# Perspectives on clinical trials in MDS in Europe

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Firenze, Oct 2024

EMSCO MYELODYSPLASTIC SYNDROMES

Université Paris Cité

UNIVERSITÉ PARIS 13

# Academic trials in the EU

- Complementary to industry sponsored trials
- Possible in one or several countries, thanks to recent EU directives on clinical trials
- Several countries involved for rare entities, or when « lobbying » is needed on companies to obtain a drug, or when rapid response is desired


EMSCO
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SYNDROMES


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MIELODISPLASTICHE


D·MDS
Deutsche MDS-Studiengruppe


GESMD

# Perspectives on clinical trials in MDS in Europe

- Recently completed  cooperative EMSCO studies
- Current studies
- How can we  envisage the future ?

# Perspectives on clinical trials in MDS in Europe

- Recently completed  cooperative EMSCO studies

- Current studies

- How can we  envisage the future ?

ARTICLE OPEN

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MYELODYSPLASTIC NEOPLASMS

# Prospective validation of a biomarker-driven response prediction model to romiplostim in lower-risk myelodysplastic neoplasms – results of the EUROPE trial by EMSCO

Anne Sophie Kubasch[1,2,3], Aristoteles Giagounidis[2,3,4], Georgia Metzgeroth[5], Anna Jonasova[6], Regina Herbst[7], Jose Miguel Torregrosa Diaz[8], Benoit De Renzis[9], Katharina S. Götze[2,3,10], Marie-Luise Huetter-Kroenke[11], Marie-Pierre Gourin[12], Borhane Slama[13], Sophie Dimicoli-Salazar[14], Pascale Cony-Makhoul[15], Kamel Laribi[16], Sophie Park[17], Katja Jersemann[18], Dorothea Schipp[19], Klaus H. Metzeler[1,2,3], Oliver Tiebel[20], Katja Sockel[2,3,21], Silke Gloaguen[1,2,3,18], Anna Mies[21], Fatiha Chermat[22], Christian Thiede[21], Rosa Sapena[22], Richard F. Schlenk[23,24], Pierre Fenaux[3,22,25], Uwe Platzbecker[1,2,3,26]✉ and Lionel Adès[3,22,25,26]

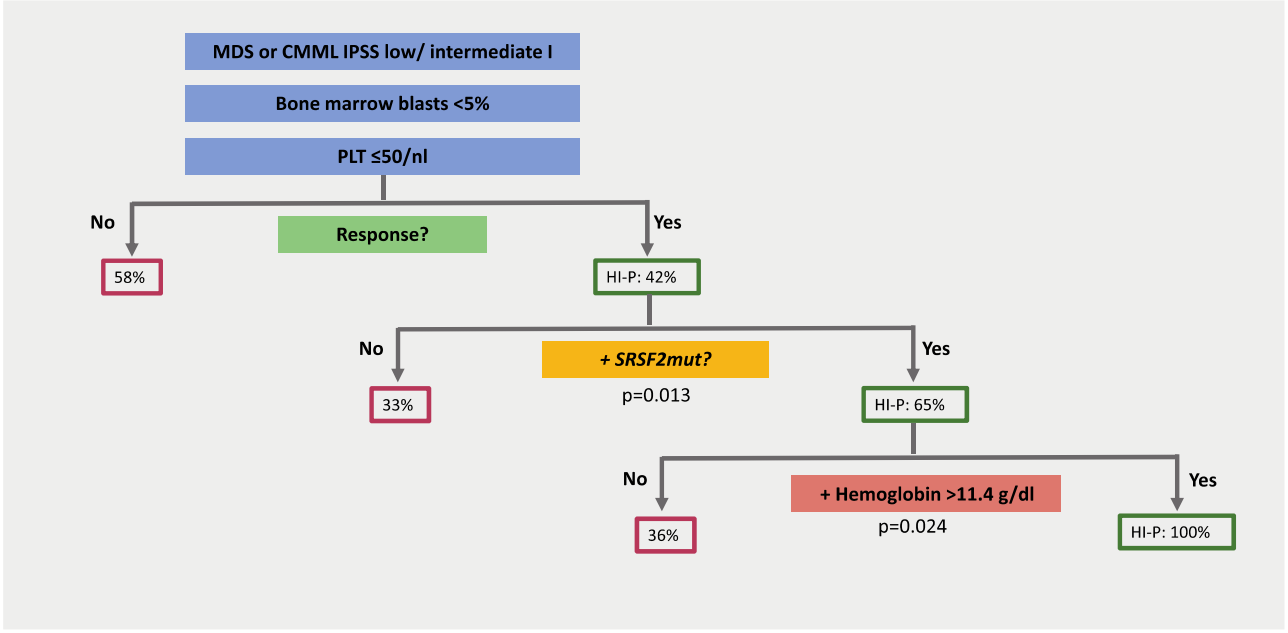



**Fig. 3 Response prediction model to Romiplostim based on the results of the EUROPE trial.** The newly developed response prediction model contains the SRSF2 mutation status in combination with platelet count and hemoglobin level (threshold 11.4 g/dl).

EMSCO MYELODYSPLASTIC SYNDROMES

# Low dose lenalidomide versus placebo in non-transfusion dependent patients with low risk, del(5q) myelodysplastic syndromes (SintraREV): a randomised, double-blind, phase 3 trial

*María Díez-Campelo*, Félix López-Cadenas*, Blanca Xicoy, Eva Lumbreras, Teresa González, Mónica del Rey González, Joaquín Sánchez-García, Rosa Coll Jordà, Bohrane Slama, Jose-Ángel Hernández-Rivas, Sylvain Thepot, Teresa Bernal, Agnès Guerci-Bresler, Joan Bargay, María Luz Amigo, Claude Preudhomme, Laurene Fenwarth, Uwe Platzbecker, Katharina S Götze, Ali Arar, Sofía Toribio, Consuelo Del Cañizo, Jesús María Hernández-Rivas, Pierre Fenaux*

## Summary

**Background** Lenalidomide is the standard of care for patients who are transfusion dependent with chromosome 5q

*Lancet Haematol* 2024;

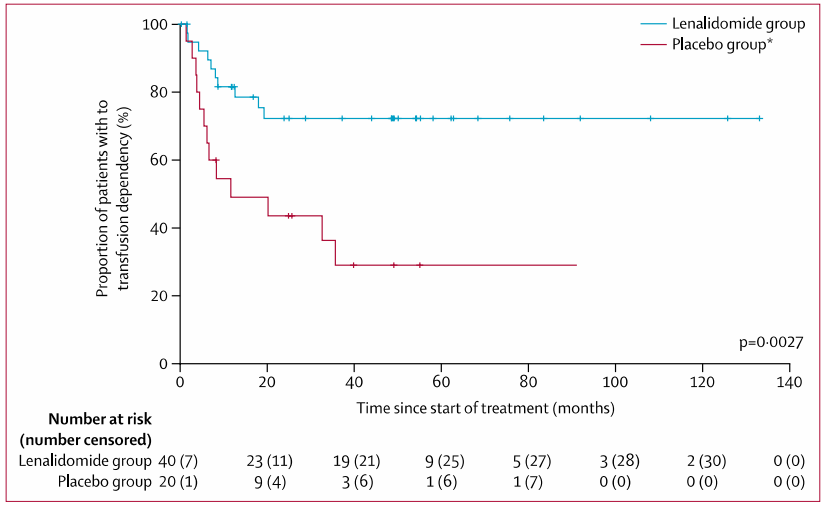


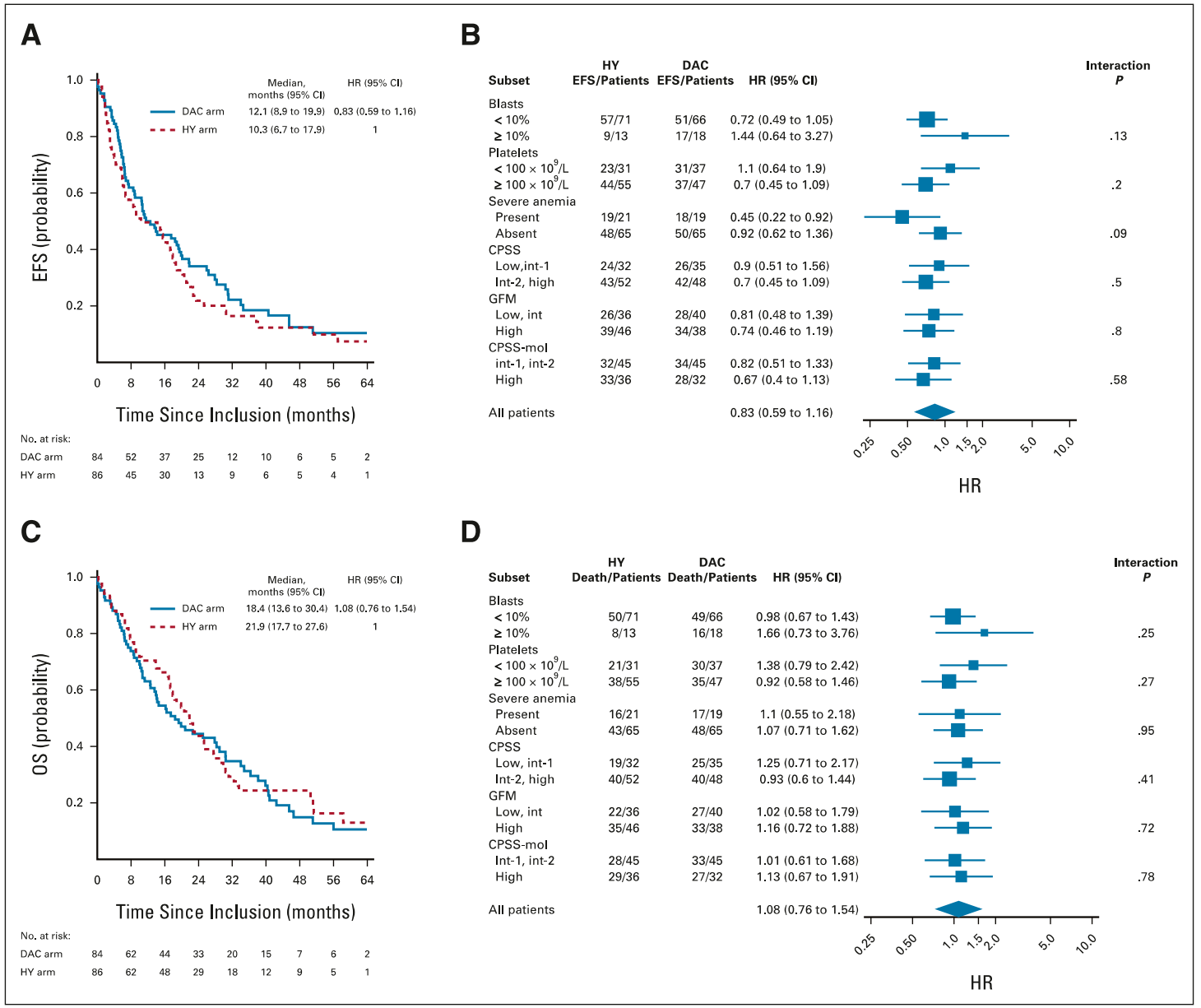

*Figure 2:* Time to transfusion dependency in the intention-to-treat population

original reports

# Decitabine Versus Hydroxyurea for Advanced Proliferative Chronic Myelomonocytic Leukemia: Results of a Randomized Phase III Trial Within the EMSCO Network

