European Perspectives on MDS Patient Management

Multi-stakeholder meeting

3 May 2017, Valencia, Spain

Palacio de Congresos de Valencia, Auditorium 3

Co-chairs:

Guillermo Sanz - Spain

Theo de Witte - The Netherlands

This project has received funding from the European Union's Horizon 2020 research and innovation programme (No 634789)

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Meeting Programme

16:00	**Welcome and introduction**	***Co-chairs:*** *Guillermo Sanz (ES), Theo de Witte (NL)*
16:05	**MDS-RIGHT– Providing the right care to the right MDS patient at the right time**	*Theo de Witte (NL)*
16:15	**MDS patient management challenges and solutions** - ***Panel presentations and discussion***	
16:15	**Introductory remarks**	***Moderator:*** *David Bowen (UK)*
16:20	**Medical specialist perspective**	*Pierre Fenaux (FR)*
16:30	**MDS patient perspective**	*Sophie Wintrich (UK)*
16:40	**Nurse perspective**	*Corien Eeltink (NL)*
16:50	**Regulatory/HTA perspective**	*David Bowen (UK)*
17:00	**Industry perspective**	*Margaret Doyle (IE), Alberto Vasconcelos (CH)*
17:15	**Discussion**	*All*
17:25	**MDS patient management recommendations & interactive online support**	*Eva Hellström-Lindberg (SE)*
17:35	**Discussion**	*All*
17:45	**MDS-RIGHT/MDS-Europe online platform**	*Alex Smith (UK)*
17:50	**Discussion**	*All*
17:55	**Closing remarks**	*Guillermo Sanz (ES), Theo de Witte (NL)*
18:00	**Meeting close**	

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16:00 - 16:05

Welcome and introduction

Co-chairs:

Guillermo Sanz[1] & Theo de Witte[2]

[1] Haematology specialist - Hospital La Fe, Valencia, Spain
[2] MDS-RIGHT project coordinator - Radboudumc, Nijmegen, The Netherlands

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16:00 - 16:05

Stakeholders

*The following **European stakeholders** were invited to join us for this meeting:*

- *Medical specialists caring for MDS patients*
- Nurses and social workers caring for MDS patients
- MDS and blood disorder patient advocates
- Medical researchers and MDS co-operative study groups
- Healthcare authorities, regulators, HTA experts
- Pharmaceutical companies

MDS-RIGHT Stakeholder meeting

Wednesday, May 3rd, 2017, 16.00-18.00 hrs CET

Venue: Palacio de Congresos de Valencia - Room: tbc

Avda. Cortes Valencianas, nº 60, E-46015 Valencia, Tel.: +34 963179400

www.palcongres-vlc.com

Meeting goals:

- Generate endorsement of accepted evidence-based guidelines & raise awareness *(Task 6.3)*
- Obtain insights on general MDS challenges & solutions across Europe
- Stimulate European MDS stakeholder information exchange & involvement in MDS-RIGHT
- Obtain stakeholder feedback on MDS treatment algorithm interactive tool (TAIT)
- Gain advice on how best to further improve the MDS-RIGHT/MDS-Europe website

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16:05 - 16:15

MDS-RIGHT – Providing the right care to the right MDS patient at the right time

Theo de Witte

MDS-RIGHT project coordinator
Radboudumc, Nijmegen, The Netherlands

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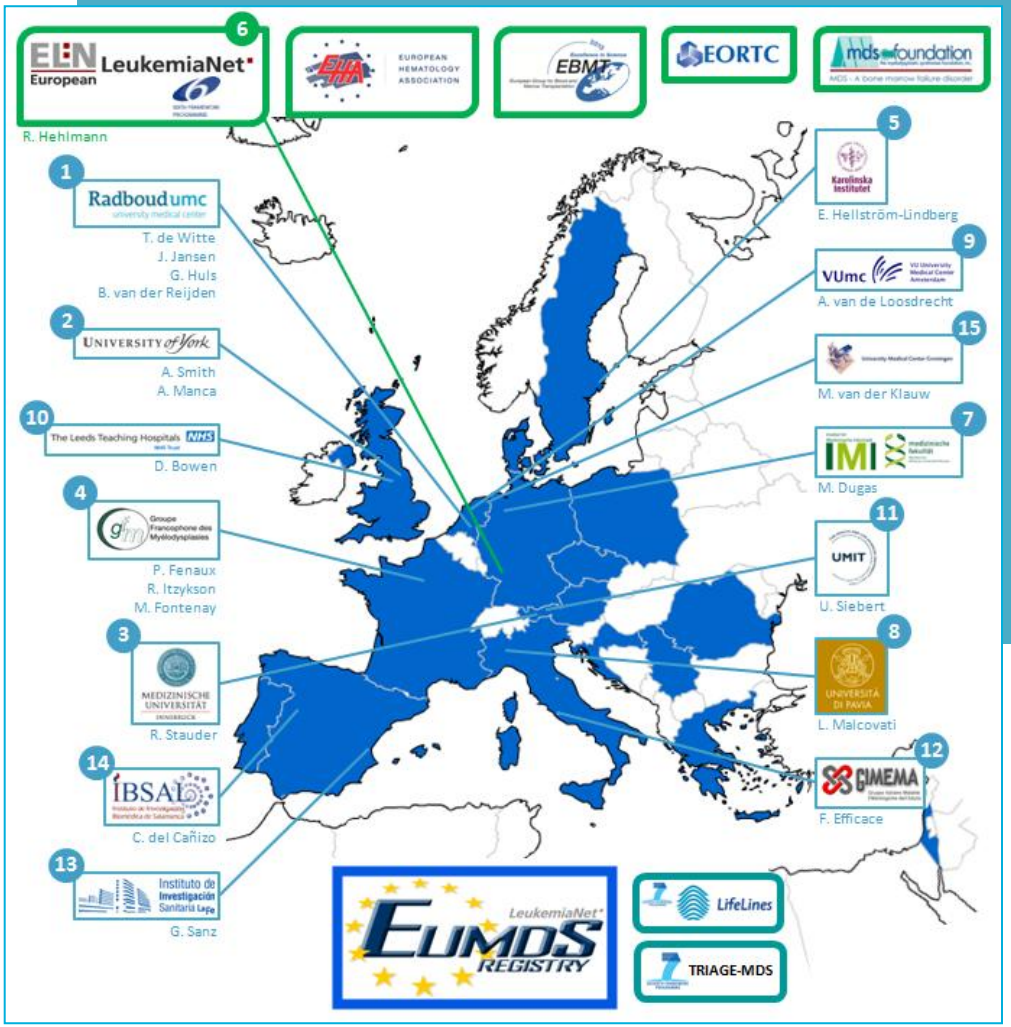
INTRODUCTION MDS-RIGHT



MDS-RIGHT stakeholder meeting

May 3rd 2017,
Valencia, Spain

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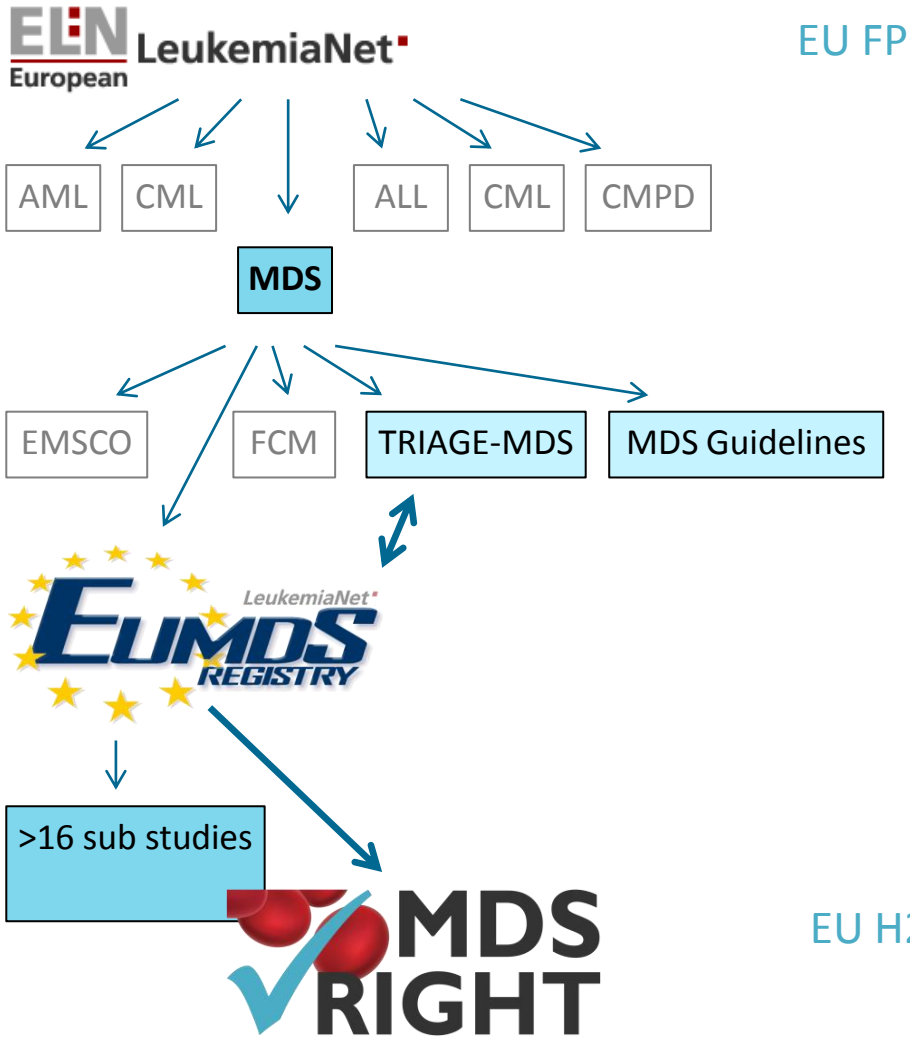
General introduction



EU FP6 grant – European Network for Leukemias
start: 1-1-2004 (6 m€ - 86 mnd)

WP8 Coördinator: Theo de Witte
various sub projects

Funding Pharma – European Registry MDS
Start: 01-04-2008

EU H2020 grant – Personalising Health and Care
Start: 1-5-2015 (6m€ - 60 mnd)

Introduction

EU Horizon 2020-funded 'Personalising Health and Care' research project

- Goals:
  - To assess (epi)genetic abnormalities and compare outcomes, costs and approaches to the diagnosis and treatment of MDS and anaemia in the elderly (>65 years of age)
  - To develop more effective and safer evidence-based, tailored interventions for elderly patients with anaemia and/or lower-risk MDS, leading to better treatment compliance and more cost-effective use of healthcare resources
- Project duration / budget: 1 May 2015 - 30 April 2020 / 6,000,000 EUR
- Project coordination / partners: Stichting Katholieke Universiteit (Radboud university medical center), Nijmegen, The Netherlands / 15 project partners
- MDS data: European MDS Registry (www.eumds.org): Prospective, observational data on >2,000 lower-risk MDS patients from 16 EU countries + Israel)
- Reference population: LifeLines 3-generation representative observational follow-up study in northern NL, incl. >14,000 individuals >65 years of age (www.LifeLines.nl)
- Project website www.mds-right.eu - launched in April 2016

Introduction

Background and Rationale

- MDS: Chronic bone marrow malignancies , predominant in the elderly, complicated by severe anaemia (AoE = anaemia of the elderly, i.e., frail people >65 years of age)
- Lower-risk MDS in ca. 20% of cases with AoE = about 2 million European citizens
- Significant impact on quality-adjusted survival
- Continuously growing burden of disease (ageing population; newly identified MDS cases among those diagnosed with AoE)
- Increasing financial burden on patients and healthcare systems

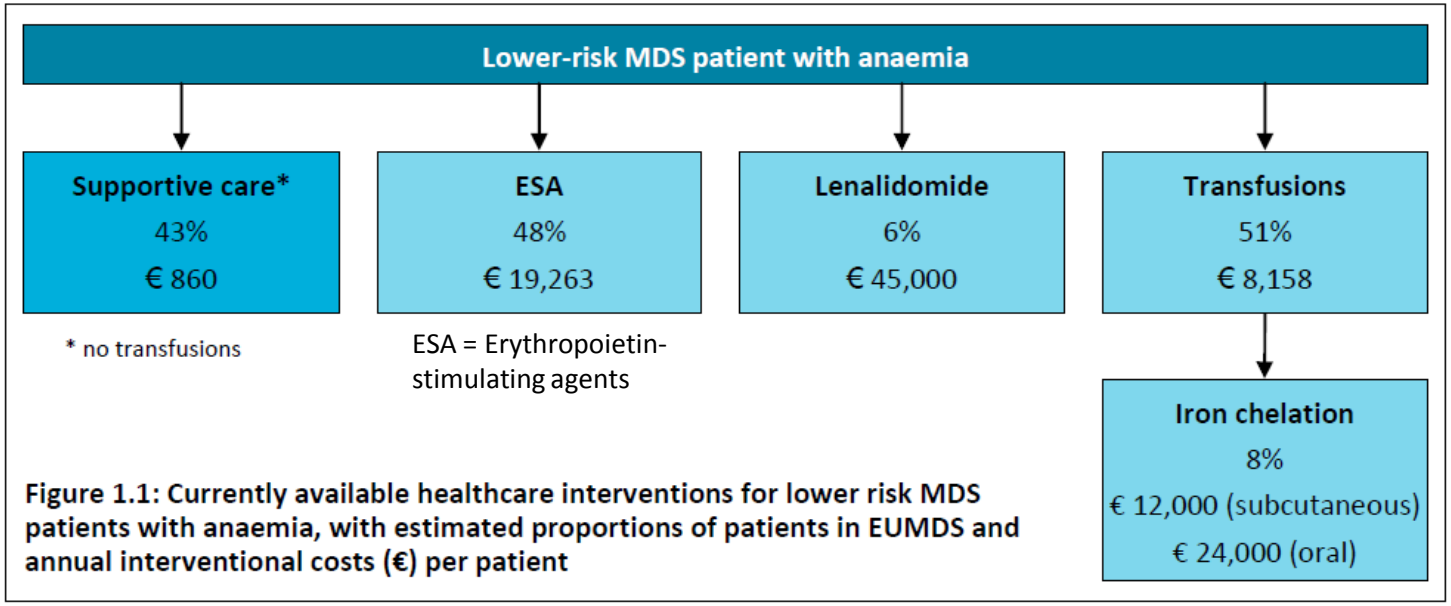


Figure 1.1: Currently available healthcare interventions for lower risk MDS patients with anaemia, with estimated proportions of patients in EUMDS and annual interventional costs (€) per patient

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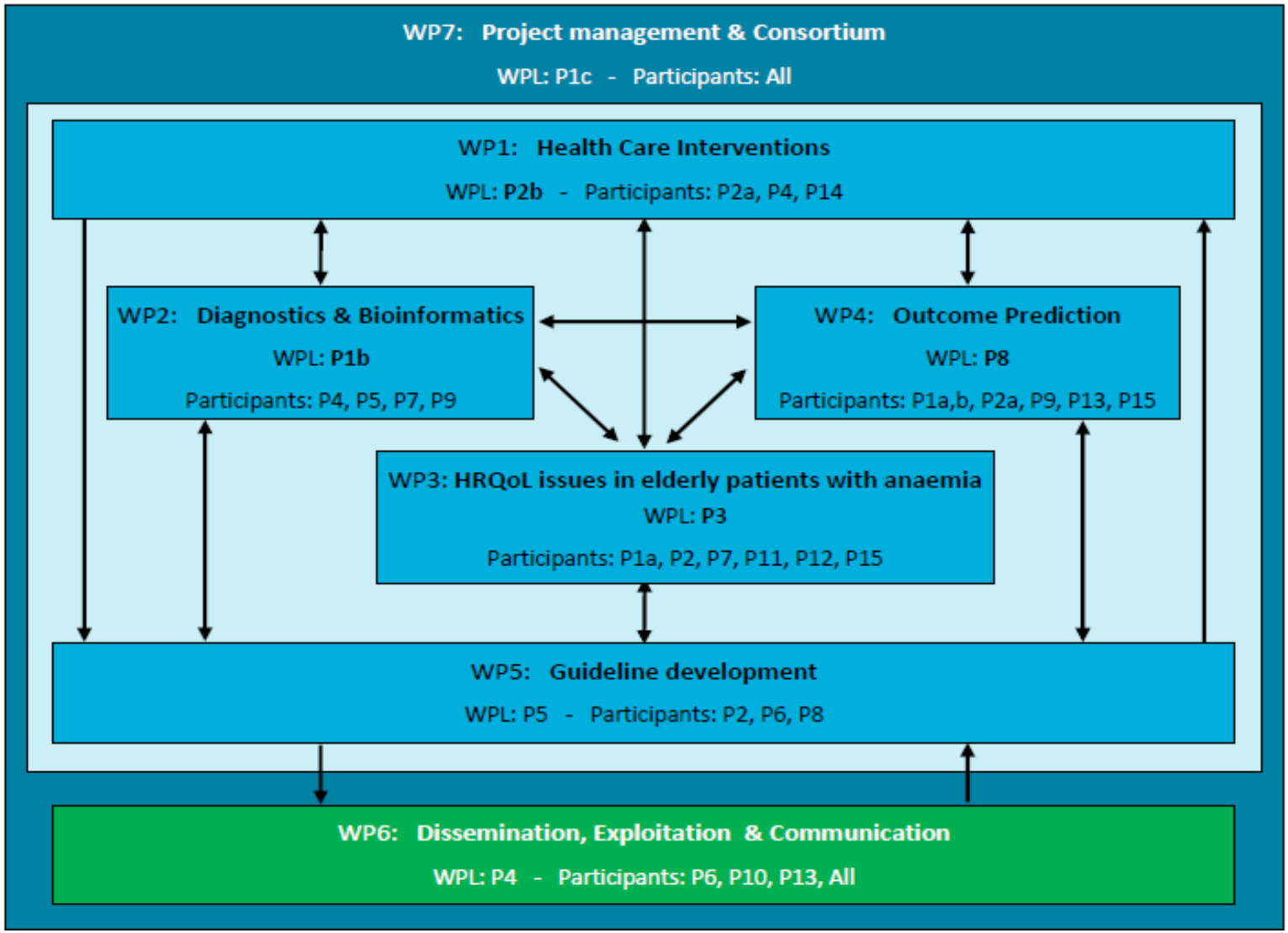
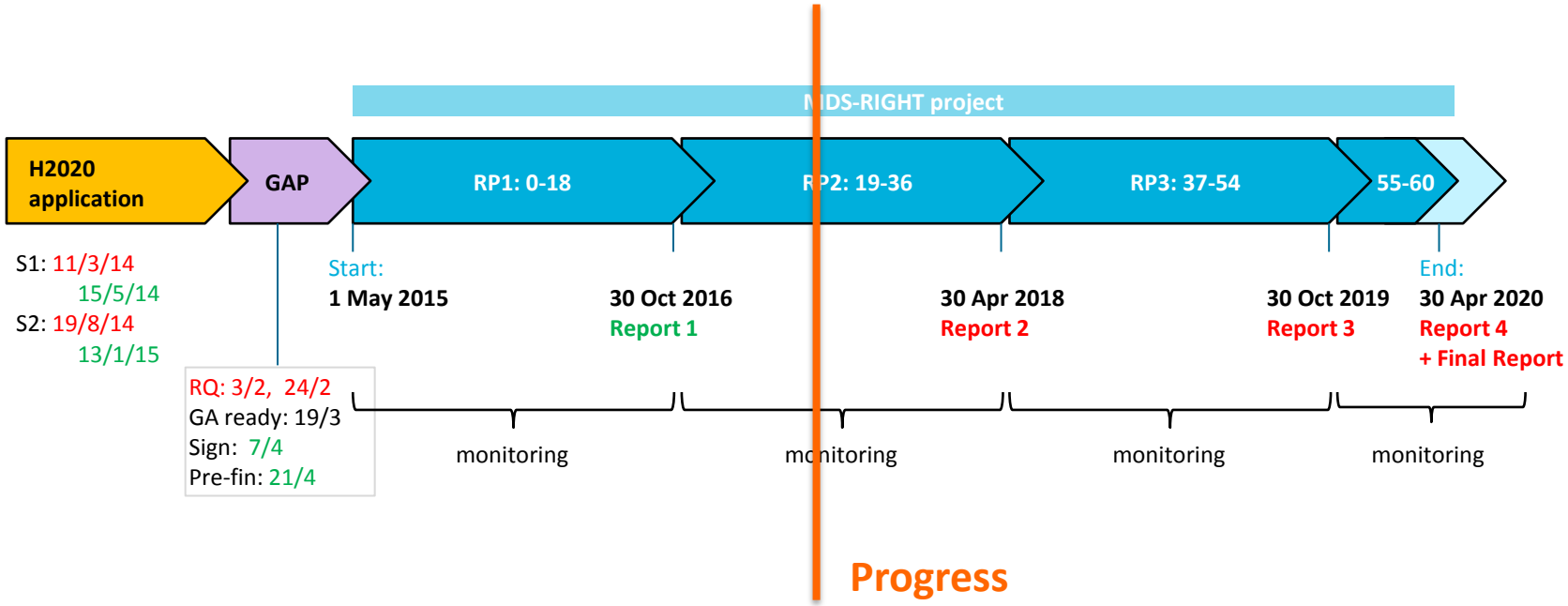
Design of MDS-RIGHT



MDS-RIGHT project - Timelines

- Start project: May 1st 2015
- Duration: 60 months
- Reporting periods: **18**, **36**, 54 and 60 months
- Meeting prior to official Kick-off in Vienna 11 June 2015:
  - Preparation meeting (GA): 2 Feb 2015 - Mannheim
  - Preparation KO meeting (WPLs): 1 May 2015 - Washington



Legend: Deadlines Outcome / Finilized

General introduction and Welcome (1)

1. MDS-RIGHT started officially on May 1st 2015.

2. Three successful meetings 2016:
   - ELN Annual meeting Mannheim, 1-3 February, 2016

     Progress of action points of the WPs during the first 18 months.

   - Meeting during MDS course ESH, Estoril 14 April 2016

     Launch of Website

   - October Meeting (Amsterdam, 15-16 Oct 2016)

     Focus on development of interactive guidelines (WP5) and the dissemination plan, including the Website structure (WP6)

     New CRFs for collecting data on Health economics and New Outcome Core sets

     Progress of 18 months report

     Involvement of patrons as stakeholders of MDS-Right

Dissemination plan

WP6 leader: Pierre Fenaux (PF)

Dissemination, Exploitation & Communication

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Dissemination Progress (WP6)

Task 6.2: Creation of a discussion platform & common website for communication with stakeholders

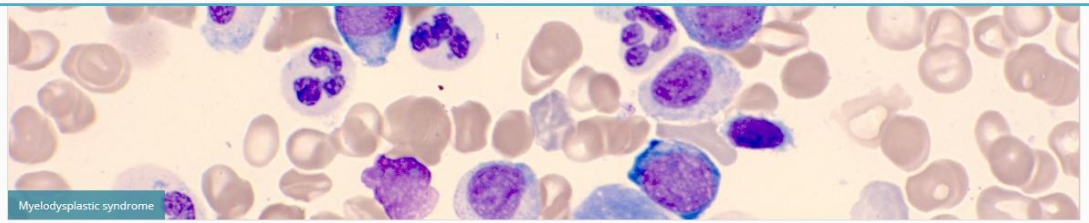
MDS EUROPE

- Home
- MDS-Right
  - Overview
  - Partners
  - Documents
- Legal statements

Home

MDS EUROPE

User login



Welcome

Welcome to MDS Europe - the online home of the MDS-RIGHT project and the future hub for all European MDS (myelodysplastic syndromes) information and guidance.

On our pages you will find detailed information about MDS-RIGHT including the project's work packages, deliverables and the extensive team of project partners.

Coming soon:

MDS Resources - pulling together a wide range of resources for patients, researchers and medical staff from across Europe
Clinical Trials - information about all European MDS-related clinical trials
Publications - the most important MDS publications, accessible from one place
European MDS recommendations - European and National guidelines for the management of MDS
Therapeutic Algorithm Interactive Tool - up-to-date, evidence-based information and regulatory guidance on the management of MDS

Check back often - the site will be regularly updated.

News

MDS EUROPE in Estoril

Come and meet us and find out more about MDS EUROPE at the European LeukaemiaNet booth at the European

MDS-RIGHT pages now live!

