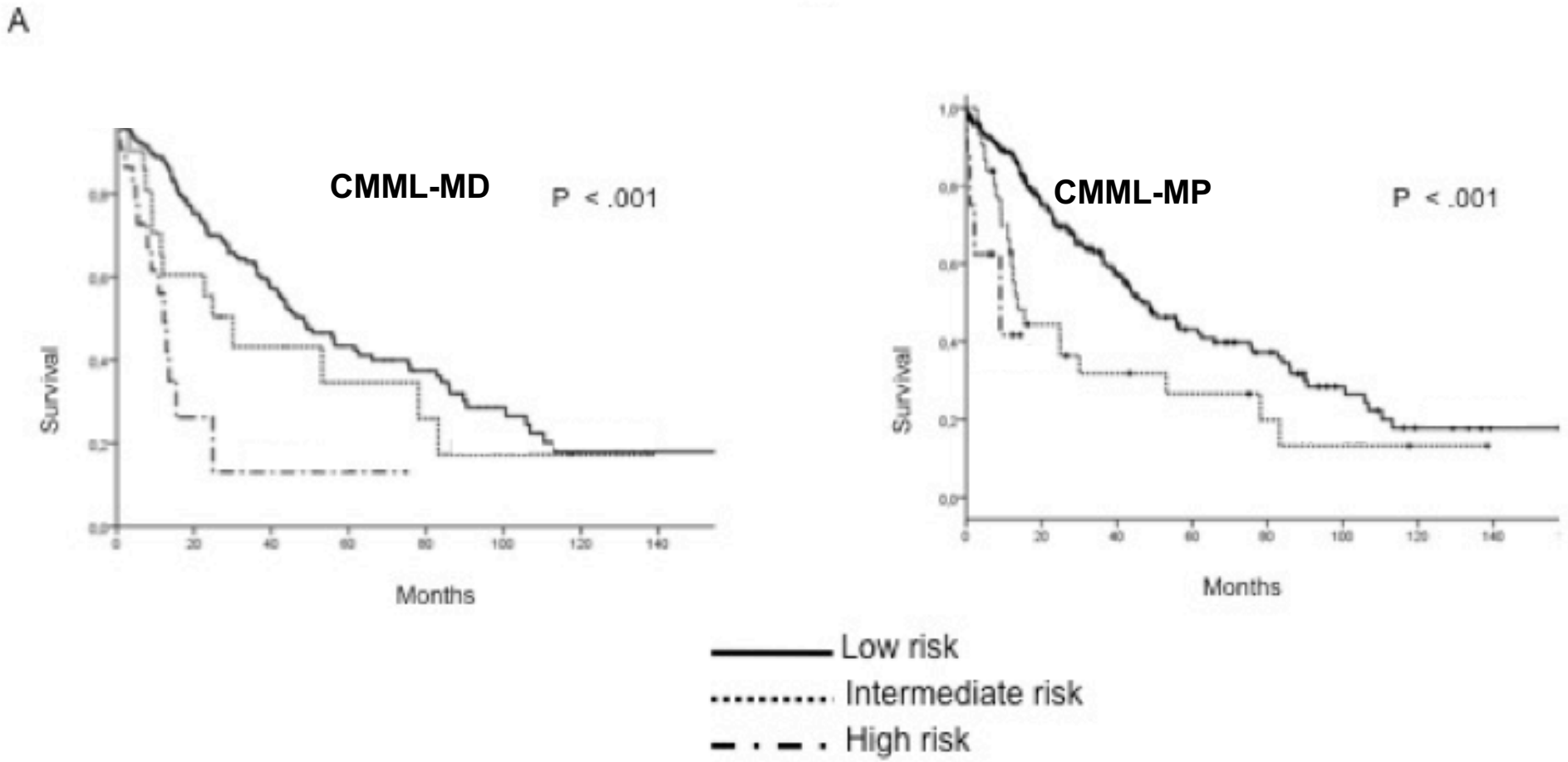
Low risk:
- normal or –Y (single)

High risk:
- abn chr 7, complex, +8

Intermediate risk:
- all others

Meldi et al, JCI, 2015
Such *et al.,* Haematologica 2011

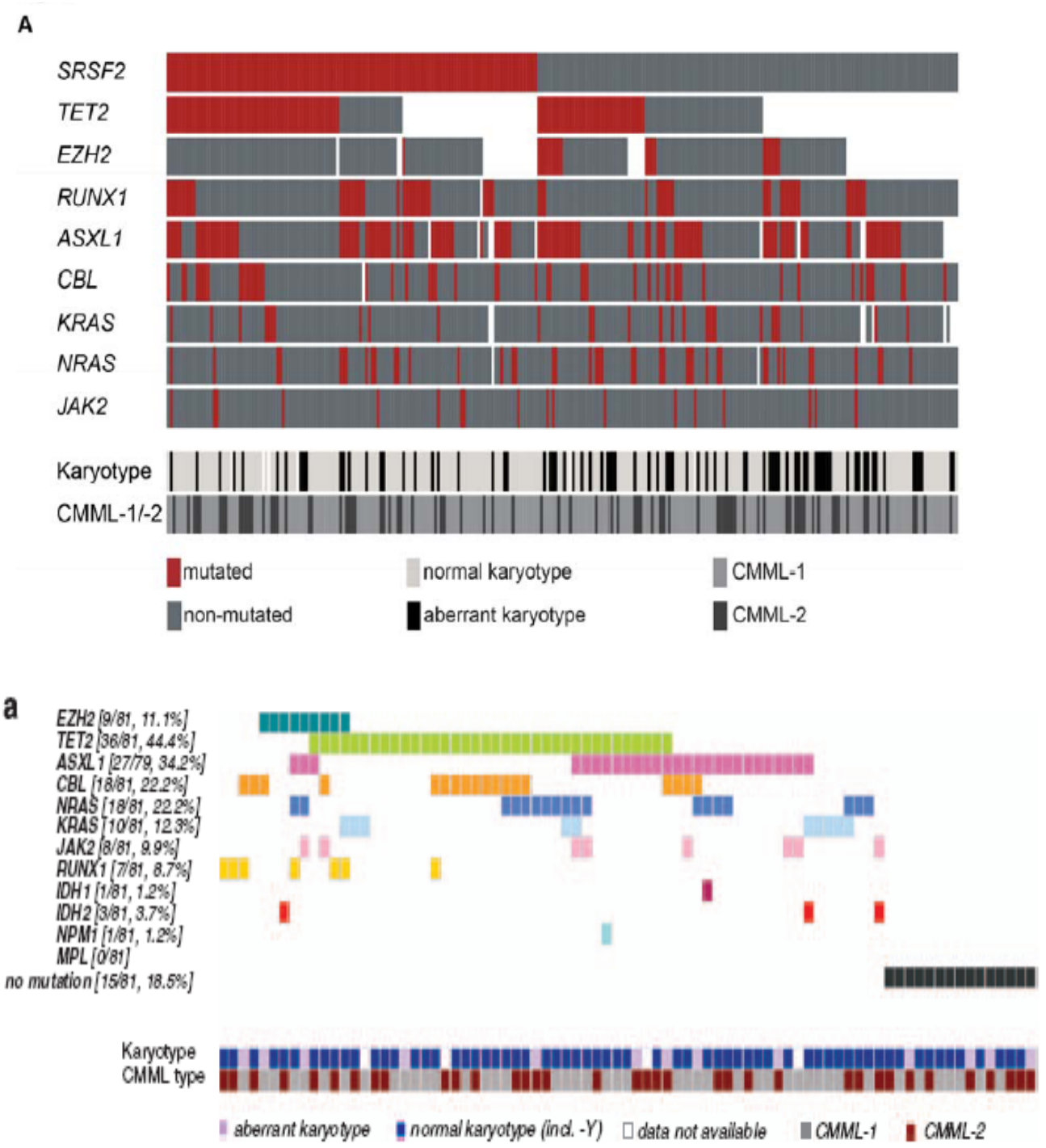
Cytogenetic risk groups are predicting outcome in CMML MD and CMML MP



Such *et al.*, Haematologica 2011

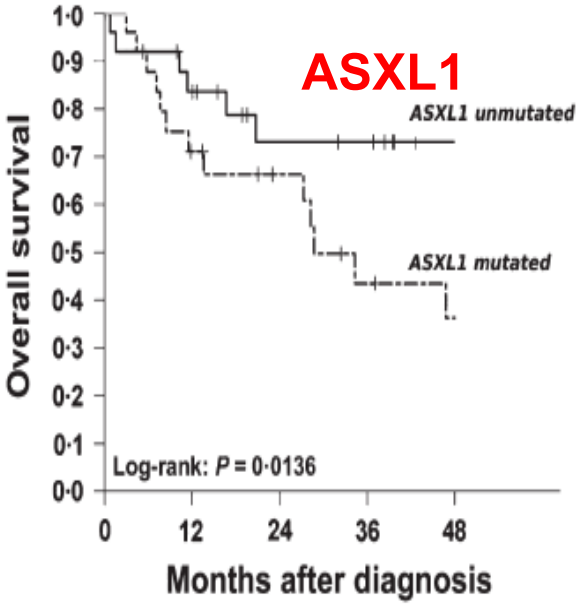
Molecular mutations in CMML

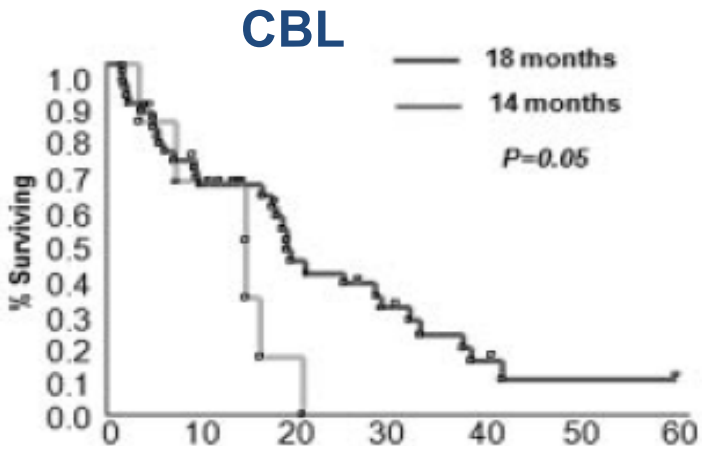
GENES	frequency
TET2	36 - 61%
SRSF2	28 - 47 %
ASXL1	27 - 52%
RUNX1	9 - 37%
CBL	5 - 19%
RAS	11 - 27%
EZH2	6 - 10%
JAK2	1 - 13%
DNMT3A	4 - 10%
IDH1/2	5 - 10%
SF3B1	5%
U2AF1	4 - 8%