Raphael Itzykson, MD, PhD[1,2,3]; Valeria Santini, MD[4,5]; Sylvain Thepot, MD[3,6]; Lionel Ades, MD, PhD[1,3,7]; Cendrine Chaffaut, MSc[8]; Aristoteles Giagounidis, MD[9,10]; Margot Morabito, BSc[11]; Nathalie Droin, PhD[11]; Michael Lübbert, MD[10,12]; Rosa Sapena, PhD[3]; Stanislas Nimubona, MD[3,13]; Jean Goasguen, MD[14]; Eric Wattel, MD, PhD[3,15]; Gina Zini, MD, PhD[16,17]; Jose Miguel Torregrosa Diaz, MD[3,18]; Ulrich Germing, MD[10,19]; Anna Maria Pelizzari, MD[5,20]; Sophie Park, MD, PhD[3,21]; Nadja Jaekel, MD[10,22]; Georgia Metzgeroth, MD[10,23]; Francesco Onida, MD[5,24]; Robert Navarro, MD[3,25]; Andrea Patriarca, MD[5,26]; Aspasia Stamatoullas, MD[3,27]; Katharina Götze, MD[10,28]; Martin Puttrich, MSc[10,29]; Sandra Mossuto, MSc[5]; Eric Solary, MD[3,11,30]; Silke Gloaguen, MSc[10,31]; Sylvie Chevret, MD, PhD[6]; Fatiha Chermat, DMD[3]; Uwe Platzbecker, MD[10,31]; and Pierre Fenaux, MD, PhD[1,3,7]

EMSCO
MYELODYSPLASTIC SYNDROMES



LETTER OPEN

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MYELODYSPLASTIC NEOPLASM

# Efficacy and safety of bemcentinib in patients with advanced myelodysplastic neoplasms or acute myeloid leukemia failing hypomethylating agents- the EMSCO phase II BERGAMO trial

A. S. Kubasch[1,2,3], P. Peterlin[3,4], T. Cluzeau[3,5], K. S. Götze[2,3,6], K. Sockel[2,7], R. Teipel[7], M. Jentzsch[1], H. Attalah[8], M. Sebert[8,9], F. Chermat[8], S. Gloaguen[2,3], M. Puttrich[10], M. Cross[1], M. Schneider[1], S. Kayser[11,12], D. Schipp[13], A. Giagounidis[2,3,14], I. Tirado-Gonzalez[15], A. Descot[15], A. van de Loosdrecht[3,16], A. Weigert[1], K. H. Metzeler[1], P. Fenaux[3,8,9], H. Medyouf[15,17,18,19], U. Platzbecker[1,2,3,19] ✉ and L. Ades[3,8,9,19]



Leukemia (2020) 34:1182–1186
https://doi.org/10.1038/s41375-019-0645-z

LETTER

Immunotherapy

# Single agent talacotuzumab demonstrates limited efficacy but considerable toxicity in elderly high-risk MDS or AML patients failing hypomethylating agents

Anne Sophie Kubasch[1,2,3] · Freya Schulze[2,3,4] · Aristoteles Giagounidis[2,3,5] · Katharina S. Götze[2,3,6] · Jan Krönke[2,3,7] · Katja Sockel[2,3,4] · Jan Moritz Middeke[2,3,4] · Fatiha Chermat[3,8] · Silke Gloaguen[2,3] · Martin Puttrich[3,9] · Carmen Weigt[3,9] · Doreen William[10,11] · Pierre Fenaux[3,8,12] · Richard F. Schlenk[3,11,13] · Christian Thiede[3,4] · Sebastian Stasik[3,4] · Anna Mies[3,4] · Lionel Adès[3,8,12] · Uta Oelschlägel[2,3,4] · Uwe Platzbecker[1,2,3]

# Perspectives on clinical trials in MDS in Europe

- Recently completed  cooperative EMSCO studies
- Current studies
- How can we  envisage the future ?


# GESMD

# CLINICAL TRIALS

**María Díez Campelo**
**mdiezcampelo@usal.es**

GESMD GRUPO ESPAÑOL DE SÍNDROMES MIELODISPLÁSICOS

# HOME TRANSFUSION VERSUS HOSPITAL TRANSFUSION IN PATIENTS DIAGNOSED WITH LOWER RISK MDS: A PHASE III CLINICAL TRIAL

*Coord.: Fernando Ramos MD MPH PhD, Hospital Universitario de León (Spain)*

*Courtesy of Dr Ramos*

# MDS-TRANSF@HOME

## 6.1. SELECTION CRITERIA

### 6.1.1. Inclusion Criteria.

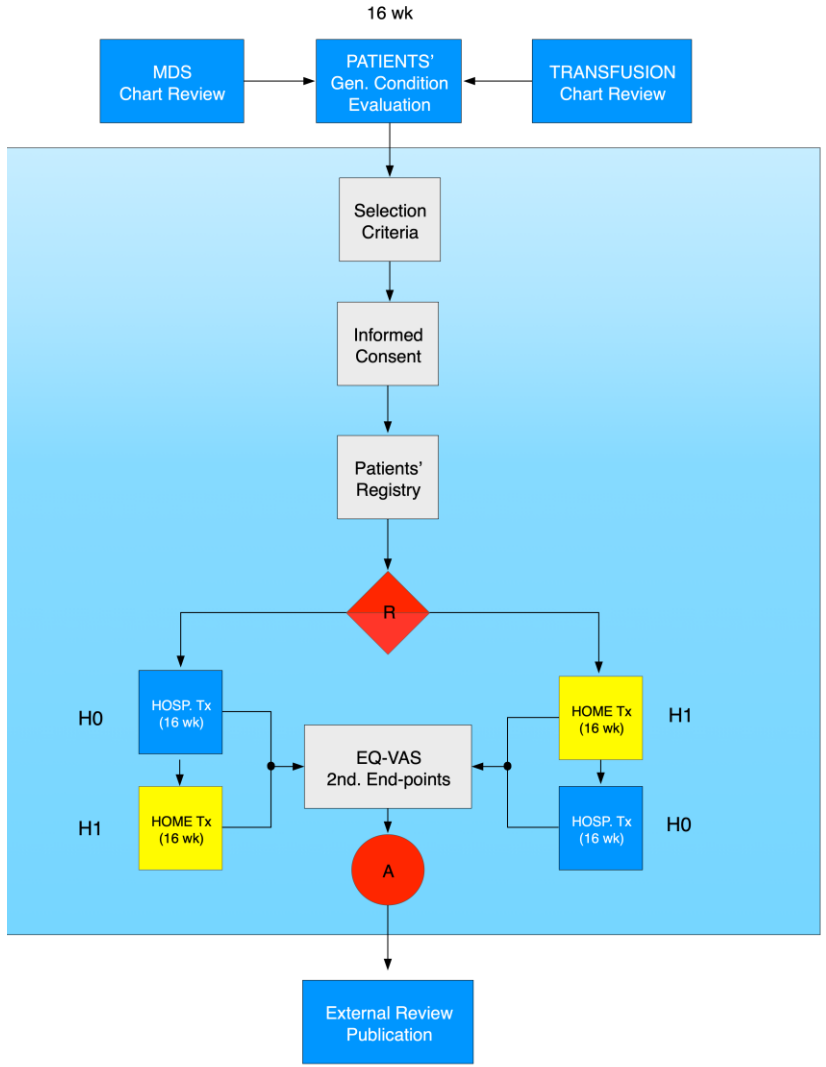
Eligible patients will have to fullfill ALL the following conditions:

1. MDS diagnosis (WHO 2017 criteria), no time limits.
2. BMA available in the last 12m ( or willing to repeat before inclusion)
3. Age 65+ years, or 50-64 AND MDS-CI score >1
4. IPSS-R score up to 3.5, calculated (date of BMA) in the last 12m
5. Available transfusion and Hb records in the last 16 wk
6. Mean pre-Tx Hb <100 g/L in the last 16 wk (availability: 90% + episodes)
7. Informed consent

### 6.1.1. Exclusion Criteria.

Eligible patients MUST NOT incur in ANY of the following situations:

1. Prior severe transfusion reactions or alloinmunization.
2. MDS treatment (ESAs, lenalidomide, HMA) initiated in the last 16 wk.
3. Active neoplasm (on therapy/therapy in the last 3 months). See exceptions.
4. Major surgery in the last 4wk.
5. BMT in the last 2y or receiving immunosuppresive therapy
6. Concurrent participation in other clinical trial.