Find out more about the MDS-RIGHT project and how this feeds into MDS EUROPE

Work packages

Find detailed information about the work packages and deliverables for the MDS-RIGHT project

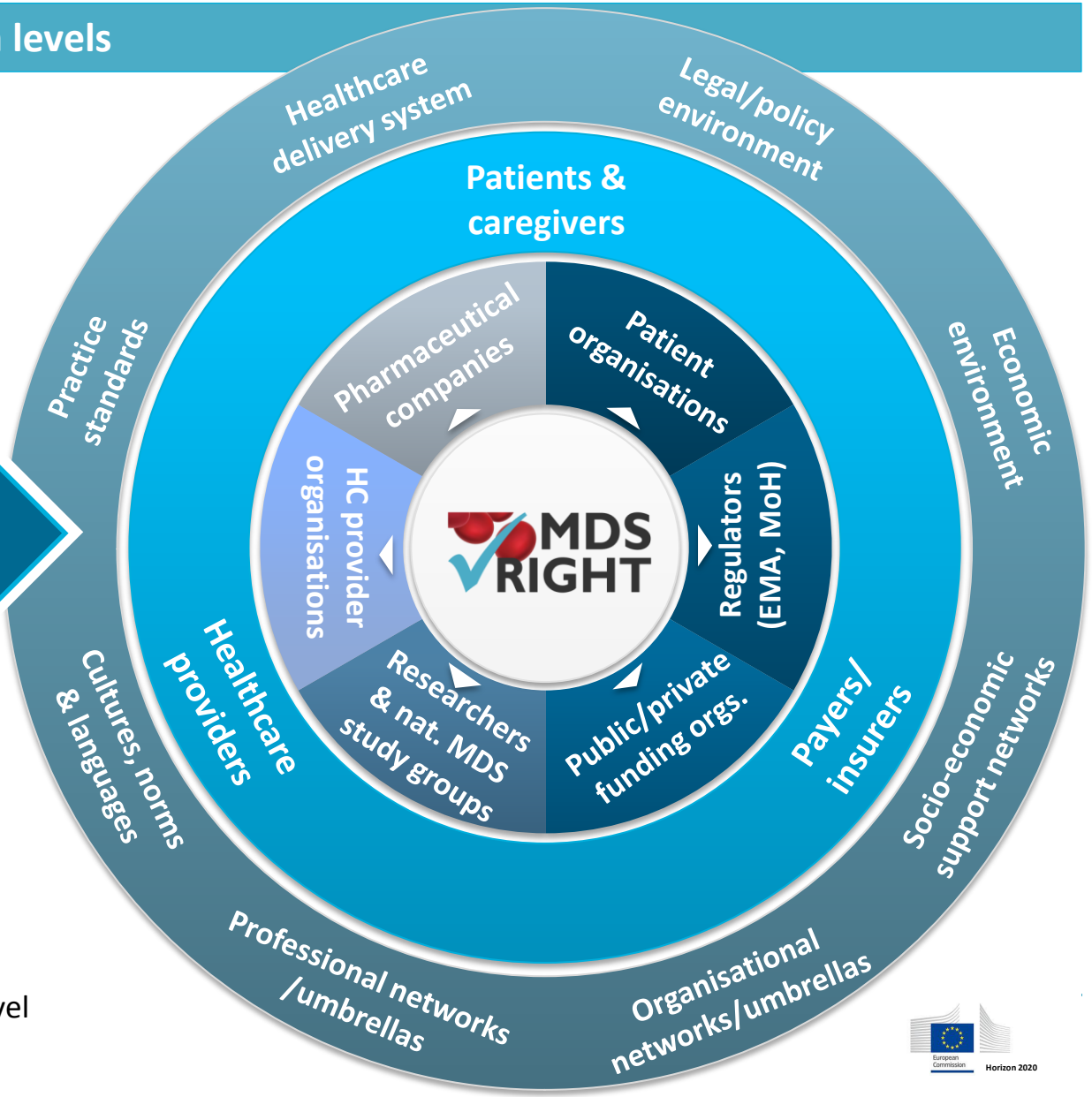
MDS-RIGHT partners

Explore our partners map to find out more about the institutions and teams working to carry out the MDS-RIGHT

Dissemination Plan (WP6)

MDS-RIGHT dissemination levels

New European MDS competence network



= Research dissemination

= Main stakeholder level

= Main end-user level

= 'Macro' environment level

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MDS-RIGHT General conclusions

- The MDS-RIGHT project is progressing well
- The early deliverables and milestones appeared feasible and have been accepted by the Horizon 2020 commission
- The first stakeholders meeting of MDS-RIGHT will give you an overview of the perspectives by the involved major stakeholders and some examples of our dissemination platforms

16:15-17:25

MDS patient management challenges and solutions

- Panel presentations and discussion -

Moderator: *David Bowen*

Honorary Professor of Myeloid Leukaemia Studies & Consultant Haematologist
St. James's University Hospital, Leeds, United Kingdom

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Panel presentations and discussion

MDS patient management challenges and solutions

16:15	Introductory remarks	***Moderator:***	*David Bowen*
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17:00	Industry perspective	*Margaret Doyle*	*& Alberto Vasconcelos*
17:15	Discussion		*All*

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16:20-16:30

Medical specialist perspective

- Panel presentation -

Pierre Fenaux

Haematology specialist
St. Louis Hospital, Paris, France

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MDS: medical specialist perspective

- **Where are we ?**
- **What do we need ?**

MDS: medical specialist perspective

- **Where are we ?**
- What do we need ?

MDS: medical specialist perspective

MDS : how far did we improve diagnosis, prognostic factors and treatment ?

- **Diagnosis**
  - Morphology
  - Cytogenetics
  - Somatic mutations
  - (Flow cytometry)

- **Prognostic factors**
  - IPSS and R-IPSS
  - Somatic mutations
  - (Flow cytometry)

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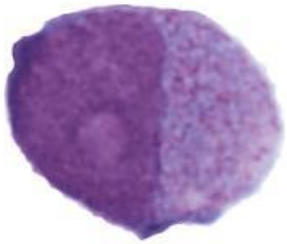
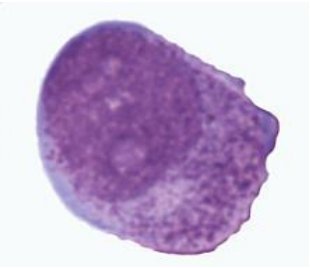
Blasts in MDS (J Goasguen)

Agranular blast		Agranular blast with basophilic cytoplasm fine chromatin and nuleoli
Granular blast		A subtype but with azurophilic granulations and **absence of Golgi zone**
Promyelocyte		Azurophilic granulations and A **clear visible Golgi zone** characteristic in promyelocytes
Myelodysplastic promyelocyte		Promyelocyte with an irregular distribution of granulations and reduced number of granules

Blast cells in MDS (J Goasguen)

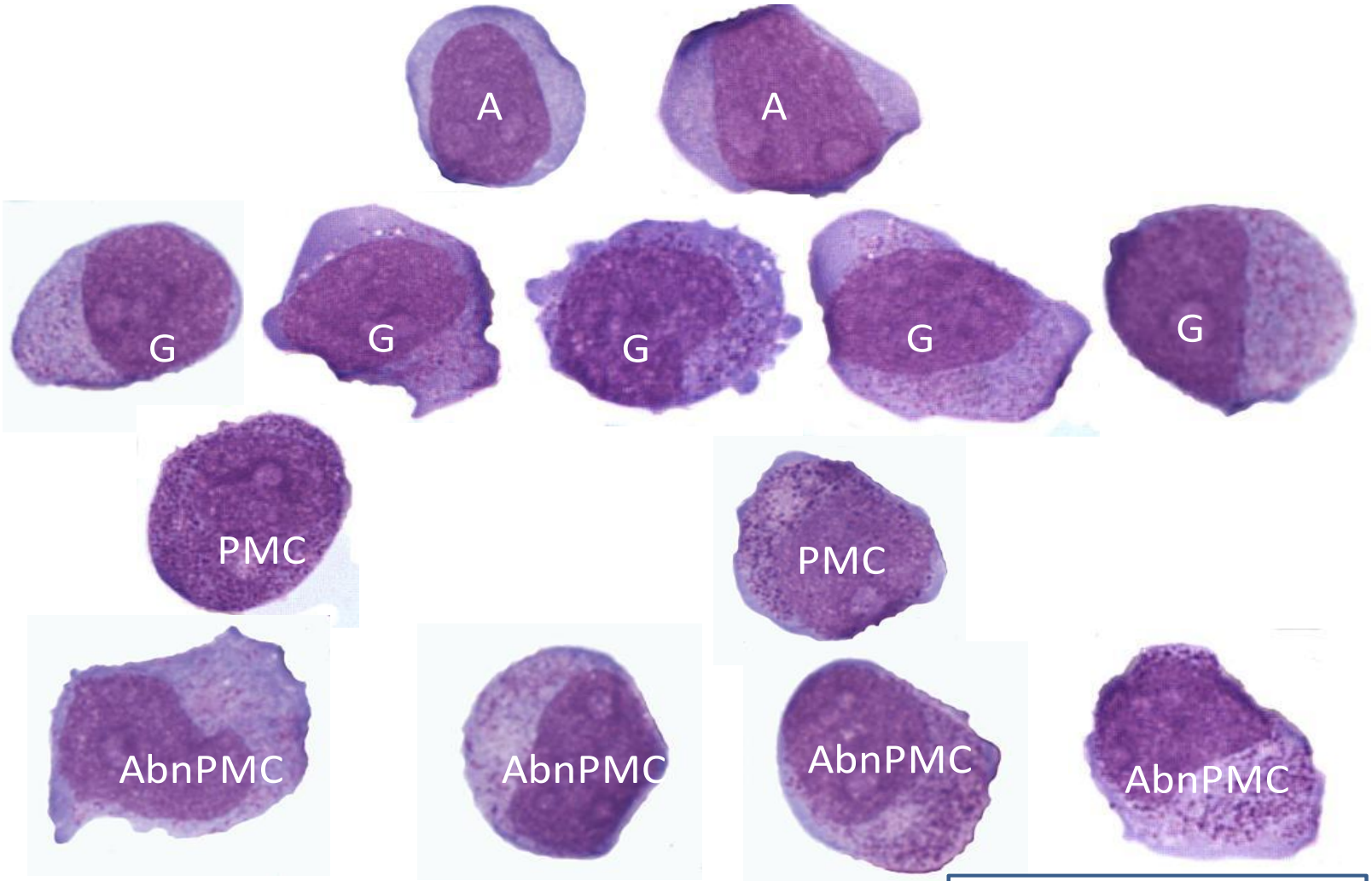


Photo: JeanE Goasguen

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MDS: medical specialist perspective

Diagnostic role of cytogenetics: MDS without significant dysplasias?

- Elderly woman with moderate anemia and del 5q
- Thrombocytopenia and del 20q
- Moderate Cytopenias and -7 ou +8

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OPEN

Leukemia (2014) **28**, 241–247

www.nature.com/leu

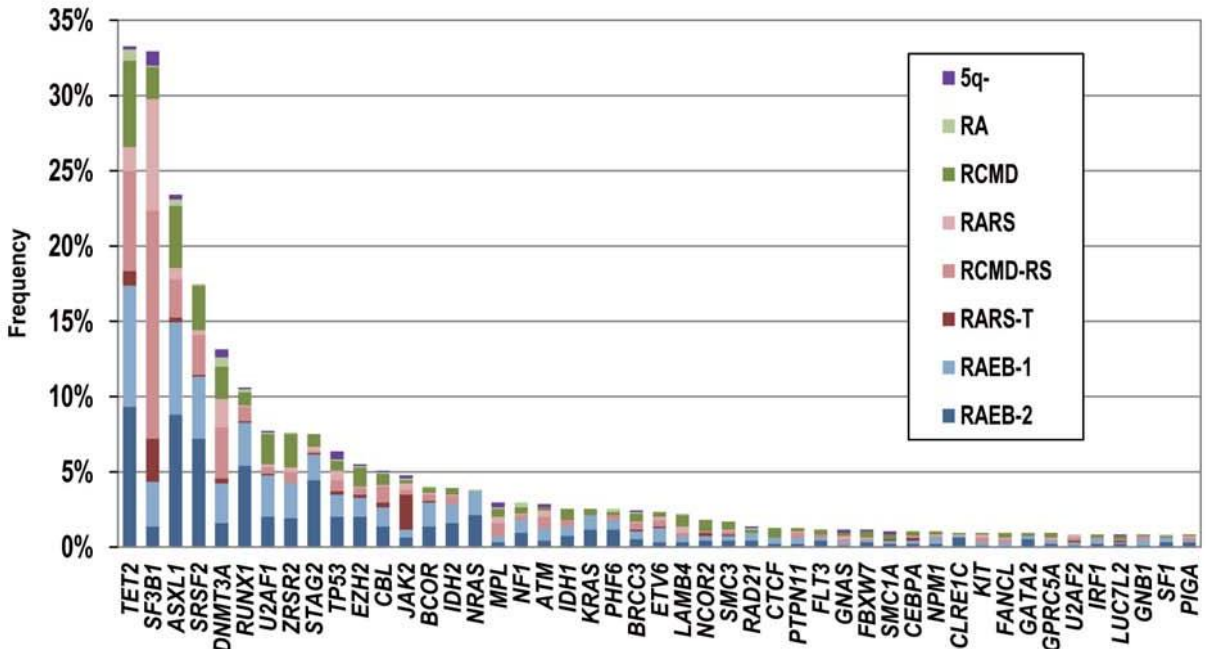
MDS RIGHT

LEADING ARTICLE

Landscape of genetic lesions in 944 patients with myelodysplastic syndromes

T Haferlach[1,10], Y Nagata[2,4,10], V Grossmann[1,10], Y Okuno[2,10], U Bacher[1], G Nagae[3], S Schnittger[1], M Sanada[2,4], A Kon[2,4], T Alpermann[1], K Yoshida[2,4], A Roller[1], N Nadarajah[1], Y Shiraishi[6], Y Shiozawa[2,4], K Chiba[6], H Tanaka[5], HP Koeffler[7,8], H-U Klein[9], M Dugas[9], H Aburatani[3], A Kohlmann[1], S Miyano[5,6], C Haferlach[1], W Kern[1,10] and S Ogawa[2,4,10]

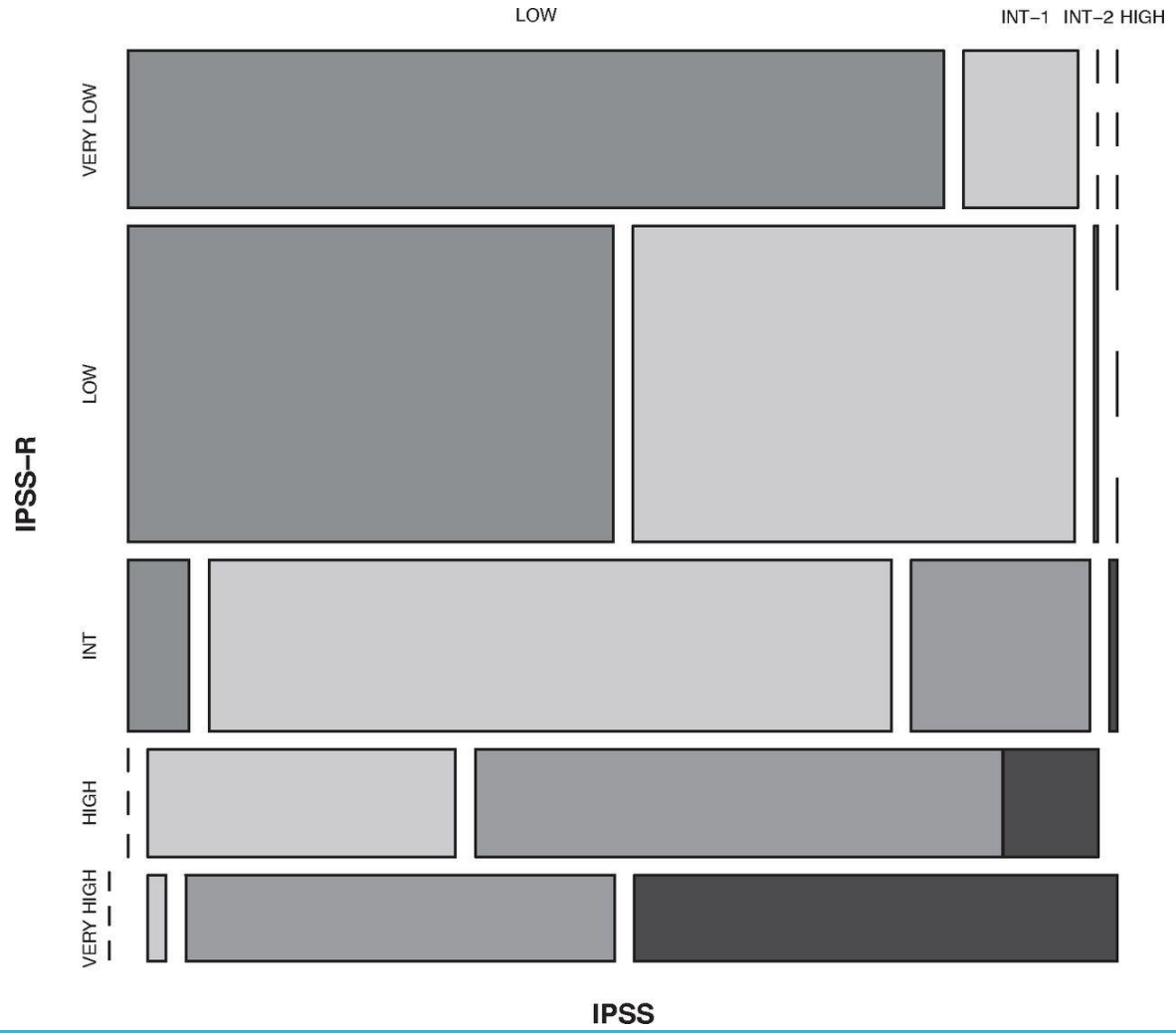
- 944 patients 104 genes
- **89.5% had at least one mutation** (median, 3 per patient; range, 0-12).
- 47 genes significantly mutated
- **TET2, SF3B1, ASXL1, SRSF2, DNMT3A, and RUNX1 mutated in >10% of cases.**



Comparison of IPSS-R and IPSS

subgroups within the IWG-PM database patient cohort

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Greenberg P L et al. Blood 2012;120:2454-2465

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Prognostic value of mutations

	HR (95% CI)	p-value
Age		
≥55 yrs vs. <55 yrs	**1.81 (1.20-2.73)**	**0.004**
IPSS Risk Group		
Int1 vs. Low	**2.29 (1.69-3.11)**	**<0.001**
Int2 vs. Low	**3.45 (2.42-4.91)**	**<0.001**
High vs. Low	**5.85 (3.63-9.40)**	**<0.001**
Mutational Status - Present vs. Absent		
TP53 Mutation	**2.48 (1.60-3.84)**	**<0.001**
EZH2 Mutation	**2.13 (1.36-3.33)**	**<0.001**
ETV6 Mutation	**2.04 (1.08-3.86)**	**0.029**
RUNX1 Mutation	**1.47 (1.01-2.15)**	**0.047**
ASXL1 Mutation	**1.38 (1.00-1.89)**	**0.049**

Bejar R et al. NEJM (2011) 364:2496-506.

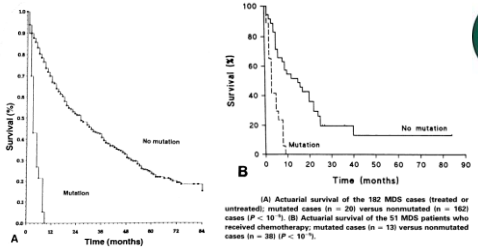
Prognosis of TP53/p53 mutations

with all available treatments

blood 1994 84: 3148-3157

p53 mutations are associated with resistance to chemotherapy and short survival in hematologic malignancies

E Wattel, C Preudhomme, B Hecquet, M Vanrumbeke, B Quesnel, I Dervite, P Morel and P Fenaux



(A) Actuarial survival of the 182 MDS cases (treated or untreated); mutated cases (n = 20) versus nonmutated (n = 162) cases ($P < 10^{-3}$). (B) Actuarial survival of the 51 MDS patients who received chemotherapy; mutated cases (n = 13) versus nonmutated cases (n = 38) ($P < 10^{-3}$).

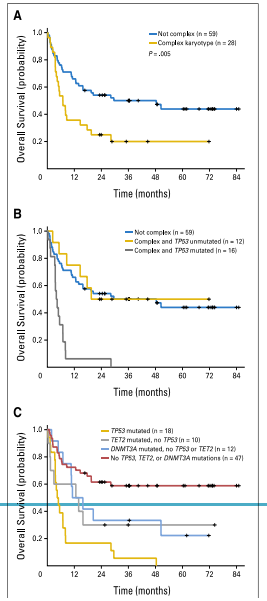
Groupe Francophone des Myélodysplasies

VOLUME 32 · NUMBER 25 · SEPTEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

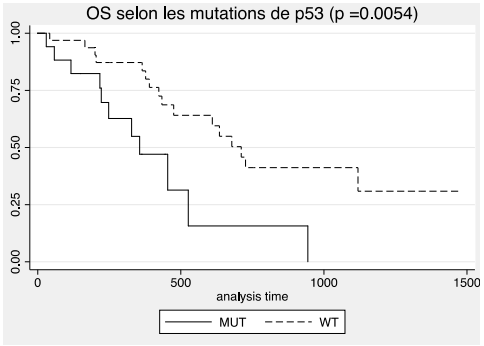
Somatic Mutations Predict Poor Outcome in Patients With Myelodysplastic Syndrome After Hematopoietic Stem-Cell Transplantation

Rafael Bejar, Kristen E. Stevenson, Bennett Caughey, R. Coleman Lindsley, Brenton G. Mar, Petar Stojanov, Gad Getz, David P. Steensma, Jerome Ritz, Robert Soiffer, Joseph H. Antin, Edwin Alyea, Philippe Armand, Vincent Ho, John Koreth, Donna Neuberg, Corey S. Cutler, and Benjamin L. Ebert



TP53 mutations and results of AZA in MDS

(Bally, Leuk Res, 2013)



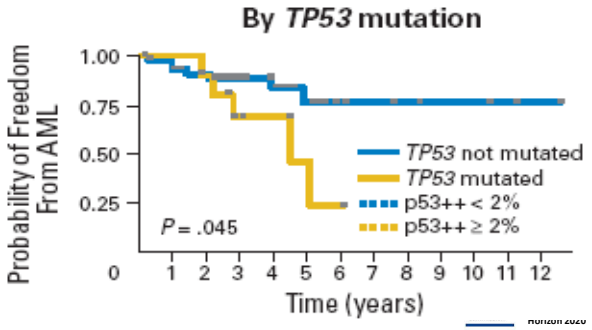
Groupe Francophone des Myélodysplasies

VOLUME 29 · NUMBER 15 · MAY 20 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

TP53 Mutations in Low-Risk Myelodysplastic Syndromes With del(5q) Predict Disease Progression

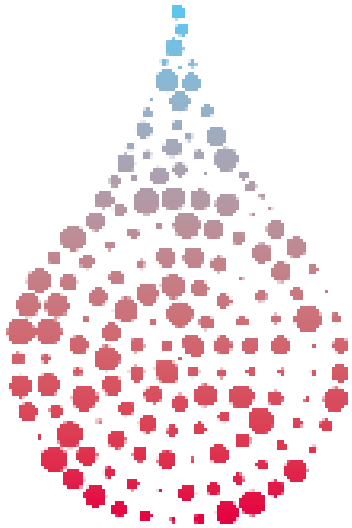
Martin Jädersten, Leonie Saft, Alexander Smith, Austin Kulasekararaj, Sabine Pomplun, Gudrun Göhring, Anette Hedlund, Robert Hast, Brigitte Schlegelberger, Anna Porwit, Eva Hellström-Lindberg, and Ghulam J. Mufti



MDS: medical specialist perspective

Prognostic factors of HMA treatment in higher risk MDS

- EU funded HARMONY project
- About 3000 high risk MDS/CMML studied, 1000 of whom had NGS
- Also testing flow cytometry, epigenetic studies, etc.



HARMONY

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MDS: medical specialist perspective

MDS : how far did we improve diagnosis, prognostic factors and treatment ?

