Lessons from the EUMDS Registry:
an observational study in lower-risk MDS

https://mds-europe.eu

Twitter: @MDS_EUROPE

EUMDS Registry - Introduction

- **Design:** Prospective observational study collecting longitudinal data every 6 months

- **Aim:** To describe demographics, clinical characteristics, disease-management, treatment outcomes and HRQoL in newly diagnosed MDS patients

- **History:** Initiative of European LeukemiaNet MDS Working Party (WP8)
  Feasibility study 2007
  Start Registry April 2008 in 11 countries
  Newly diagnosed Lower-risk MDS

- **Where are we now?**
  >2680 patients from 147 centres across 18 countries
  Valuable source containing wide variety of clinical data and HRQoL
  34 sub studies & 2 large research projects
  Publications & Presentations

EUMDS Registry
Recent developments

- New protocol extended to High-risk MDS since 2017

- Increased recruitment target

- Extended follow-up

- Addition of molecular analysis

- Set up of electronic data transfer from national registries

- Update of CRFs & definition of data subsets

- Set A: **Core data** (Mandatory) and **General extended data**

- Set B: **Study specific data**

- Analyses & manuscript drafting

- Promotion of collaboration with Patrons

Participating countries

Austria	Reinhard Stauder
Czech Republic	Jaroslav Cermák
France	Pierre Fenaux
Germany	Ulrich Germing
Greece	Argiris Symeonidis
Italy	Luca Malcovati
Netherlands	Saskia Langemeijer
Romania	Aurelia Tatic
Spain	Guillermo Sanz
Sweden	Eva Hellström-Lindberg
United Kingdom	David Bowen *(Co-chair)*
Denmark *(2009)*	Mette S. Holm
Portugal *(2010)*	Antonio Medina Almeida
Poland *(2010)*	Krzysztof Mądry
Israel *(2012)*	Moshe Mittelman
Republic of Serbia *(2013)*	Aleksandar Savic
Croatia *(2013)*	Njetočka Gredelj Šimec
Switzerland (*2018*)	Nicolas Bonadies

Project Coordination   Theo de Witte *(Chief Investigator & Chair)*

Project Management   Radboudumc Nijmegen, NL - Corine van Marrewijk
Data Management & Statistics   University of York, UK - Alex Smith

Recruitment

Cumulative inclusion - Overall
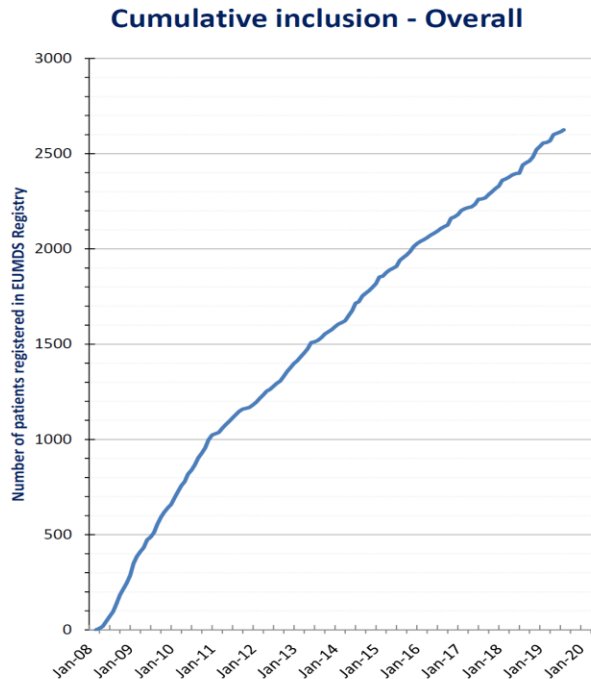
Annual accrual rates

Year	Number of patients
2008	245
2009	394
2010	359
2011	170
2012	210
2013	198
2014	223
2015	213
2016	156
2017	149
2018	204
2019	104

18 countries
147 centres
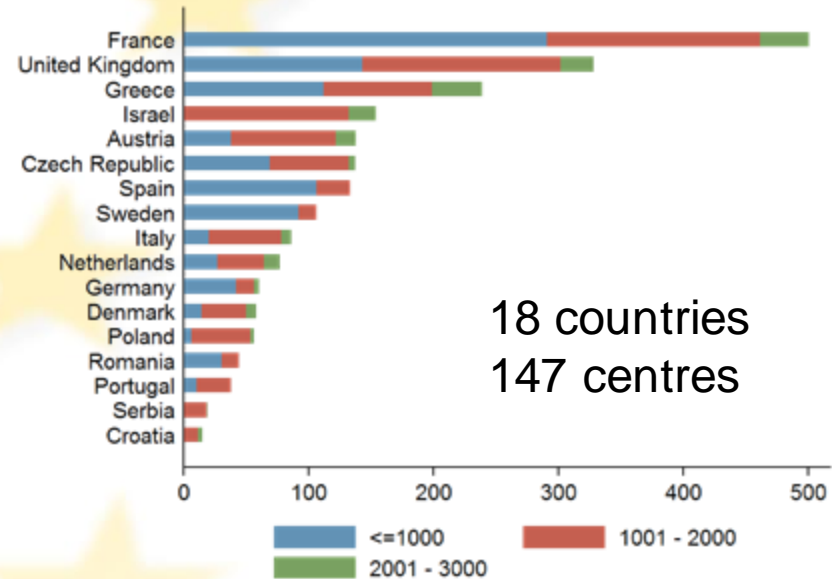
Recruited >2,680

- Median time between diagnosis & inclusion = 43 days
- Total Visits = 11,014
- Mean visits per subject = 4 (1-17)
- Median time between visits = 182 days

Disease Management

Treatment n (%)	1st Visit	Any Visit
Transfusion	624 (30.0)	1,101 (52.1)
ESA	331 (15.7)	958 (45.3)
Chelators	15 (0.7)	199 (9.4)
G-CSF	30 (1.4)	203 (9.6)
Lenalidomide	8 (0.4)	116 (5.5)
Prednisone	47 (2.2)	114 (5.4)
Demethylating	4 (0.2)	131 (6.2)
Immunosuppressives	4 (0.2)	41 (2.0)
Hydroxyurea	6 (0.3)	47 (2.2)

Progress Sub-studies and Projects

- **Overview with IPSS-R (De Swart L)**: Br J Haemat 2015

- **ESA (Garelius HK):** Journal of Internal Medicine 2017

- **Cytomorphology (De Swart L):** Ann Haematology 2017

- **Iron sub study (De Swart L):** Haematologica 2018

- **Kinetics of cytopenias (Itzykson R)**: Blood Advances 2018

- **HRQoL (Stauder R):** Leukemia 2018

- **Transfusion (De Swart L):** Haematologica 2019

- **Chelation (Hoeks M):** Haematologica 2019

- **Triage-MDS and MDS-Right projects:** to be completed in 2020

- **Association of AoE with HRQoL and survival (Wouters H):** Haematologica 2019

- **Dynamics of clonal hematopoiesis in AoE (Van Zeventer I)** Blood in press 2020