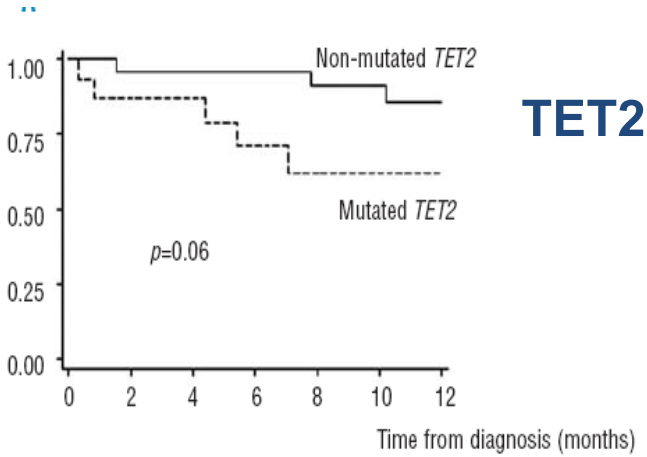


Meggendorfer *et al.* Blood 2012; Grossmann *et al.* Leukemia 2011

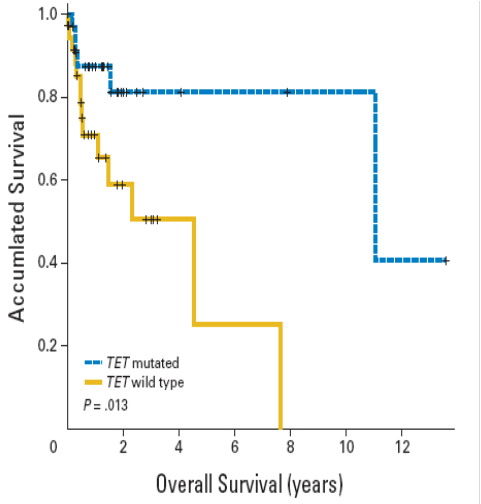
Prognostic relevance of different somatic mutations

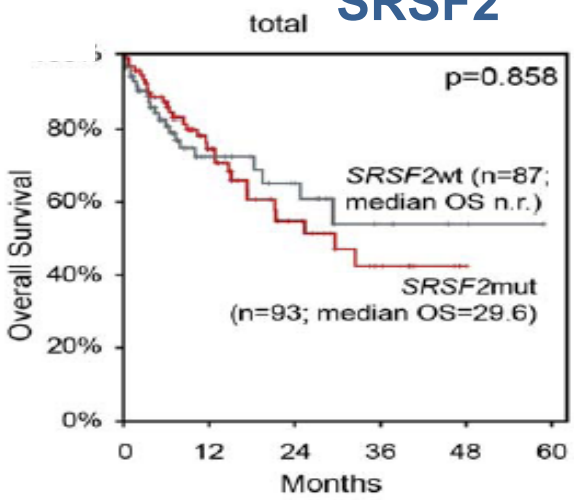






TET2





SRSF2

Meggendorfer *et al.* Blood 2012

Geisi-Boyer et al. BJH 2010

Jankowska *et al.,* Blood 2011

Kosmider et al.,Haematologica. 2009

Kohlmann et al, JCO 2010

Regular Article

blood

MYELOID NEOPLASIA

Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia

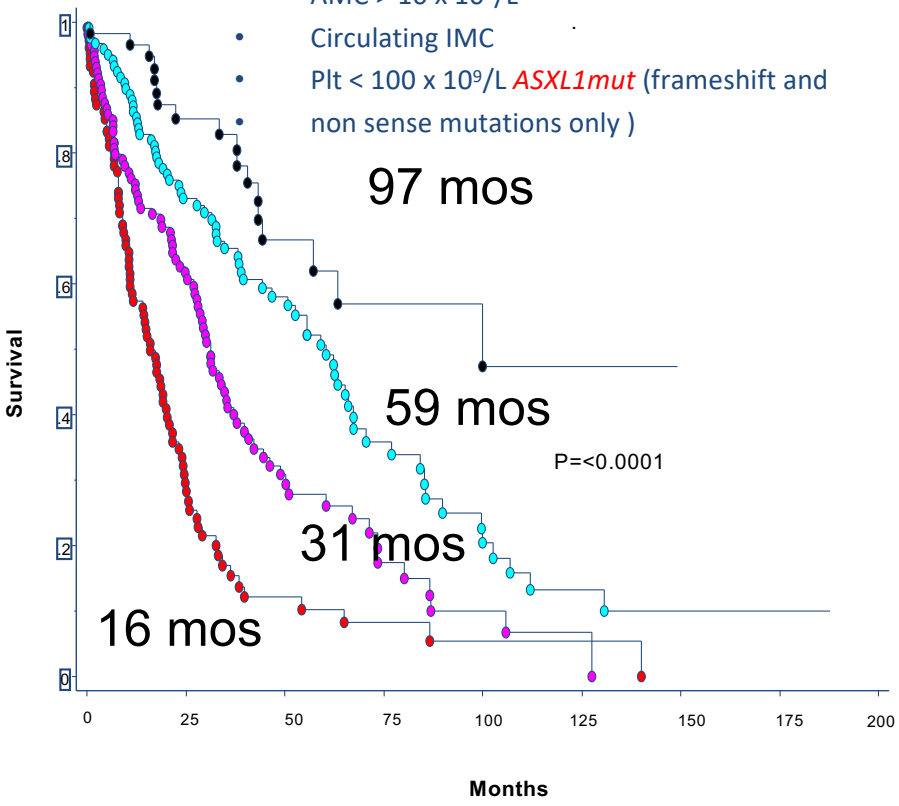
Chiara Elena,[1,2] Anna Gallì,[2] Esperanza Such,[3] Manja Meggendorfer,[4] Ulrich Germing,[5] Ettore Rizzo,[6] Jose Cervera,[3] Elisabetta Molteni,[1] Annette Fasan,[4] Esther Schuler,[5] Ilaria Ambaglio,[2] Maria Lopez-Pavia,[3] Silvia Zibellini,[2] Andrea Kuendgen,[5] Erica Travaglino,[2] Reyes Sancho-Tello,[7] Silvia Catricalà,[2] Ana I. Vicente,[8] Torsten Haferlach,[4] Claudia Haferlach,[4] Guillermo F. Sanz,[3] Luca Malcovati,[1,2,*] and Mario Cazzola[1,2,*]

« mutations in RUNX1, NRAS, SETBP1, and ASXL1 were independently associated with overall survival (OS) »

OS according to Prognostic scores including ASXL1

Molecular Mayo

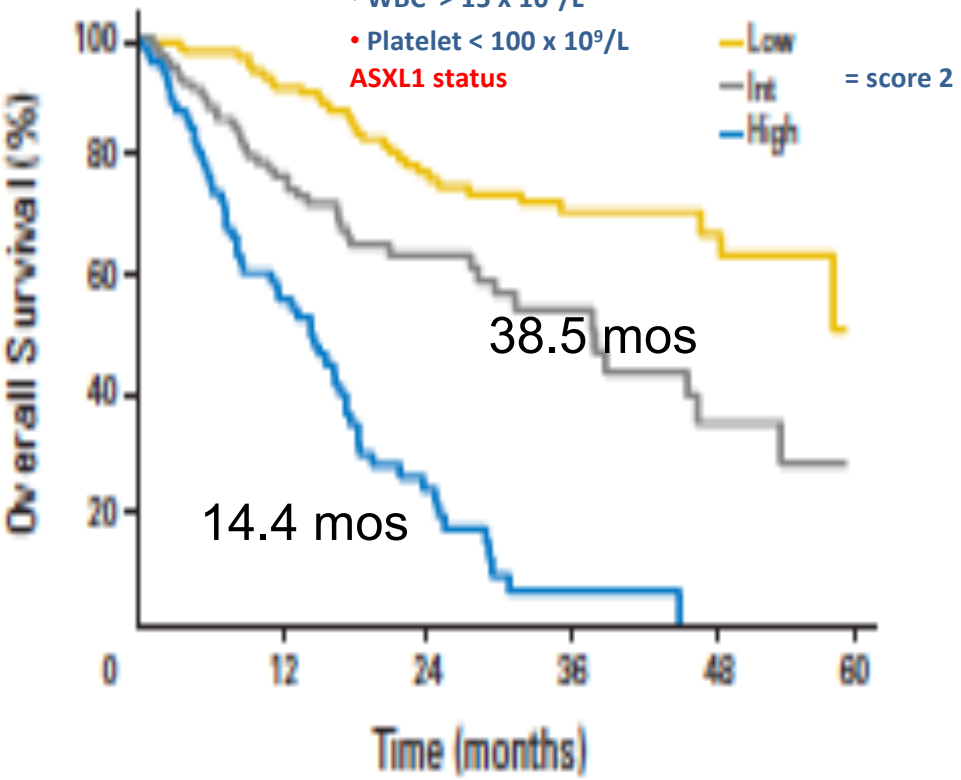
- Hb < 10 g/dl
- AMC > 10 x 10^9/L
- Circulating IMC
- Plt < 100 x 10^9/L *ASXL1mut* (frameshift and non sense mutations only)