- Allogeneic SCT
- Hypomethylating agents
- Erythropoietic stimulating agents
- Lenalidomide

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MDS: medical specialist perspective

Outcome of higher-risk MDS according to donor availability: *M Robin, Leukemia, 2014*

- **163 patients** : 21%no donor; 71% HLA-matched donor (34% sibling and 37% unrelated) and 9% patients HLA mismatched donor
- **117 patients treated by AZA and 40 by CT.** marrow blasts < 10% achieved in 68% and 57% for patients without and with donor

Groupe Francophone des Myélodysplasies

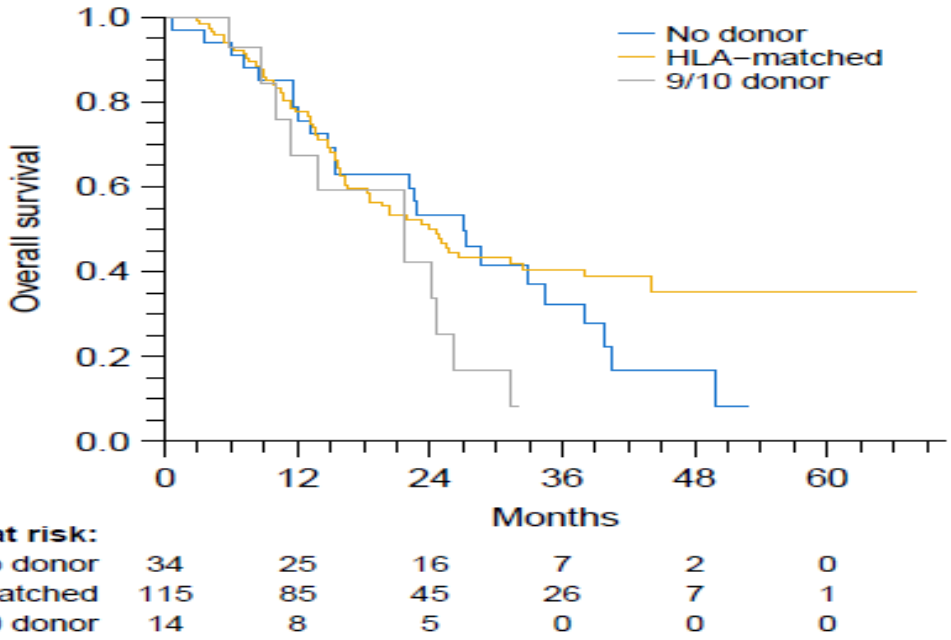

Figure 1: Overall survival according to donor group.

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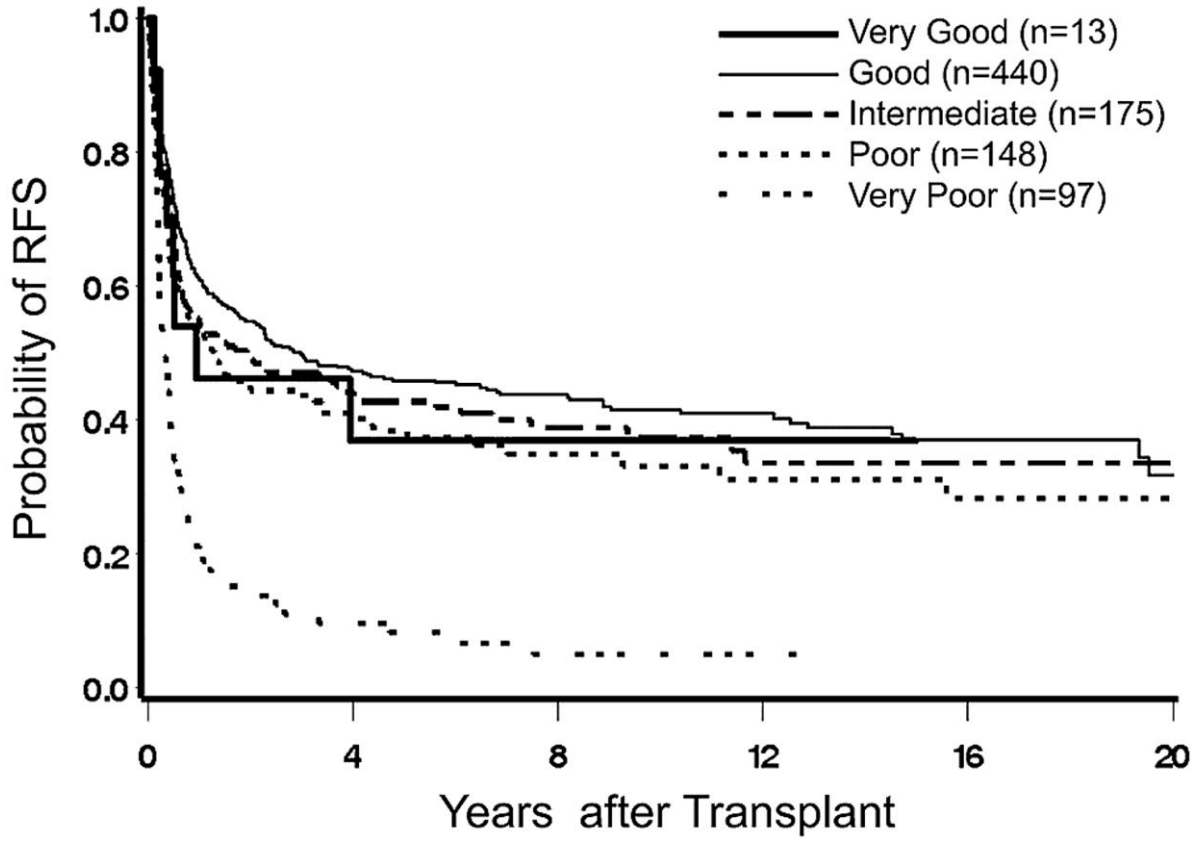
MDS: medical specialist perspective

Allo SCT and very poor karyotype IPSS-R)

blood

JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Survival by 5-group cytogenetic classification.



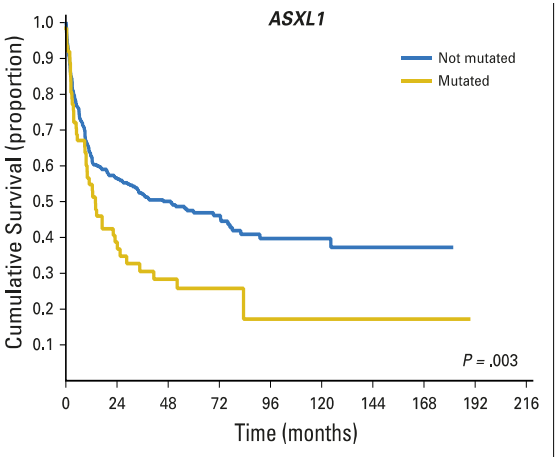
Deeg H J et al. Blood 2012;120:1398-1408

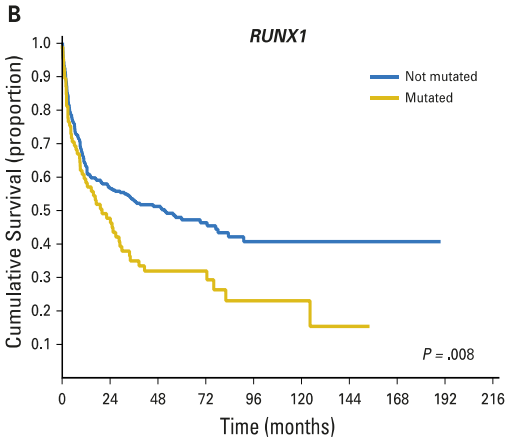
Published Ahead of Print on September 6, 2016 as 10.1200/JCO.2016.67.3616
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2016.67.3616

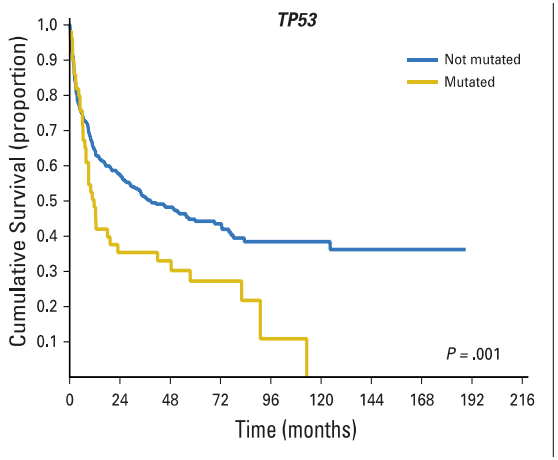
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Clinical Effects of Driver Somatic Mutations on the Outcomes of Patients With Myelodysplastic Syndromes Treated With Allogeneic Hematopoietic Stem-Cell Transplantation

Matteo G. Della Porta, Anna Galli, Andrea Bacigalupo, Silvia Zibellini, Massimo Bernardi, Ettore Rizzo, Bernardino Allione, Maria Teresa van Lint, Pietro Pioltelli, Paola Marenco, Alberto Bosi, Maria Teresa Voso, Simona Sica, Mariella Cuzzola, Emanuele Angelucci, Marianna Rossi, Marta Ubezio, Alberto Malovini, Ivan Limongelli, Virginia V. Ferretti, Orietta Spinelli, Cristina Tresoldi, Sarah Pozzi, Silvia Luchetti, Laura Pezzetti, Silvia Catricalà, Chiara Milanesi, Alberto Riva, Benedetto Bruno, Fabio Ciceri, Francesca Bonifazi, Riccardo Bellazzi, Elli Papaemmanuil, Armando Santoro, Emilio P. Alessandrino, Alessandro Rambaldi, and Mario Cazzola

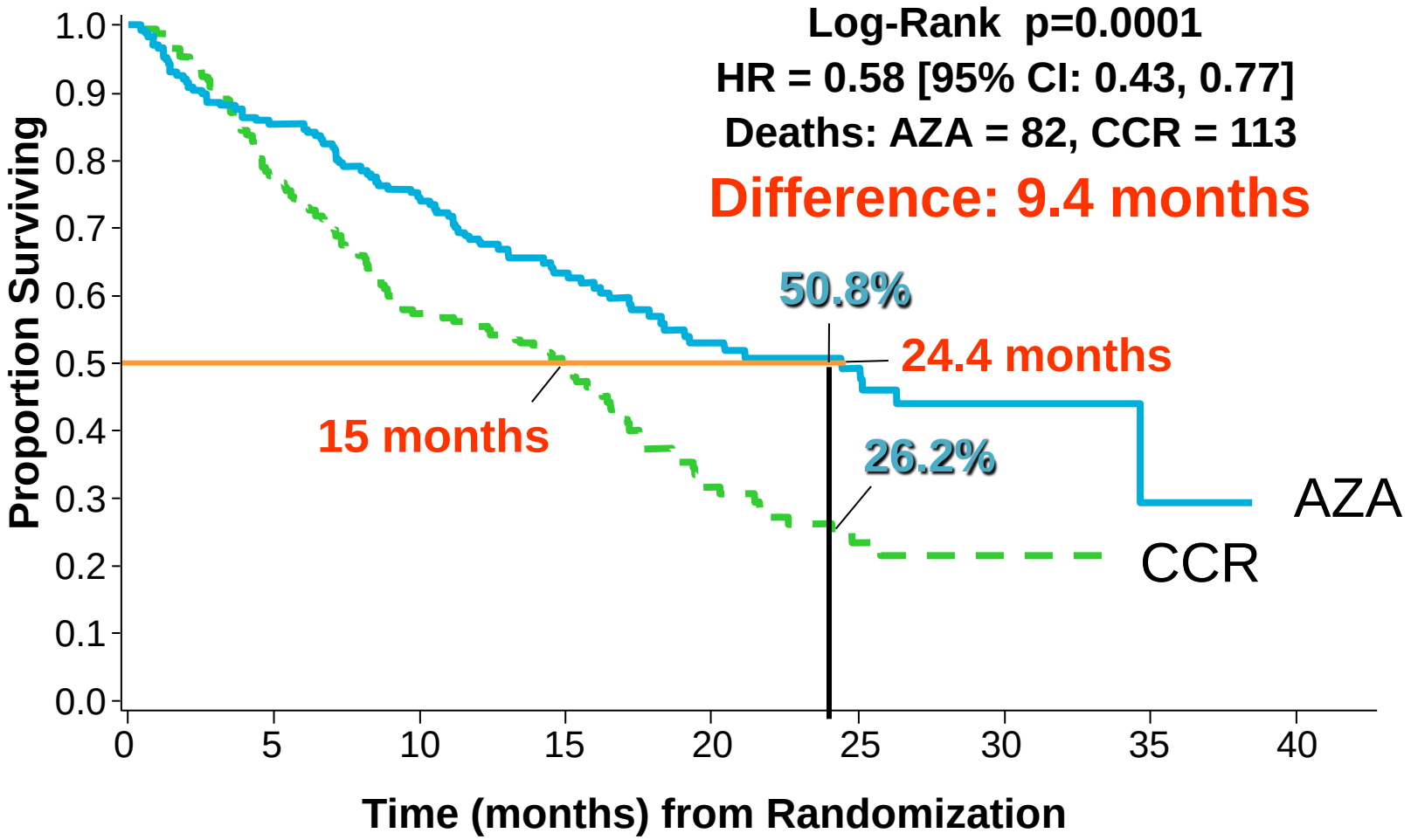






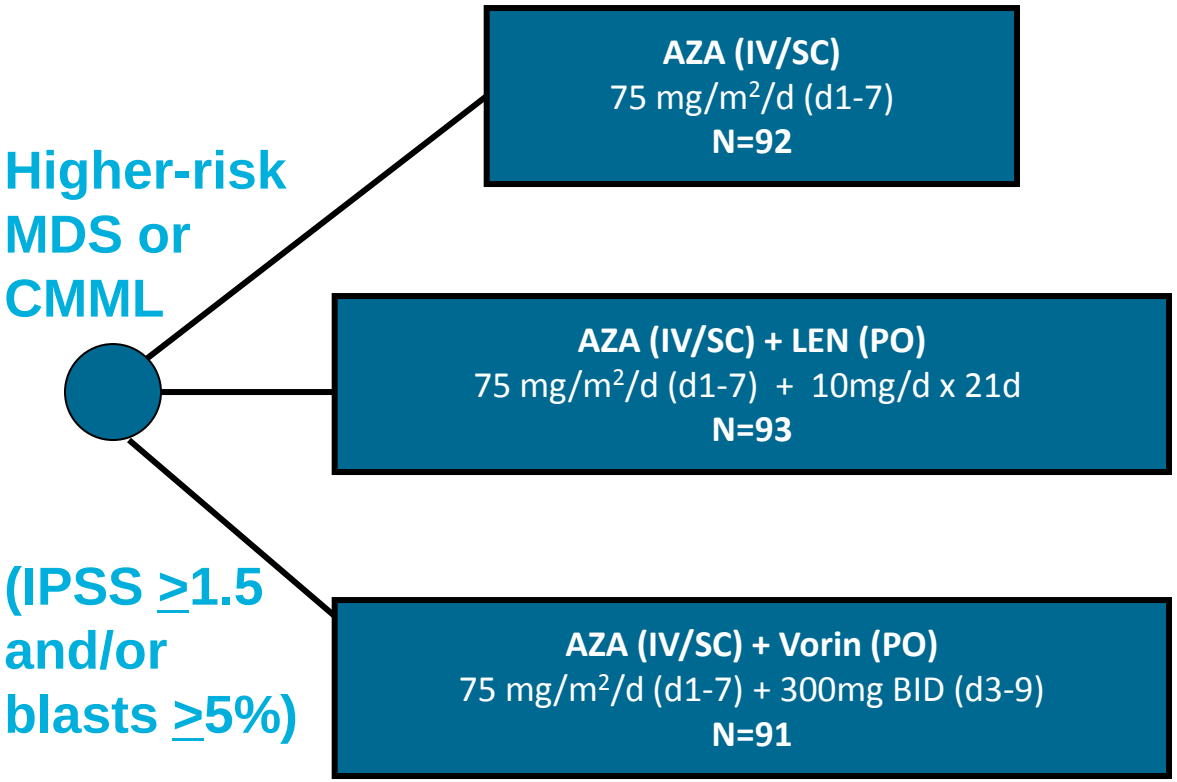
MDS: medical specialist perspective

AZA 001 trial:Overall Survival: Azacitidine vs CCR *(Lancet Oncol, 2009)*



MDS: medical specialist perspective

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

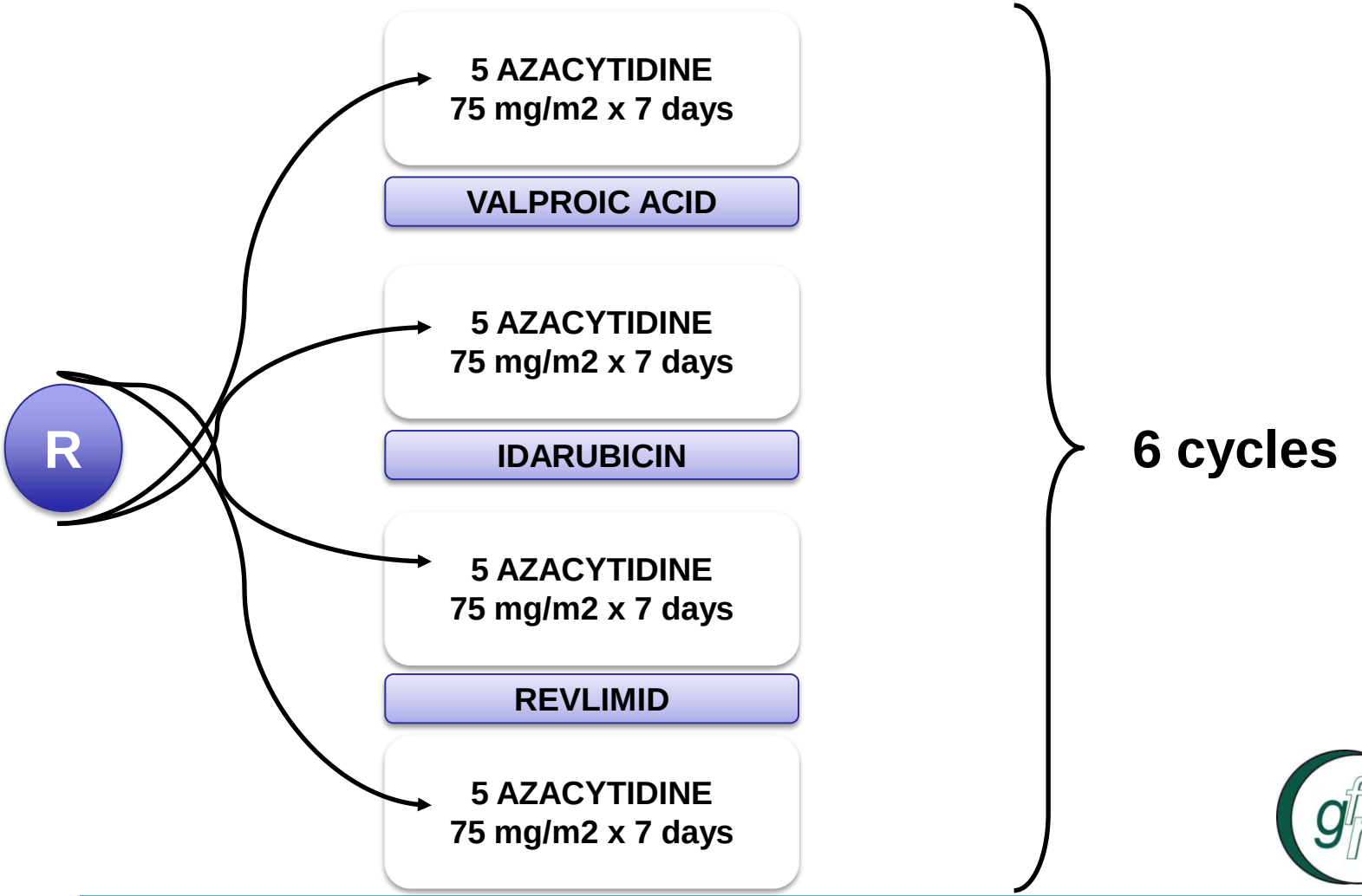
03/2012 – 06/2014

Sekeres et al. ASH 2014: LBA - 5

Horizon 2020

MDS: medical specialist perspective

High risk MDS 1st line AZA PLUS trial «pick the winner»



Groupe Francophone des Myélodysplasies

Horizon 2020

VOLUME 29 · NUMBER 24 · AUGUST 20 2011

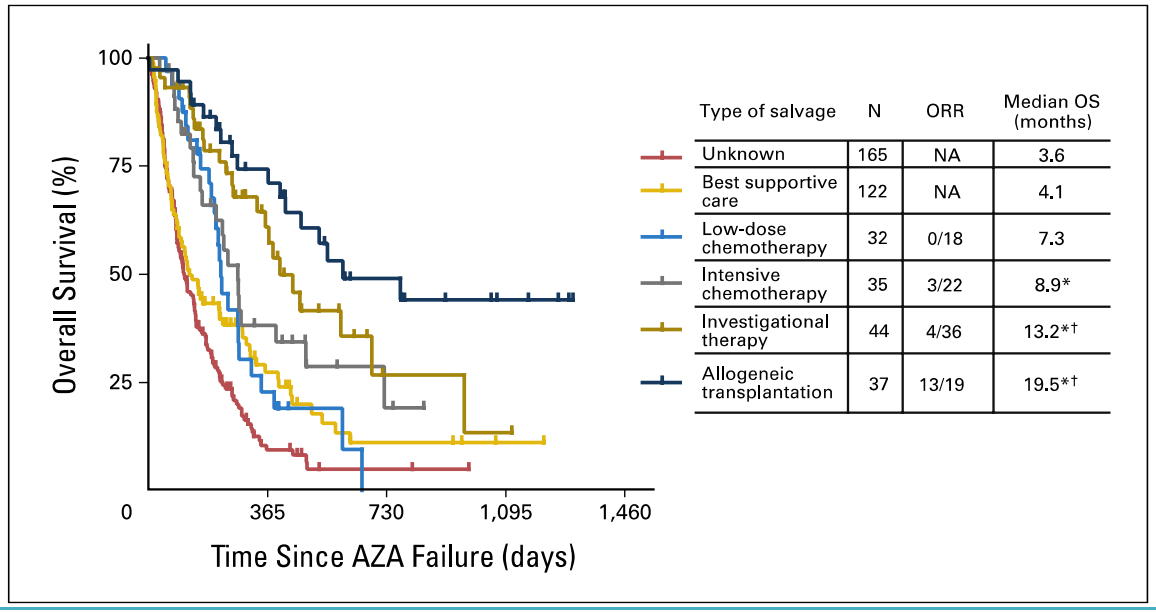
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcome of High-Risk Myelodysplastic Syndrome After Azacitidine Treatment Failure

Thomas Prébet, Steven D. Gore, Benjamin Esterni, Claude Gardin, Raphael Itzykson, Sylvain Thepot,

Prébet et al



Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

New drugs in higher-risk MDS

- Intensive HMA regimens (AZA,DAC)
- New HMAs (guadecitabine, oral AZA)
- IDH1 , IDH2 inhibitors
- Polo like kinase inhibitors (Rigosertib)
- Anti CD 33, anti CD 123 MoAb (and double antibodies)
- Anti bcl2 (Venetoclax)
- Checkpoint inhibitors (anti PD-1, anti PD-L1, anti CTLA4)
- Spliceosome inhibitors (SRSF2)