Treatment: ESA (any visit)
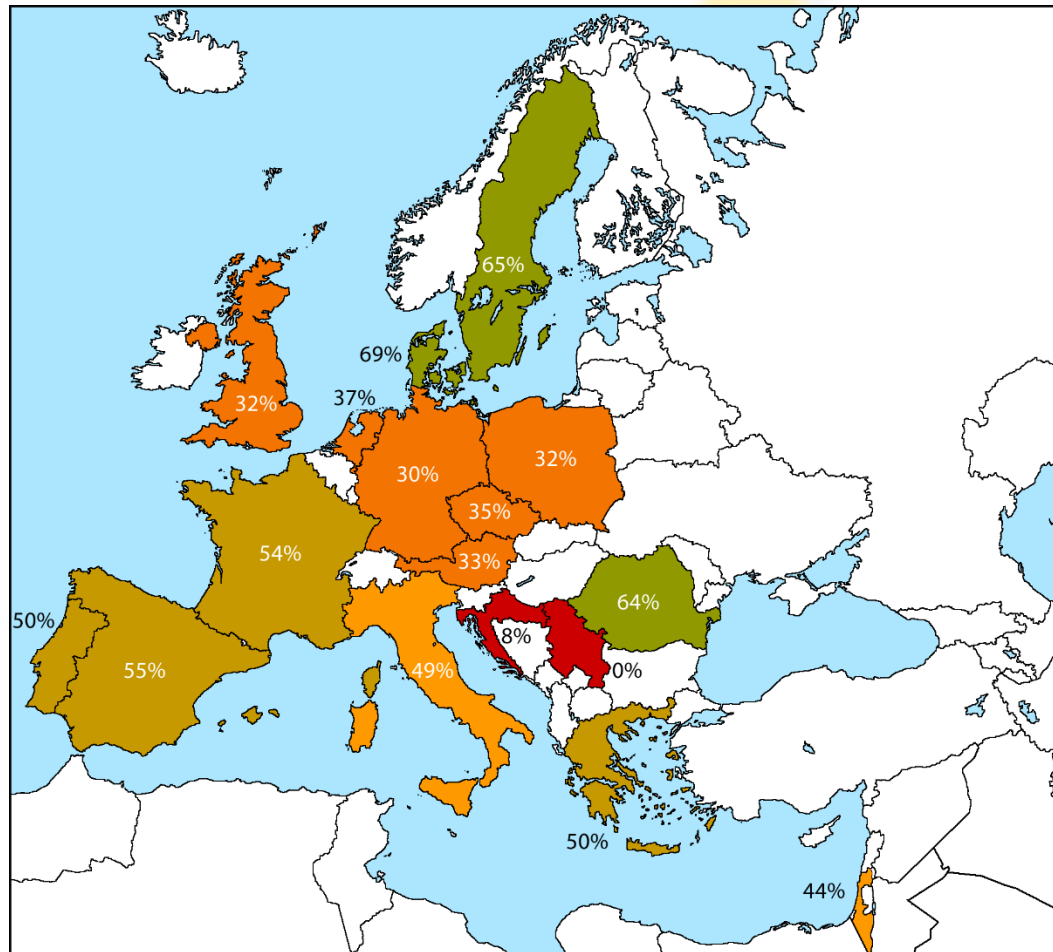
ERYTHROPOIESIS STIMULATING AGENTS SIGNIFICANTLY DELAY THE ONSET OF A REGULAR TRANSFUSION NEED IN NON-TRANSFUSED PATIENTS WITH LOWER-RISK MDS

HEGE KG GARELIUS, W. THOMAS JOHNSTON, ALEXANDRA G SMITH, SOPHIE PARK, LOUISE DE SWART, PIERRE FENAUX, ARGIRIS SYMEONIDIS, GUILLERMO SANZ, JAROSLAV CERMAK, REINHARD STAUDER, LUCA MALCOVATI, MOSHE MITTELMAN, ARJAN VAN DE LOOSDRECHT, CORINE VAN MARREWIJK, DAVID BOWEN, SIMON CROUCH, THEO DE WITTE, AND EVA HELLSTRÖM-LINDBERG FOR THE EUMDS STUDY GROUP IN
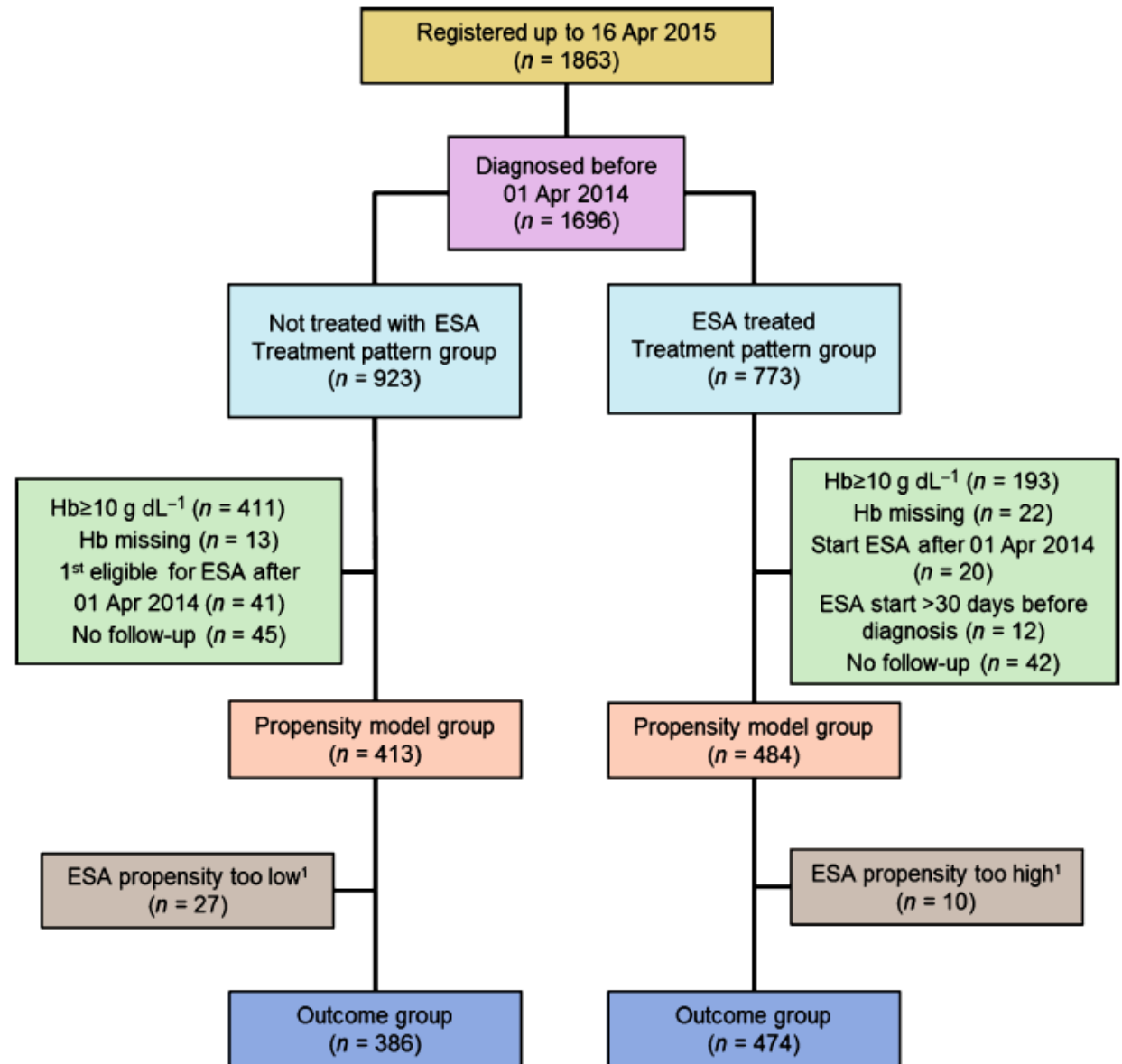
ESA treated pts:

Outcome measured from start of treatment

Untreated pts:

Outcome measured from "pseudostart" Hb <10 g/dl or start of transfusion need

Registered up to 16 Apr 2015 ($n = 1863$)

Diagnosed before 01 Apr 2014 ($n = 1696$)

Not treated with ESA Treatment pattern group ($n = 923$)

ESA treated Treatment pattern group ($n = 773$)

Hb≥10 g dL^{-1} ($n = 411$)
Hb missing ($n = 13$)
1st eligible for ESA after 01 Apr 2014 ($n = 41$)
No follow-up ($n = 45$)

Hb≥10 g dL^{-1} ($n = 193$)
Hb missing ($n = 22$)
Start ESA after 01 Apr 2014 ($n = 20$)
ESA start >30 days before diagnosis ($n = 12$)
No follow-up ($n = 42$)

Propensity model group ($n = 413$)

Propensity model group ($n = 484$)

ESA propensity too low[1] ($n = 27$)

ESA propensity too high[1] ($n = 10$)

Outcome group ($n = 386$)

Outcome group ($n = 474$)