GFM

- Age > 65 yrs
- Anemia (M < 10 g/dL, F < 11 d/dL)
- WBC > 15 x 10^9/L
- Platelet < 100 x 10^9/L

ASXL1 status = score 2



Patnaik et al. Leukemia. 2014;28(11):2206

Itzykson R et al. JCO. 2013;31(19):2428-36

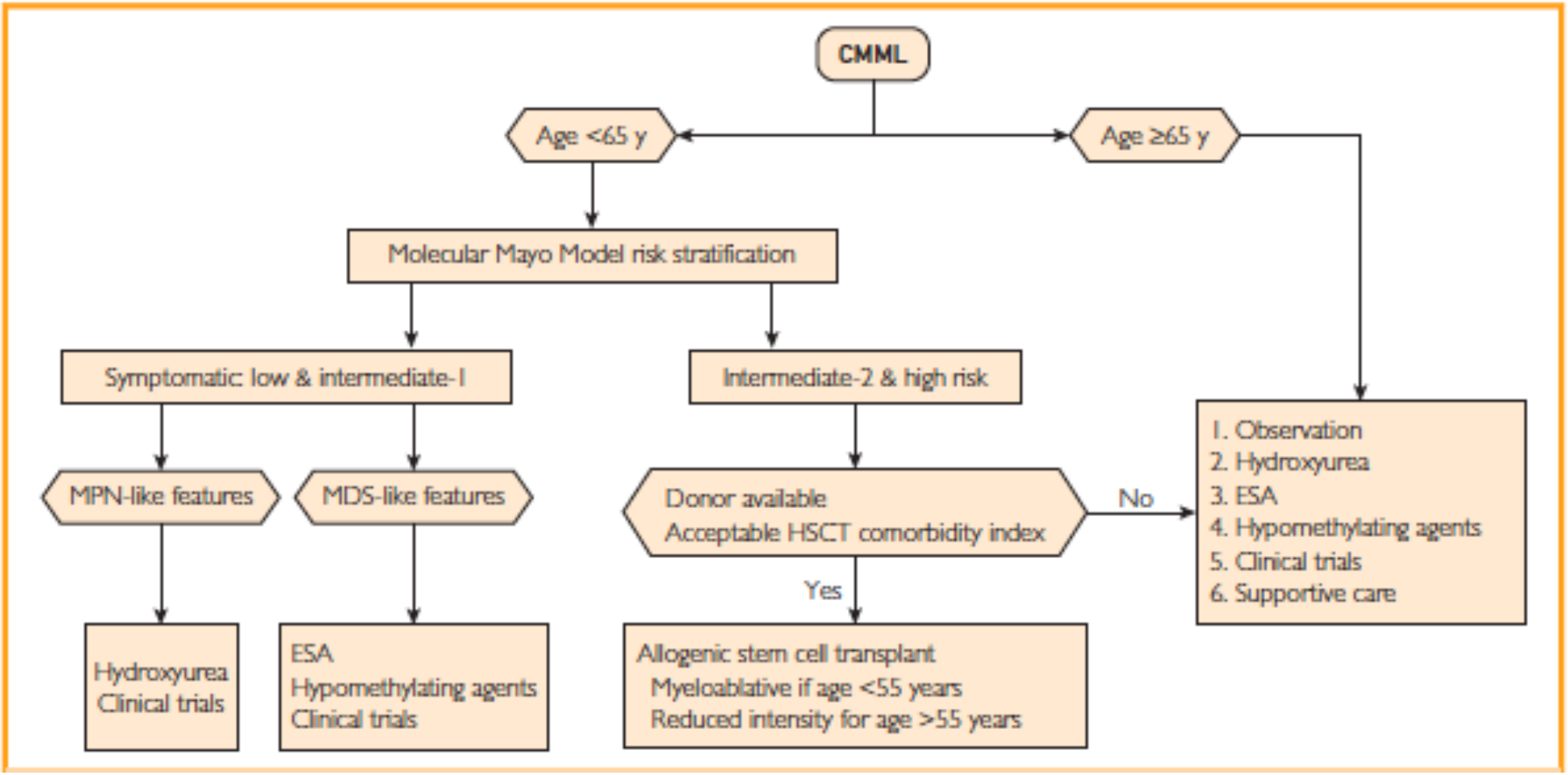
An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults

Michael R. Savona,[1] Luca Malcovati,[2] Rami Komrokji,[3] Ramon V. Tiu,[4] Tariq I. Mughal,[5] Attilio Orazi,[6] Jean-Jacques Kiladjian,[7] Eric Padron,[3] Eric Solary,[8] Raoul Tibes,[9] Raphael Itzykson,[7] Mario Cazzola,[2] Ruben Mesa,[9] Jaroslaw Maciejewski,[4] Pierre Fenaux,[7] Guillermo Garcia-Manero,[10] Aaron Gerds,[4] Guillermo Sanz,[11] Charlotte M. Niemeyer,[12] Francisco Cervantes,[13] Ulrich Germing,[14] Nicholas C. P. Cross,[15] and Alan F. List,[3] on behalf of the MDS/MPN International Working Group

Table 2. Proposed criteria for measurement of treatment response in adult MDS/MPN

CR (presence of all of the following improvements)*
Bone marrow: ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity*
Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤grade 1 fibrosis)†
Peripheral blood‡
WBC ≤10 × 10^9 cells/L
Hgb ≥11 g/dL
Platelets ≥100 × 10^9/L; ≤450 × 10^9/L
Neutrophils ≥1.0 × 10^9/L
Blasts 0%
Neutrophil precursors reduced to ≤ 2%
Monocytes ≤1 × 10^9/L
Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
Provisional category of CR with resolution of symptoms:‡ CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia*