*Courtesy of Dr Ramos*

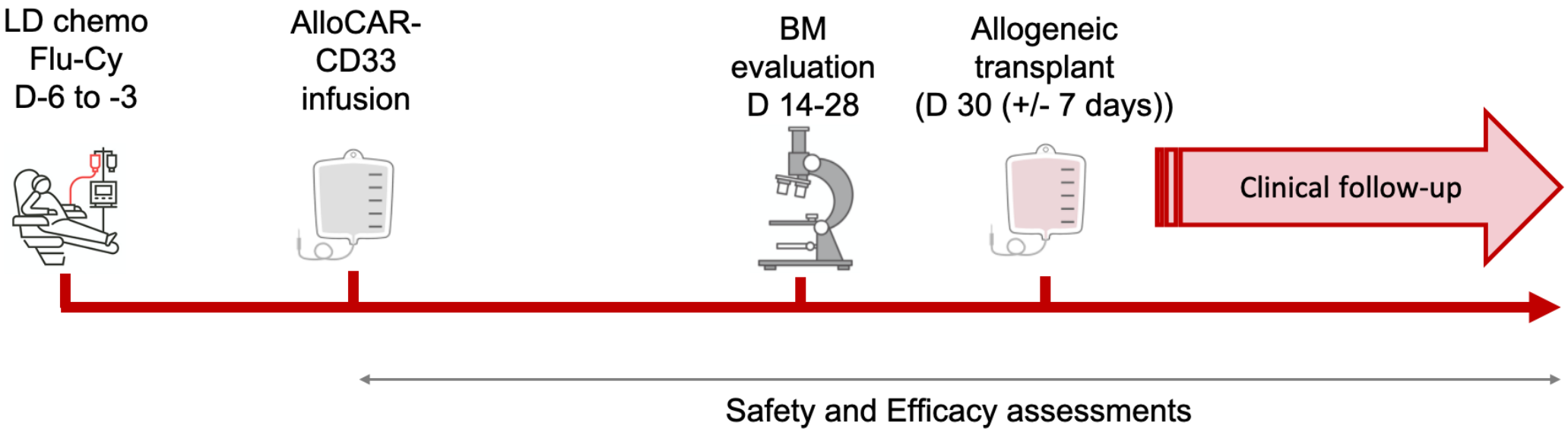
# Allogeneic CD33 CAR-T

Ana Alfonso Piérola

Clínica Universidad de Navarra

*Courtesy of Dr Alfonso*

## Design




LD: Cyclophosphamide 300 mg/m$^2$ + fludarabine 30 mg/m2 on days −5, −4 and −3

*Courtesy of Dr Alfonso*

## Manufacturing Centers

- **Dose escalation phase**: Clínica Universidad de Navarra
- **Expansion phase**:
  - Clínica Universidad de Navarra
  - Hospital Clínico Universitario de Salamanca
  - Hospital Universitario y Politécnico de La Fe

## Infusion centers

- Clínica Universidad de Navarra (IP: Ana Alfonso-Piérola)
- Hospital Clínico Universitario de Salamanca (IP: María Diez Campelo)
- Hospital Universitario y Politécnico de La Fe (IP: Pau Montesinos)
- Hospital Universitario Vall d'Hebron (IP: David Valcárcel)
- Hospital Universitario de Navarra (IP: Maite Zudaire)
- Hospital 12 de Octubre (IP: Pilar Martinez)
- Hospital Clínico Universitario Virgen de la Arrixaca (IP: Miguel Blanquer)

*Courtesy of Dr Alfonso*

# FISIM CLINICAL TRIALS

**Valeria Santini**

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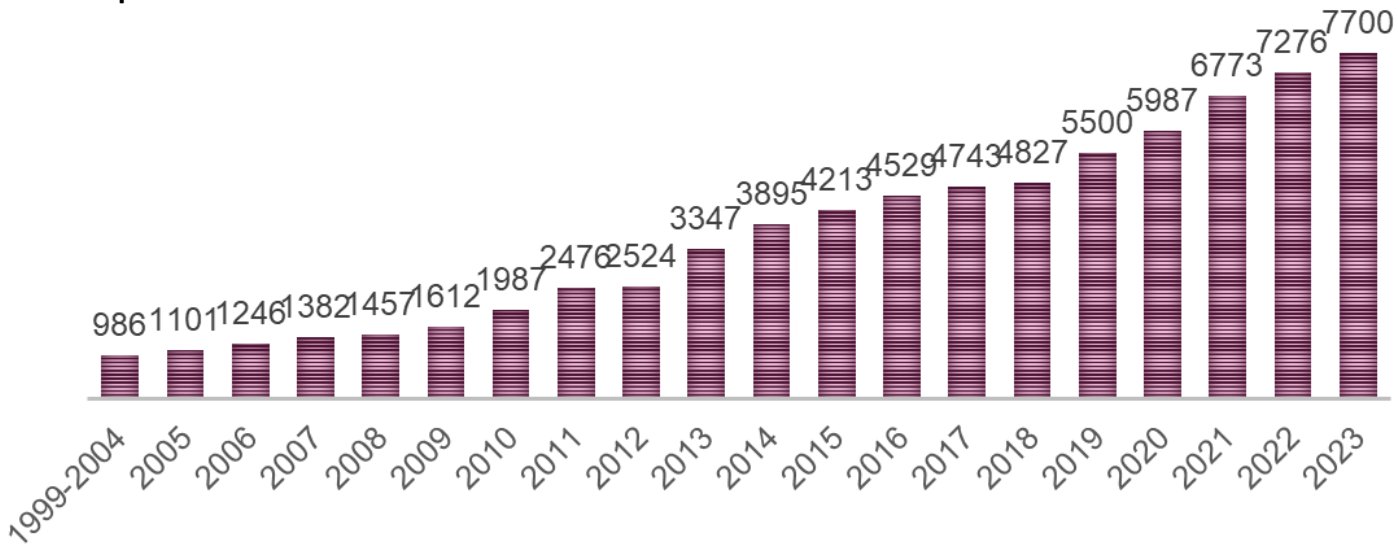
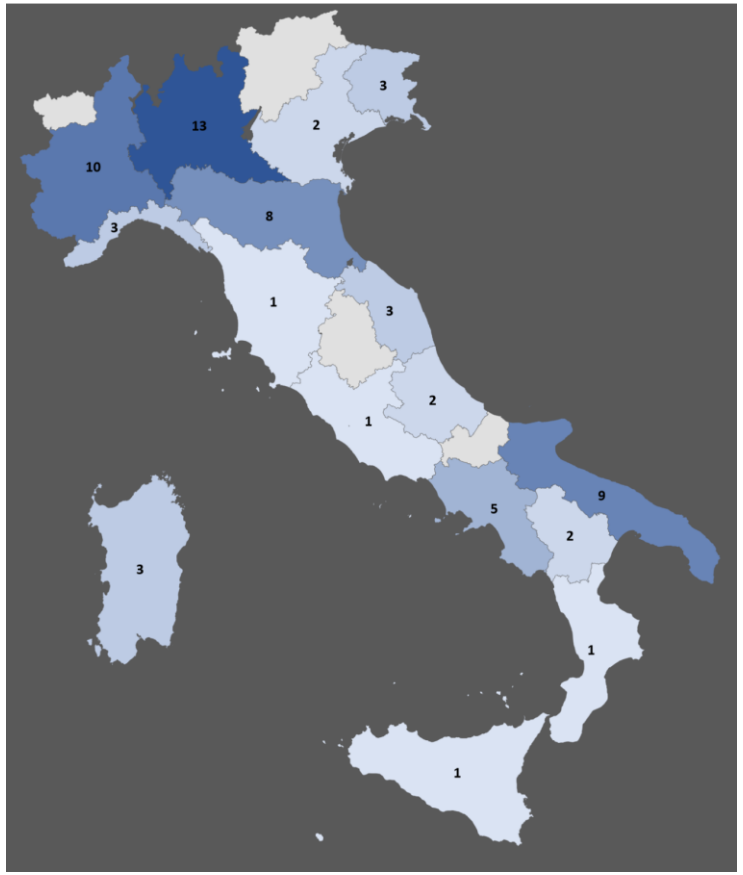
MIELODISPLASTICHE

# FISiM-MDS: Registry

Adult patients affected with myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms enrolled in the Italian network of pathology registry

- **Study design**: pathology registry. 7700 patients with MDS and MDS/MPN from 67 Italian centers within 24 Years
- **Objectives**:
  - Census of all cases of MDS diagnosed by FISiM centers
  - Record the most important clinical-laboratory information, the treatment and follow up of the patients-> real-world picture
  -Carry out biological, clinical and observational studies to improve the prognosis of MDS patients.



# FISIM Clinical trials

## Recently completed studies

- Iron-mediated tissue damage in acquired ineffective erythropoiesis
- Hypocellular myelodysplastic syndromes (h-MDS)
- Real-world study on luspatercept in MDS-RS
- Lenalidomide discontinuation in MDS del(5q)- Harmony

## Ongoing trials

Observational trials

- Lower risk MDS with predominant thrombocytopenia
- FISIM-MDS NGS

Phase II trials

- Low risk MDS: REMARK
- High risk CMML: PATROL

## Work in progress

FISIM
FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Pilo et al. Leu Res 2022 ; Calabretto G et al. Leukemia 2022; Lanino L et al. Am J *Hematol*. 2023;

# FISIM ongoing trials

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# Lower risk MDS with predominant thrombocytopenia

## Impact of the thrombocytopenia severity on the clinical evolution in patients with “lower risk” (very low-low-intermediate IPSS-R) myelodysplastic syndrome: retrospective study from disease registry

(Anna Calvisi, Enrico Balleari)

**Study design**: Multicenter, retrospective observational study. Patients with MDS from 67 Italian centers

**Patients population:**

- MDS at IPSS –r very low, low or intermediate
- thrombocytopenia <100000/mmc at diagnosis
- Available data on molecular characterization , treatment and outcome

**Endpoints**

- Progression free survival
- Overall survival
- Time to AML
- Response to treatments

According to platelets level at diagnosis:

- 100-50000/µl
- 50-30000/µl
- <30000/µl

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

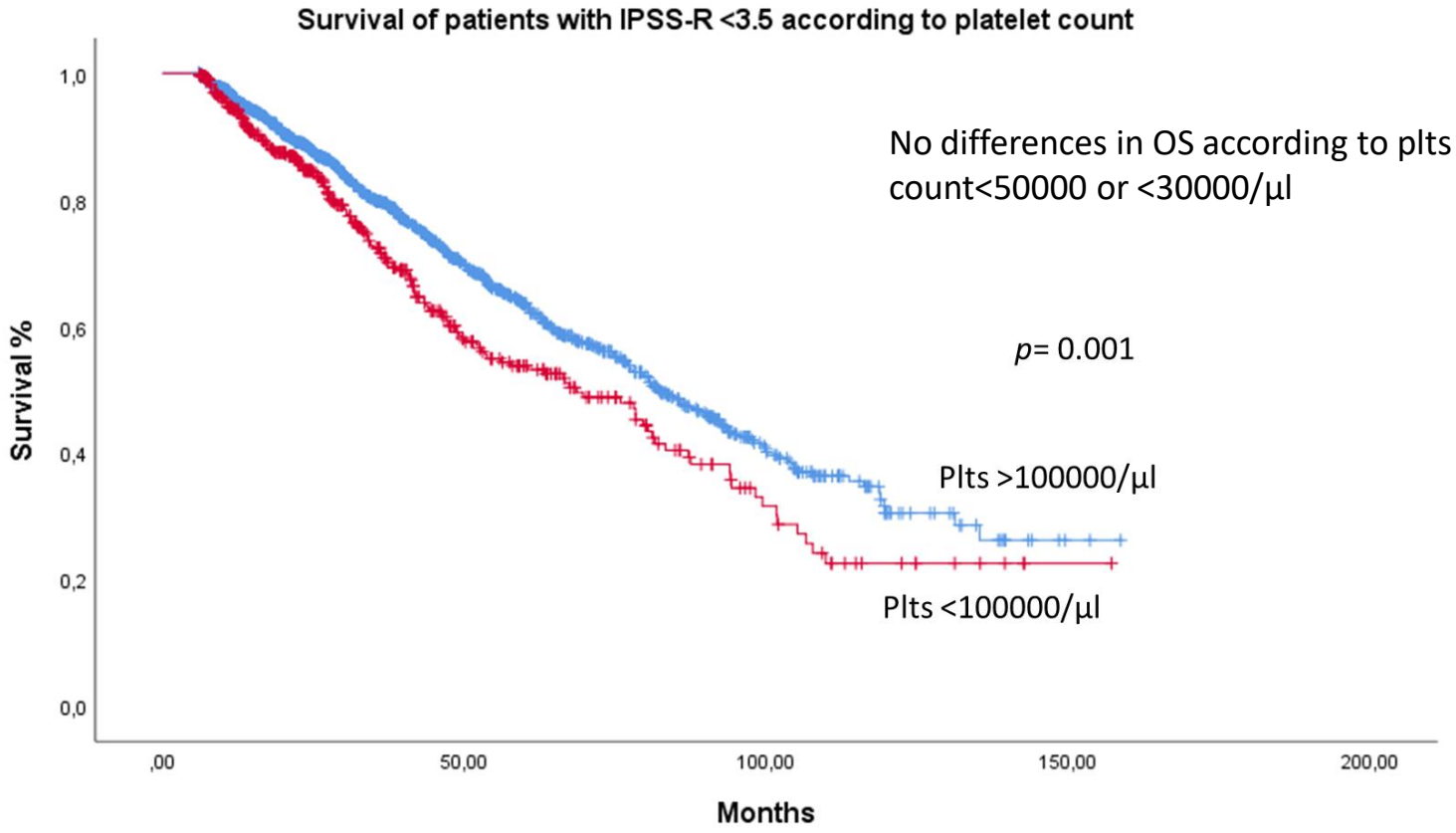
# Lower risk MDS with predominant thrombocytopenia

**1905** pts with IPSS-R <3.5 and follow up >=6 months

⇩

**479** patients with plts<100000/µl

| PLTS/µl | N° |
|---|---|
| 50000-100000 | 350 |
| 30000-50000 | 76 |
| <30000 | 53 |




Ongoing data cleaning for PFS, molecular characterization , coexisting immunological disorders and therapy

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

# FISiM-NGS-MDS

(Prof. Matteo Della Porta)

- **Study design**: No-profit, prospective observational study. 882 patients with MDS from 28 Italian participating centers within 5 Years

- **Objectives**:

  Primary:

  define the clinical utility of mutational screening in the diagnostic work-up and classification of MDS defined according to WHO criteria and to IPSS-R risk categories, developing precision medicine program in MDS patients based on real-world data

  Secondary:

  - assess the implementation of diagnostic and therapeutic guidelines in a real world context
  - evaluate the impact of specific interventions
  - identify predictors of response to specific treatments

# FISiM-NGS-MDS

**Inclusion criteria:**

- Age ≥ 18 years
- Diagnosis of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasms (chronic myelomonocytic leukemia, CMML) according to 2016 WHO classification criteria
- Ability to give informed consent according to ICH/EU GCP, and national/local regulations.

**Exclusion criteria**:

- Lack of written informed consent
- Lack of biological samples (blood, bone marrow aspirate)

FISiM
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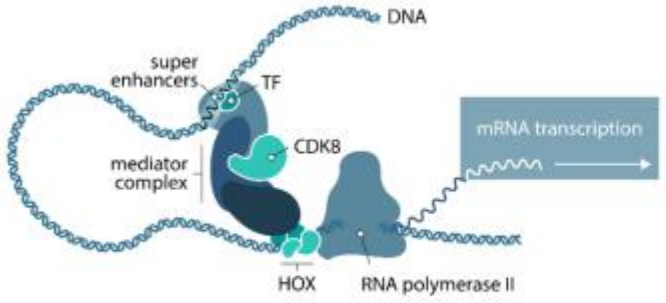
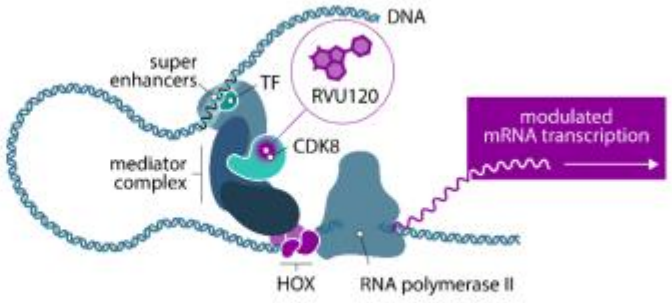
# REMARK

## A phase II, open-label, multicenter study of orally administered RVU120 for the treatment of anemia in patients with lower-risk myelodysplastic neoplasms (MDS)

- RVU120 is a highly selective type I ATP-competitive kinase inhibitor targeting Cyclin-Dependent Kinase 8 (CDK8) and its paralog Cyclin-Dependent Kinase 19 (CDK19)
- First clinical data support the rationale for use of RVU120 in MDS and indicate a strong erythroid differentiation potential of RVU120 in CD34+ cells with acquired MDS/AML-like genetic aberrations resulting in erythroid dysfunction
- This potential activity in erythroid differentiation provides a compelling argument to investigate RVU120 in an anemia-driven lower-risk MDS patient population.




CDK8/19 mediator promotes AML growth




CDK8/19 inhibition by RVU120 triggers differentiations and apoptosis

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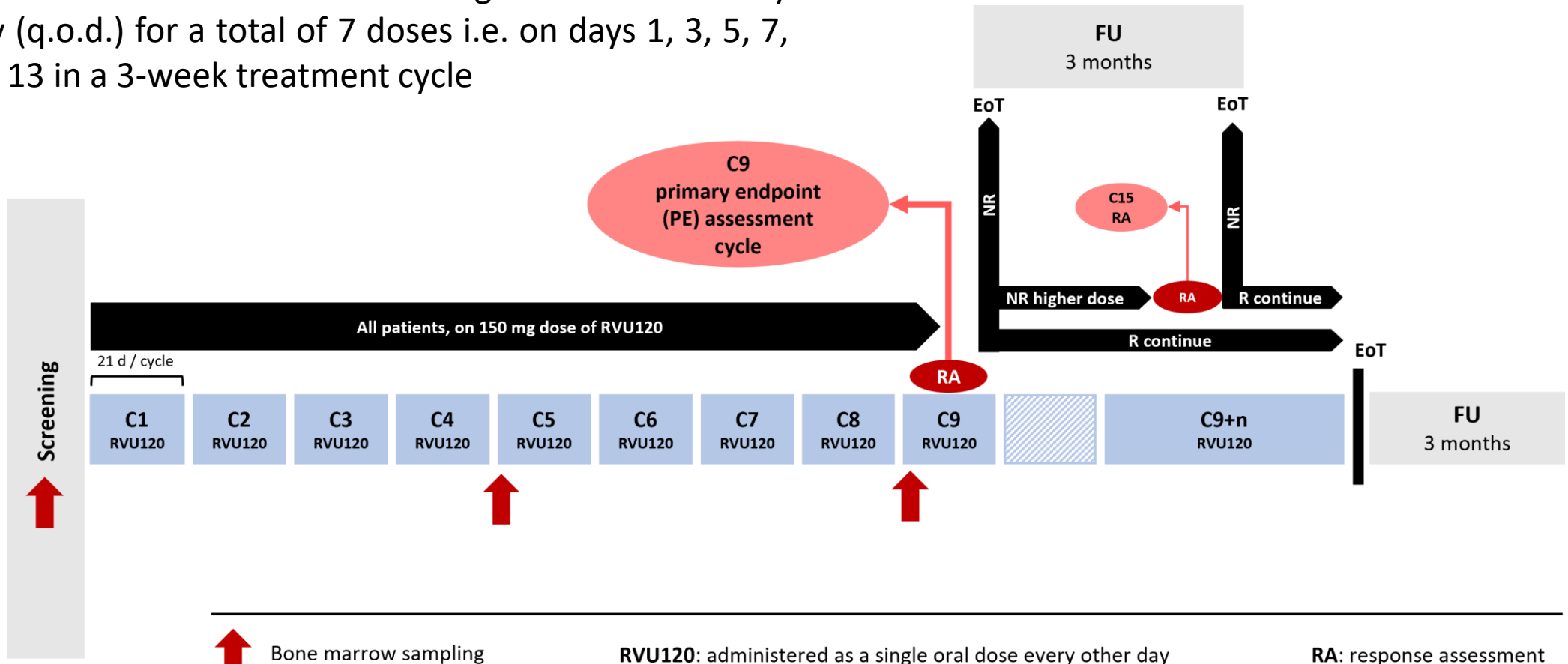
# REMARK

RVU120 will be administered as a single oral dose every other day (q.o.d.) for a total of 7 doses i.e. on days 1, 3, 5, 7, 9, 11 and 13 in a 3-week treatment cycle




Bone marrow sampling

**RVU120**: administered as a single oral dose every other day (q.o.d.) for a total of 7 doses, i.e. on days 1, 3, 5, 7, 9, 11 and 13 in a treatment cycle of 21 days.