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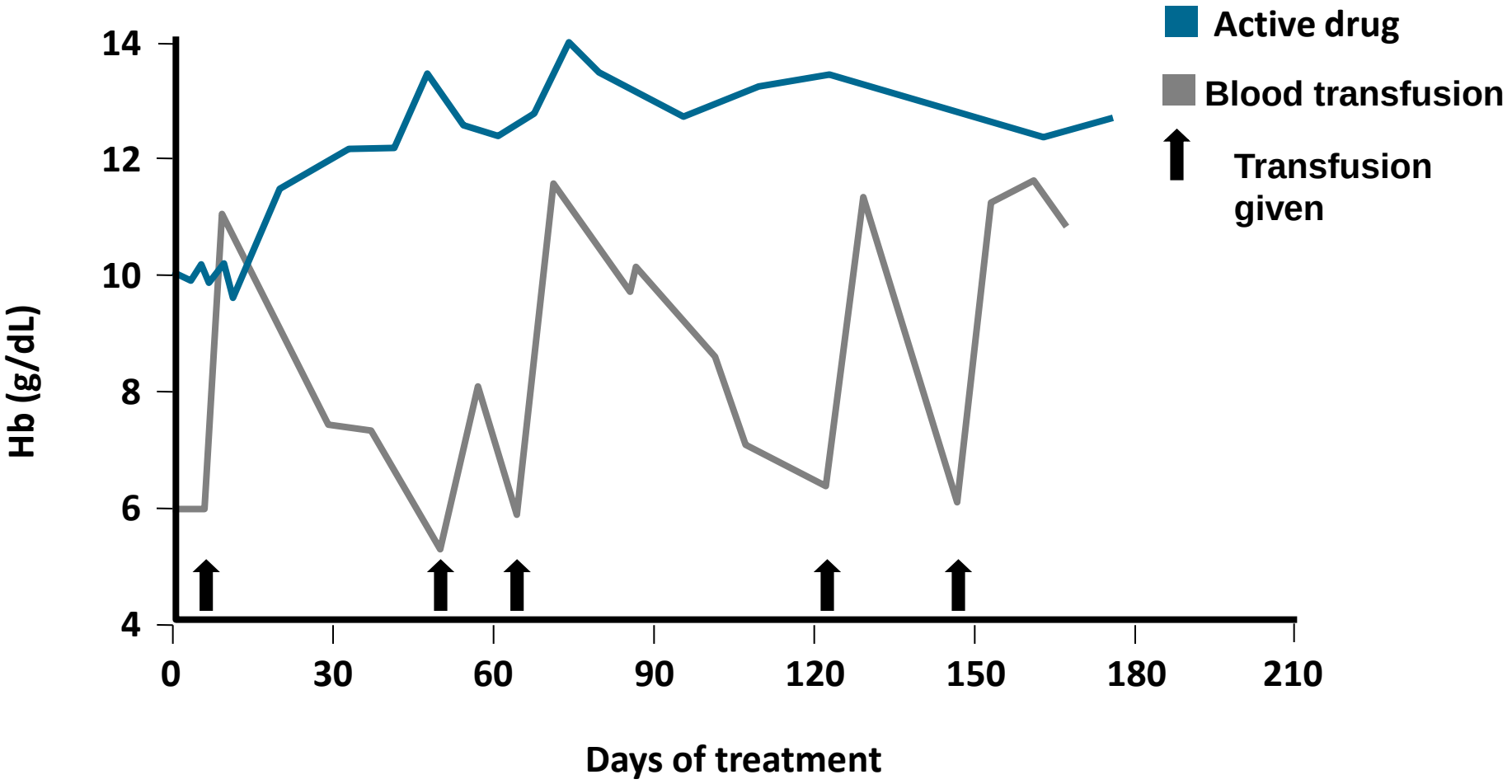
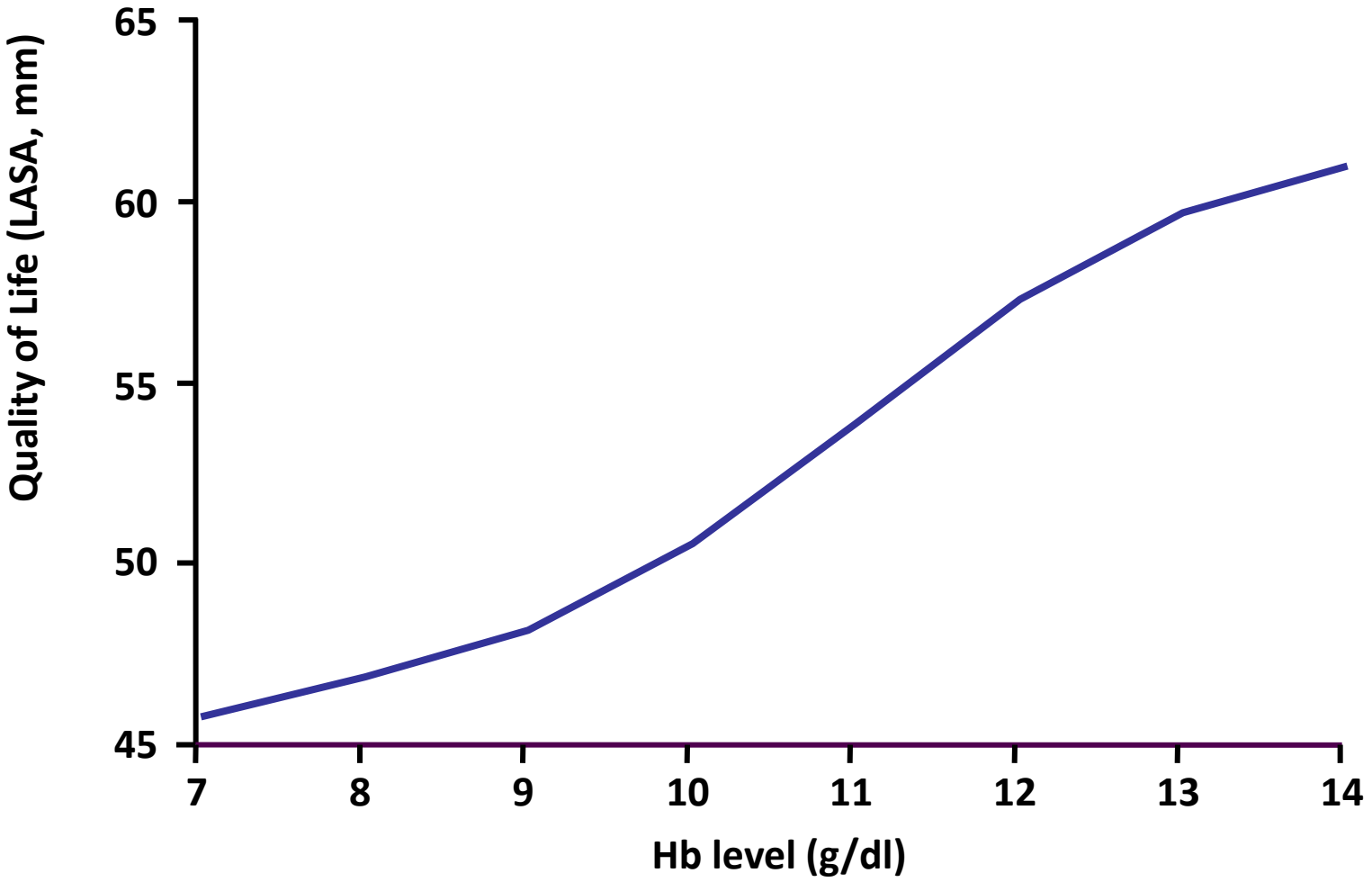
Treatment of anemia in lower risk MDS



Quality of Life is correlated to Hb levels



Crawford et al. *Cancer* 2002; 95: 888–95

LASA: Linear Analog Scale Assessment

Horizon 2020

MDS: medical specialist perspective

EPO +/- G-CSF in MDS: prognostic factors of respons *(Park, Kelaidi, Blood 2007)*

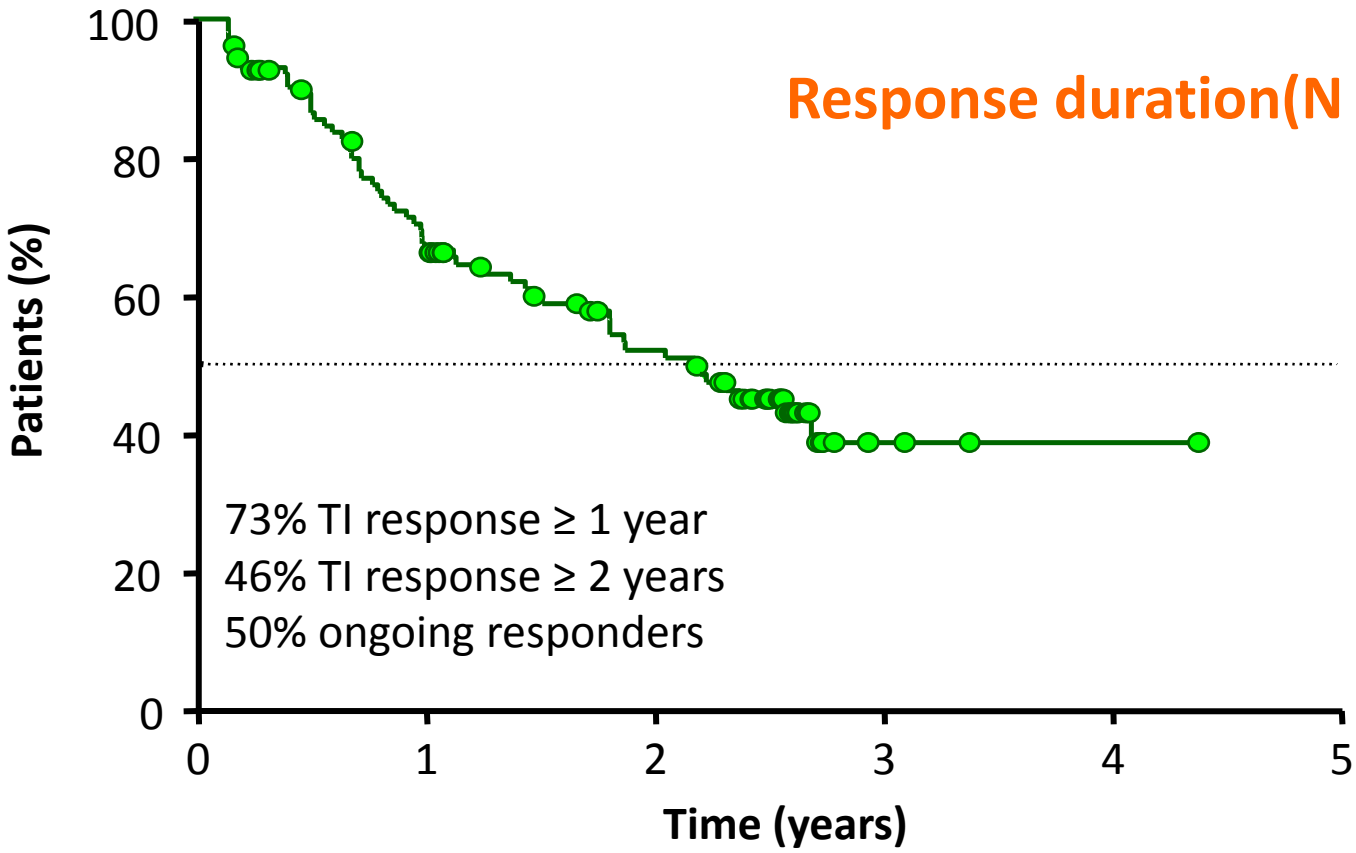
- N=403 pts treated with EPO+/- G-CSF or Darbepoetin alpha
- Hb<10g/dl (54%transfused)
- **63% response (43% major, 20% minor)**
- **Median response duration: 24 months**

Groupe Francophone des Myélodysplasies

Horizon 2020

MDS: medical specialist perspective

Lenalidomide Erythroid Response: lower risk Del 5q *(List, NEJM 2006)*



● **Censored patients who remain TI at time of data cut-off or discontinuation of study**

List AF, et al. Updated data presented at ASH Annual Meeting, 2006 [Abstract 251].

VOLUME 26 · NUMBER 15 · MAY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

MDS RIGHT

Factors Affecting Response and Survival in Patients With Myelodysplasia Treated With Immunosuppressive Therapy

Elaine M. Sloand, Colin O. Wu, Peter Greenberg, Neal Young, and John Barrett

129 pts

- 24% response (CR+PR) to ATG
- **48% response to ATG+ CsA**
- 8% response to CsA
- 31% responses were complete

Prognostic factors of response :

- Younger age (<60 y)
- Recent onset of transfusions
- HLA DR 15
- ATG+ CsA
- IPSS low or int 1

If compared to IPSS database: immunosuppression improves survival in younger patients

European Commission Horizon 2020

A randomized phase II trial of azacitidine +/- epoetin-β in lower-risk myelodysplastic syndromes resistant to erythropoietic stimulating agents

Sylvain Thépot,[1*] Raouf Ben Abdelali,[2*] Sylvie Chevret,[3] Aline Renneville,[2] Odile Beyne-Rauzy,[4] Thomas Prébet,[5] Sophie Park,[6] Aspasia Stamatoullas,[7] Agnes Guerci-Bresler,[8] Stéphane Cheze,[9] Gérard Tertian,[10] Bachra Choufi,[11] Laurence Legros,[12] Jean Noel Bastié,[13] Jacques Delaunay,[14] Marie Pierre Chaury,[15] Laurence Sanhes,[16] Eric Wattel,[17] Francois Dreyfus,[6] Norbert Vey,[5] Fatiha Chermat,[18] Claude Preudhomme,[2] Pierre Fenaux[19] and Claude Gardin[1] on behalf of the Groupe Francophone des Myélodysplasies (GFM)

Haematologica 2016
Volume 101(8):918-925

- **93 pts**
- Mainly “purely anemic patients”
- Randomized phase II trial AZA+/- EPO beta
  In patients CLEARLY resistant to ESAs (at least 12 weeks using 60000 U/ w EPO or 250ug/w Darbepoetin)
- 33% responses, transfusion independence in 19% of patients

Horizon 2020

MDS: medical specialist perspective

LEN+/-EPO in lower risk MDS resistant to EPO (ITT population, n=129)

	LEN + EPO N = 65	LEN N = 64	
Erythroid response (IWG 2006)	40 %	23.4 %	RR1.7 p= 0.043

- Median response duration was 18.1 and 15.1 months in the L and LE arms, respectively (P = 0.47)
- Low baseline serum EPO level and a G polymorphism of CRBN gene predicted HI-E.

Groupe Francophone des Myélodysplasies

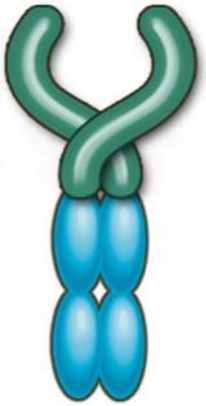
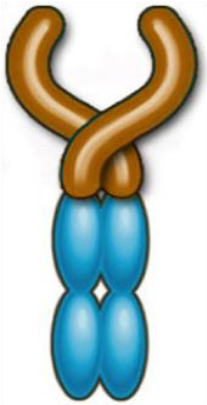
Horizon 2020

Novel Ligand Traps TGFβ Superfamily Ligands

ACE-011 *(Sotatercept)* and ACE-536 *(Luspatercept)*

Fusion protein with ligand trap activity toward the activin type 2 receptors

Drug does not bind EPO receptors

	ACE-011 (Sotatercept)	
	 Extracellular Domain of ActRIIA; Fc Domain of human IgG_1 Antibody	 Modified Extracellular Domain of ActRIIB; Fc Domain of human IgG_1 Antibody
Heme effect	+	+
Bone effect	+	−

Horizon 2020

MDS: medical specialist perspective

- Where are we ?
- **What do we need ?**

MDS: medical specialist perspective

What do we need ?

- **Diagnosis:**
  - Trained morphologists and cytogeneticists
  - NGS
- **Prognosis:**
  - large international studies like HARMONY
- **Treatment**
  - ++++ New drugs, and companies willing to have them approved in MDS
  - Help from companies for academic trials
  - International cooperation
  - Help from patient support groups

Horizon 2020

Groupe Francophone des Myélodysplasies

- Activates clinical trials in MDS
  - (35 centers in France and Belgium + Switzerland)
- Website: www. gfmgroup.org
- Online registry of French MDS cases
- Close cooperation with:
  - a patient support group
  - the International MDS Foundation
  - the European Leukemia Net

Groupe Francophone des Myélodysplasies

Horizon 2020

16:30-16:40

MDS patient perspective

- Panel presentation -

Sophie Wintrich

Chief Executive/Patient Liaison of the MDS UK Patient Support Group
King's College Hospital, London, United Kingdom

MDS RIGHT

European Commission
Horizon 2020

MDS patient perspective

Who is MDS Alliance?

- Umbrella organisation of national MDS patient groups
- 6 founding members
- Established to promote collaboration, shared information, and increased awareness of MDS worldwide
- Currently 25 members – fully checked and validated
- A shared pool of knowledge, skills and resources
- Training and assistance opportunities for junior groups

European Commission Horizon 2020

MDS patient perspective

Audience and Aims of MDSA

- **Our audiences:**
  - patients/relatives/clinicians/regulatory/HTA-payers
- **Our aims = to help improve & promote:**
  - Strategic and accelerated pace of research
  - shared and collaborative research
  - Increased clinical trials
  - Better REAL patient data – Increased evidence - QOL data
  - Increased access to more effective therapies - espec in low-risk MDS
  - Knowledge of clinical guidelines

Based on our experience with EMA and HTA's

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MDS patient perspective

Data is key

Solutions = robust registries

- **Projects like EU MDS Right (also ERN & Harmony)** with special emphasis on:
  - widespread use of molecular analysis – **EMA and HTA**
  - Use of robust QOL tools (*QUALMS, but also QOL-e – not just EQ5D!)* – **EMA and HTA**
  - Tissue banking & well-kept databases – effective, accurate & truly usable
  - Increased essential 'real-world' data (community data vs limited trial data)
  - Improved cross border system for patients and samples
  - strengthened collaboration with patients, clinicians, researchers and pharma industry

- **FOR**
  - Better understanding of MDS
  - Refined and more accurate prognostic tools
  - Hope for **AND ACCESS** to a larger choice of treatment
  - More personal treatments
  - Less “wasted” time for patients
  - **Financially viable access** to treatments with more assured response rate

ROBUST DATA is a must

Non-response rates = hard to cope with

European Commission Horizon 2020

16:40-16:50

Nurse perspective

- Panel presentation -

Corien Eeltink

Clinical Nurse Specialist
VU medical center, Amsterdam, the Netherlands

MDS RIGHT

European Commission
Horizon 2020


VUmc

Nurse perspective

Heterogeneous Population

- MDS
- Higher incidence among older population
- Fit versus frail
- Increased life expectancy versus Quality of Life

Horizon 2020

Nurse perspective

Supplemented with:

- **Living conditions**
- **Literacy**
- **Vision and hearing screening**
- **NCCN distress thermometer and problem list**
- **Medication adherence**
- **Quality of Life**
- **Social network (presence of adequacy of caregiver) and Quality of Life of the caregiver**
- **Access to transportation**
- **Meaning of life**

Nurse perspective

original articles

Annals of Oncology

Annals of Oncology 24: 1306–1312, 2013
doi:10.1093/annonc/mds619
Published online 4 January 2013

Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study

C. Kenis[1], D. Bron[2], Y. Libert[3], L. Decoster[4], K. Van Puyvelde[5], P. Scalliet[6], P. Cornette[7], T. Pepersack[8], S. Luce[9], C. Langenaeken[10], M. Rasschaert[11], S. Allepaerts[12], R. Van Rijswijk[13], K. Milisen[14,15], J. Flamaing[14,16], J.-P. Lobelle[17] & H. Wildiers[18,19*]

Table 2.

Results of the screening

SCREENING	Instrument	Score	*n*	%	95% CI
Geriatric profile	G8 (0–17) (*n* = 1967)	Absence of a geriatric profile: score >14	576	29.3	27.3 –31.3
		Presence of a geriatric profile: score ≤14	1391	70.7	68.7 –72.7

- The assessment detected unknown geriatric problems in 51.2% of patients.
- The treatment decision was influenced in 25.3% of patients.

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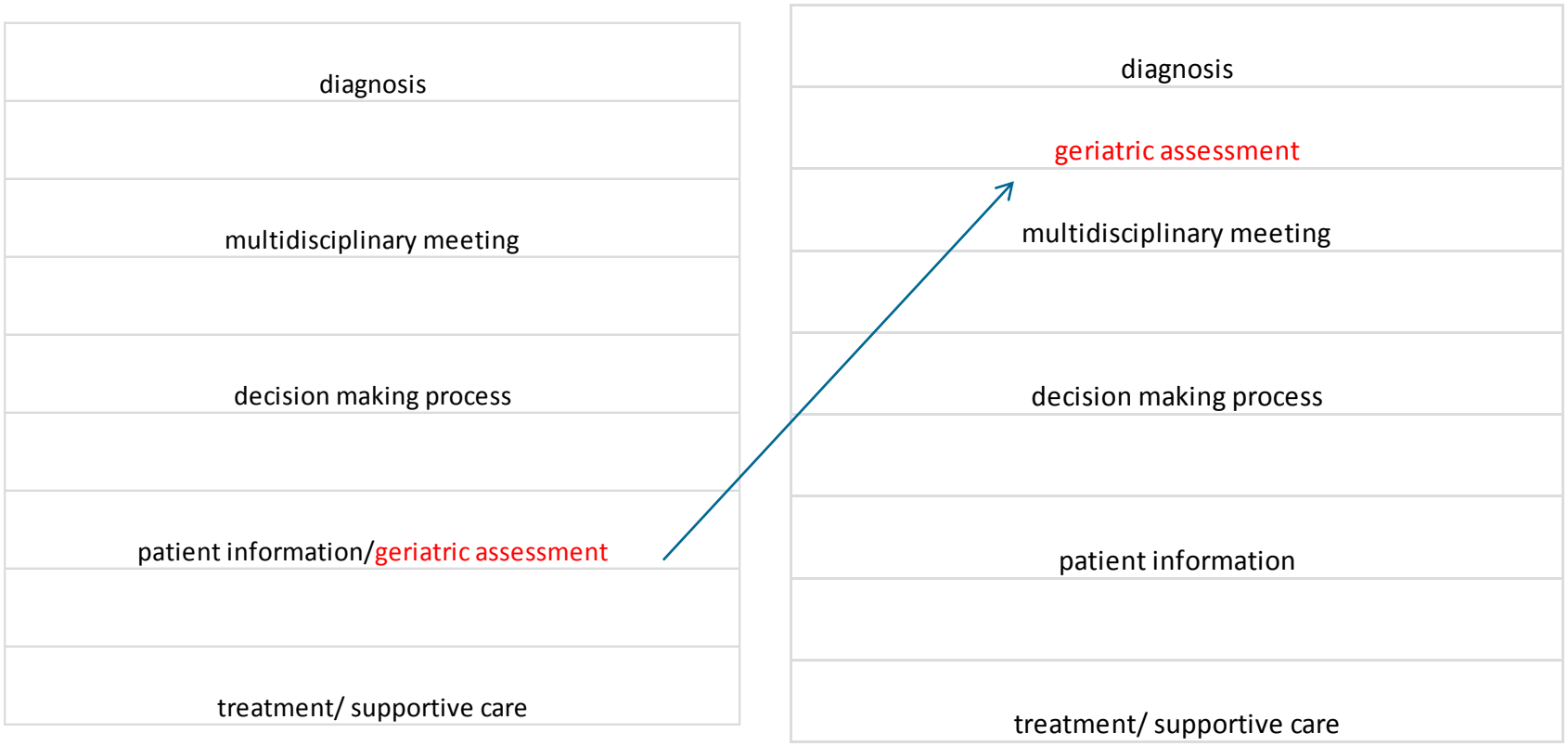
Nurse perspective



Nurse perspective

Interpretation of Quality of Life results is complicated

Technical Summary

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

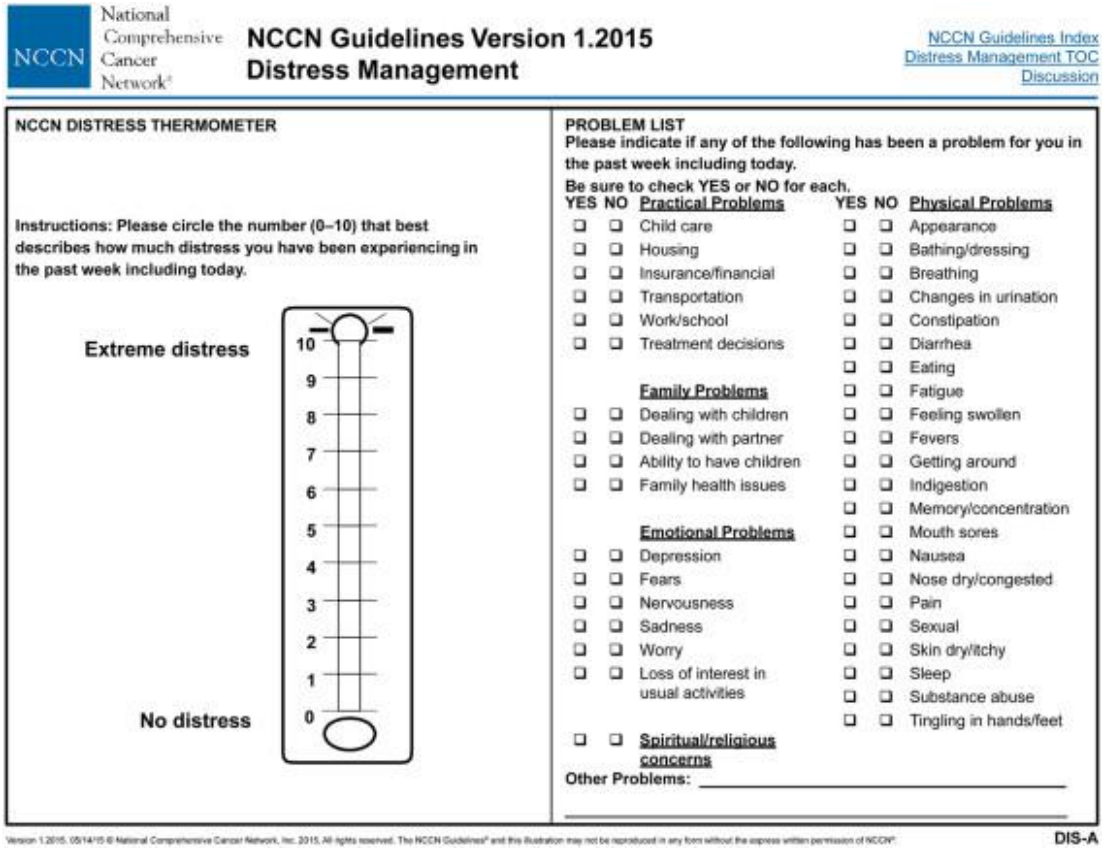
Symptom scales / items: $S = \{(RS-1)/range\} \times 100$

Global health status / QoL: $S = \{(RS-1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

EORTC QLQ-C30 (version 3)

Nurse perspective



National Comprehensive Cancer Network

NCCN Guidelines Version 1.2015
Distress Management

NCCN Guidelines Index
Distress Management TOC
Discussion

NCCN DISTRESS THERMOMETER

Instructions: Please circle the number (0–10) that best describes how much distress you have been experiencing in the past week including today.