Survival after start or pseudostart of ESA treatment

Difference in survival
Overall: p=0.09
**Untransfused: p=0.07**
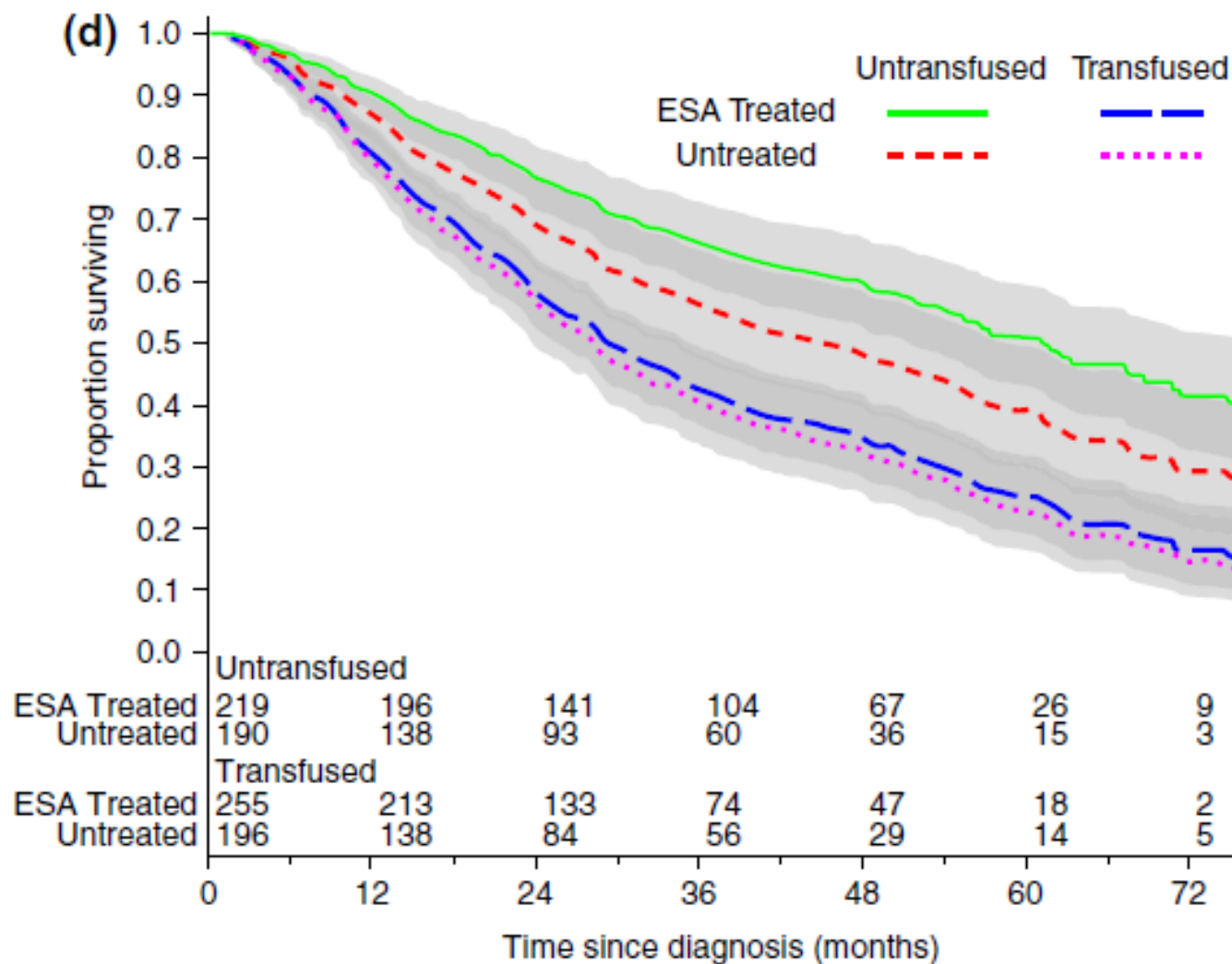
Conclusions ESA treatment in lower-risk MDS

- ESA is an effective treatment for the anemia of lower-risk MDS

- ESA treatment significantly delays the time to onset of a regular transfusion need

  - Significantly more effective if initiated before the onset of a regular transfusion need

- If initiated before the onset of transfusion – associated with improved survival (p=0.07)

- Major differences between European countries with regard to Hb level at start of ESA

- Major differences in the rules for reimbursement for ESA

  - Transfusion need mandatory in some countries

Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European LeukemiaNet study

Reinhard Stauder, Ge Yu, Karin A. Koinig, Tim Bagguley, Pierre Fenaux, Argiris Symeonidis, Guillermo Sanz, Jaroslav Cermak, Moshe Mittelman, Eva Hellström-Lindberg, Saskia Langemeijer, Mette Skov Holm[1], Krzysztof Mądry, Luca Malcovati, Aurelia Tatic, Ulrich Germing, Aleksandar Savic, Corine van Marrewijk, Agnès Guerci-Bresler, Elisa Luño, Jackie Droste, Fabio Efficace, Alex Smith, David Bowen, Theo de Witte[2]

Number of MDS patients included per country completion rate of EQ5D
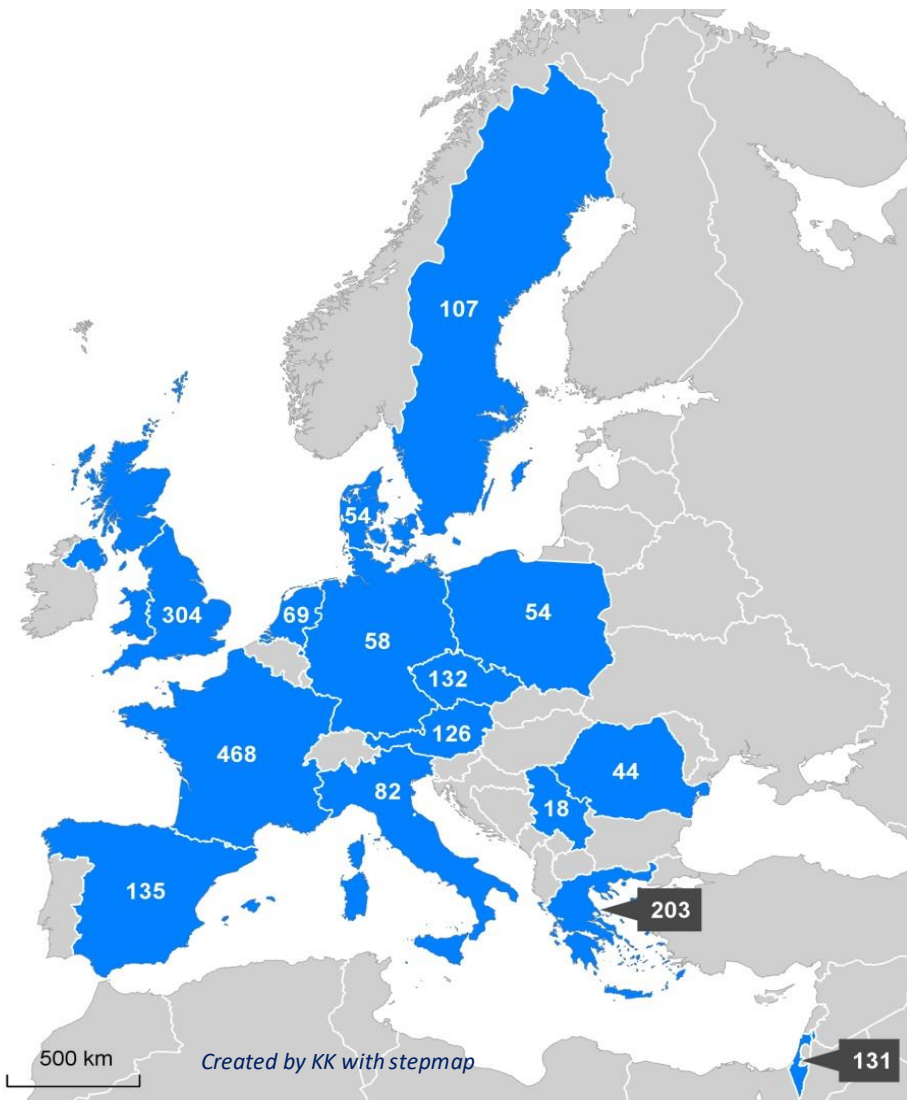
Completion rate: 85%
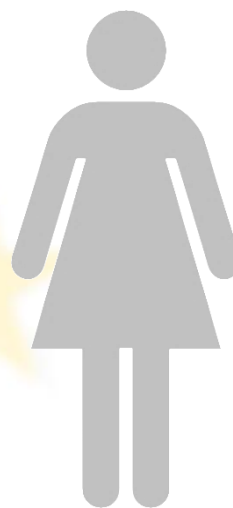
Mobility

Self care

Usual activities

Pain / discomfort

Anxiety / depression

VAS – self rated health

pinterest.com

Association of impaired HRQoL in MDS-patients with disease characteristics and survival

	EQ-5D: Index			EQ-5D: VAS		
Haemoglobin (g/dL)		**<0.001**				**<0.001**
>=10	0.77	0.22	909	72.71	19.44	893
<10	0.70	0.23	765	65.79	20.31	755
Red Blood Cell Transfusion		**<0.001**				**<0.001**
No	0.76	0.22	1160	71.74	19.56	1137
Yes	0.69	0.24	523	64.94	20.57	520
Cox Regression Analyses	HR	P*		*HR*		P*
Univariate analysis	0.51	**<0.001**		0.99		**<0.001**
Multivariate (b)	0.65	0.030		0.99		0.002

Conclusions in first manuscript of HRQoL

This study analysed prospectively patient-reported outcome HRQoL in IPSS lower-risk MDS at diagnosis, and compared this outcome in MDS with age- and sex matched healthy populations.