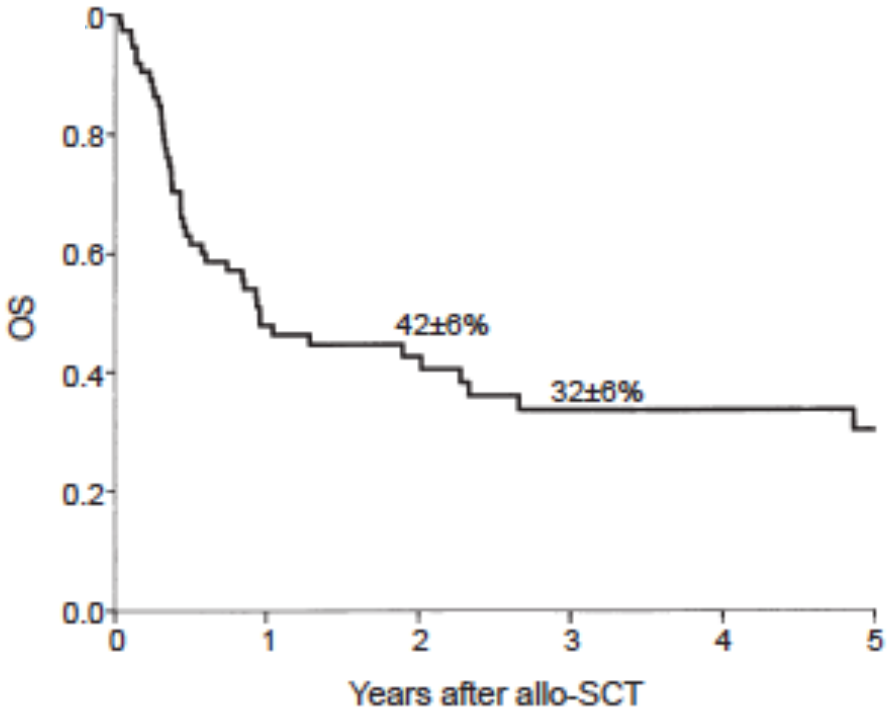
Therapeutic recommendations for CMML



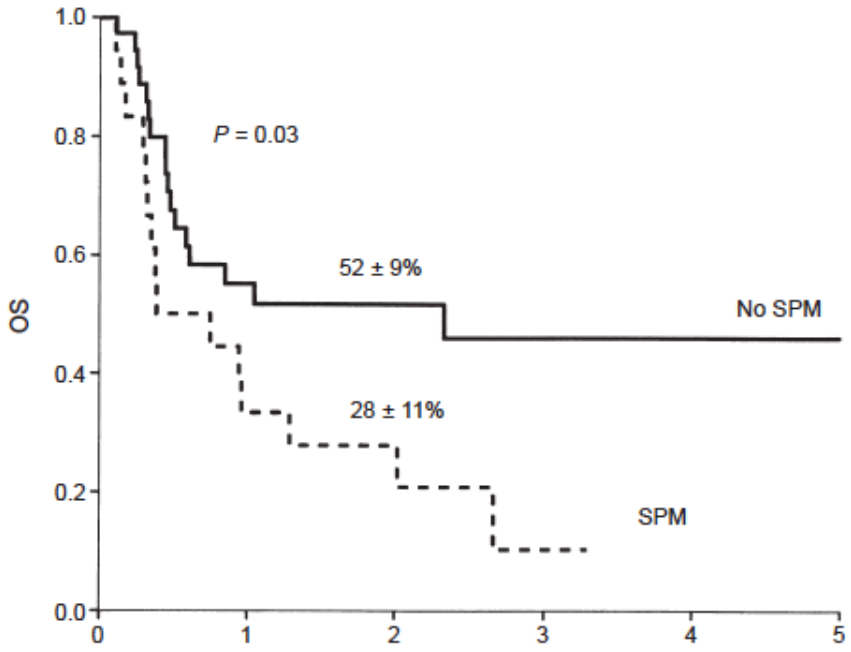
Patnaik et al; 2016

OS in CMML after allogeneic HSCT

overall

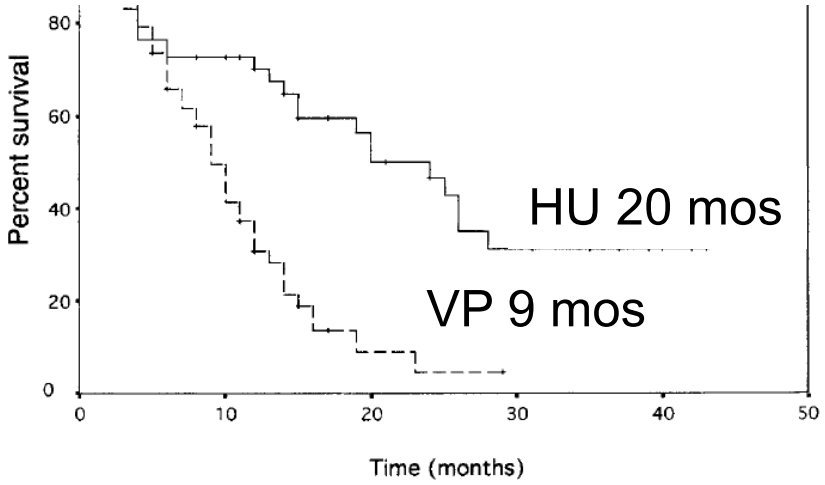


according spleen size

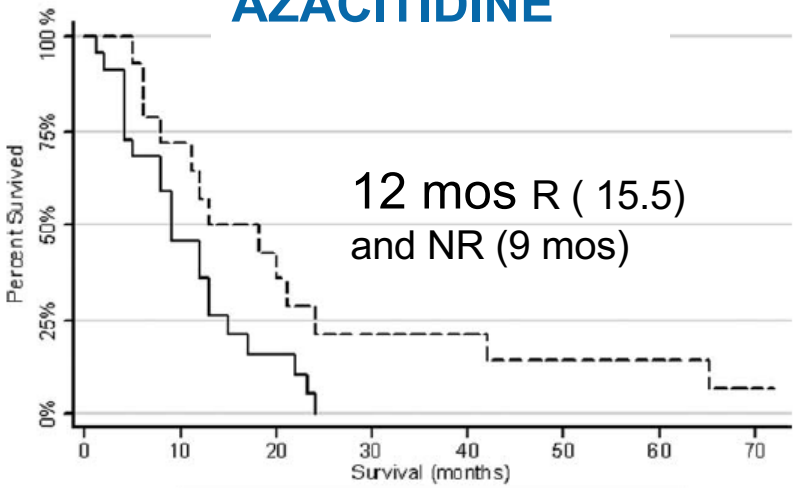


Park S, et al., Eur J Haematol. 2013

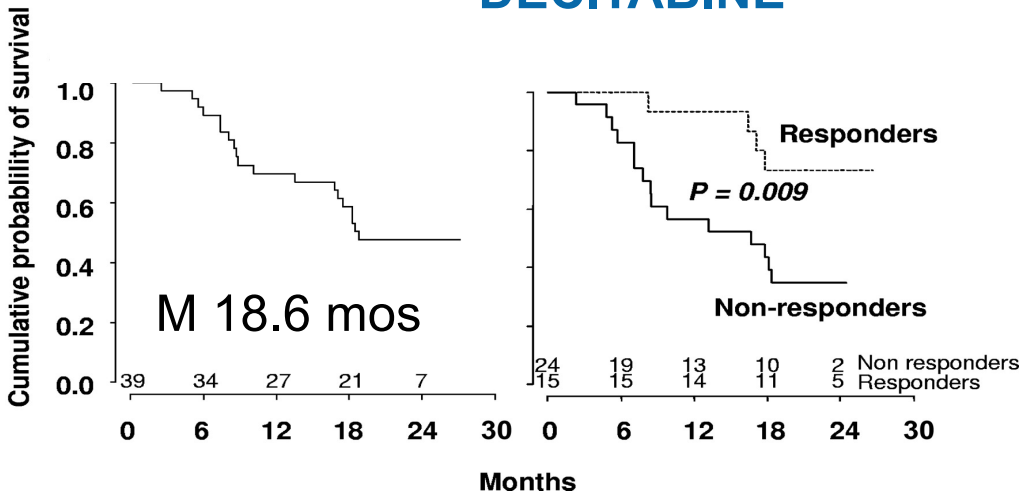
OS in CMML after therapy

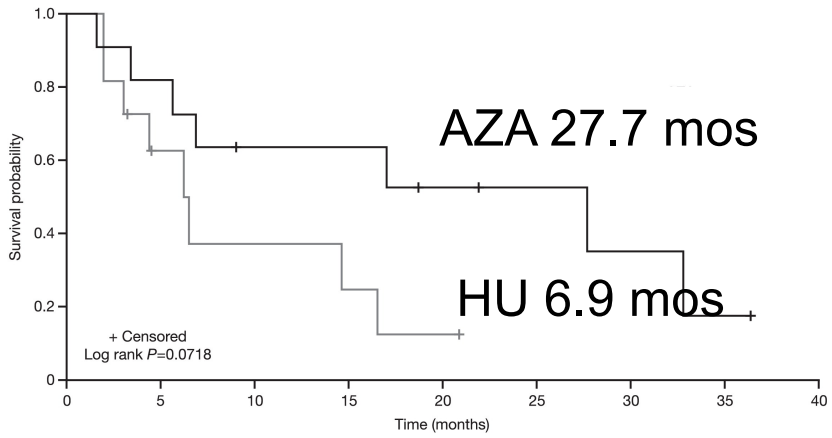


AZACITIDINE



DECITABINE





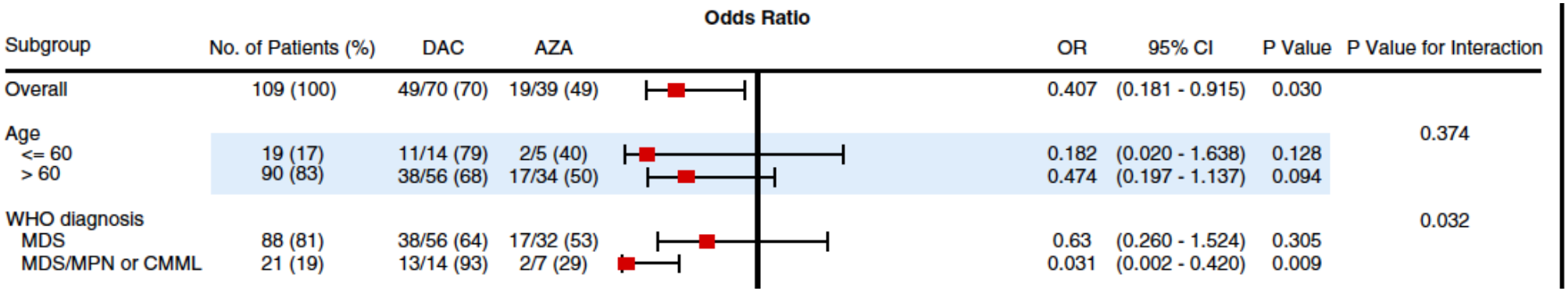
Wattel et al, Blood 1996
Braun et al., Blood 2011

Costa et al, Cancer 2011;
Pleyer et al., Leuk Res 2014

Low-Dose Decitabine or Azacitidine in MDS/MPN

- **Bayesian adaptive randomization: DAC vs. AZA**
- **Regimens:**
  - DAC 20 mg/m^2 IV D1-3 every 4 weeks
  - AZA 75 mg/m^2 IV/SC D1-3 every 4 weeks
- **Response assessment by modified IWG 2006**

	Overall	DAC	AZA
MDS/MPN-U	6 (5)	2 (3)	4 (10)
CMML	16 (14)	10 (14)	6 (15)



Jabbour et al , Blood. 2017 Sep 28;130(13):1514-1522.

A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia

V Santini, B Allione, G Zini, D Gioia, M Lunghi, A Poloni, D Cilloni, A Sanna, E Masiera, M Ceccarelli, O Abdel-Wahab, A Terenzi, E Angelucci, C Finelli, F Onida, A M Pelizzari, D Ferrero, G Saglio, M Figueroa, A Levis

Santini et al; Leukemia. 2018 Feb;32(2):413-418.