Extreme distress 10 9 8 7 6 5 4 3 2 1 **No distress** 0

PROBLEM LIST
Please indicate if any of the following has been a problem for you in the past week including today.
Be sure to check YES or NO for each.

YES	NO	Practical Problems
❑	❑	Child care
❑	❑	Housing
❑	❑	Insurance/financial
❑	❑	Transportation
❑	❑	Work/school
❑	❑	Treatment decisions
		Family Problems
❑	❑	Dealing with children
❑	❑	Dealing with partner
❑	❑	Ability to have children
❑	❑	Family health issues
		Emotional Problems
❑	❑	Depression
❑	❑	Fears
❑	❑	Nervousness
❑	❑	Sadness
❑	❑	Worry
❑	❑	Loss of interest in usual activities
❑	❑	**Spiritual/religious concerns**

YES	NO	Physical Problems
❑	❑	Appearance
❑	❑	Bathing/dressing
❑	❑	Breathing
❑	❑	Changes in urination
❑	❑	Constipation
❑	❑	Diarrhea
❑	❑	Eating
❑	❑	Fatigue
❑	❑	Feeling swollen
❑	❑	Fevers
❑	❑	Getting around
❑	❑	Indigestion
❑	❑	Memory/concentration
❑	❑	Mouth sores
❑	❑	Nausea
❑	❑	Nose dry/congested
❑	❑	Pain
❑	❑	Sexual
❑	❑	Skin dry/itchy
❑	❑	Sleep
❑	❑	Substance abuse
❑	❑	Tingling in hands/feet

Other Problems: _____

DIS-A

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Horizon 2020

Nurse perspective

Nursing roles

- Patient education and patient information
- Upfront Geriatric Assessment
- Understanding of Quality of Life
- Case manager
- Nursing research

Nurse perspective

In conclusion

- A full GA is time-consuming but detects unknown geriatric problems in older patients
- A two-step approach: a short screening test followed by geriatric evaluation for patients at risk can lead to many older patients still needed to be assessed by GA
- Involve dedicated nurses in your plans and provide adequate training
- Quality of Life is an important outcome, therefore results should be available to discuss with every patient

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16:50-17:00

Regulatory/HTA perspective

- Panel presentation -

David Bowen

Honorary Professor of Myeloid Leukaemia Studies & Consultant Haematologist
St. James's University Hospital, Leeds, United Kingdom

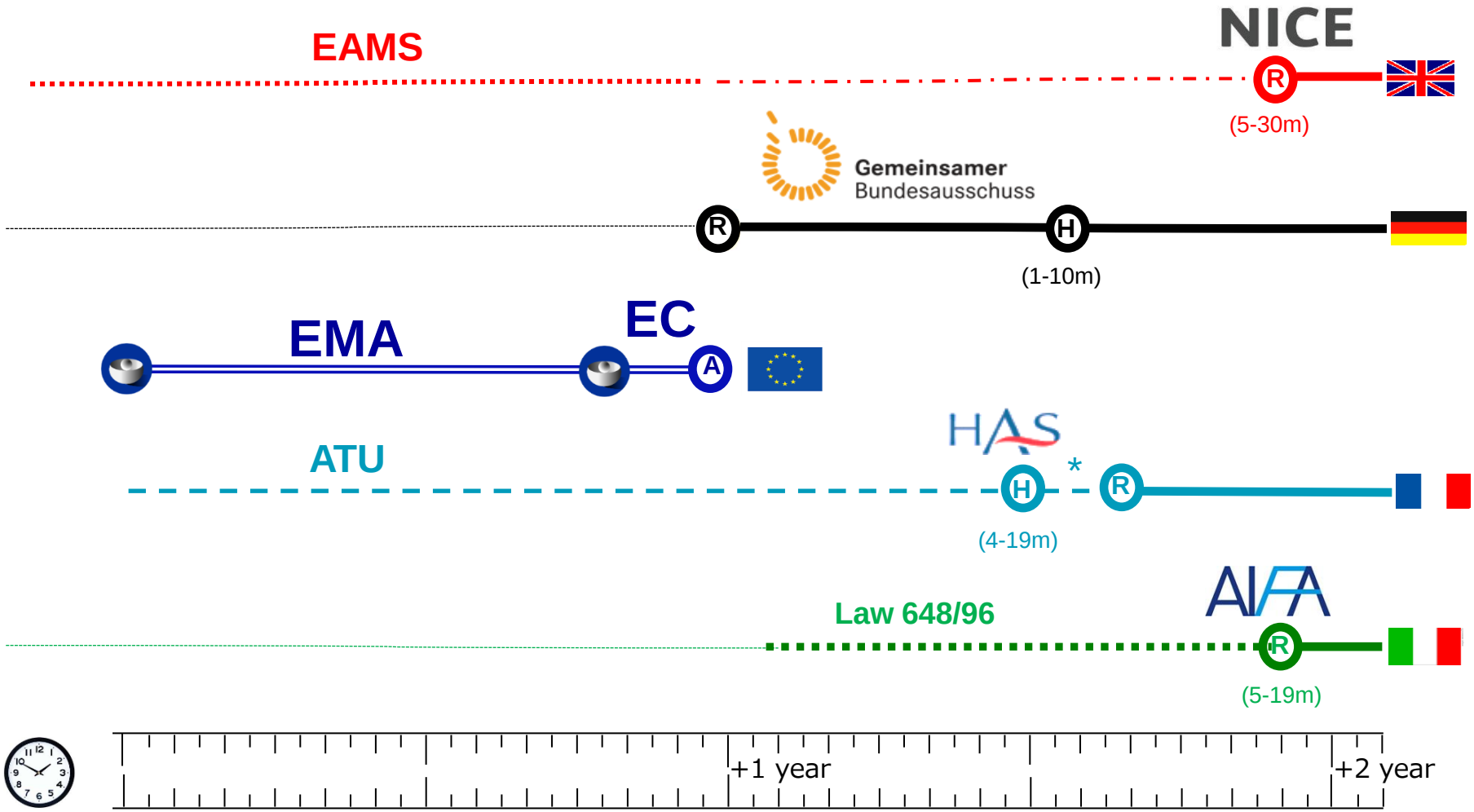
MDS RIGHT

European Commission
Horizon 2020

My background

justification for giving this presentation

- **MDS clinician / researcher**
- Member of National Institute for Health and Care Excellence **(NICE) Technology Appraisal Committee** member since 2013
- Seconded as National Expert to Scientific Advice Unit (Geriatric Medicines & Adaptive Pathways), **European Medicines Agency** for 12 months (2015)



Martinalbo et al, Early market access of oncologic drugs in the EU, Annals of Oncology online 2015

Stakeholder targets (for this talk)

- **Pharmaceutical companies**
- **Regulatory authorities**
  - EMA
  - National Competent Authorities
- **Health Technology Assessment Bodies**
- **Payers**

How EUMDS / MDS-RIGHT could assist:

Pharmaceutical companies

- **Assist with trial design**
  - Prevalence of sub-populations of MDS
  - Outcomes with current standard of care
- **Regulatory submission**
  - Supportive data for clinical trials (e.g. outcomes of SOC arm)
- **Post marketing commitment**
  - Real-world data (RWD) (*prospective*)
    - demographics including co-morbidity
    - outcome
    - QoL

Early access tools: Overview

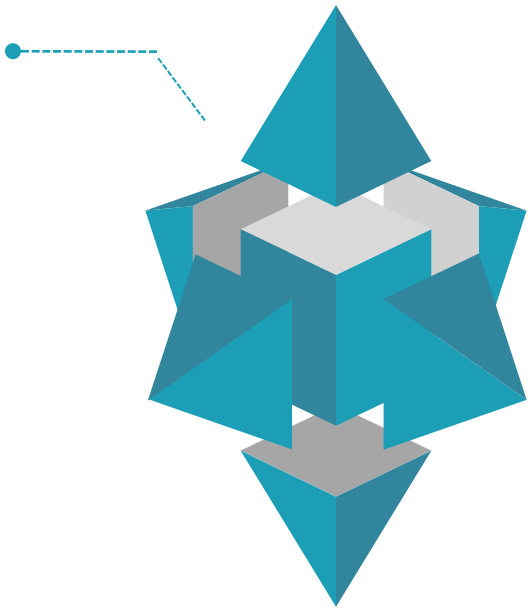
PRIME

Major public health interest, unmet medical need.

Dedicated and reinforced support.

Enable accelerated assessment.

Better use of existing regulatory & procedural tools.



Adaptive Pathways

Scientific concept of development and data generation.

Iterative development with use of real-life data.

Engagement with other healthcare-decision makers.

Accelerated Assessment

Major public health interest, unmet medical need.

Reduce assessment time to 150 days.

Conditional MA

Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations.

Early approval of a medicine on the basis of less complete clinical data.

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How EUMDS / MDS-RIGHT could assist:

Regulators

- **Prospective RWD** to assist early Scientific Advice (EMA/NCA)

- **Implementation of Adaptive Pathways concepts**
  - Real world data (RWD) collection
  - Elements of pharmacovigilance (second primary malignancies / specific safety signals captured by comorbidity)

How EUMDS / MDS-RIGHT could assist

Health Technology Assessment

- **Country specific outcome data**
- **Comparative effectiveness**
  - Academic Evidence Review Groups
- **Resource Utilisation**
  - Comparator
- **Prospective outcome data with longer follow up than clinical trials**
  - Validity of extrapolation models for outcomes (reduce uncertainty)

How EUMDS / MDS-RIGHT could assist:

Payers

- **Assist in HTA evaluation**
- **Provide ongoing outcome data for regular re-evaluation of 'value'**

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Regulatory/HTA perspective

Conclusion

- **EUMDS is the only prospective registry for low risk MDS**
- **Now amended to include**
  - high-risk MDS
  - Health economics
  - Expanded QoL
- **A unique resource**

Horizon 2020

17:00-17:07

Industry perspective (1)

- Panel presentation -

Margaret Doyle

Global Medical Affairs Director, Haematology
Janssen, Pharmaceutical Companies of Johnson & Johnson, Dublin, Ireland

MDS RIGHT

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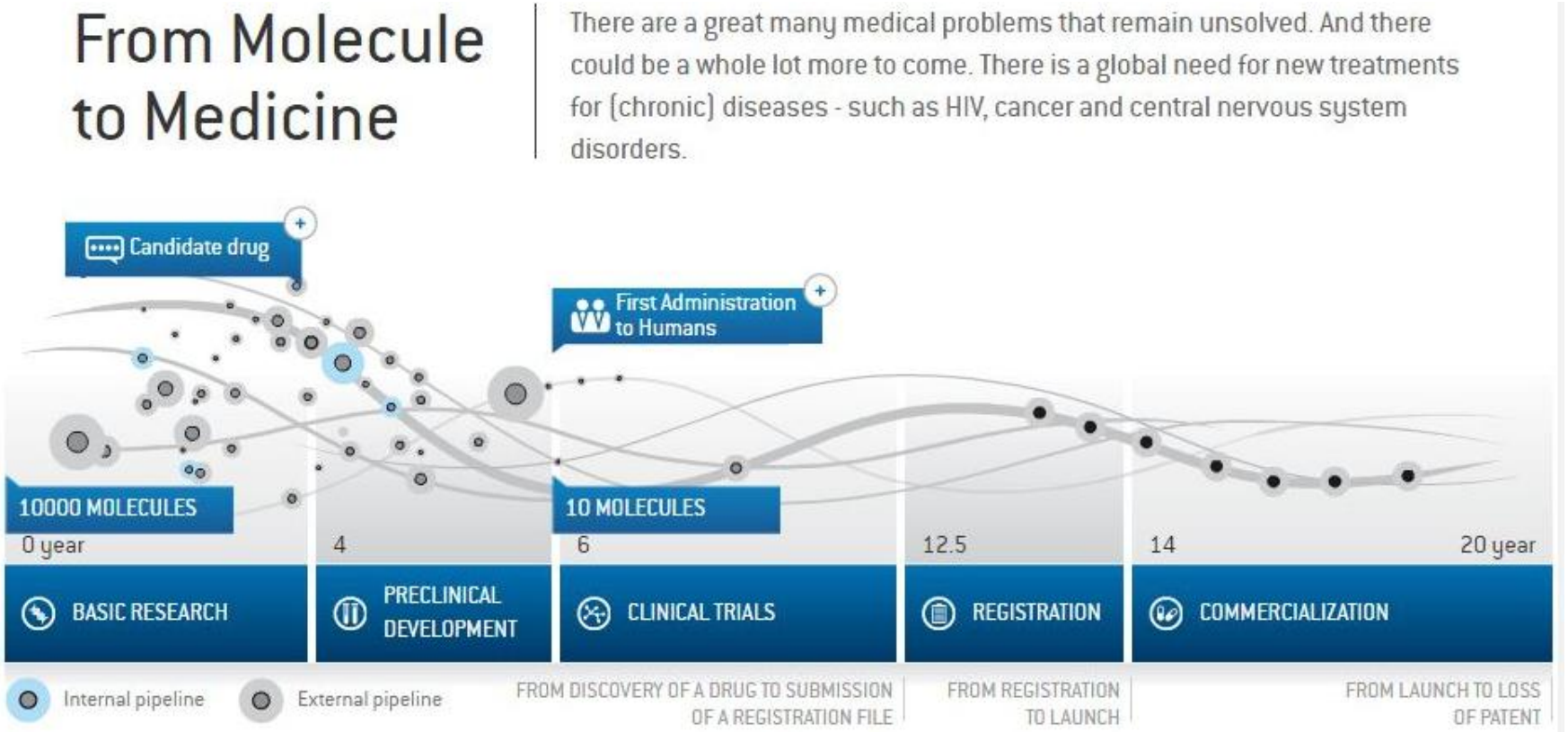
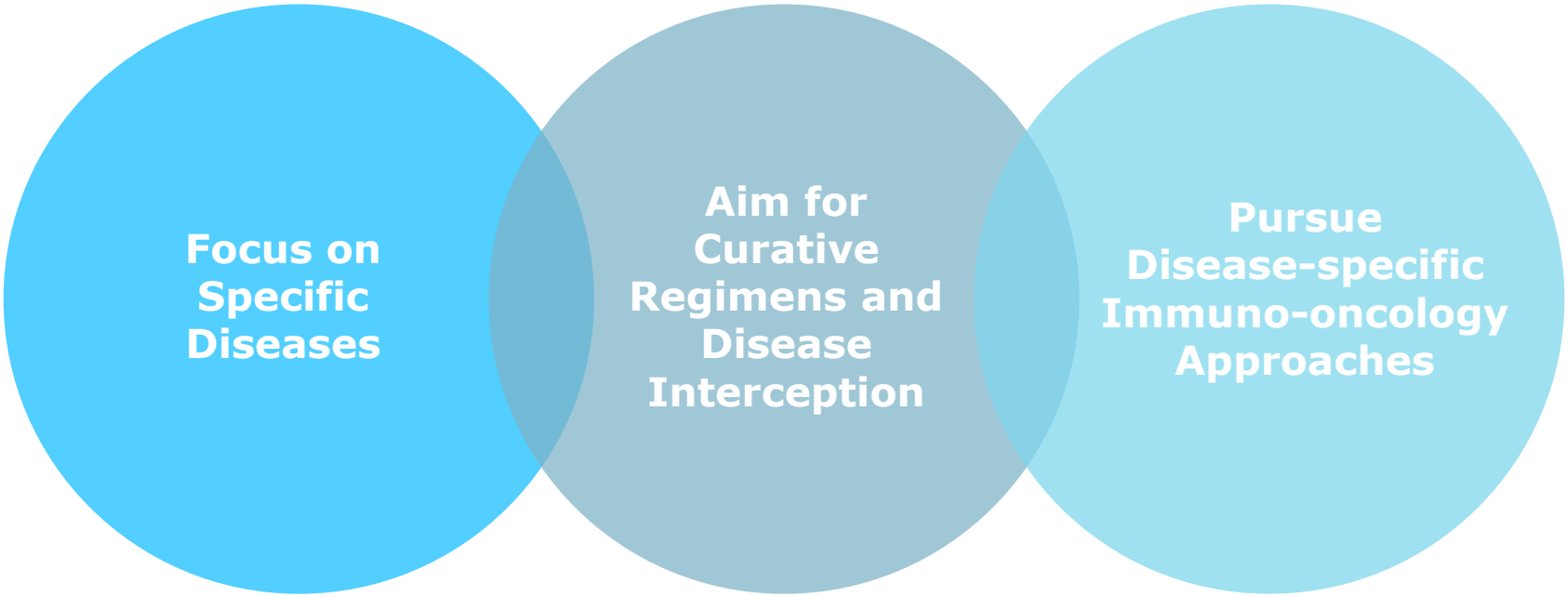
Horizon 2020

Industry perspective



Industry perspective

Janssen's Vision: The Elimination of Cancer



Horizon 2020

Industry perspective

Leveraging Novel Science in Areas of Large Unmet Need

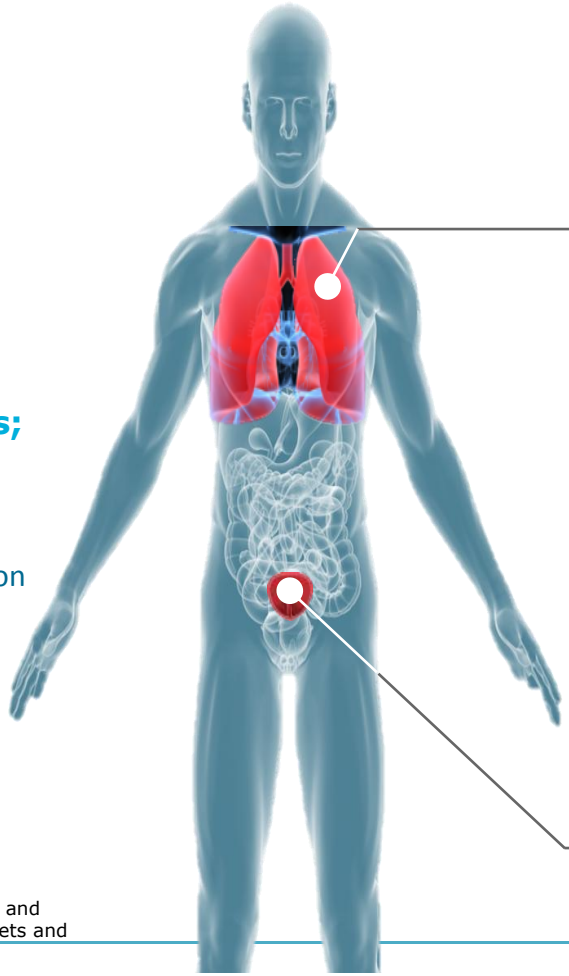
- *Massive Need Remains: 8⁺ Million Deaths, 14⁺ Million New Diagnoses Each Year WW*

Heme Malignancies

Complex group of diseases with many types and subtypes, one of which is:

Myelodysplastic Syndromes; 37,820 patients*

*Diagnosed Incident Patient Population (US+G5; 2019 projections)



Lung Cancer

The most common cancer worldwide

Prostate Cancer

Most common cancer among men in the US

Source: AML-Kantar Health 2017, MDS-Decision Resources Disease and Landscape Forecast MDS, 2015, MF-Decision Resources Niche Markets and Rare Disease, 2015.

European Commission Horizon 2020

Industry perspective

The Challenges We Need to Address

How do we:

- Address the true unmet needs of patients?
- Understand outcomes and deficiencies of current therapies today?
- Shorten time for regulatory approval & market access?

Industry perspective

An Opportunity in our Common Goals

Industry perspective

An Opportunity in our Common Goals through Collaboration

- Provide **timely access to innovative drugs**
- **Collect data** to improve our understanding and **find new ways to treat disease**
  - Increase the number of patients enrolled in clinical trials
  - Enhance translational programs to accelerate clinical development; identify early benefits of new treatments
  - Improved trial design flexibility as the science evolves
  - Overcome current deficiencies in our understanding of therapies and solutions

THANK YOU!

When we see something special in oncology research, we will go to the ends of the earth to get it done.”

Craig Tendler, M.D. VP, LATE DEVELOPMENT & GLOBAL MEDICAL AFFAIRS

“We’re striving to change expectations of what a cancer diagnosis means. Together with our partners, we are focused on delivering solutions that make a positive impact on people’s health”

Jane Griffiths, Ph.D. COMPANY GROUP CHAIRMAN, EMEA

European Commission
Horizon 2020

17:08-17:15

Industry perspective (2)

- Panel presentation -

Alberto Vasconcelos

Director, Medical Affairs Myeloid Disease Lead for Europe, Middle East & Africa (EMEA)
Celgene , Boudry, Switzerland

MDS RIGHT

European Commission
Horizon 2020

Industry perspective (2)

Celgene is committed to changing the course of human health through bold pursuits in science and transformational medicines.

“Extraordinary claims require extraordinary evidence”

Carl Sagan

Industry perspective (2)

Randomized clinical trials

- Often need to exclude groups such as patients with given comorbidities, children, pregnant women, chronic disease patients, very elderly/frail

Industry perspective (2)

Randomized, controlled clinical trials:

- Limited power to detect rare drug adverse events
- Sometimes not able to assess long-term safety or effectiveness
- Some hypothesis impossible to test for ethical reasons

→ No matter how well designed, geographically broad, long follow-up, flawless monitoring & data collection, no single trial, or cluster of trials, is ever capable of answering all the relevant questions!