Patients experience profound age- and sex-dependent restrictions in different HRQoL-dimensions.

Distinct demographic and disease parameters are associated with reduced HRQoL.

In addition, these results may provide a benchmark in the evaluation of new interventional options aimed at improving HRQoL outcomes.

Impact of red blood cell transfusion dose density on progression-free survival in lower-risk myelodysplastic syndromes patients

Louise de Swart, Simon Crouch, Marlijn Hoeks, Alex Smith, Saskia Langemeijer, Pierre Fenaux, Argiris Symeonidis, Jaroslav Čermák, Eva Hellström-Lindberg, Reinhard Stauder, Guillermo Sanz, Moshe Mittelman, Mette Skov Holm, Luca Malcovati, Krzysztof Mądry, Ulrich Germing, Aurelia Tatic, Aleksandar Savic, Antonio Medina Almeida, Njetočka Gredelj-Šimec, Agnes Guerci-Bresler, Odile Beyne-Rauzy, Dominic Culligan, Ioannis Kotsianidis, Raphael Itzykson, Corine van Marrewijk, Nicole Blijlevens, David Bowen and Theo de Witte, on behalf of the EUMDS Registry Participants

Aim

- Assess the effect of RBCT dose density on PFS
- Hypothesis: transfusional iron may be toxic and associated with oxidative stress → BM failure, genetic damage, increased risk for progression or premature death

Results

- 1267 patients included in the analyses

- 317 patients died without progression

- In 162 patients the disease had progressed

- Median survival after progression 5.3 months

- Progression-free survival was significantly associated with age, EQ-5D index, baseline WHO classification, bone marrow blast count, cytogenetic risk category, number of cytopenias, and country.

Progression-free survival after landmark of visit 3 (1 year)

De Swart, et al: Haematologica 2020; 105:632-9
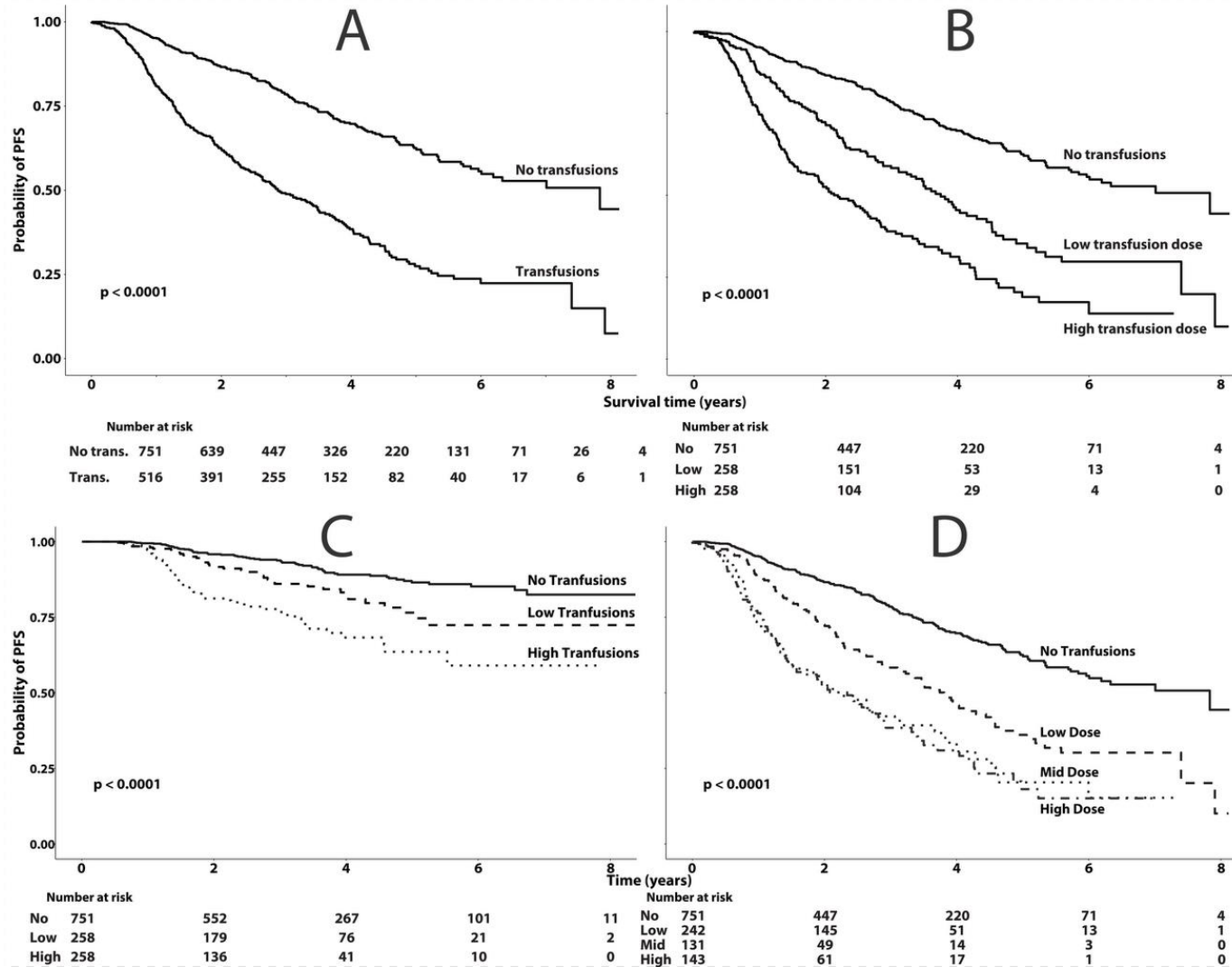
Impact of red blood cell transfusion density on progression-free survival in Lower-Risk MDS patients
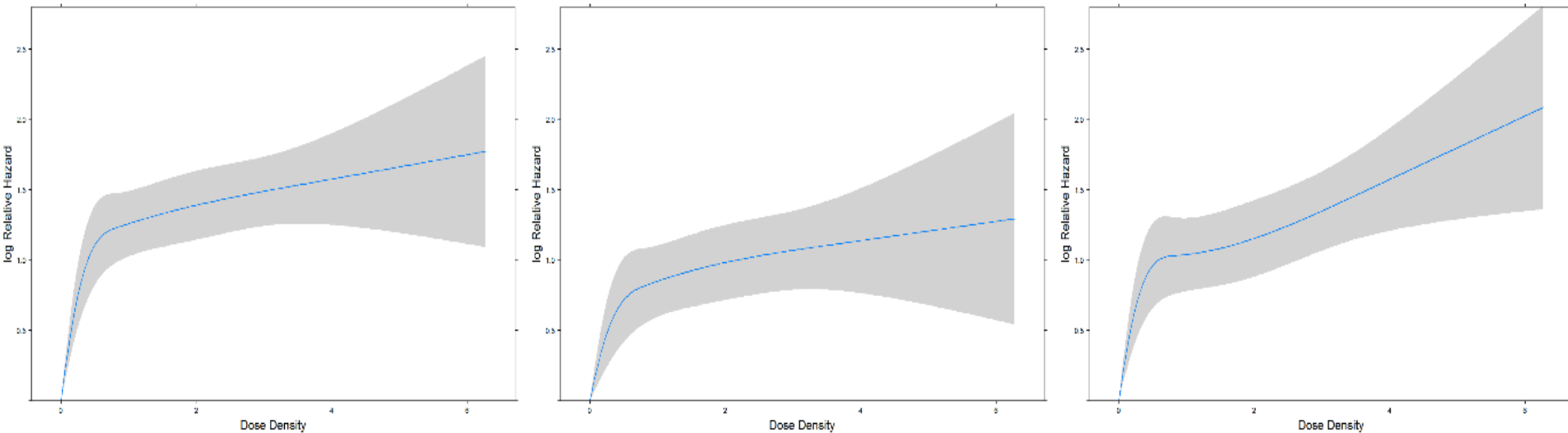
A: Univariate analysis of influence of dose density on progression-free survival
B: Dose density effect on PFS in a multivariate regression model unadjusted for the three treatment variables
C: Dose density effect on PFS in a multivariate regression model adjusted for treatment with either ESA, Iron Chelation Therapy or Lenalidomide