**RA**: response assessment
**PE**: primary endpoint
**R**: responder
**NR**: non-responder
**FU**: follow-up

# PATROL

## Phase II study of Azacitidine (AZA) combined with venetoclax (VEN) and Tagraxofusp (TAG) in patients with higher-Risk chrOnic myelomonocytic Leukemia (CMML): the PATROL trial

- **Indication:** Higher-risk CMML (CPSS risk intermediate-2 or high), no prior HMA treatment

- **Study design**: Open-label, single-arm multicenter, phase II study. 30 patients (to end up with min. 21 evaluable subjects) from 12 sites (4 Germany, 4 Italy, 4 Spain)

- **Objectives**:
  Primary:
  - efficacy and toxicity of the combination of AZA with VEN and TAG in the studied patient population

  Secondary:
  - Tolerability and safety of the combination; Overall survival (OS), time to leukemia transformation (TLT), median duration of response until EOT; Proportion of patients achieving hematologic improvement at 3 months (IWG 2006 criteria); Proportion of patients achieving transfusion independence at 3 months (IWG 2006 criteria); Change of quality of life at 3 months compared to baseline; Biomarkers of resp

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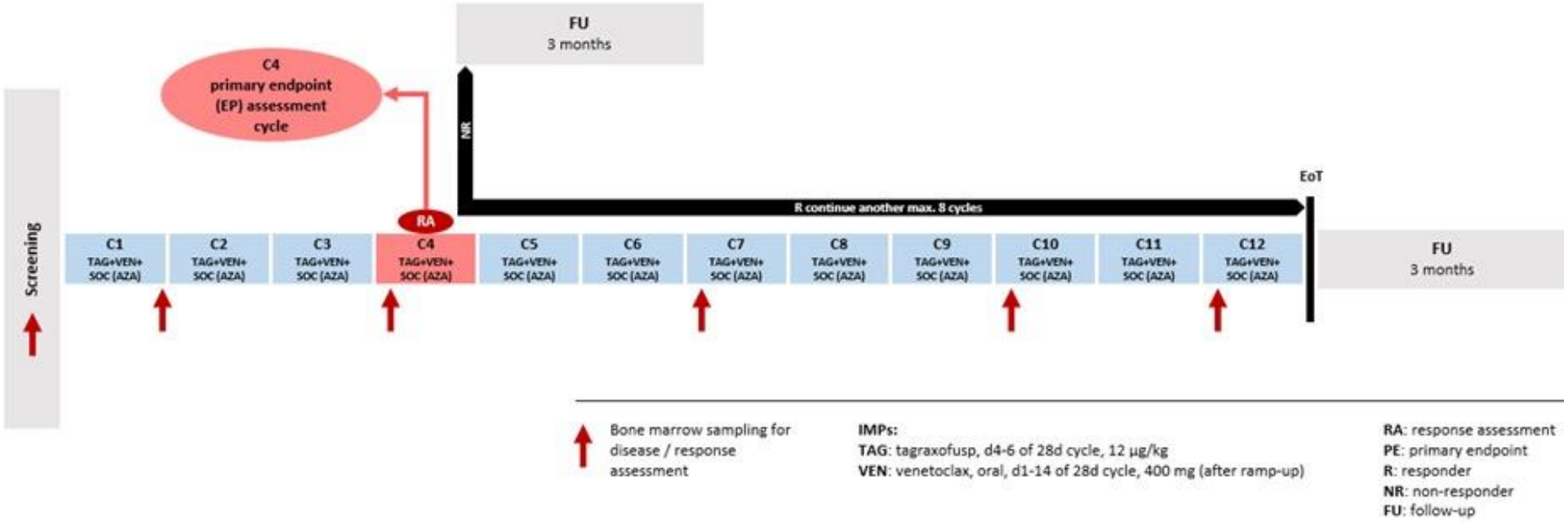
# PATROL

**Study treatments**:

Cycle: Q28

IMPs: TAG: 12µg/kg IV on days 4-6; VEN: Oral intake 400mg on days 1-14 (after ramp-up)

Backbone: standard of care - AZA




**Time plan**: Min of ~12 Wks of treatment (until EP assessment in C4: response rate defined as CR or mCR or PR rate after 3 mths of treatment).

For responders: treatment for a max of ~12 mths in total (max. ~8 further mths after EP assessment), followed by 3 mths of FU.

For non-responders: treatment stops after ~14 Wks after EP assessment carried out in C4 followed by 3 mths of FU.

The study is financially supported by Stemline Corporation and Abbvie

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Cooperative Group

D·MDS
Deutsche MDS-Studiengruppe

# Clinical trials of the D-MDS and EMSCO platforms

09 / 2024

# Active trials

| LR/HR | Acronym | Title | IMP | Countries | Sample size | Status |
|---|---|---|---|---|---|---|
| LR | REMARK | *A phase II, open-label, multicenter study of orally administered RVU120 for the treatment of anemia in patients with lower-risk myelodysplastic neoplasms (MDS)* | **RVU120** |  | N=41 (single arm) | Recruiting **N=0/41** |
| LR | LUSPLUS | *A phase IIIb, open-label, single arm study to evaluate the efficacy and safety of luspatercept in patients with lower-risk MDS and ring-sideroblastic phenotype (MDS-RS)* | **Luspatercept** |  | N=70 (single arm) | Recruiting **N=41/70** |
| LR | LENNON | *A phase II, open-label, single arm study to evaluate the efficacy of luspatercept in erythropoiesis-stimulating agent naive lower-risk MDS patients with or without ring sideroblasts who do not require RBC transfusions* | **Luspatercept** |  | N=30 (single arm) | Recruiting **N=9/30** |
| HR | PALOMA | *Primary comparison of liposomal anthracycline based treatment versus conventional care strategies before allogeneic stem cell transplantation in patients with higher risk MDS and oligoblastic AML* | **CPX-351** (Vyxeos®) (random. vs. CCR) |  | N=150 (two arms) | Recruitment completed |
| HR | IMPRESS | *A phase II study evaluating the efficacy and safety of imetelstat in patients with HR myelodysplastic syndromes or AML failing HMA-based therapy* | **Imetelstat** |  | N=46 (single arm) | Recruiting **N=21/46** |

# Active trials

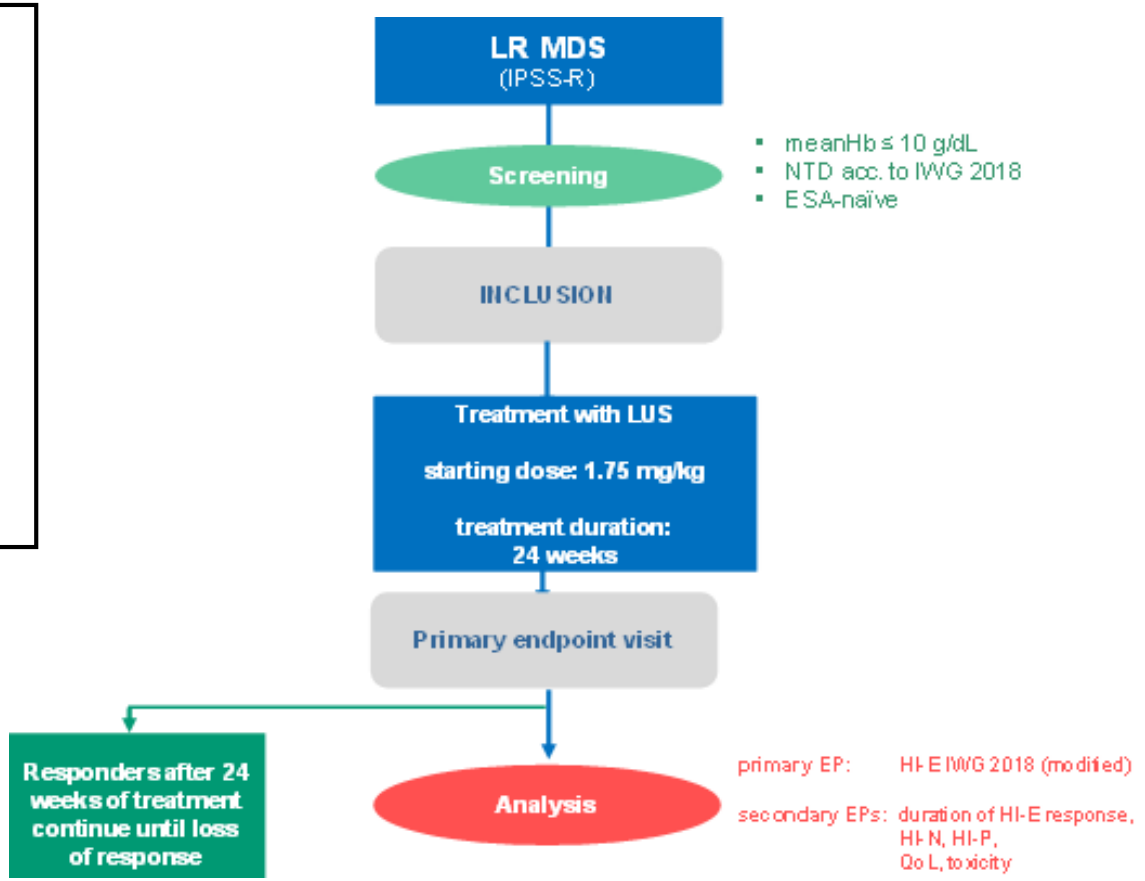
| LR/HR | Acronym | Title | IMP | Countries | Sample size | Status |
|---|---|---|---|---|---|---|
| LR | **LENNON** | *A phase II, open-label, single arm study to evaluate the efficacy of luspatercept in erythropoiesis-stimulating agent naive lower-risk MDS patients with or without ring sideroblasts who do not require RBC transfusions* | **Luspatercept** |  | N=30<br>(single arm) | Recruiting<br>**N=11/30** |