Industry perspective (2)

Industry perspective (2)

Experimental Evidence

Real World Evidence

Clinical Trials

Clinical Routine
High Quality
Registries

Industry perspective (2)

In 2014, the EMA commenced a Registry Initiative aiming to optimise the use of registries in supporting medicines authorisations.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 February 2017
EMA/69716/2017
Inspections, Human Medicines, Pharmacovigilance and Committees Division

Patient Registries Workshop, 28 October 2016

Observations and recommendations arising from the workshop

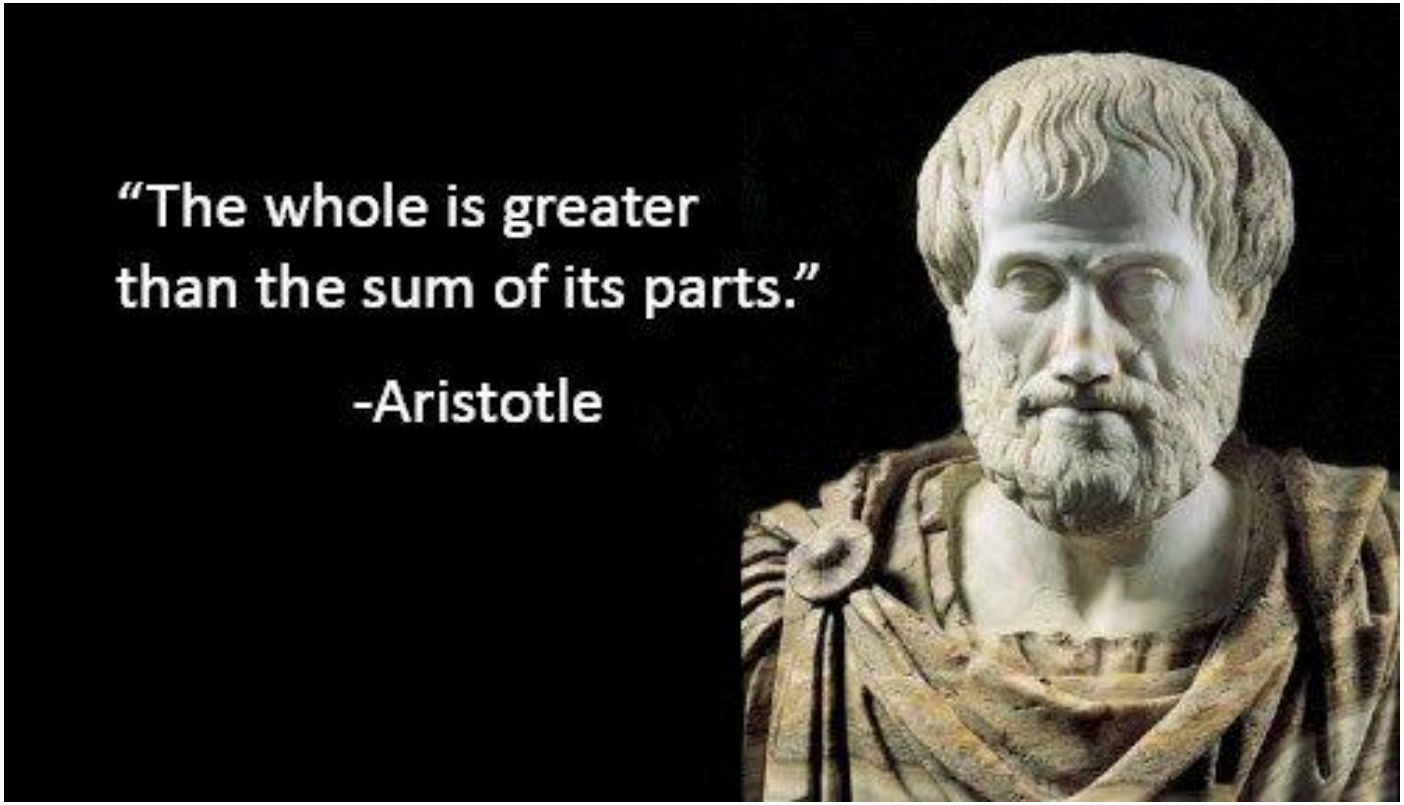
Industry perspective (2)

The European Medicines Agency Registry Initiative is based on the recognition of the need for information across the life cycle of medicinal products in order to better understand disease characteristics and progression, to understand current clinical care and collect data on the effectiveness and safety of medicines beyond what is available from the evidence supporting the marketing authorisation.

Such evidence is generally derived from randomised controlled studies, which in order to investigate efficacy, are conducted in tightly defined populations and often exclude patients in whom the medicine may be used when the product is marketed.

EMA may require the marketing authorisation applicant or holder (MAA/MAH) to provide evidence on disease outcomes, effectiveness and safety unavailable from clinical trials. There are multiple real world evidence sources of potential value, including registries, typically patient registries as defined in the EMA's Patient Registry Initiative.

Industry perspective (2)



Industry perspective (2)

17:15-17:25

MDS patient management challenges and solutions

- Panel discussion -

Moderator: David Bowen

MDS RIGHT
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Horizon 2020

17:25 - 17:35

MDS patient management recommendations and interactive online support

Eva Hellström-Lindberg

Haematology specialist
Karolinska Institute - Huddinge University Hospital, Huddinge, Sweden

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MDS patient management recommendations

Who needs them?

- MDS specialists
  - In order to establish national guidelines
- Hematologists
  - In order to establish local therapeutic routines
- Internists / trainees
- Patients and relatives
- Patient organizations
- Health care systems – regulators
- Researchers
- Pharma
- Others

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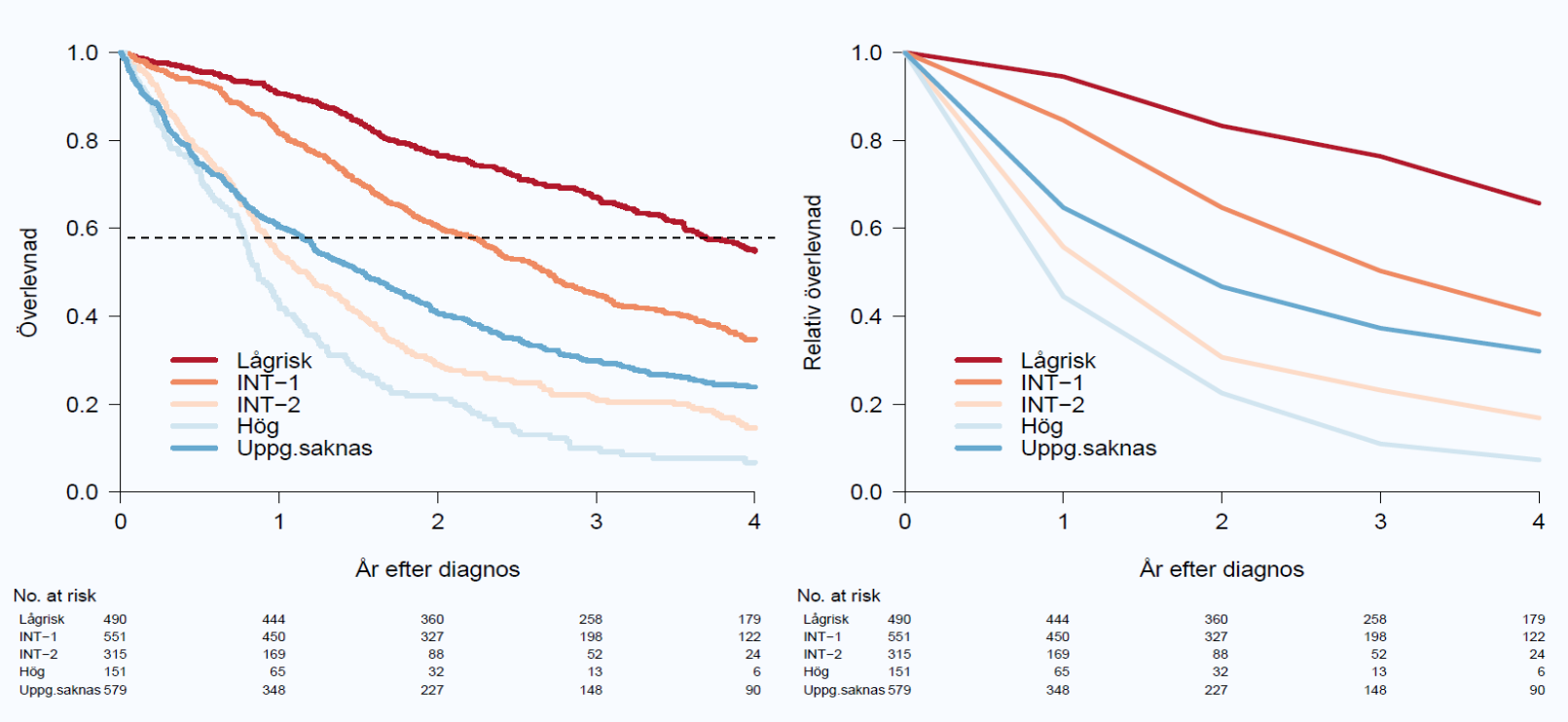
MDS patient management recommendations



50% of patients are transfusion-dependent at diagnosis

Important to make right treatment decisions upfront

(*2200 patients from the Swedish population-based registry 2009-2014*)

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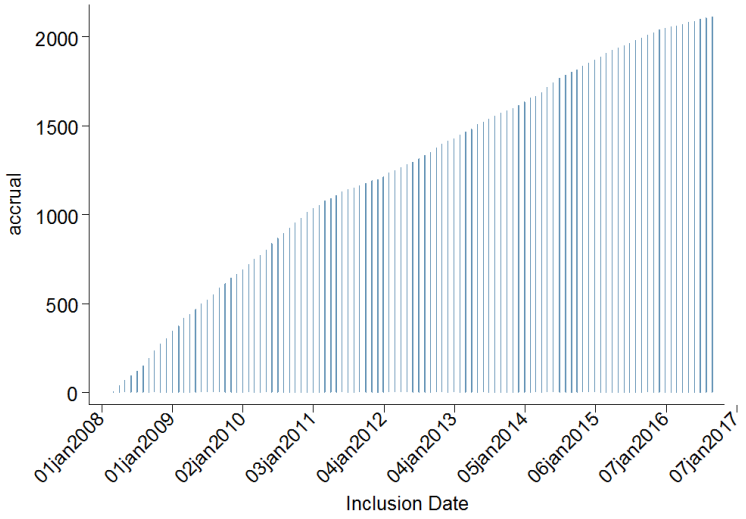
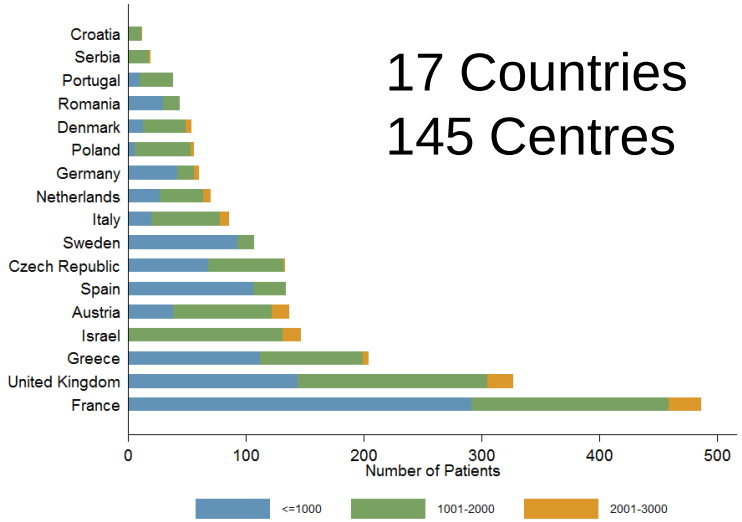
MDS patient management recommendations

What have we learned from EU MDS Registry?





17 Countries
145 Centres

Recruited = 2,161 MDS IPSS Low and INT-1

- Transfusions, co-morbidities, treatment, disease progression, survival, quality of life

Expanded registry from 2017

- all MDS subtypes and more details regarding treatment, outcome and health economy

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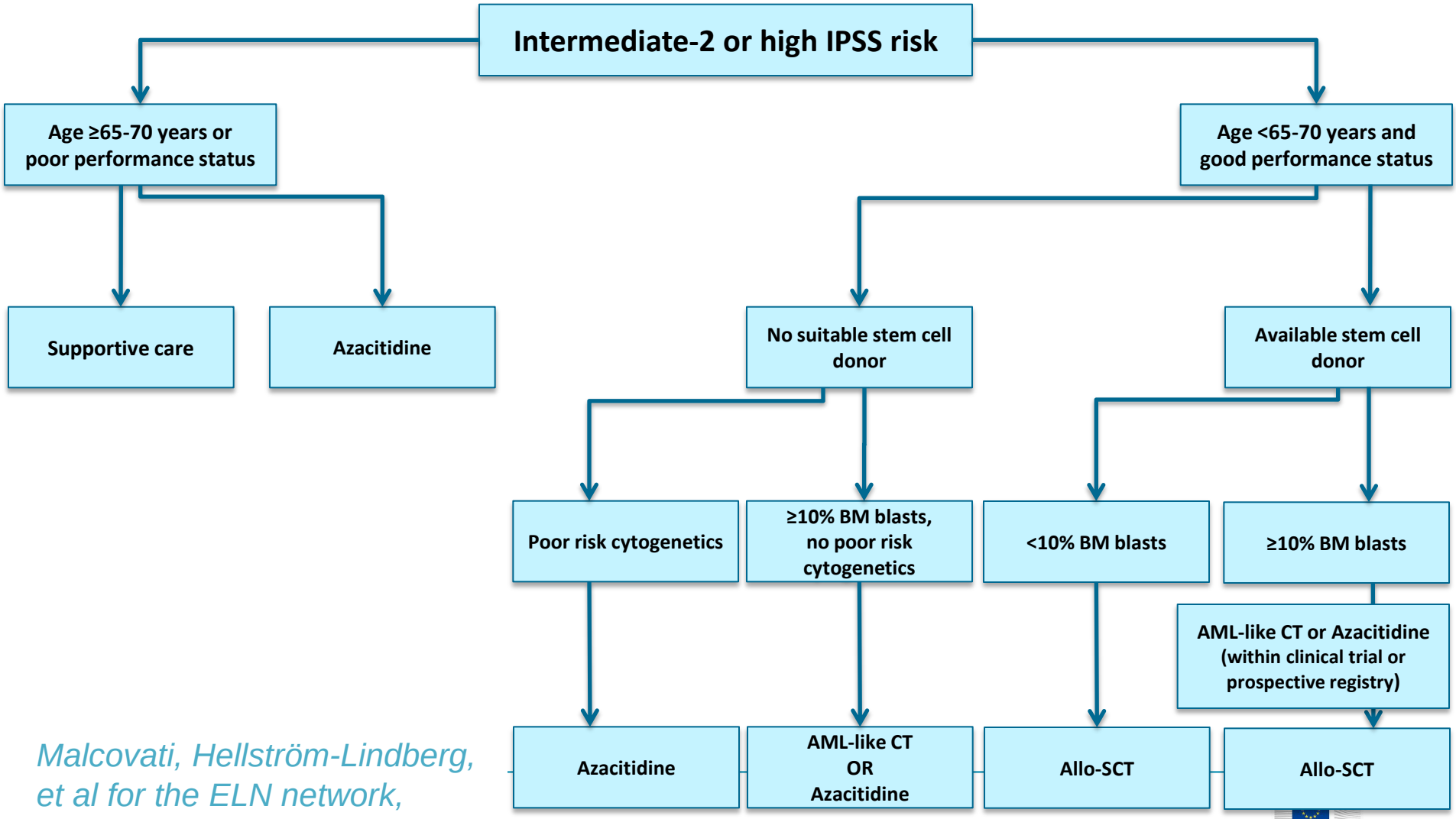
MDS patient management recommendations

Therapeutic Algorithm for Patients with Primary MDS and Int-2 or High IPSS Score (ELN)



Malcovati, Hellström-Lindberg, et al for the ELN network, Blood 2013

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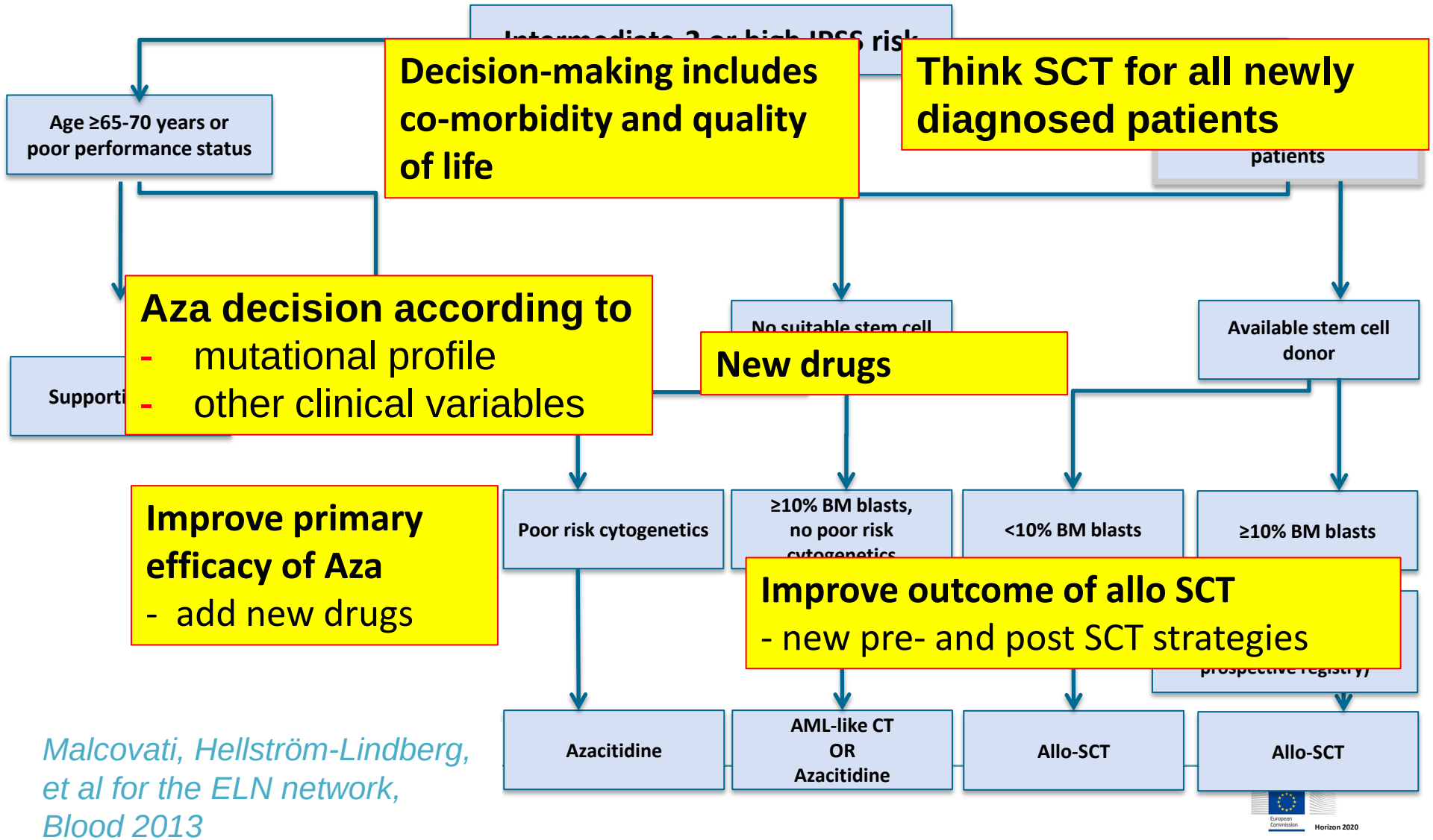
MDS patient management recommendations

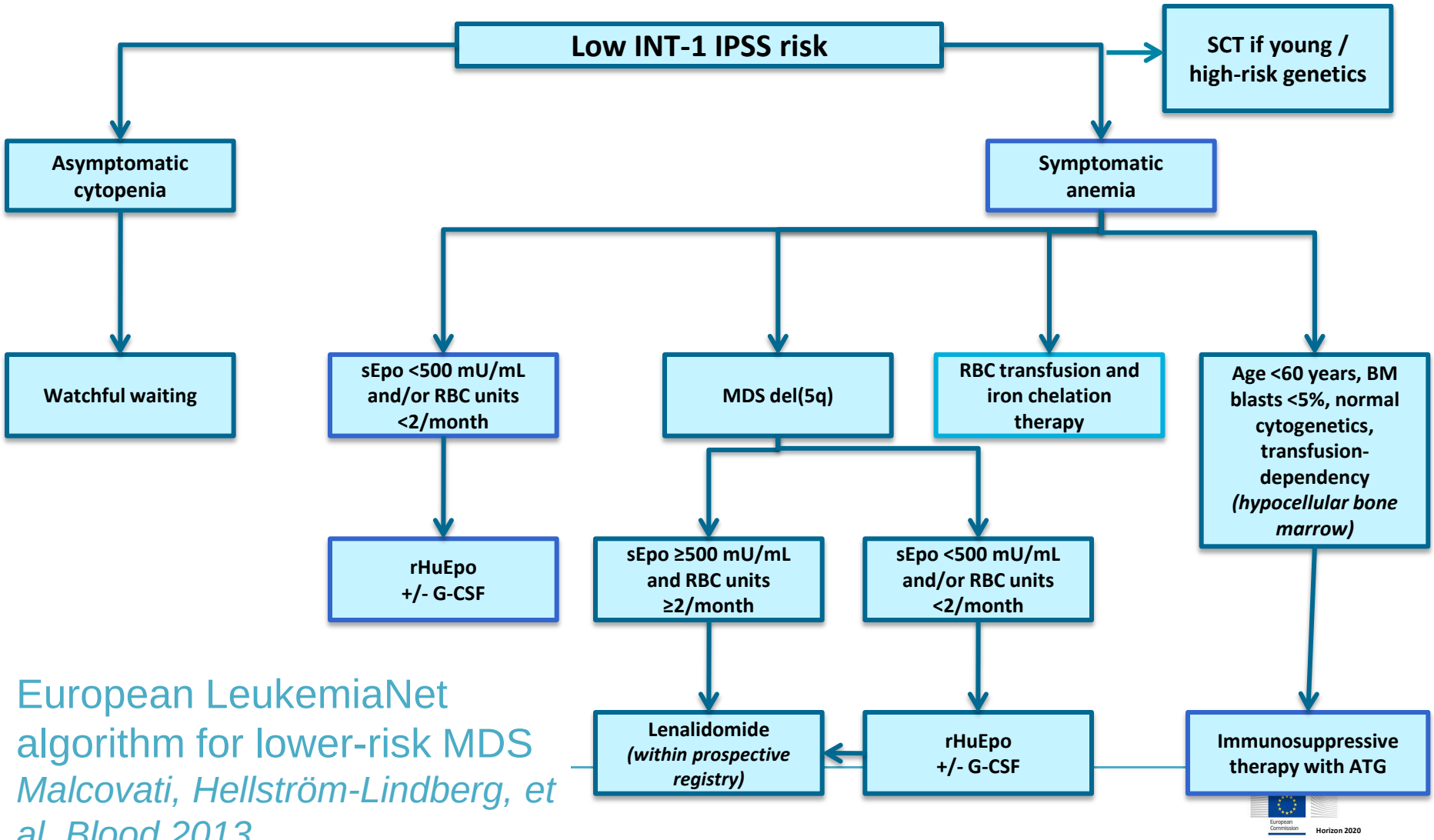
2017-2020 strategies to improve outcome for patients with higher-risk MDS



Malcovati, Hellström-Lindberg, et al for the ELN network, Blood 2013

MDS patient management recommendations

Therapeutic Algorithm for Patients with Primary MDS and Low or INT-1 IPSS Score (ELN)



European LeukemiaNet algorithm for lower-risk MDS

Malcovati, Hellström-Lindberg, et al, Blood 2013

MDS patient management recommendations

Conclusions ESA treatment in lower-risk MDS

ESA treatment:

- Effective treatment for the anaemia of lower-risk MDS
- 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