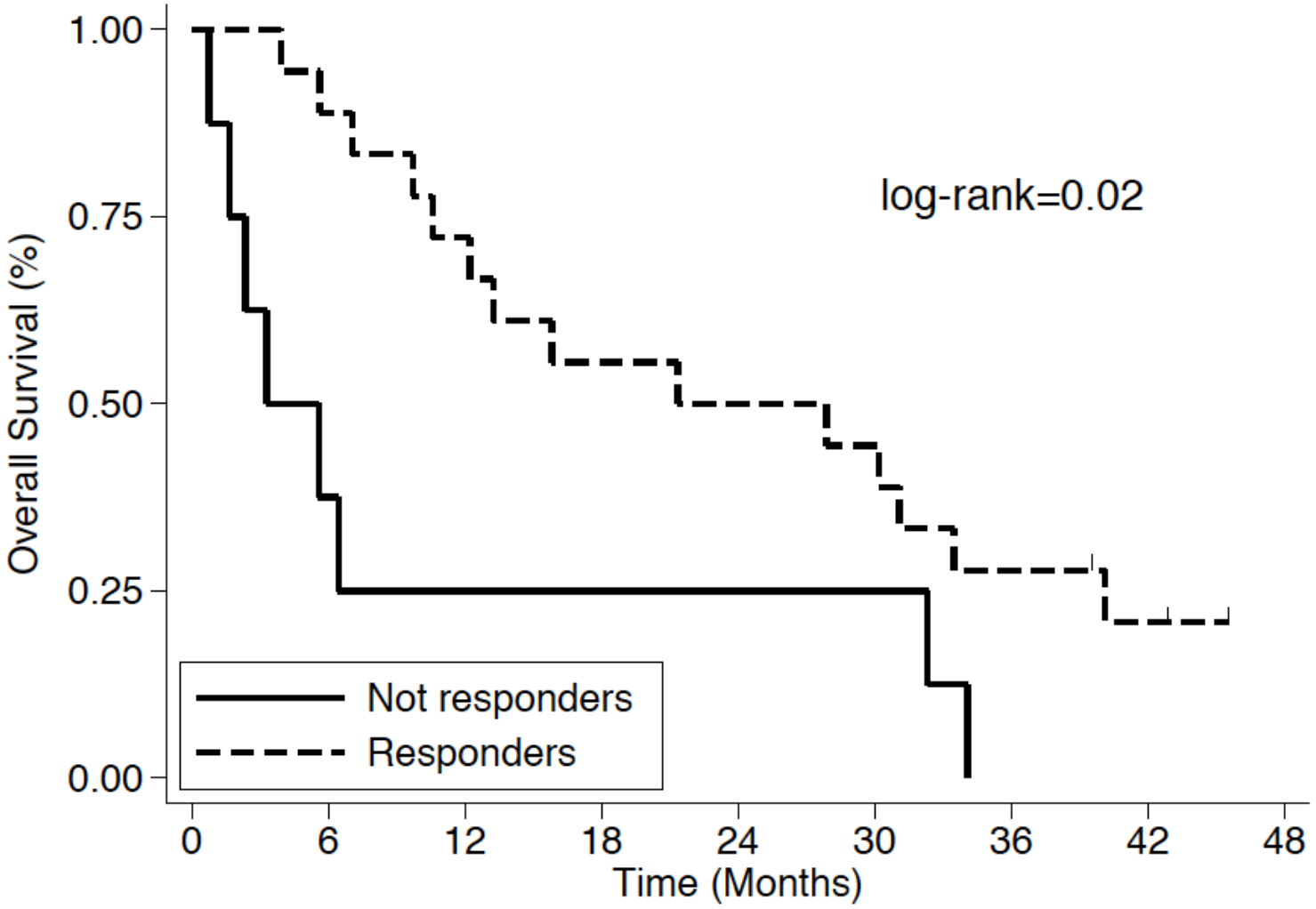
FONDAZIONE
ITALIANA
SINDROMI
MIELODISPLASTICHE

Response to decitabine in CMML patients (7% ORR in TP53 mut)

	Number (%) of patients									
	ITT (n = 42)		CMML-1[a] (n = 26)		CMML-2[a] (n = 16)		dCMML (n = 14)		pCMML (n = 28)	
ORR	20	(47.6)	15	(57.6)	5	(31.25)	9	(64.3)	11	(39.3)
CR	7	(16.6)	5	(19.2)	2	(12.5)	3	(21.4)	4	(14.3)
mCR	8	(19.0)	6	(23.1)	2	(12.5)	4	(28.6)	4	(14.3)
PR	1	(2.4)	0	(0.0)	1	(6.2)	0	(0.0)	1	(3.5)
HI	4	(9.5)	4	(15.3)	0	(0.0)	2	(14.2)	2	(7.2)
SD	9	(21.4)	4	(15.3)	5	(31.3)	0	(0.0)	9	(32.1)
PD	13	(31.0)	7	(26.9)	6	(37.5)	5	(35.7)	8	(28.6)

Santini et al, Leukemia 2017

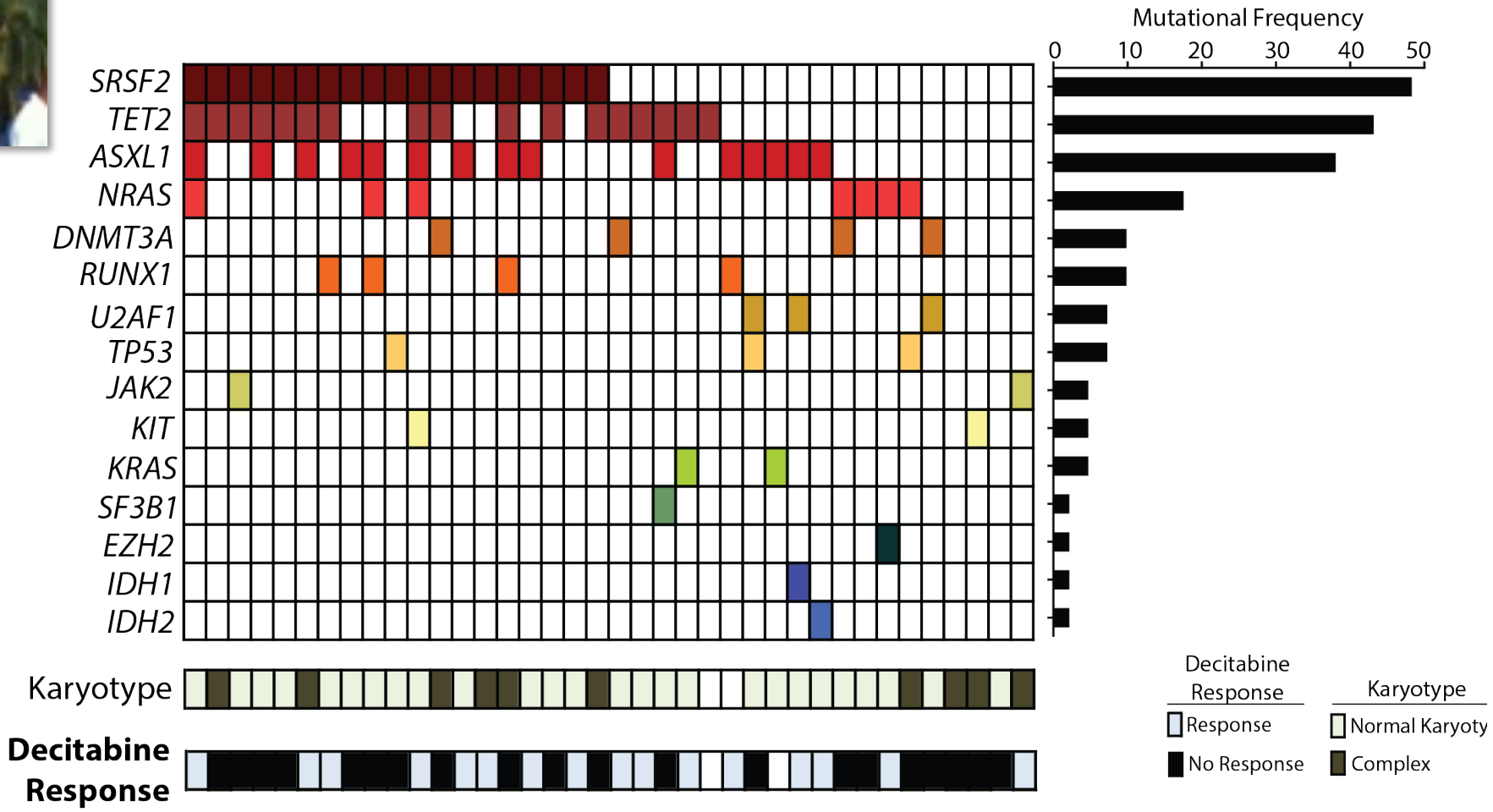
Overall survival according to Response to DAC



At risk:									
Not responders	8	3	2	2	2	2	0	0	0
Responders	18	16	13	10	9	8	5	3	1

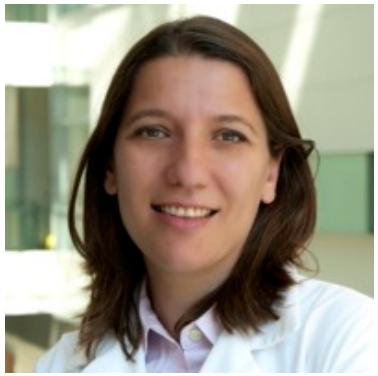
Mutational profiles do not correlate with response to DAC