Conclusions

- The new outcome parameter 'Transfusion dose density' allows to incorporate longitudinal changes of transfusion intensity in the evaluation of the impact of transfusions on outcome

- Transfusion dependency may be considered as an indicator of inferior progression-free survival, even at relatively low transfusion dose densities of < 0.75 units per month or < 3 units per 16 weeks as defined in the revised IWG
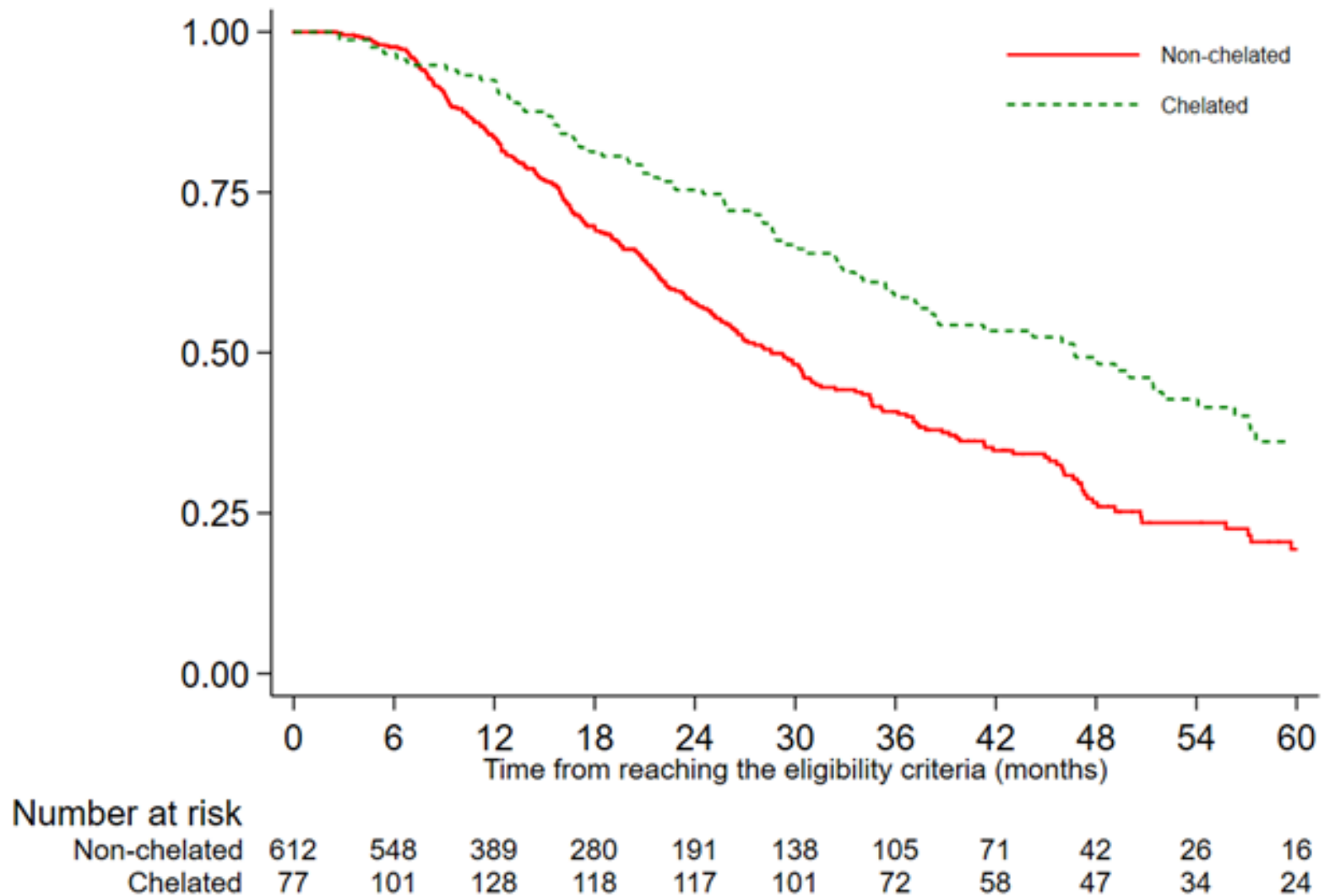
Management of iron overload in patients with MDS

- The aims of iron chelation therapy are to:
  - Prevent iron-related organ damage
  - Improve bone marrow (BM) function
  - Improve survival

- Two medications are approved by the EMA to reduce iron levels in patients with transfusion-dependent anemia
  - Deferasirox; an oral medication taken once daily
  - Deferoxamine; a subcutaneous infusion administered 5–7 days a week
  - Deferiprone: not available in all European countries

1. Jabbour E et al. Oncologist 2009;14:489–96
2. Rose C, et al. Blood 2007;110:(Abstract 249)

Results

Results

Number at risk

Non-chelated	612	548	389	280	191	138	105	71	42	26	16
Chelated	77	101	128	118	117	101	72	58	47	34	24

Hoeks, et al: Haematologica 2020; 105:640-52
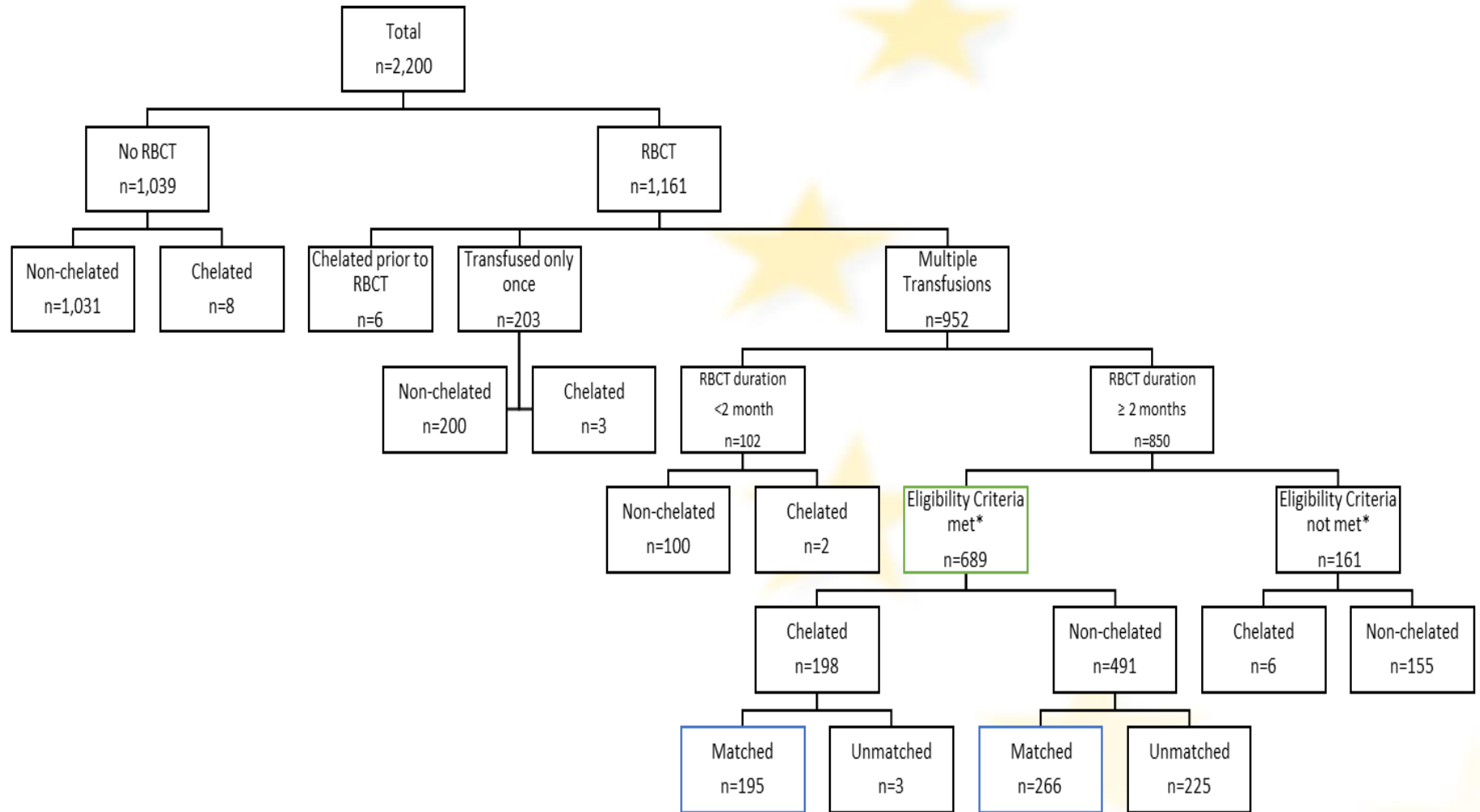
Results