**Main IN**

- MDS diagnosis according to WHO classification
- Very low, low or intermediate risk disease with up to 3.5 points according to IPSS-R
- Non-transfusion-dependent for RBC according to IWG 2018
- Symptomatic anemia: mean baseline-Hb < 10 g/dL

**Main OUT**

- Secondary MDS
- Known clinically significant anemia due to lack of iron, vitamin B12 or folic acid, autoimmune disease, hereditary hemolytic anemia or GI bleeding
- Prior allogeneic or autologous stem cell transplantation
- ECOG > 2
- Prior treatment with ESA



# Active trials

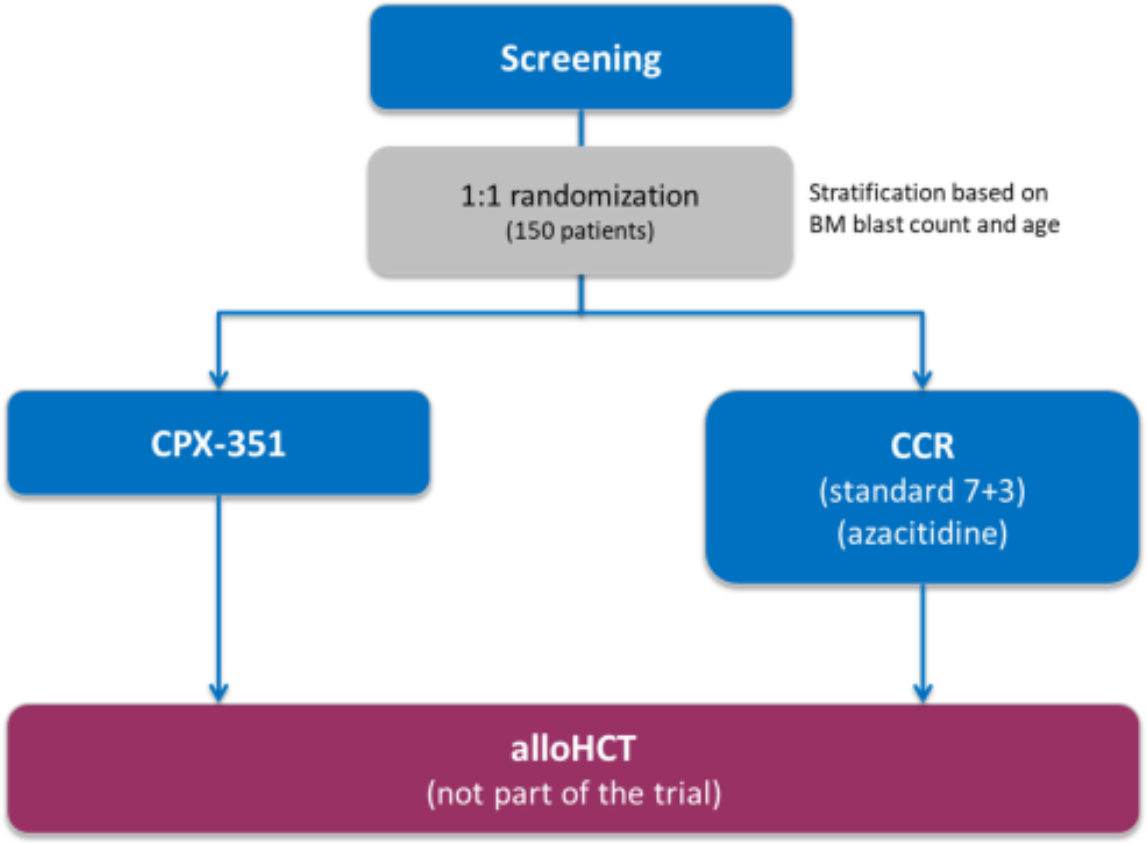
| LR/HR | Acronym | Title | IMP | Countries | Sample size | Status |
|---|---|---|---|---|---|---|
| HR | **PALOMA** | *Primary comparison of liposomal anthracycline based treatment versus conventional care strategies before allogeneic stem cell transplantation in patients with higher risk MDS and oligoblastic AML* | **CPX-351** (Vyxeos®) (random. vs. CCR) | | N=150 (two arms) | Recruitment completed |

**Main IN**

- Higher-risk MDS or oligoblastic non-proliferative AML up to 29% of bone marrow blasts
- IPSS intermediate or high
- BM blasts ≥ 10%
- alloSCT intended within the next 6 months

**Main OUT**

- History of MPN or combined MDS/MPN
- Prior treatment with either CPX-351, HMAs, cytarabine or intensive chemotherapy for higher-risk MDS or AML
- AML with t(15;17), PML-RARA; AML with t(8;21), RUNX1-RUNX1T1, AML with inv(16)/t(16;16), CBFβ-MYH11; AML with biallelic CEBPA mutation; AML with mutated NPM1
- Patients with prior cumulative anthracycline exposure of greater than 368 mg/m2 daunorubicin (or equivalent)



# Active trials

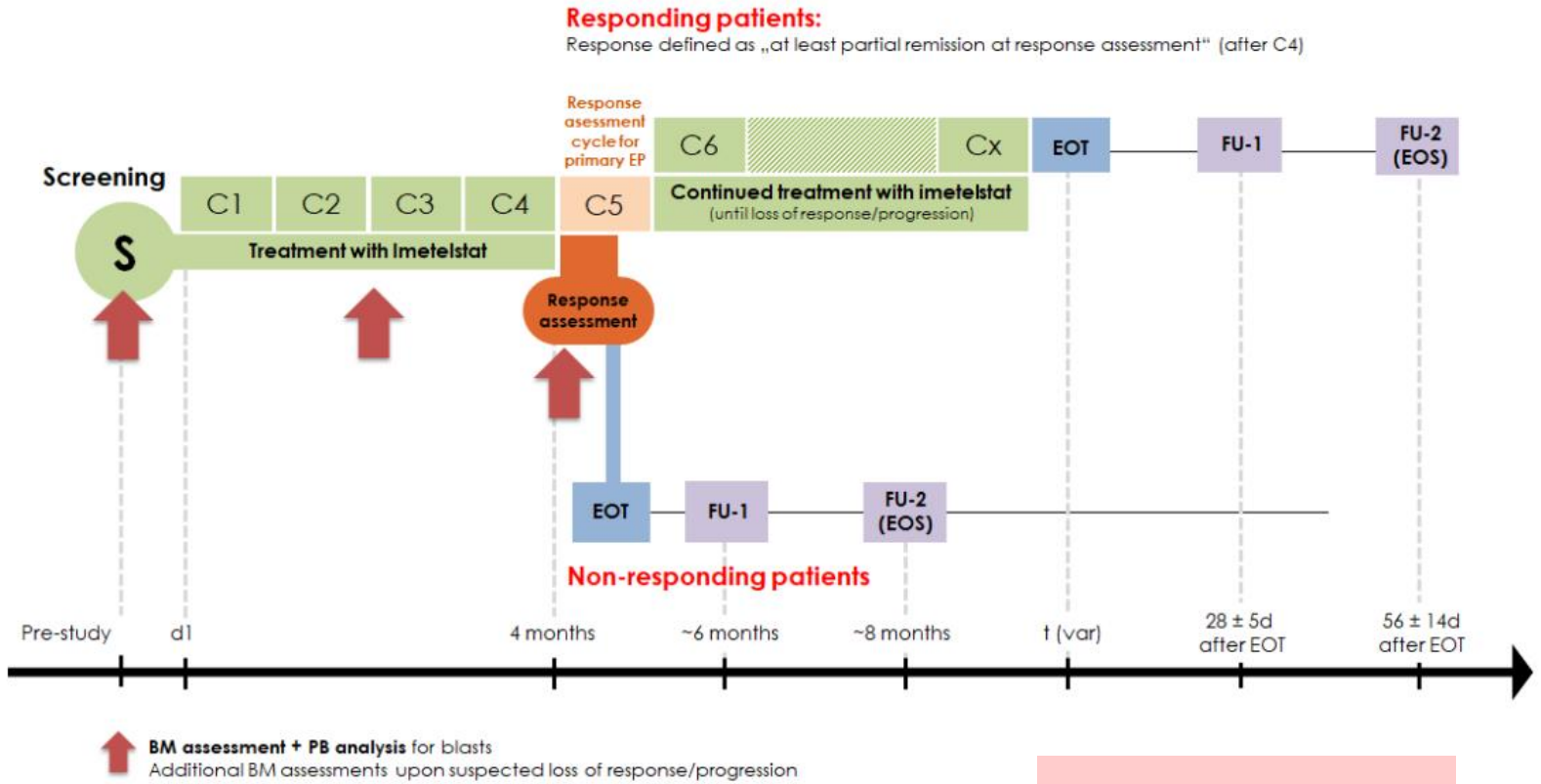
| LR/HR | Acronym | Title | IMP | Countries | Sample size | Status |
|---|---|---|---|---|---|---|
| HR | **IMPRESS** | *A phase II study evaluating the efficacy and safety of imetelstat in patients with HR myelodysplastic syndromes or AML failing HMA-based therapy* | **Imetelstat** | | N=46 (single arm) | Recruiting **N=23/46** |

**Main IN**

- Diagnosis of AML or MDS according to WHO 2016 classification
- ≥ 5 % BM blasts at screening
- At least one cytopenia
- Refractory / relapsed / intolerant re. HMA
- Not eligible for HSCT