Garelius et al, for EU MDS Registry 2017, Journal of Internal Medicine

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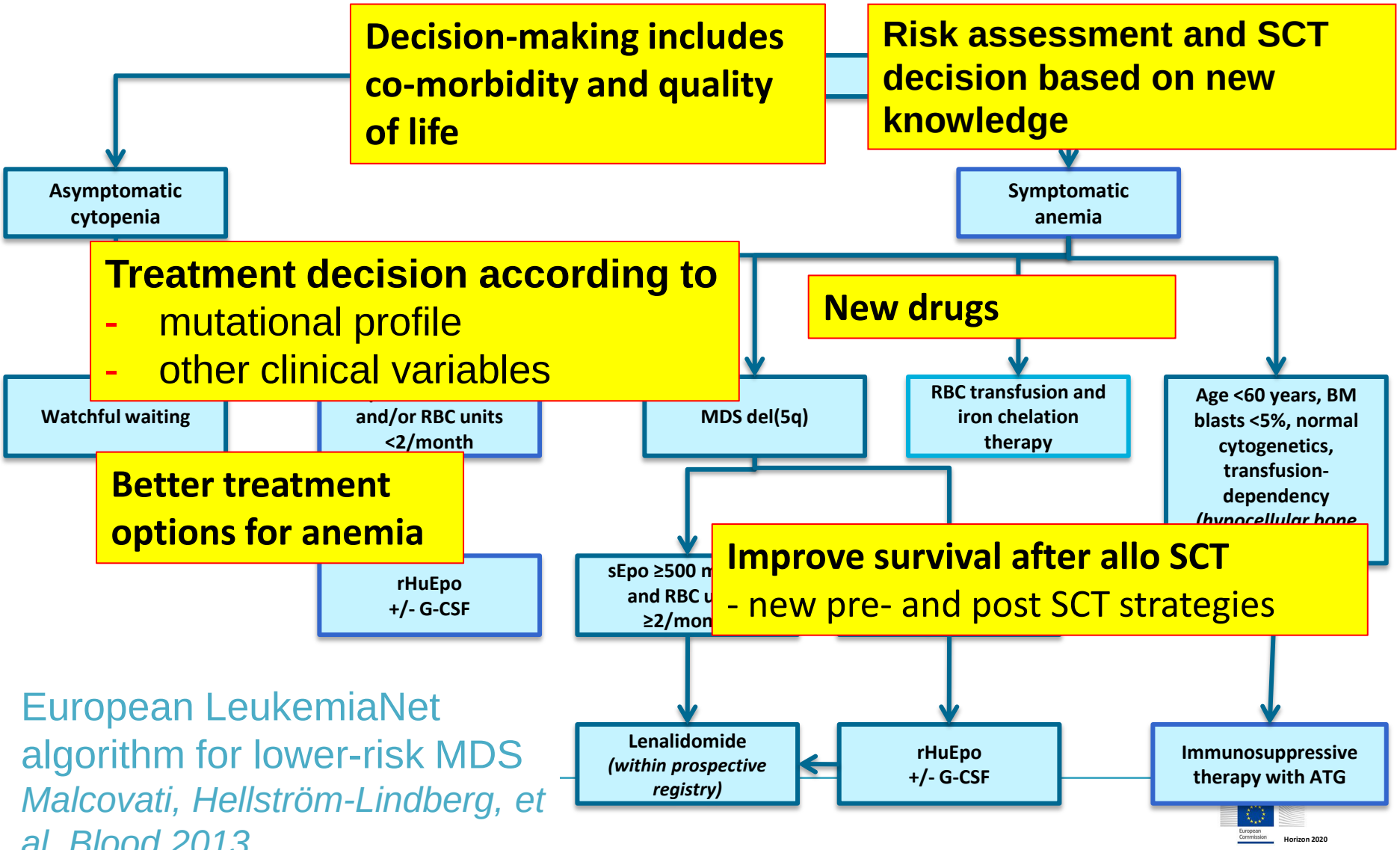
MDS patient management recommendations

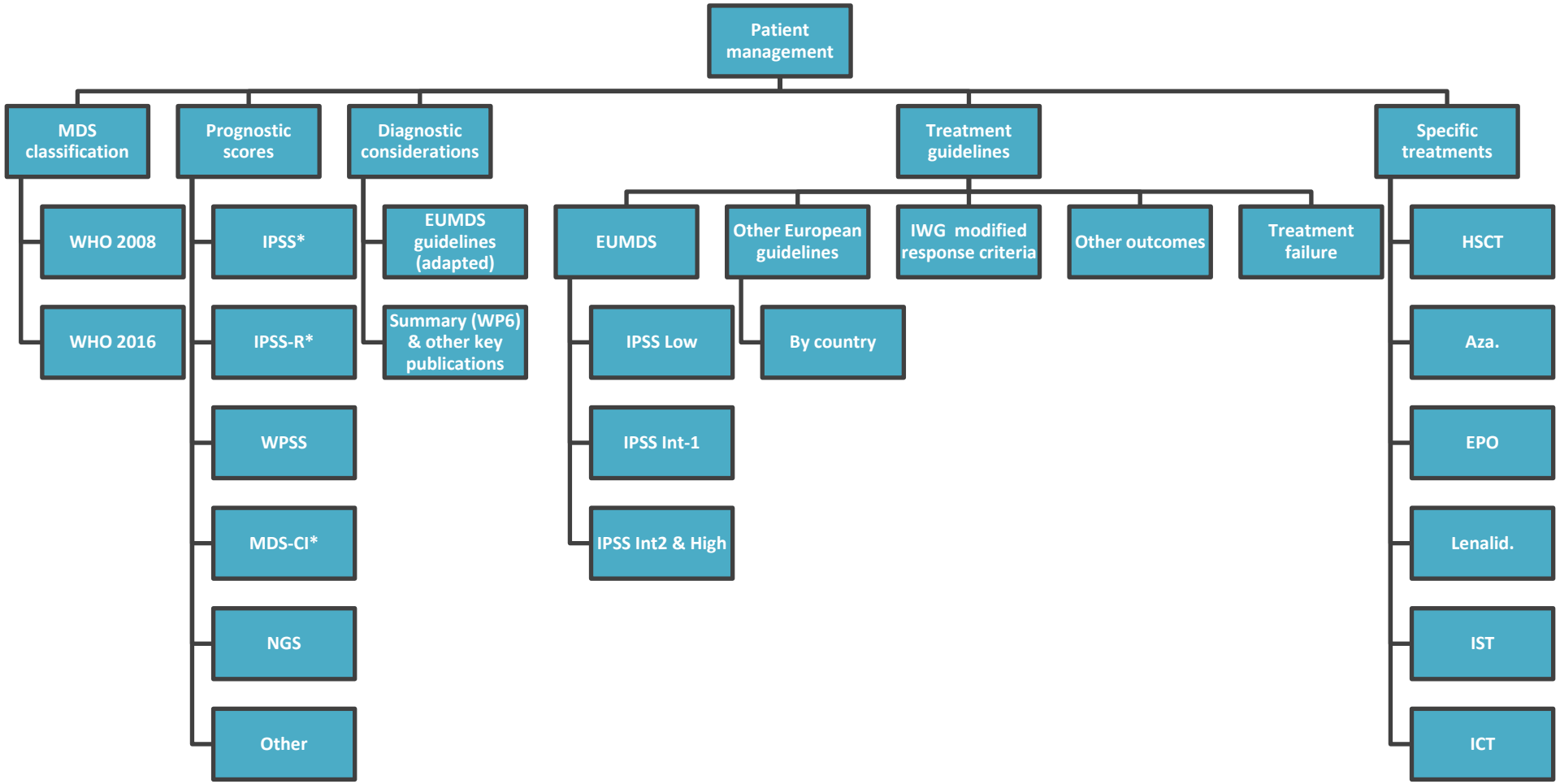
2017-2020 strategies to improve outcome for patients with lower-risk MDS



European LeukemiaNet algorithm for lower-risk MDS
Malcovati, Hellström-Lindberg, et al, Blood 2013

MDS patient management recommendations

MDS-RIGHT Patient management



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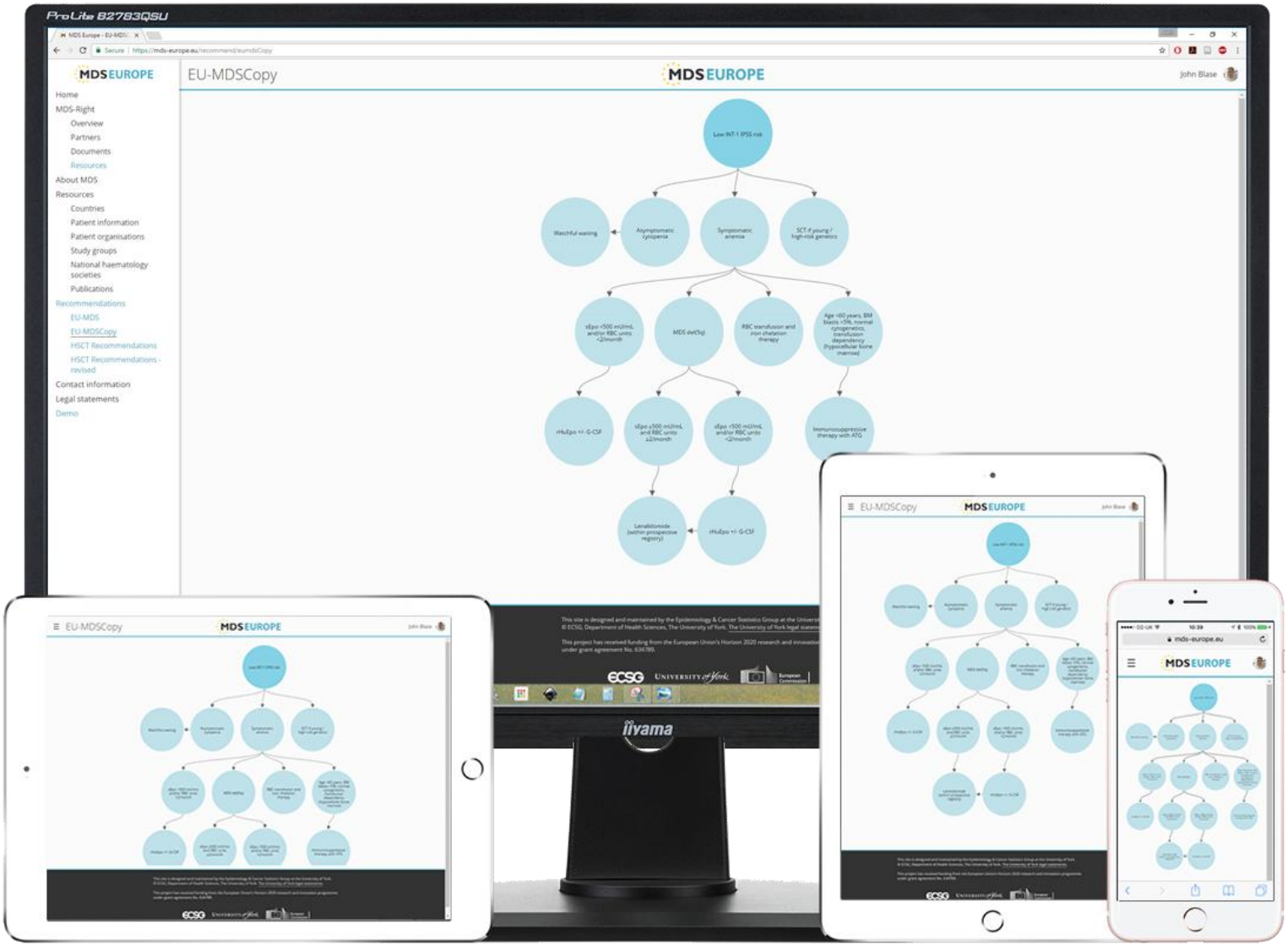
MDS patient management recommendations



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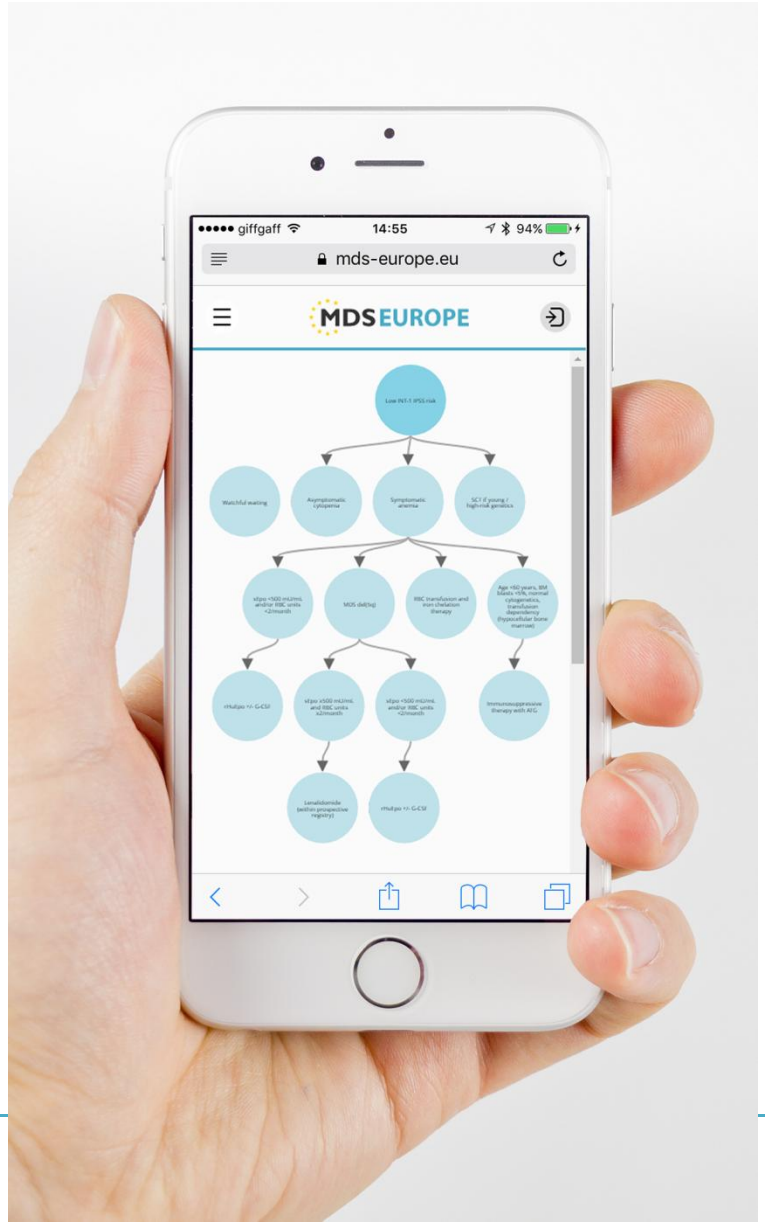
Horizon 2020

MDS patient management recommendations



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17:35-17:45

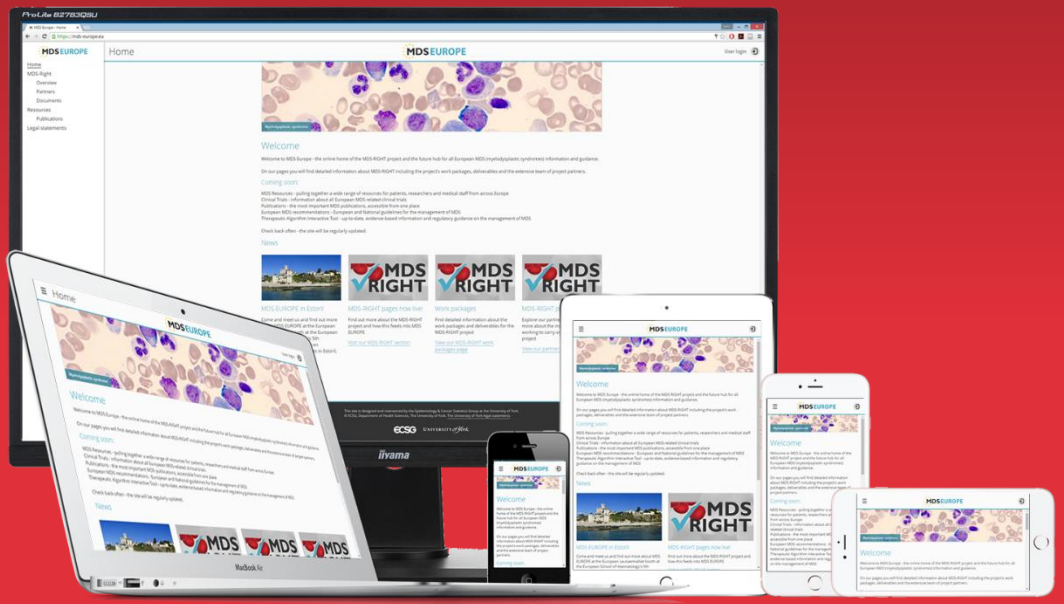
MDS patient management recommendations and interactive online support

- discussion -

European Commission
Horizon 2020

17:45 - 17:50

MDS-RIGHT / MDS Europe online platform



Alex Smith

Senior Research Fellow, Epidemiology & Cancer Statistics Group
University of York , York, United Kingdom

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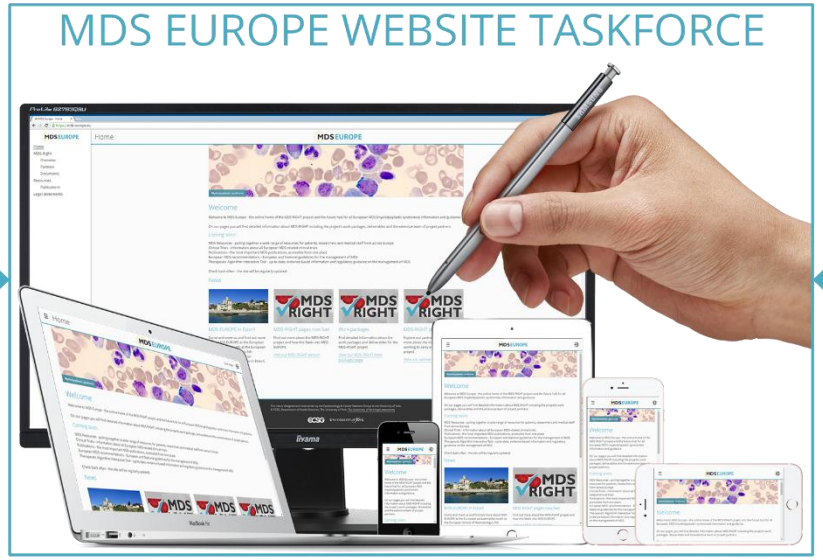
MDS Europe online platform

- **Aim:**
  - Creation of platform and website for communication with stakeholders
- **Collaborative**
  - e.g. MDS stakeholders were polled on their preferred domain names
- **Task force established:**
  - Theo de Witte, Eva Hellström-Lindberg, Pierre Fenaux, Martin Dugas
  - Robert Schäfer
  - Corine van Marrewijk, Karien Croezen
  - John Blase, William Curson, Dan Painter, Alex Smith
- **Soft Launch April 2016**

Website taskforce

Collaborative

11 members
6 centres
5 countries



Broad expertise

Haematologists
Researchers
Communications experts
Technical specialists
Project management

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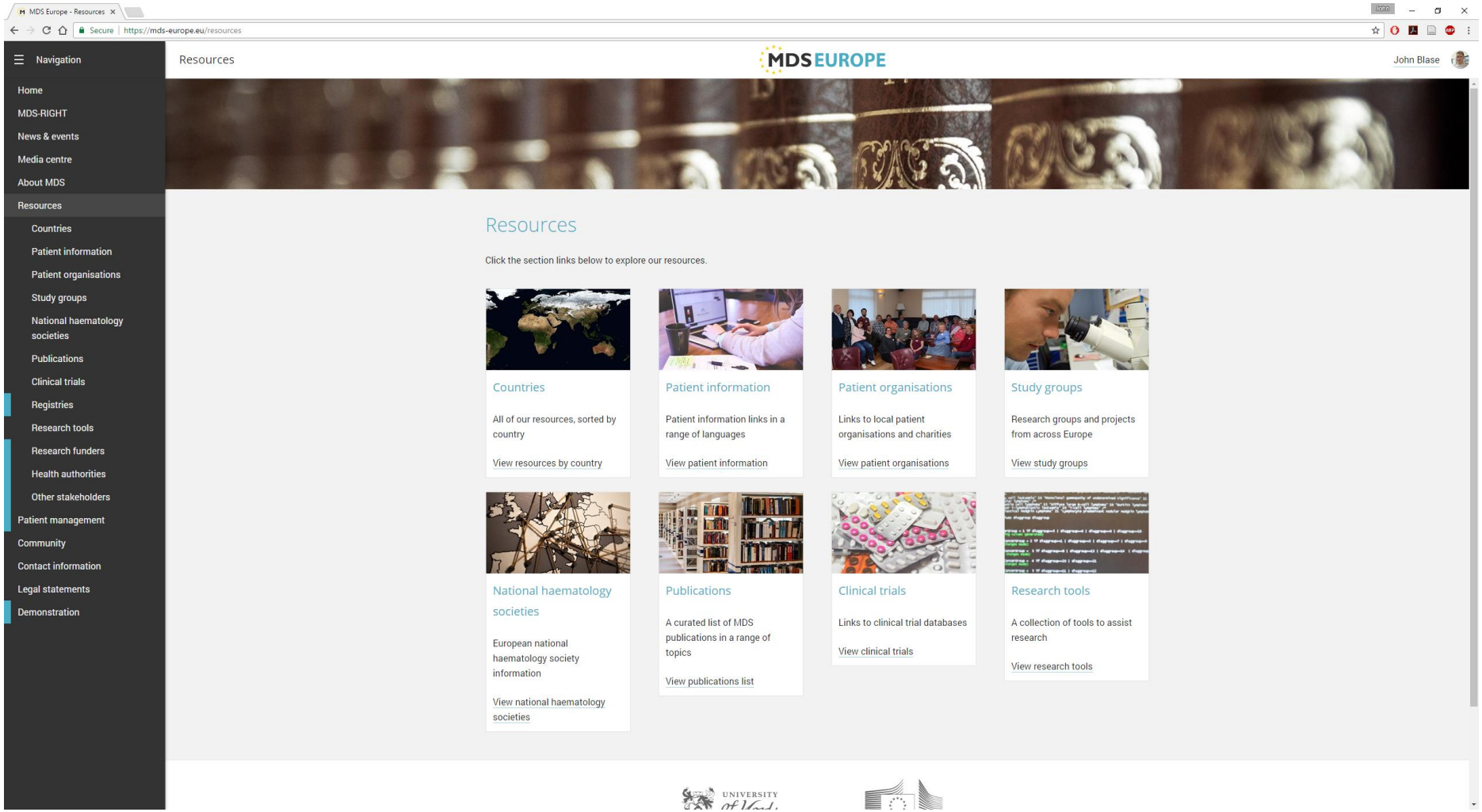
Horizon 2020

MDS Europe



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Community – discussion articles

MDS patients speak out

MDS EUROPE

User login

MDS patients speak out

Connaitre et combattre les myélosdysplasies (CCM)

Patrick Festy

11 April 2017

When questioned about our disease, we and our doctors speak first of fatigue, but most words that are used — weariness, tiredness, numbness, heavy legs, stiff muscles, short breath — are not strong enough.

One patient describes it aptly:

> "It's more a sensation of exhaustion than tiredness. I asked: Why am I like this? Why can't I do the things I should be doing? I was told: You are tired, that's normal, you are over 60, you are a grandparent, you want to continue to be active, but it's normal. No, I felt, it's not normal. I am not tired, I am totally exhausted. Something is wrong with me."

The widow of an MDS patient said:

> "Few of those they share their lives with or who assist them can comprehend the harassing fatigue that MDS patients suffer. My husband used to say: "We wonder if the specialists who are caring for us understand what this fatigue is really like."