	Non-chelated	Chelated
Total	266	195
Overall survival		
Unadjusted	1	0.59 (0.45-0.79)
Adjusted	1	0.43 (0.27-0.66)

-Matched by age, sex, country, RBCT intensity, ferritin level, comorbidity, performance status, and IPSS-R
-Adjusted for age, sex, comorbidity, performance status, RBCT intensity, number of RBC units transfused, IPSS-R, and presence of ringed-sideroblasts
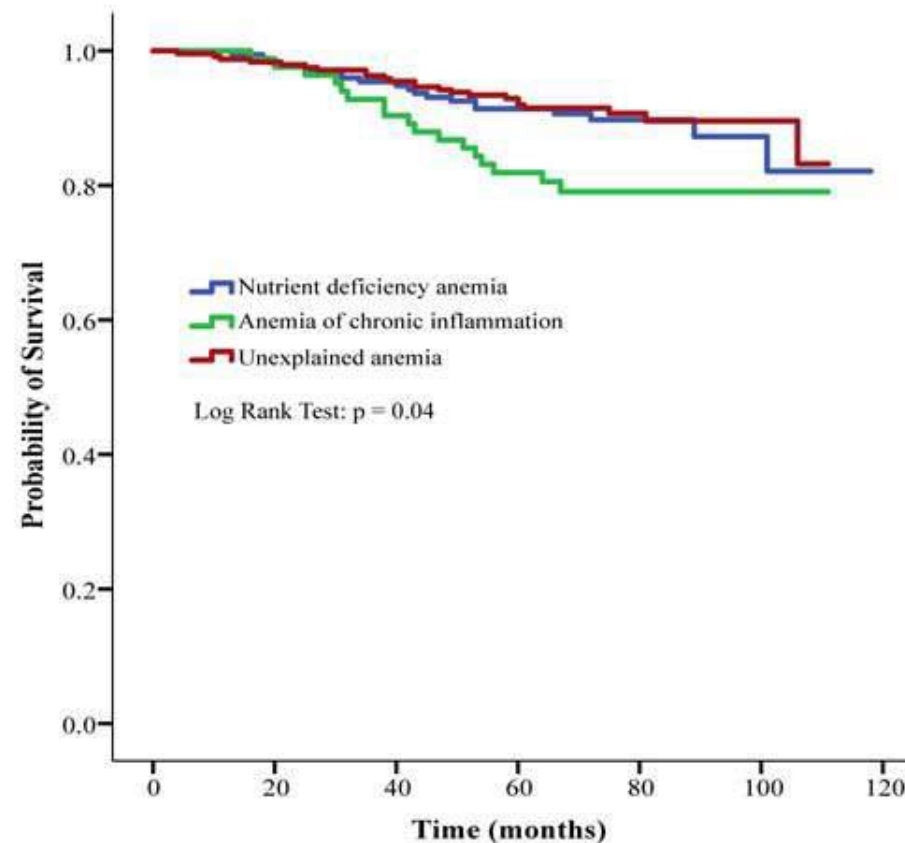
Results

Kaplan-Meijer curve

Cox model

Results

Haemoglobin
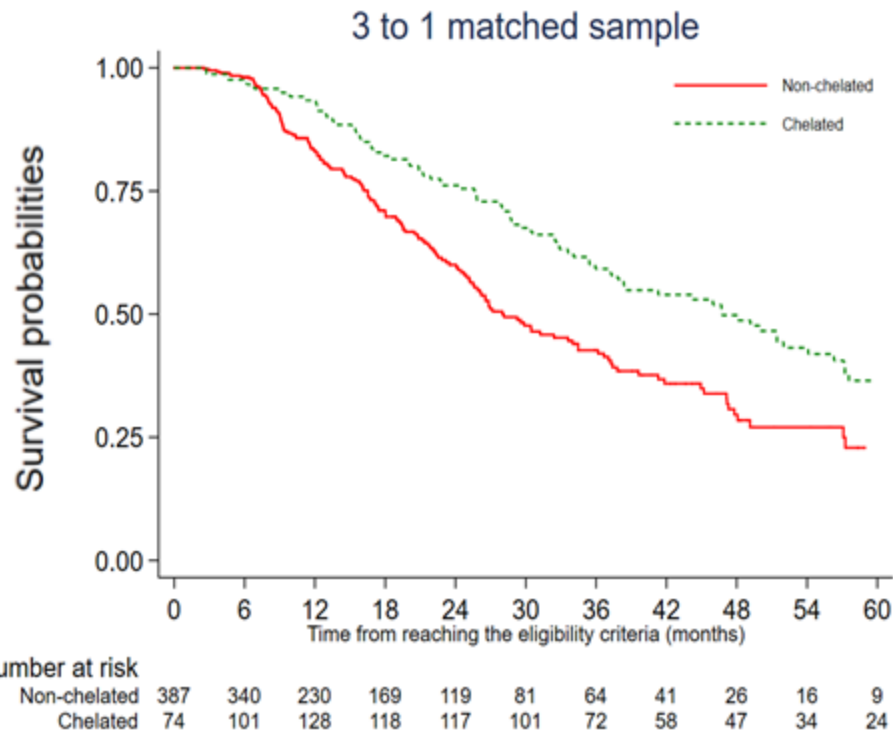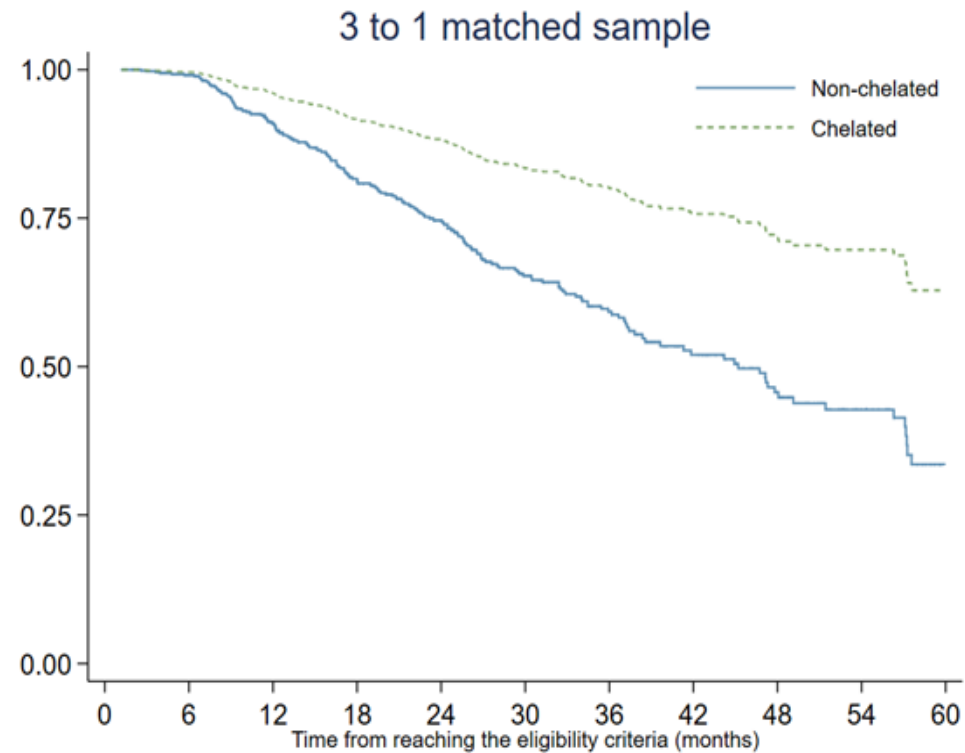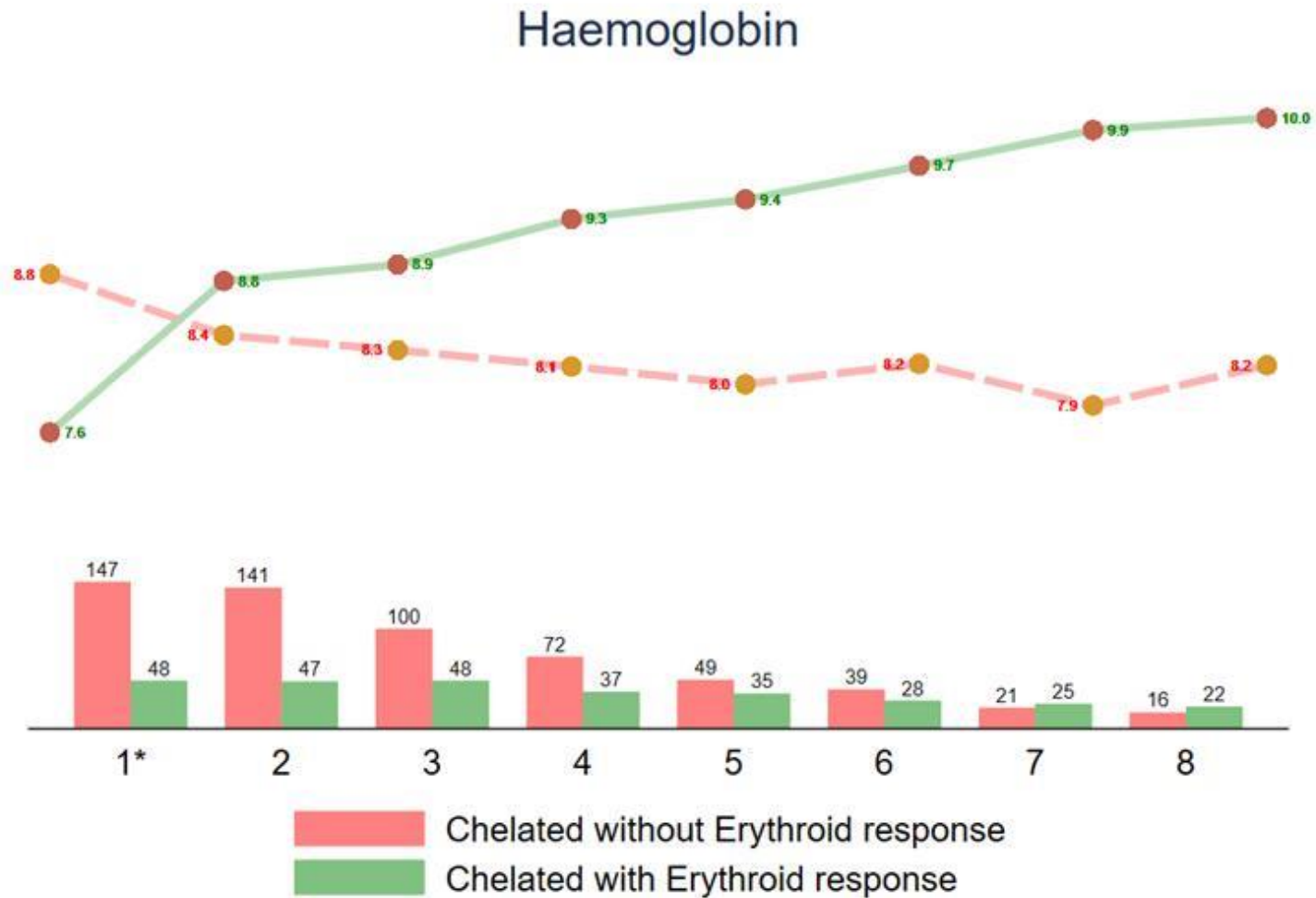
Conclusions