**Main OUT**

- Prior history of intensive chemotherapy or HSCT
- Prior treatment with imetelstat
- Clinically significant cardiovascular disease




**Amendment** → increased dosing frequency (every 2 weeks instead of every 4 weeks)

**Results of interim analysis submitted to ASH**

## Trials in preparation

| LR/HR | Acronym | Title | IMP | Countries | Sample size | Status |
|---|---|---|---|---|---|---|
| CMML | **PATROL** | *A Phase II study of Azacitidine (AZA) combined with Venetoclax (VEN) and Tagraxofusp (TAG) in patients with higher higher-risk chronic myelomonocytic leukemia (CMML)* | **Tagraxofusp** (in comb. with AZA and VEN) |  | N=24 (single arm) | Finalizing protocol and contact negotiations |

# Completed trials

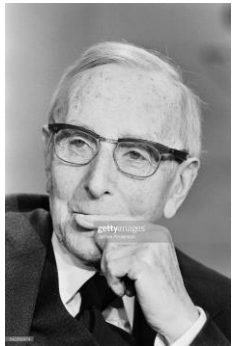
| LR/HR | Acronym | Title | IMP | Countries | Sample size | Status |
|---|---|---|---|---|---|---|
| | | | | | | |
| LR | LUCAS | *A Phase II, Open-Label, Multicenter Study of Orally Administered CA-4948 for the Treatment of Anemia in Patients With Very Low, Low or Intermediate Risk Myelodysplastic Syndromes (MDS)* | **Emavusertib (CA-4948)** |  | N=38/84 | • Not yet published, prematurely terminated<br>• Translational work submitted to ASH |
| LR | CANFIRE | *A Phase II, Single-Arm, Open-Label Study to Assess the Efficacy and Safety of Canakinumab for the Treatment of Anemia in Patients With IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes or MDS/MPN* | **Canakinumab** | | N=11/41 | • Not yet published, prematurely terminated<br>• Translational work submitted to ASH |

# GFM clinical trials Oct 2024

Groupe Francophone des Myélodysplasies

Université Paris Cité

UNIVERSITÉ PARIS 13



# GFM clinical trials

- Higher risk MDS
  - First line
  - Second line or beyond
  - Allo SCT
  - CMML
  - MDS with TP 53 mutation

- Lower risk MDS
  - First line
  - Second line or beyond
  - Associated with autoimmune or auto inflammatory diseases

Groupe Francophone des Myélodysplasies

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# Onureg-Ven : A phase 1b-2 study
## (Colombe Saillard)

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| | |
|---|---|
| Target population | Previously untreated higher-risk myelodysplastic syndromes ineligible for allogenic transplantation |
| Study design | Multicenter, l phase 1b-2 study |
| Objectives of the Trial | **Primary objective** in the phase 1b is to establish maximum tolerated dose (MTD) and determine recommended phase 2 dose-schedule (RP2DS) by evaluating safety and tolerability of Onureg (CC-486) and VENETOCLAX combination, in previously untreated patients with HR-MDS not eligible for transplant.<br><br>When MTD/RP2D will be determined, phase 2 dose expansion part of the study will open for enrollment. **Primary objective in phase 2** is to assess preliminary efficacy (CR rate) of the R2PD of Onureg-VEN combination. |

| | Oral AZA | Venetoclax |
|---|---|---|
| Level -1 | 200 mg QD d1-d7 | 400 mg QD d1-d14 |
| Level 1 | 200 mg QD d1-d14 | 400 mg QD d1-d14 |
| Level 2 | 300 mg QD d1-d14 | 400 mg QD d1-d14 |

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# $IDH_1$ & $IDH_2$ inhibitors in MDS (L Adès, M Sébert)

| IDEAL STUDY | IDIOME STUDY |
| --- | --- |
| Enasidenib (AG-221; IDH2 inhibitor) | Ivosidenib (AG-120; IDH1 inhibitor) |

Cohort A: higher risk MDS who failed to achieve response after 6 cycles of AZA

Cohort B: Patients with untreated higher risk without life threatening cytopenia

Cohort C: Lower risk MDS with anemia resistant to EPO

# Impress (cooperation with the German MDS group) (L
## Adès for the GFM)

- Imetelstat in higher risk MDS ans AML having failed AZA (+/-Venetoclax)

# GFM clinical trials

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# Ongoing

**1) VENTOGRAFT: Venetoclax + AZA + DLI in MDS relapsing post allo SCT** (T Cluzeau,M Robin)

**2)Upfront allo SCT in patients with marrow blasts <15%** (M Robin)

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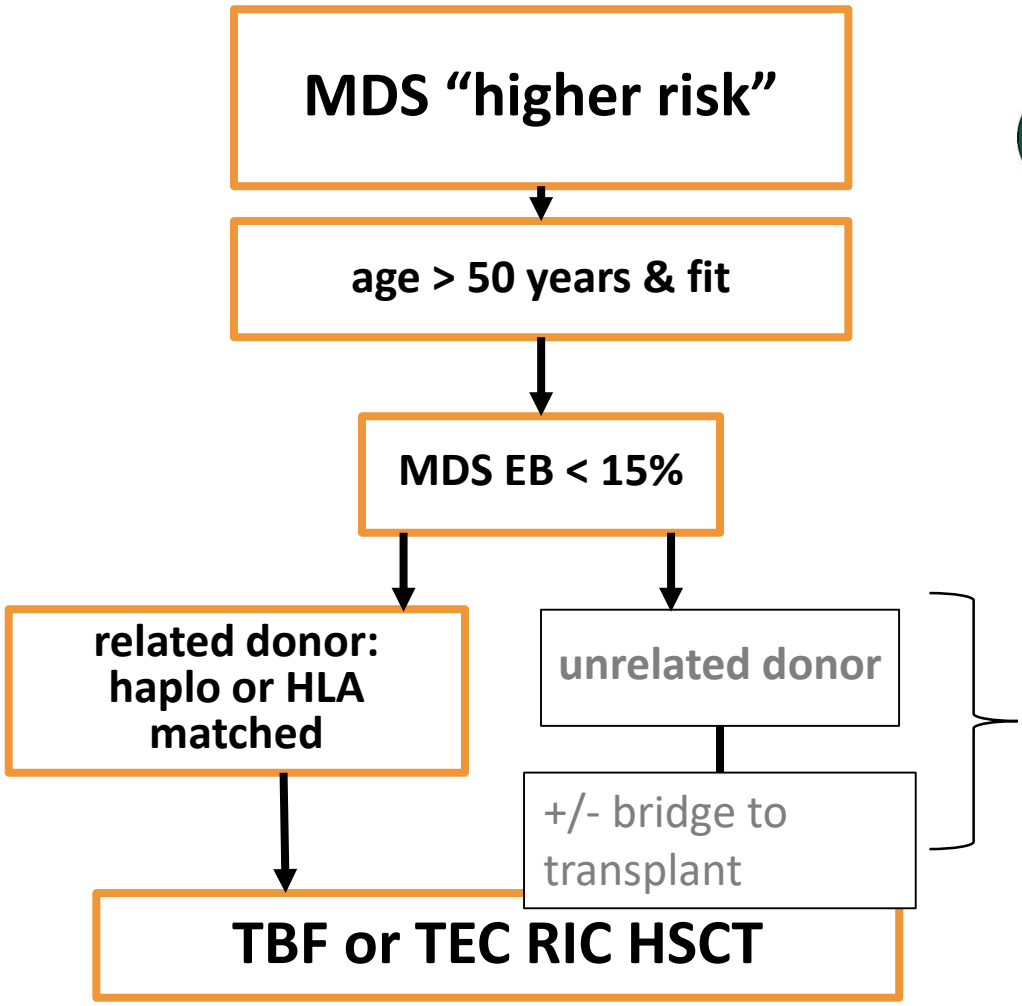


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SFGM-TC Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

# « MDS FIRST ALLO »

An uncontrolled phase 2 open-label trial

Sponsor: DRCI Hôpital Saint-Louis

HMA

HMA VEN

Other experimental arm

# GFM clinical trials

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# Advanced CMML

- AZA + VEN ( AVENHIR trial) (R Itzykson)

# GFM clinical trials

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# Higher risk MDS with TP 53 mutation

- Failure of APR 246
- Attempts at drug repurposing based on in vitro/ex vivo experiments (N Maslah; B Cassinat)

# GFM clinical trials

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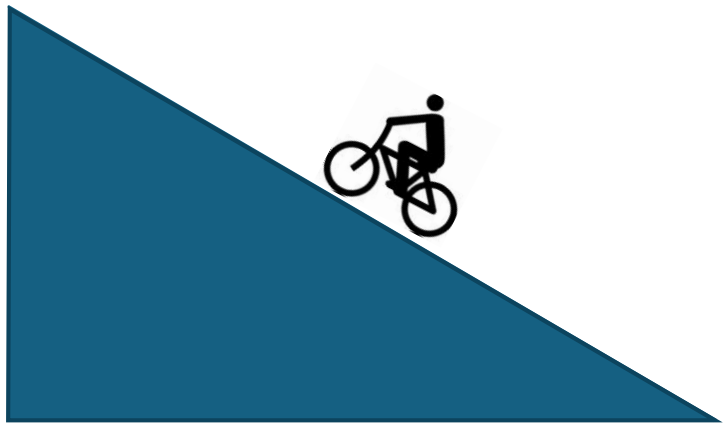
# Randomized trial evaluating early versus late introduction of Epoetin Alfa (EPREX®) in patients with low-risk myelodysplastic syndromes



## GFM-EPO-PRETAR

**Sophie PARK**
CHU de Grenoble Alpes

Numéro EudraCT: 2016-000327-10

Numéro ClinicalTrials.gov: NCT02992860

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CHU GRENOBLE ALPES

# LODEFI

## Phase II therapeutic trial evaluating low-dose deferasirox (DFX) in patients with resistant low-risk myelodysplastic syndrome (MDS) or post-erythropoiesis-stimulating agent (ESA) relapse"