Omar Waab

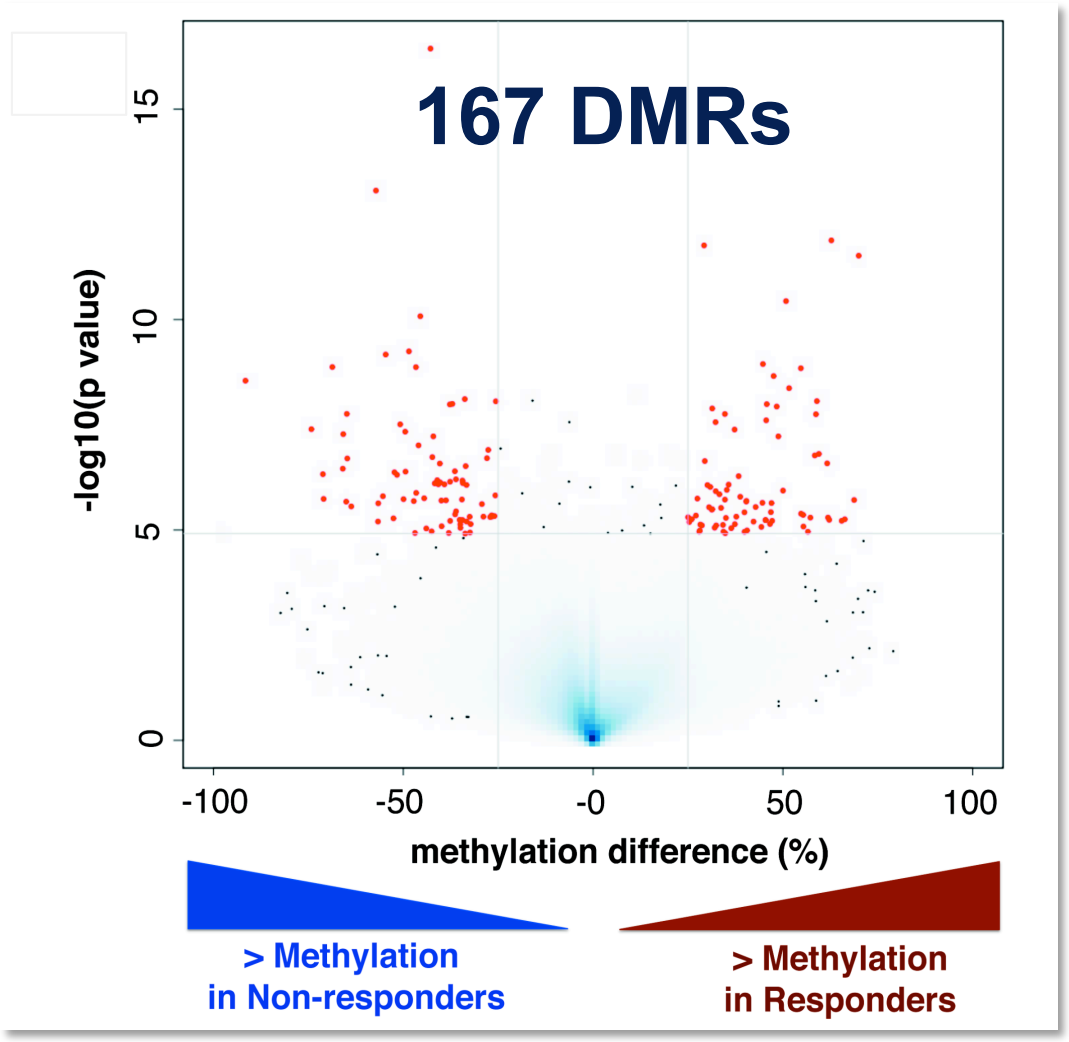


Santini et al, Leukemia 2017
Meldi et al; J Clin Invest. 2015

Distinct DNA methylation profiles at diagnosis is associated with response to DAC

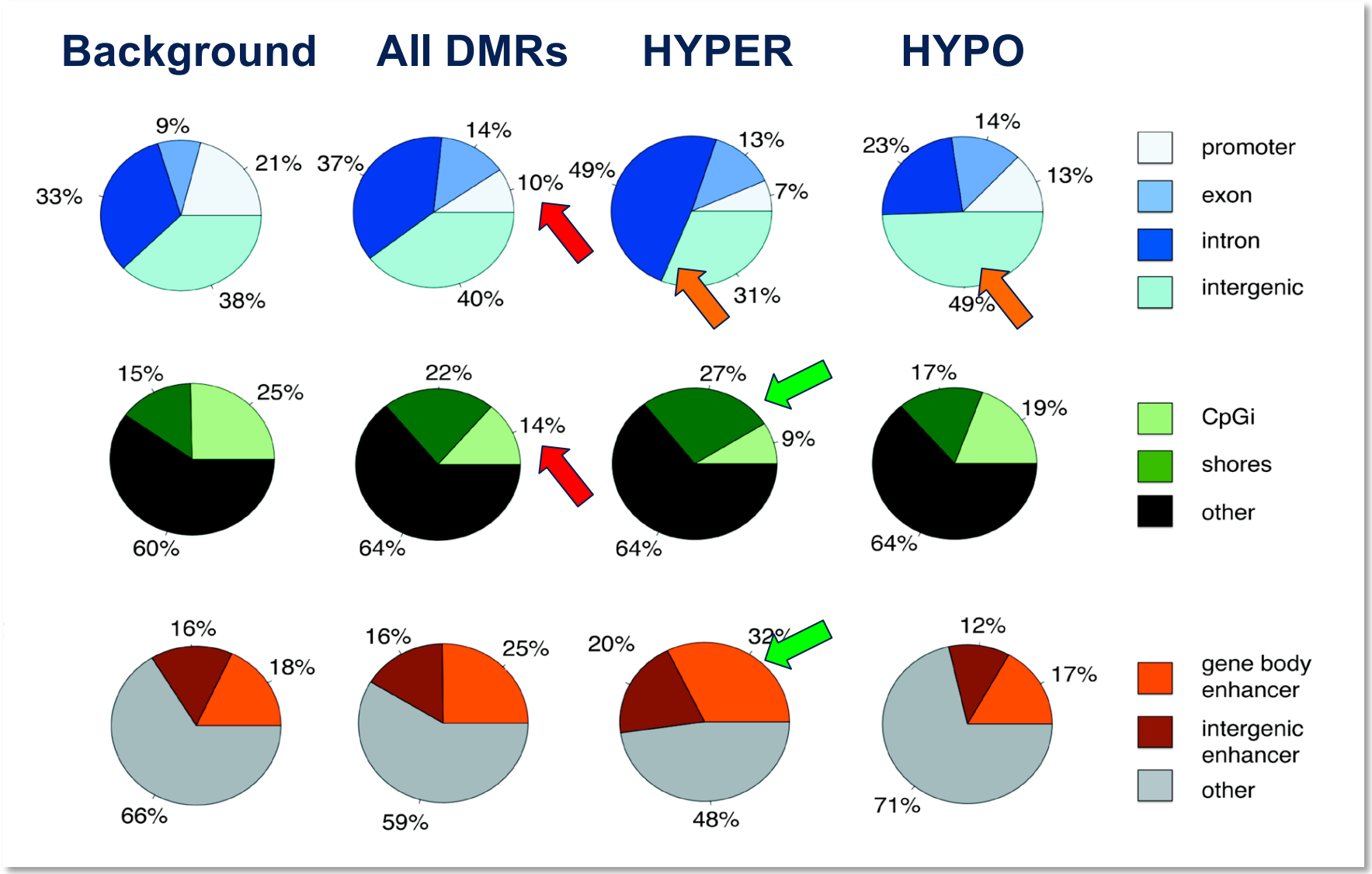


ME Figueroa
Michigan University
(now Miami U)