- Iron chelation in lower risk MDS improves outcome: better survival, increase of hematopoiesis (minority)

- Iron toxicity, as measured by LPI species and oxidative stress, may occur at low transfusion burden and in patients with prolonged ineffective erythropoiesis (mainly in patients with RS-MDS)

- Early intervention with iron chelators may be considered in patients who are prone to develop increased LPI levels

Hoeks, et al: Haematologica 2020; 105:640-52

Outcome of Anemia of the Elderly

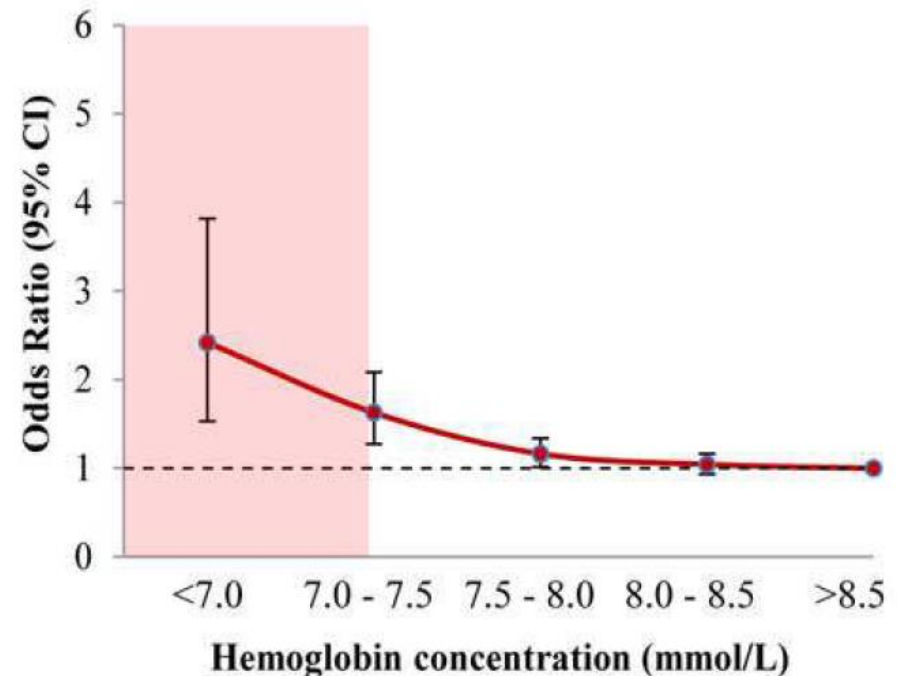Wouters, et al: Haematologica 2019; 104:468-76

Outcome of Anemia of the Elderly Gender differences?

B - Men older than 60 years
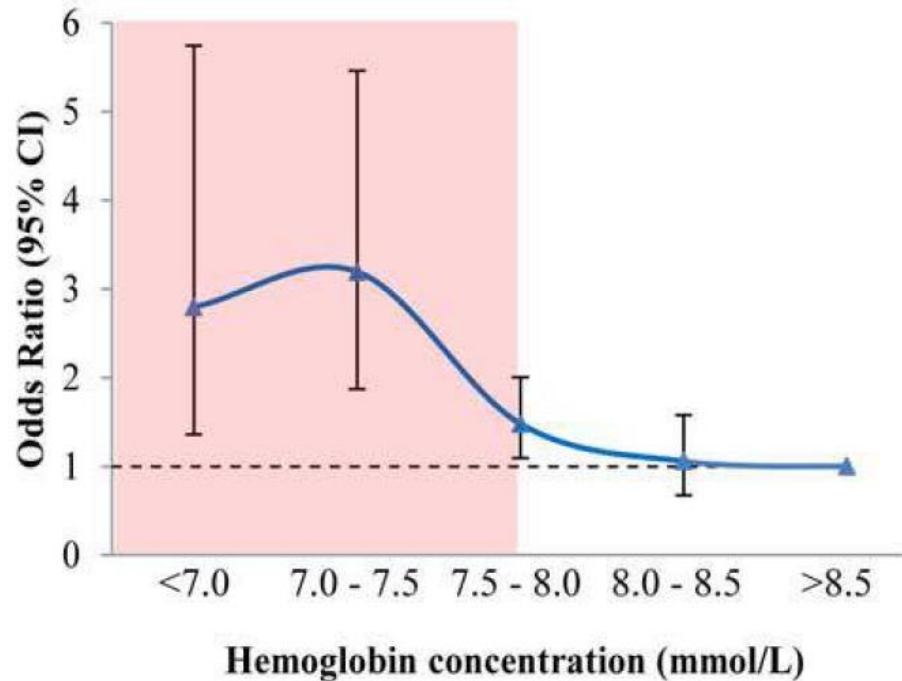
D - Women older than 60 years

Risk of having a lower total HRQoL score than the (sex- and age-specific) 25th percentile cut-off according to Hb concentrations
Red rectangles: Hb concentration below the current WHO definition of anemia.