**Pr Sophie PARK**

**Promoteur :**
**CHU de Grenoble**
**Délégation à la Recherche Clinique et à l'Innovation**
**Pavillon Dauphiné**
**CS 10217**
**38043 Grenoble Cedex 09**


Protocole en vigueur : version 8.0 du 20220304
Lettre d'information et de consentement : version 3.1 du 23/11/2018

Version 6.0 du 18062021

# Combola Trial (non sideroblastic lower risk MDS) (L Adès)

- Patients with lower risk MDS according to IPSS classification (LOW, INT-1) without RS
- failed to achieved a response or who subsequently relapse after ESA (at least 60000 U EPO-a over at least 12weeks or equivalent), without disease progression (Or ineligible to ESA defined by EPO > 500 UI/l)
- Hemogobin < 9 gr/dl or Transfusion dependant( at least 3 RBCs
- No del(5q) MDS

1º Endpoint: transfusion independence for TD dependent patients and hematological improvement For non TD dependent patient at W25

R

1

Luspatercept (ACE-536)
1.0 mg/kg q3W
with titration up to max of 1.75 mg/kg
n=63

1

Luspatercept (ACE-536)
+ ESA at the selected dose (part A)
n=63

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# GFM clinical trials

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# Treatment of VEXAS with MDS

Leukemia www.nature.com/leu

LETTER

MYELODYSPLASTIC NEOPLASM

## A Phase II prospective trial of azacitidine in steroid-dependent or refractory systemic autoimmune/inflammatory disorders and VEXAS syndrome associated with MDS and CMML

Arsene Mekinian[1,27], Lin Pierre Zhao[2,27], Sylvie Chevret[3], Kristell Desseaux[3], Laurent Pascal[4], Thibaut Comont[5], Alexandre Maria[6], Pierre Peterlin[7], Louis Terriou[8], Maud D'Aveni Piney[9], Marie-Pierre Gourin[10], Norbert Vey[11], Odile Beyne Rauzy[5], Vincent Grobost[12], Holy Bezanahary[13], Sophie Dimicoli-Salazar[14], Anne Banos[15], Stefan Wickenhauser[16], Benoit De Renzis[17], Eric Durot[18], Shanti Natarajan-Amé[19], Laurent Voillat[10], Fatiha Chermat[2], Karine Lemaire[2], Vincent Jachiet[1], Chantal Himberlin[18], Sylvain Thépot[20], Jose Miguel Torregrosa Diaz[21], Laurent Frenzel[22], Emmanuel Gyan[23], Guillaume Denis[24], Pierre Hirsch[25], Olivier Kosmider[26], Lionel Ades[2], Olivier Fain[1] and Pierre Fenaux[2]

- N=30
- 66% response on SAID
- 59% hematological response
- Identical response in VEXAS and non VEXAS patients

TO THE EDITOR:

## Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study

Maël Heiblig,[1] Marcela A. Ferrada,[2,*] Matthew T. Koster,[3,*] Thomas Barba,[4,*] Mathieu Gerfaud-Valentin,[5] Arsène Mékinian,[6] Henrique Coelho,[7] Gaelle Fossard,[1] Fiorenza Barraco,[1] Lionel Galicier,[8] Boris Bienvenu,[8] Pierre Hirsch,[9] Guillaume Vial,[10] Anne Blandine Boutin,[11] Joris Galland,[12] Guillaume Le Guenno,[13] Adrien Bigot,[14] Kenneth J. Warrington,[3] Tanaz A. Kermani,[15] Peter C. Grayson,[2] Bhavisha A. Patel,[16] David B. Beck,[17,18] Yvan Jamilloux,[5,†] Pierre Fenaux,[19,†] and Pierre Sujobert[20]

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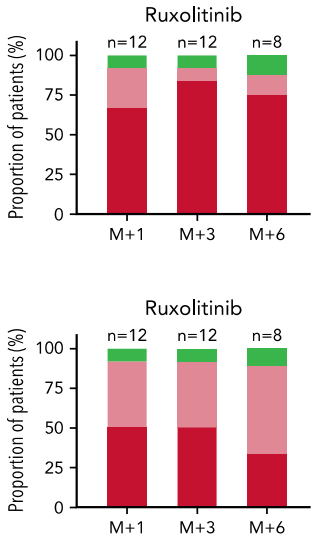

# Next steps in VEXAS with MDS (cooperation with MINHEMON/VEXAS group)

- New JAK inhibitors : Momelotinib (M Heiblig)

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# Perspectives on clinical trials in MDS in Europe

- Recently completed  cooperative EMSCO studies
- Current studies
- How can we  envisage the future ?

COMMENTARY

blood advances

TO THE EDITOR:

# An agenda to advance research in myelodysplastic syndromes: a TOP 10 priority list from the first international workshop in MDS

Maximilian Stahl,[1] Omar Abdel-Wahab,[2] Andrew H. Wei,[3] Michael R. Savona,[4] Mina L. Xu,[5] Zhuoer Xie,[6] Justin Taylor,[8] Daniel Starczynowski,[9] Guillermo F. Sanz,[10-12] David A. Sallman,[6] Valeria Santini,[13] Gail J. Roboz,[14] Mrinal M. Patnaik,[7] Eric Padron,[6] Olatoyosi Odenike,[15] Aziz Nazha,[16] Stephen D. Nimer,[8] Ravindra Majeti,[17] Richard F. Little,[18] Steven Gore,[18] Alan F. List,[19] Vijay Kutchroo,[20] Rami S. Komrokji,[6] Tae Kon Kim,[4] Nina Kim,[18] Christopher S. Hourigan,[21] Robert P. Hasserjian,[22] Stephanie Halene,[23] Elizabeth A. Griffiths,[24] Peter L. Greenberg,[17] Maria Figueroa,[8] Pierre Fenaux,[25] Fabio Efficace,[26] Amy E. DeZern,[27] Matteo G. Della Porta,[28] Naval G. Daver,[29] Jane E. Churpek,[30] Hetty E. Carraway,[31] Andrew M. Brunner,[32] Uma Borate,[33] John M. Bennett,[34] Rafael Bejar,[35] Jacqueline Boultwood,[36] Sanam Loghavi,[37] Jan Philipp Bewersdorf,[2] Uwe Platzbecker,[38] David P. Steensma,[39] Mikkael A. Sekeres,[8] Rena J. Buckstein,[40] and Amer M. Zeidan[23]

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Review

# Classification, risk stratification and response assessment in myelodysplastic syndromes/neoplasms (MDS): A state-of-the-art report on behalf of the International Consortium for MDS (icMDS)

Maximilian Stahl [a], Jan Philipp Bewersdorf [b], Zhuoer Xie [c], Matteo Giovanni Della Porta [d], Rami Komrokji [c], Mina L. Xu [e], Omar Abdel-Wahab [b], Justin Taylor [f], David P. Steensma [g], Daniel T. Starczynowski [h], Mikkael A. Sekeres [f], Guillermo Sanz [i,j,k], David A. Sallman [c], Gail J. Roboz [l], Uwe Platzbecker [m], Mrinal M. Patnaik [n], Eric Padron [c], Olatoyosi Odenike [o], Stephen D. Nimer [f], Aziz Nazha [p], Ravi Majeti [q], Sanam Loghavi [r], Richard F. Little [s], Alan F. List [t], Tae Kon Kim [u], Christopher S. Hourigan [v], Robert P. Hasserjian [w], Stephanie Halene [x], Elizabeth A. Griffiths [y], Steven D. Gore [s], Peter Greenberg [z], Maria E. Figueroa [f], Pierre Fenaux [aa], Fabio Efficace [ab], Amy E. DeZern [ac], Naval G. Daver [ad], Jane E. Churpek [ae], Hetty E. Carraway [af], Rena Buckstein [ag], Andrew M. Brunner [ah], Jacqueline Boultwood [ai], Uma Borate [aj], Rafael Bejar [ak], John M. Bennett [al], Andrew H. Wei [am], Valeria Santini [an], Michael R. Savona [u], Amer M. Zeidan [x,*]

**Table 1. Top 10 list of MDS collaborative priority research goals**

| Priority research goals |
|---|
| 1. To establish a new standard of care for frontline higher-risk MDS |
| 2. To develop better treatment options for DNA methyltransferase inhibitor (DNMTi)-refractory MDS |
| 3. To develop effective strategies for *TP53*-mutated MDS |
| 4. To advance novel treatment strategies to impact the underlying pathophysiology of lower-risk MDS |
| 5. To conduct clinical trials in a collaborative international effort with emphasis on equal access and on PROs |
| 6. To formulate unified diagnostic criteria and classification subgroups for MDS |
| 7. To establish and systematically validate clinically meaningful response criteria for MDS therapy |
| 8. To establish tools to predict, and ultimately reduce, risk of progression of CH to MDS and other hematological malignancies in clinical practice |
| 9. To establish linked clinical databases and biobanks allowing sharing of data |
| 10. To improve the development and dissemination of reliable preclinical models of MDS |

# A few additional suggestions for international clinical trials in higher risk MDS

- (Large patient numbers and surrogate endpoints)
- Avoid some exclusion criteria
- Parallel trials in different continents
  - APR 246 in MDS with TP 53 mutation (T Cluzeau, D Salmann)
  - ABNL MARRO (M Savona)
- Prespecified subgroup analysis ( based particularly on genetics)
- Avoid the systematic « intention to treat dogma »(especially for relapsing patients)
- For TP53 mutation, close cooperation with solid tumor specialists

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but what we need most is effective drugs !

Department of hematology and immunology
of Hospitals St Louis, R Debré, Avicenne
APHP and University of Paris

## Hôpital St Louis

- 7 services of adult hematology (H Dombret, N Boissel, G Socié, B Arnulf, E Oksenhendler, P Fenaux, C Thiéblemont)
- ICU (E Azoulay)
- pneumology (A Tazi)

## Hôpital Robert Debré

- pediatric hématology service (A Baruchel)
- Sickle cell disease unit(M Benkerrou)

## Hôpital Avicenne

- Adult hematology service (C Gardin)

Université de Paris

UNIVERSITÉ PARIS 13

# 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