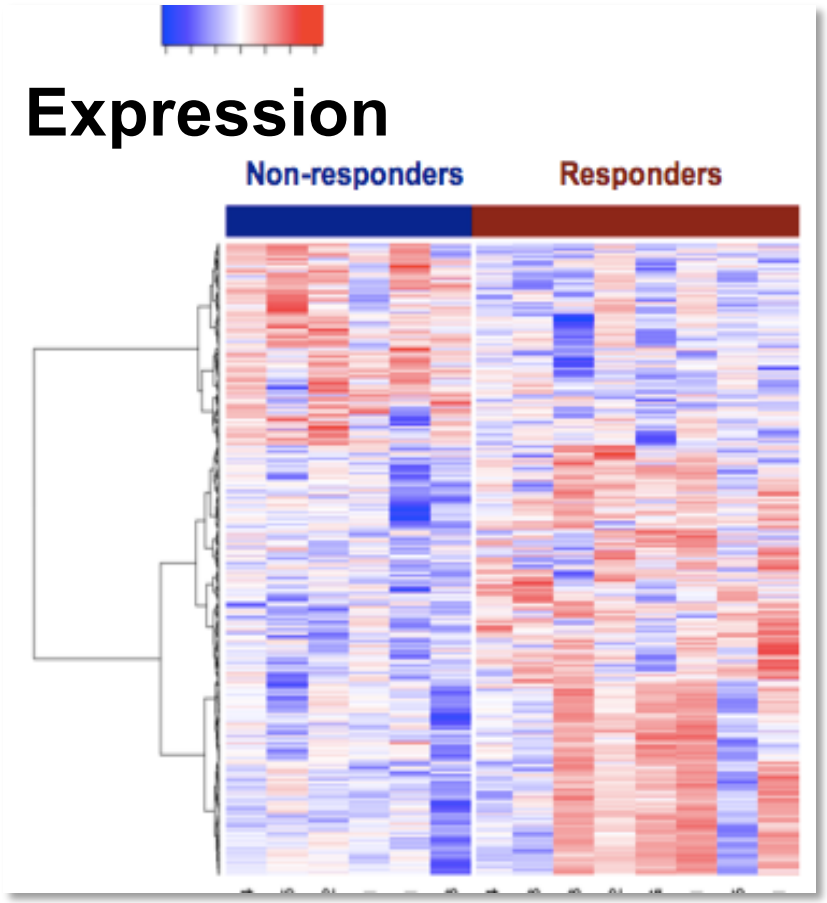
Meldi, et al. JCI 2015

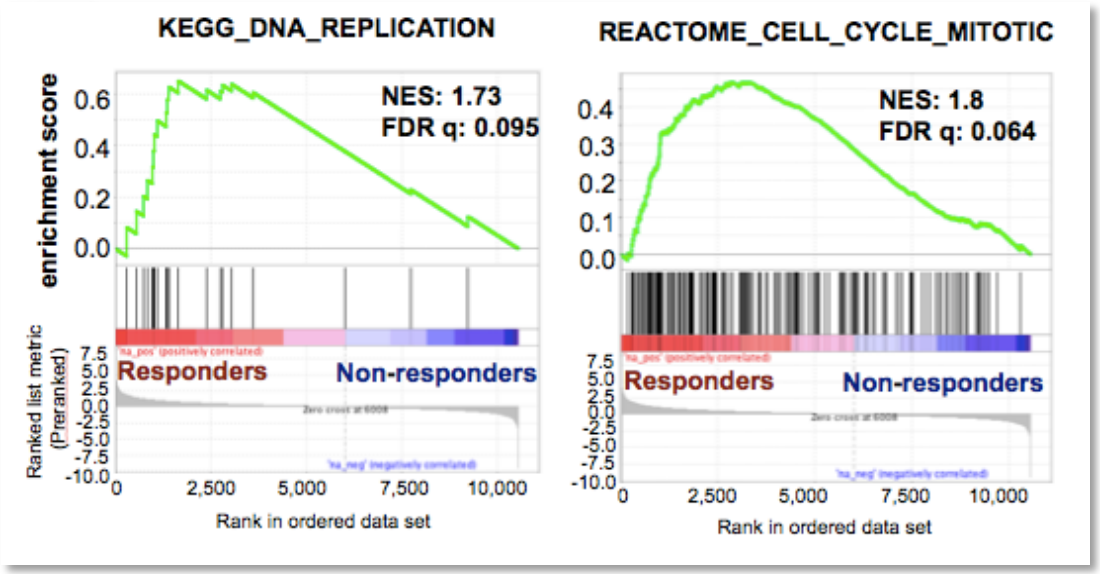
Differentially methylated regions are enriched at distal intergenic regions and enhancers