Outcome of Anemia of the Elderly Gender differences?

This large prospective population-based study indicates that anemia is associated with survival and HRQoL in older individuals, but not in younger individuals

This study challenges the definition of anemia in women >60 years, and suggests that the optimal definition of anemia, in the perspective of health-related quality of life, in women >60 years should be increased to Hb levels of <13.0 g/dL (8.0 mmol/L), comparable to men

Wouters, et al: Haematologica 2019; 104:468-76

Spectrum and dynamics of clonal hematopoiesis in anemia of older individuals
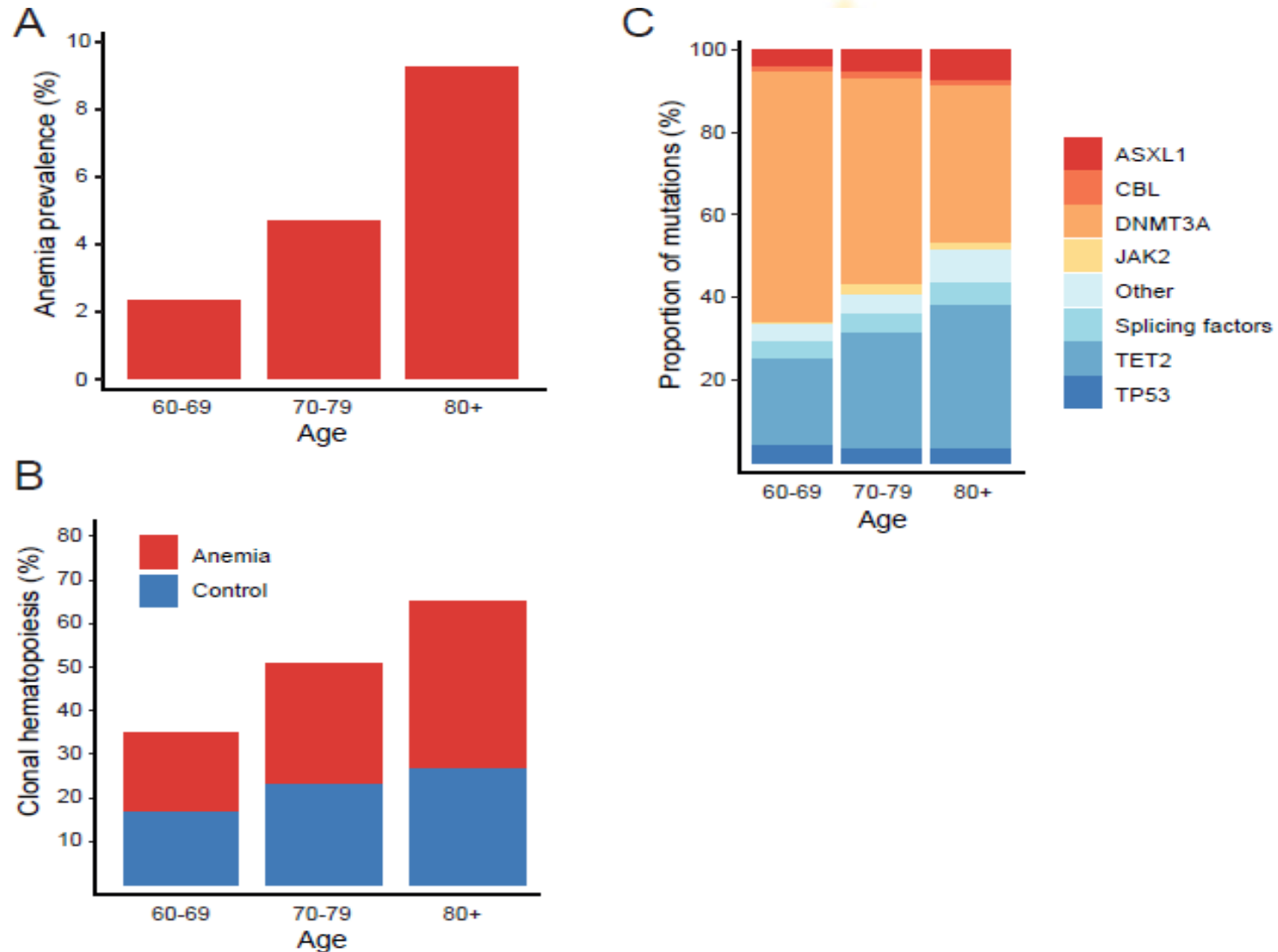
Spectrum and dynamics of clonal hematopoiesis (CH) in anemia of older individuals

CH was more frequently detected in anemic individuals (46.6%) compared to controls (39.1%) (P=0.007).

No differences were observed regarding commonly detected DTA mutations (*DNMT3A*, *TET2*, *ASXL1*) in anemic individuals compared to controls, other mutations were enriched in the anemia cohort, including *TP53* and *SF3B1*.

In contrast to individuals with nutrient deficiency (P=0.84), individuals with anemia of chronic inflammation and unexplained anemia revealed a higher prevalence of CH (P=0.035 and P=0.017 respectively) compared to their matched non-anemic controls

Spectrum and dynamics of clonal hematopoiesis in anemia of older individuals
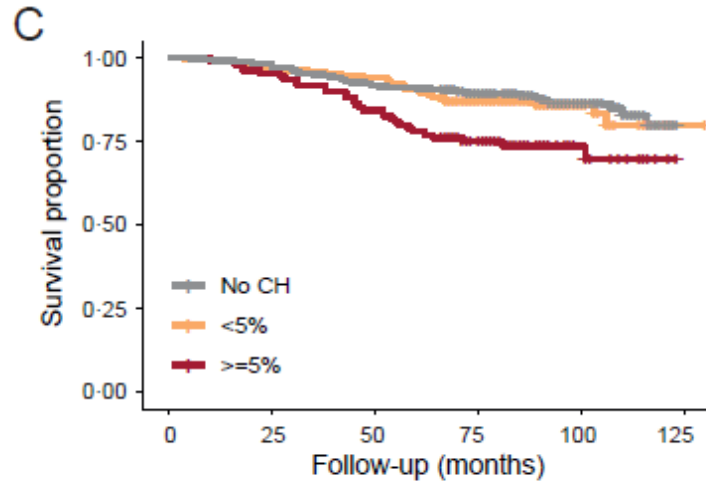
Smaller clones (<5% VAF) did not affect overall survival in contrast to larger clones.
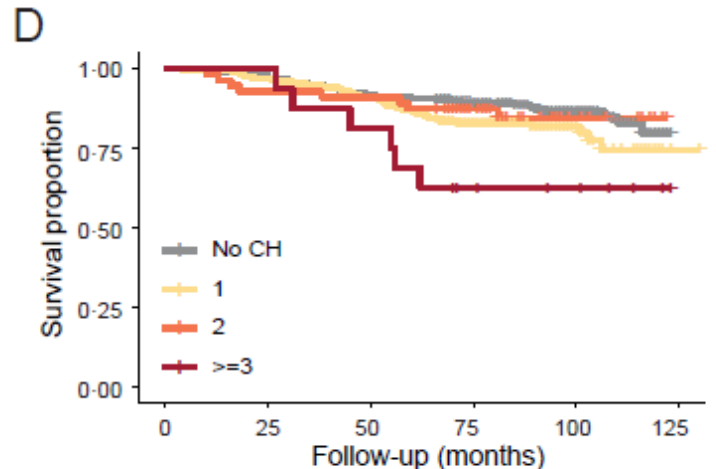
Multiple clones (>2) were associated with impaired survival

Conclusions

The EUMDS Registry is a productive European collaboration, leading to real-world observational data in a population of elderly patients who usually do not participate to clinical trials

The high quality of our Registry has resulted in an increasing flow of reports and publications

Moreover, we were able to attract support from the EU Horizon 2020 programme

We are grateful to all our patients who reported their personal feelings and to all caretakers of our patients

Acknowledgments

Chief Investigator: Theo de Witte

Database / statistics: Alex Smith and her team

Project Manager: Corine van Marrewijk

Project assistant: Rosalie Lubbers

Country Principal Investigators

Country Coordinators

Trials staff at each site

Above all patients whose participation has made this such a productive and relevant international study