But fatigue is not the whole story. For MDS patients it is associated with symptoms that do not necessarily have a clinical link to MDS but are nevertheless an

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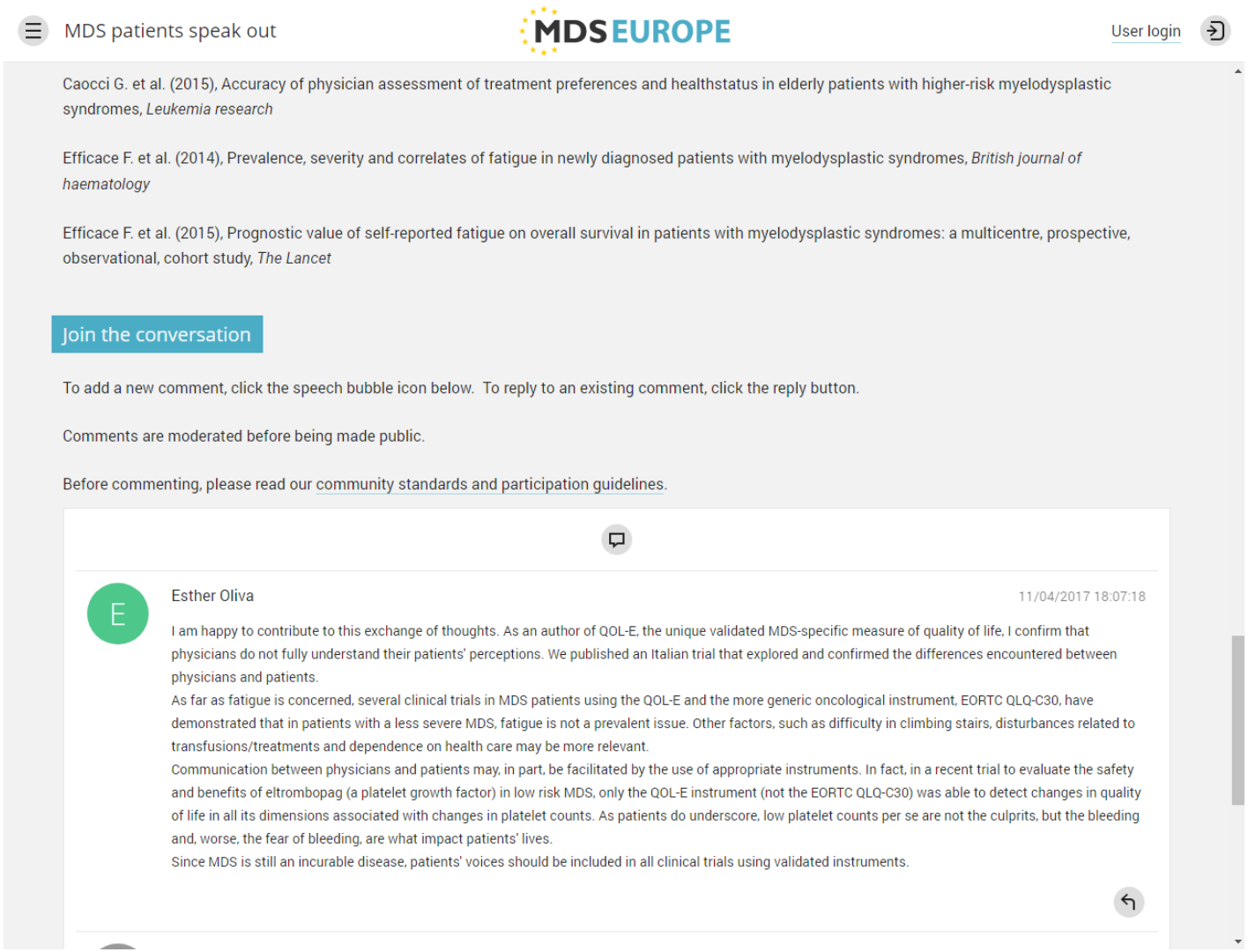
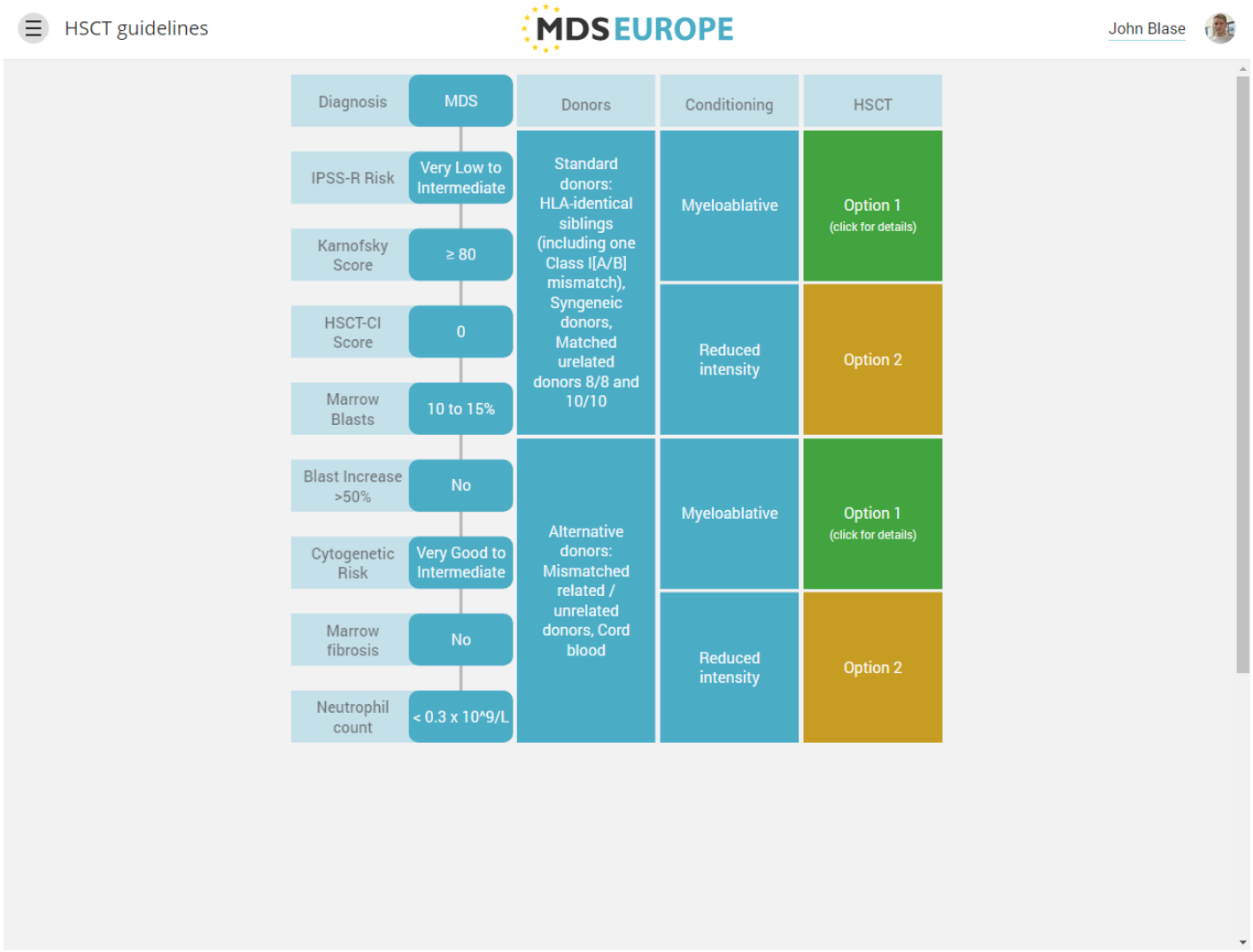
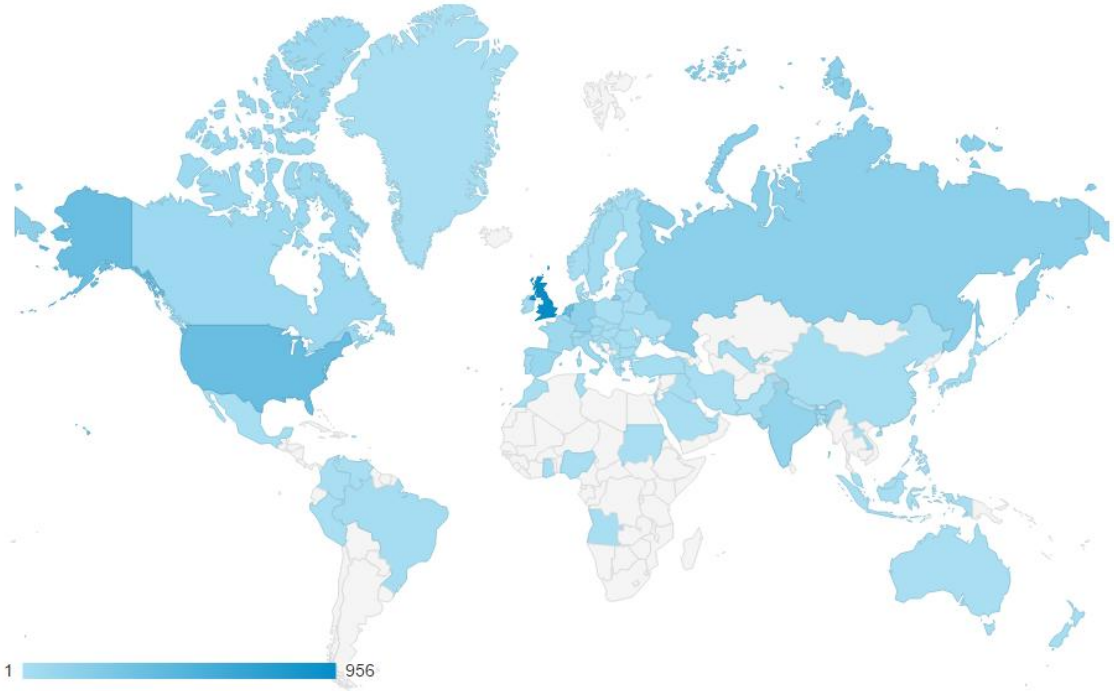
Discussion articles - comments

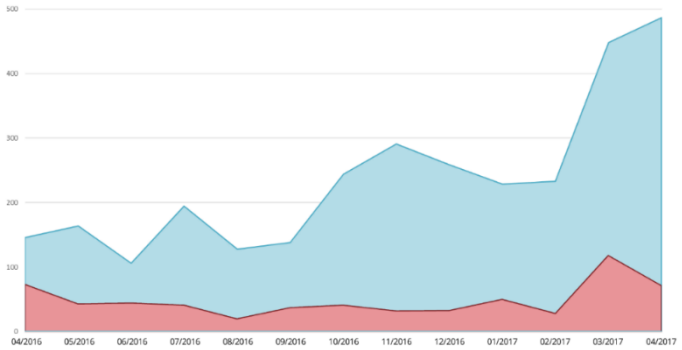


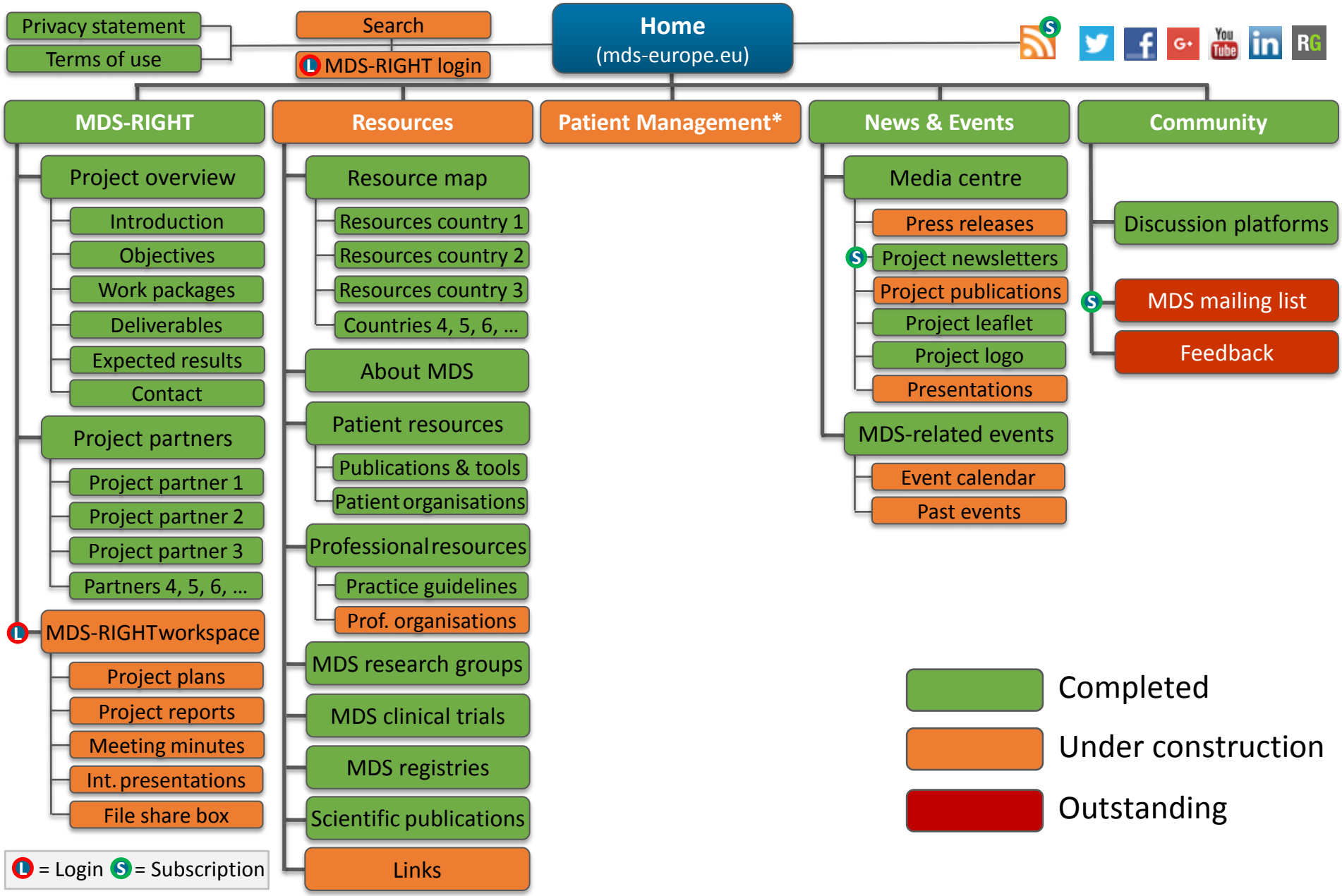
Treatment guidelines - HSCT

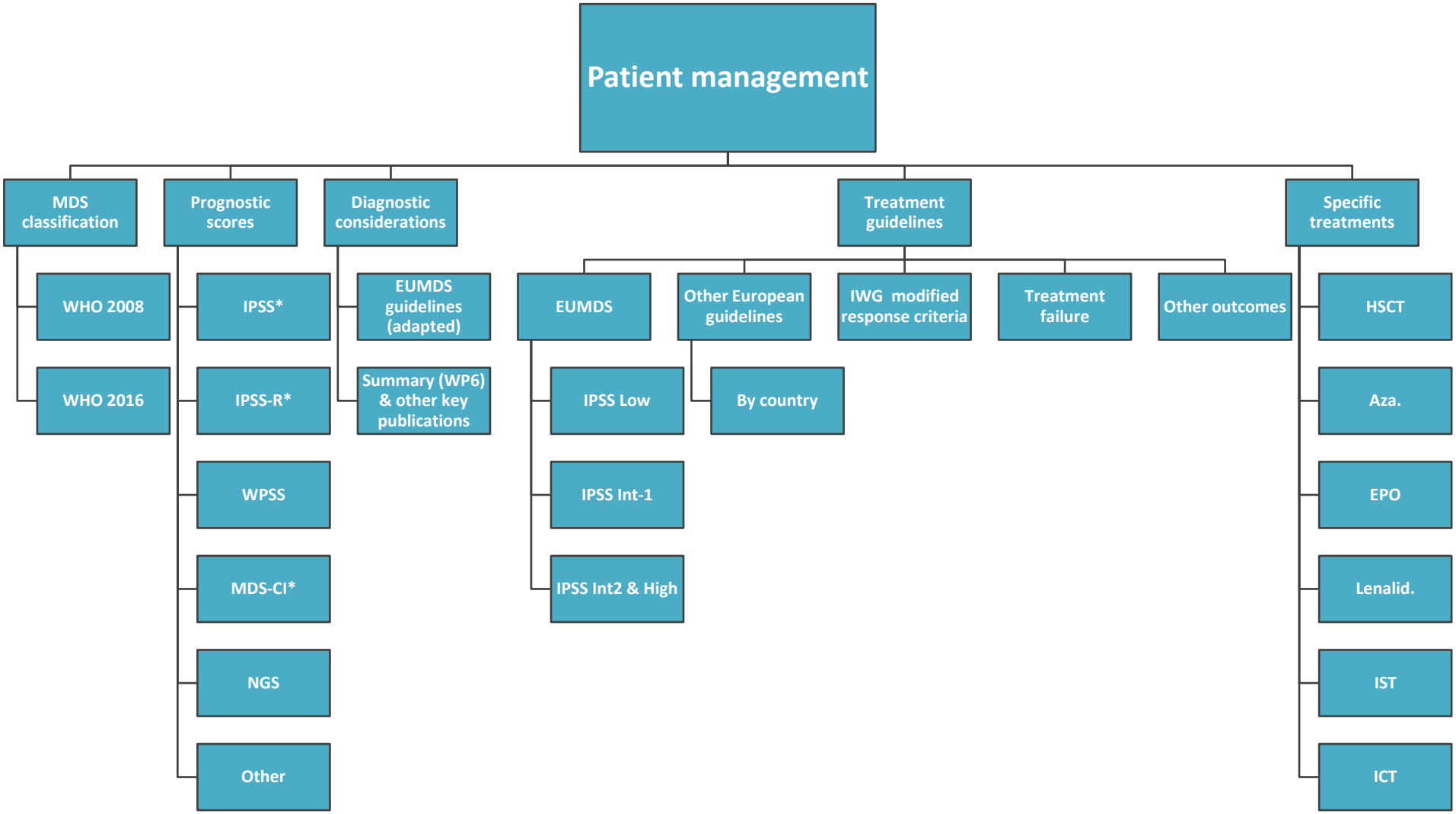


MDS Europe visitors






Privacy statement
Terms of use
Search
MDS-RIGHT login
Home
(mds-europe.eu)
MDS-RIGHT
Resources
Patient Management*
News & Events
Community
Project overview
Introduction
Objectives
Work packages
Deliverables
Expected results
Contact
Project partners
Project partner 1
Project partner 2
Project partner 3
Partners 4, 5, 6, ...
MDS-RIGHTworkspace
Project plans
Project reports
Meeting minutes
Int. presentations
File share box
Resource map
Resources country 1
Resources country 2
Resources country 3
Countries 4, 5, 6, ...
About MDS
Patient resources
Publications & tools
Patient organisations
Professional resources
Practice guidelines
Prof. organisations
MDS research groups
MDS clinical trials
MDS registries
Scientific publications
Links
Media centre
Press releases
Project newsletters
Project publications
Project leaflet
Project logo
Presentations
MDS-related events
Event calendar
Past events
Discussion platforms
MDS mailing list
Feedback
L = Login S = Subscription
Completed
Under construction
Outstanding

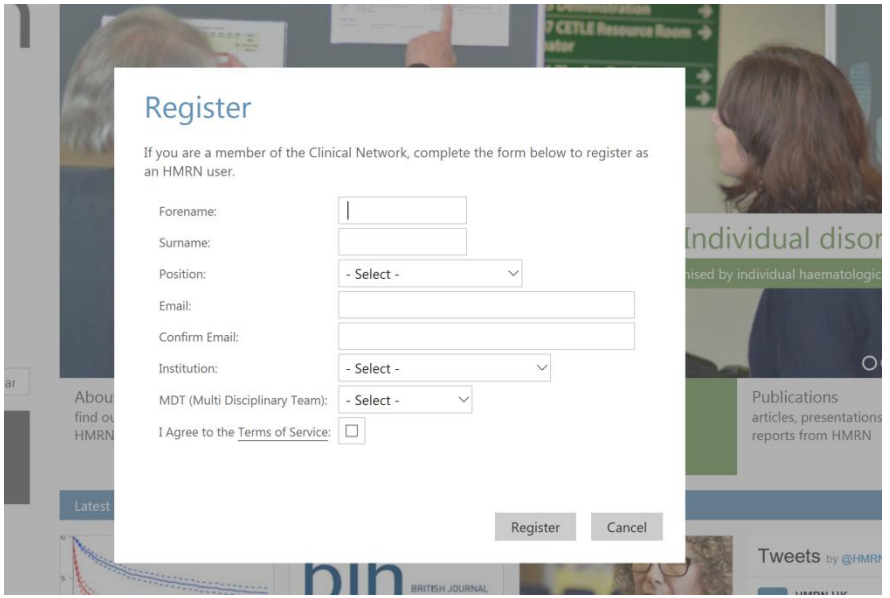

Patient management
MDS classification
WHO 2008
WHO 2016
Prognostic scores
IPSS*
IPSS-R*
WPSS
MDS-CI*
NGS
Other
Diagnostic considerations
EUMDS guidelines (adapted)
Summary (WP6) & other key publications
Treatment guidelines
EUMDS
IPSS Low
IPSS Int-1
IPSS Int2 & High
Other European guidelines
By country
IWG modified response criteria
Treatment failure
Other outcomes
Specific treatments
HSCT
Aza.
EPO
Lenalid.
IST
ICT

* calculator

MDS RIGHT workspace

Proposed content

- Document upload/download/share
- Plans
- Progress reports
- Minutes
- Internal presentations
- Study documentation

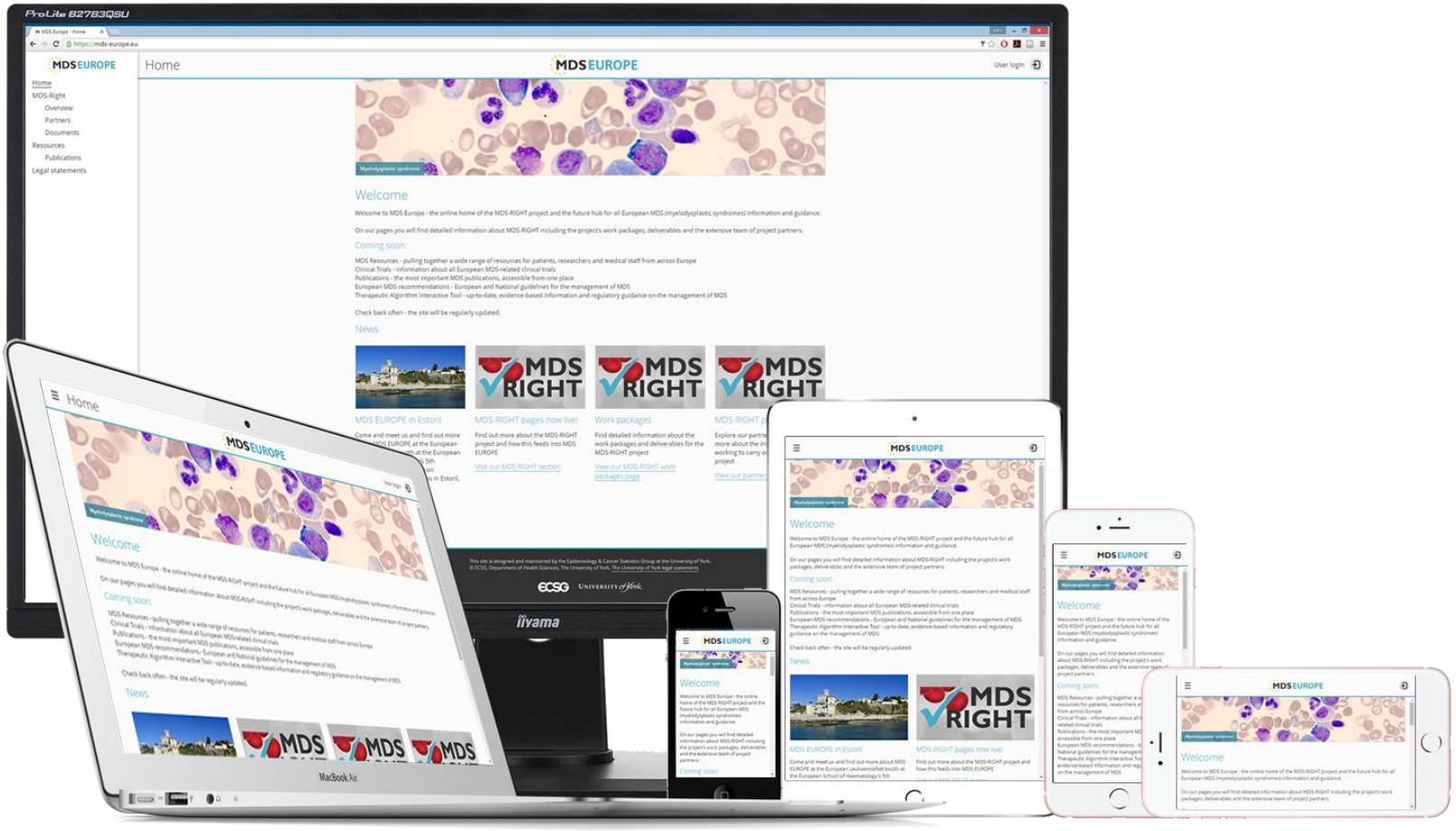


Network
- Audit committee
- Governance
- Guidelines
- SCN meetings
- Statistics
- SOPs

Files
- JSC meetings
  - Terms of reference
  - Agendas
  - Minutes
  - Correspondence
  - Other material
- Progress and results
- Study documentation
- Weekly calls

MDS Europe

- mds-europe.eu
- mds-europe.org
- mds-right.eu
- mds-right.org



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17:50-17:55

MDS-RIGHT / MDS-Europe online platform

- discussion -

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17:55-18:00

Closing remarks

Guillermo Sanz & Theo de Witte

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