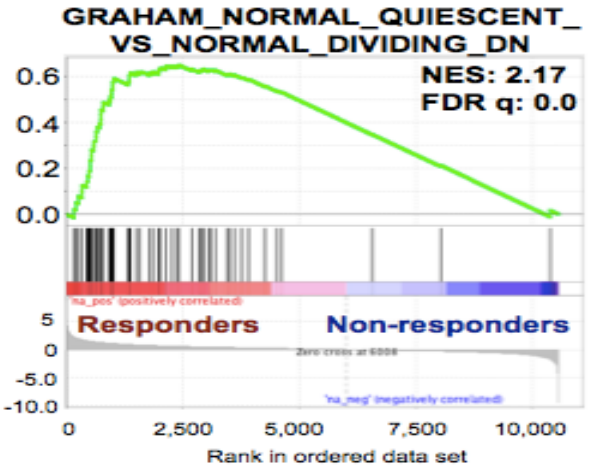


Meldi, et al. JCI 2015

Differential gene expression at diagnosis associated with response to DAC

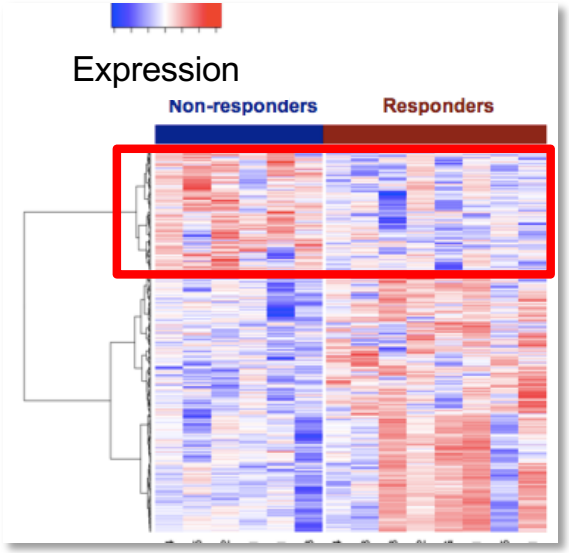


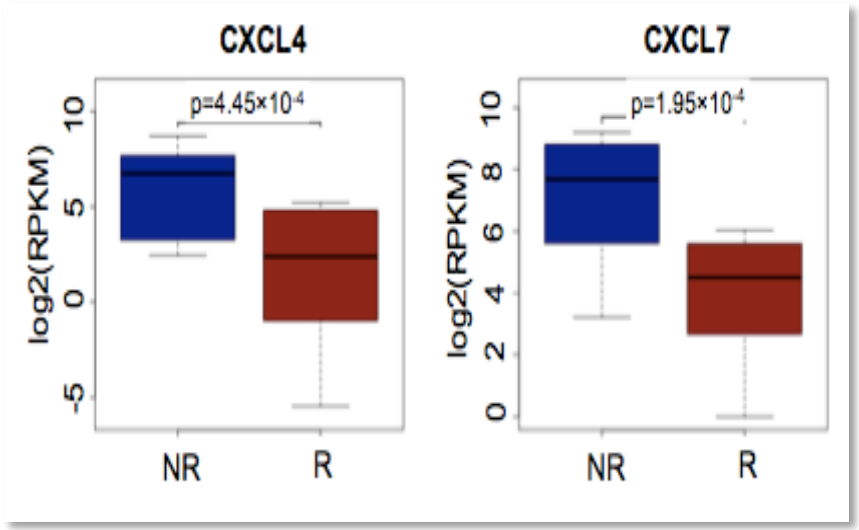


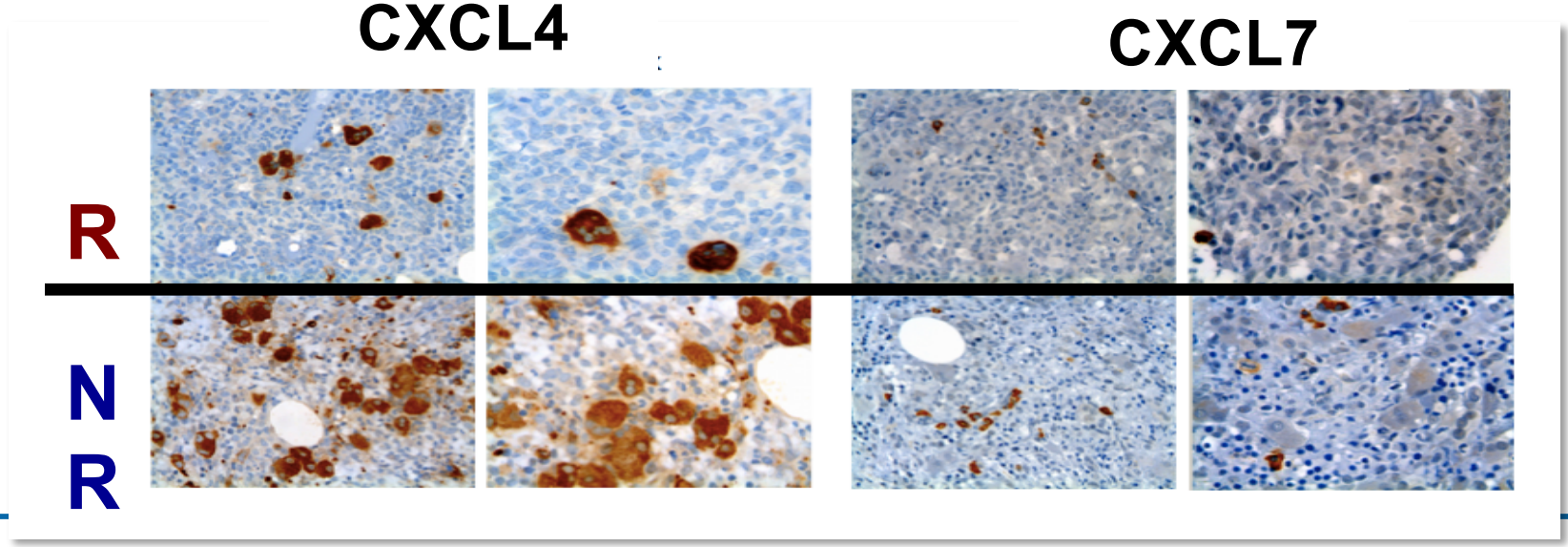


Meldi, et al. JCI 2015

CXCL4 and CXCL7 are up-regulated in the bone marrow of non-responders







Meldi, et al. JCI 2015

Response to DAC is associated with reversal of hypermethylation

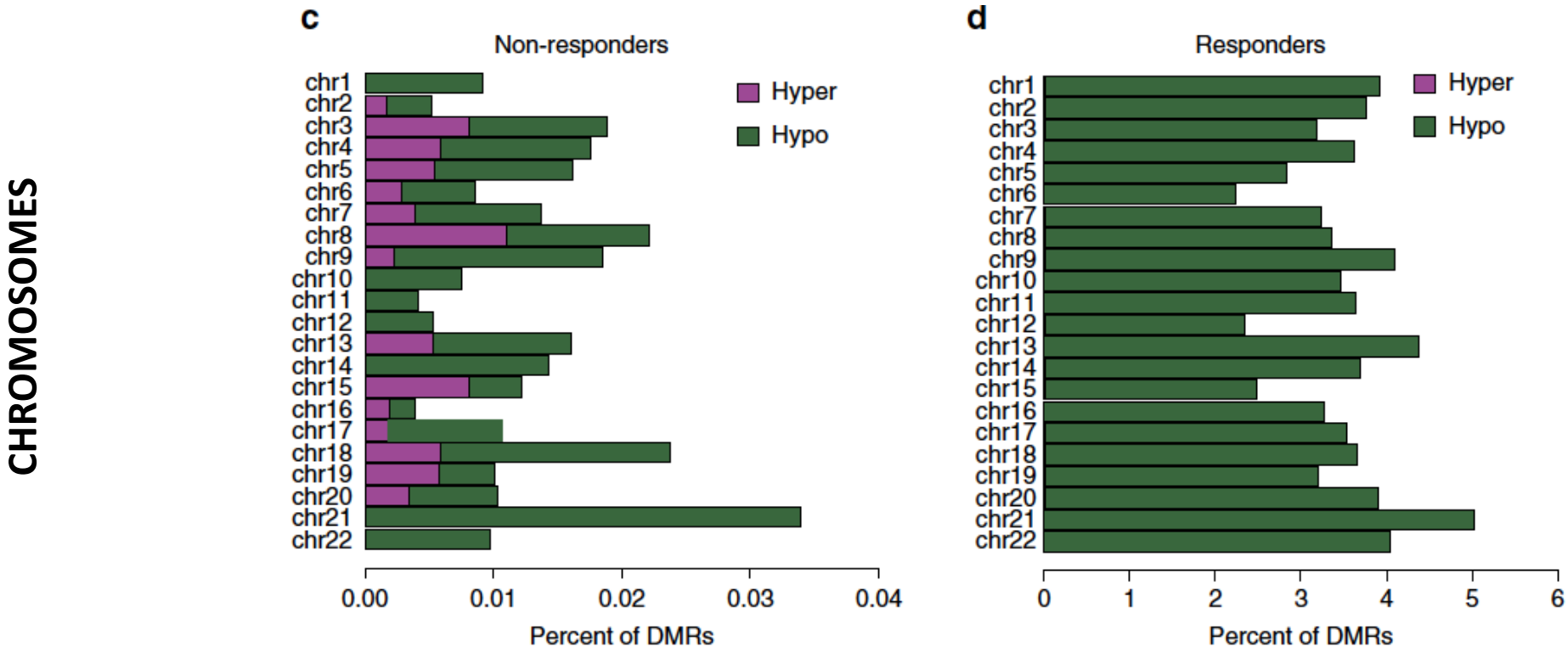
Before DAC – After DAC

- Loss of mC ≥ 25% after DAC
- Gain of mC ≥25% after DAC

Merlevede et al Nat Commun. 2016 Feb 24;7:10767

Response to DAC is associated with reversal of hypermethylation

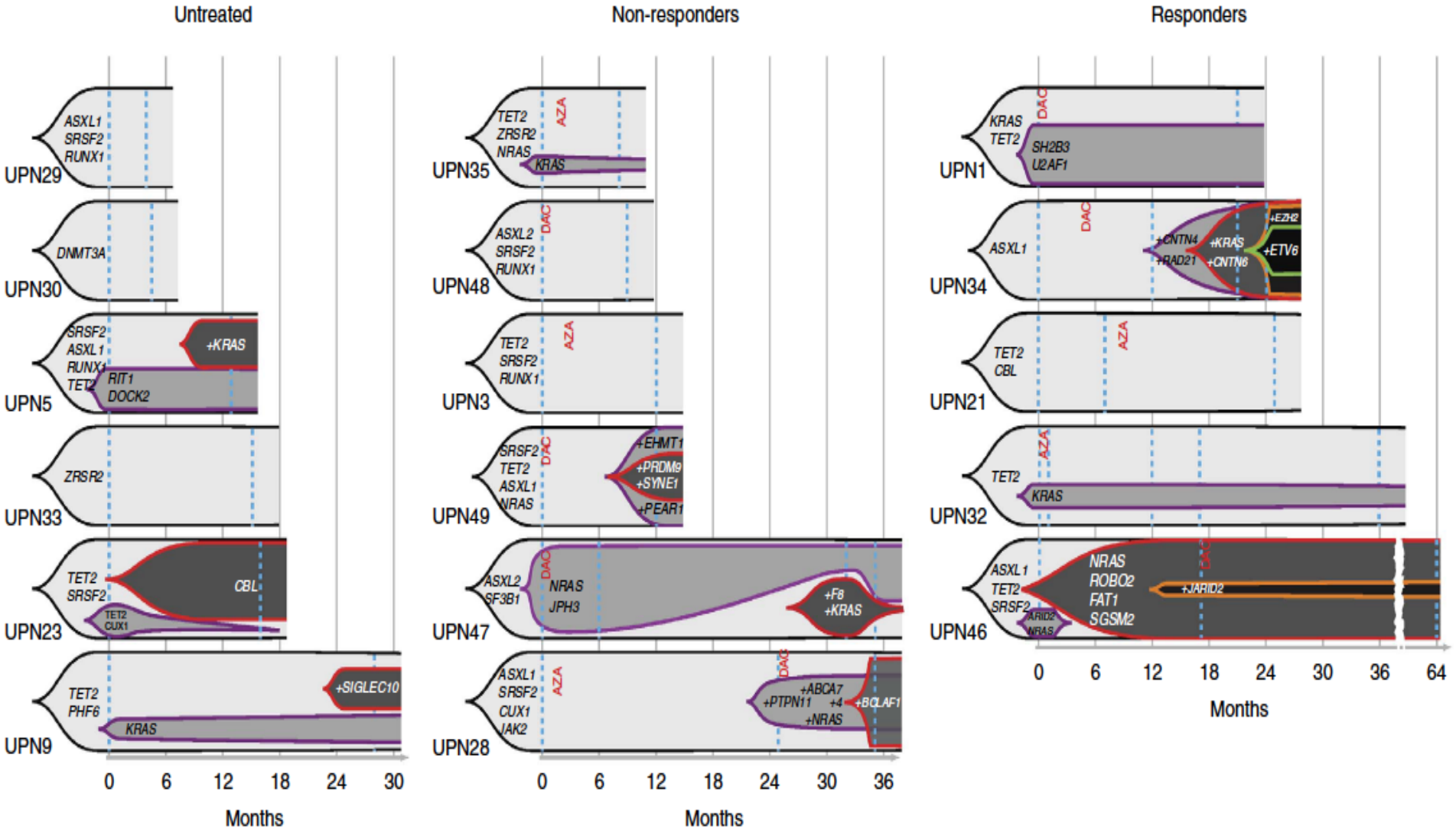
Before DAC – After DAC



- **Loss of mC ≥ 25% after DAC**
- **Gain of mC ≥25% after DAC**

Merlevede et al Nat Commun. 2016 Feb 24;7:10767.

Mutation allele burden remains unchanged after DAC



Merlevede et al Nat Commun. 2016 Feb 24;7:10767.

DACOTA trial

Primary Objective
Event free survival

DAC 20 mg/m^2 x 5 days every 28 days

Patient Randomized into Study
N = 168 1:1

Minimum 6 month treatment & follow-up

HU

Patient Population:

- **Advanced proliferative CMML**
- **Centrally confirmed diagnosis**

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Groupe Francophone des Myélodysplasies

D·MDS Deutsche MDS-Studiengruppe

EHA CMML panel

Participants:

•E Solary
•E Padron
•G F Sanz
•R Itzykson
•V Santini
•T de Witte
•U Platzbecker
•J Cortes
•A van de Loosdrecht
•F Onida
• U Germing
•D Bowen
• N Cross
•L Malcovati,
•P Fenaux, Steering Committee Chair

EHA Executive Office:

•C Smand
•G Rojková

UNIVERSITÀ DEGLI STUDI FIRENZE

DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

Azienda Ospedaliero Universitaria Careggi

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

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Antonella Poloni

Emanuele Angelucci

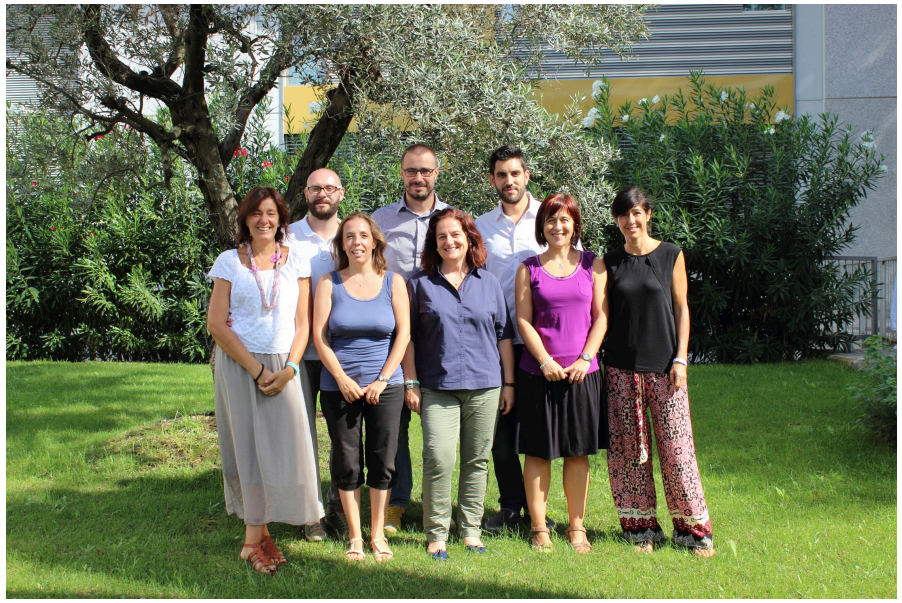
Carlo Finelli

Alessandro Levis

Ana Valencia

Alessandro Sanna

Valeria Santini



Omar Abdel-Wahab

MEMORIAL SLOAN-KETTERING CANCER CENTER • ESTABLISHED 1884 •

Institute Gustave Roussy, Paris

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