MDS Newsletter

Issue # 11
September 2017

EMSCO
MYELODYSPLASTIC SYNDROMES

Motivation und Mission

The goal of the MDS Newsletter is to promote new knowledge and to support the exchange of information in the clinical research, diagnostics and therapy of myelodysplastic syndromes (MDS).

The newsletter is particularly directed towards clinicians, scientists and industry developers of therapies for MDS.

Kind regards,

Silke Gloaguen in the name of the EMSCO team

Good news for MDS: EPREX® Marketing Authorisation extended to anaemia in LR MDS

Janssen-Cilag International announced on March 24th that the French health authority ANSM has approved EPREX (epoetin alfa) for the treatment of symptomatic anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1 risk MDS) who display with low serum erythropoietin (<200 mU/mL).

The ANSM acted as the reference Member State within the Mutual Recognition Procedure (MRP), which has now concluded and resulted in an extension to the marketing authorisation for EPREX. Upon the conclusion of the extension procedure within the MRP the other European health authorities are required to implement the new indication into their national Summary of Product Characteristics (SmPC) and package leaflet within 30 days.

This approval was based on results from the international Phase 3, randomised, double-blind, placebo-controlled, multicentre study, EPOANE 3021 along with three registry studies from across Europe.

EPOANE 3021 demonstrated the efficacy and safety of EPREX as a treatment for anaemia, in adult patients with low or intermediate-1-risk MDS, as classified

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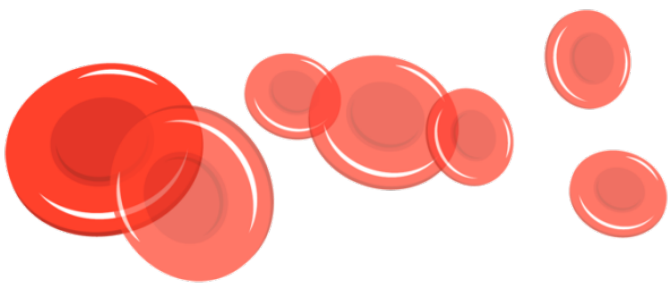

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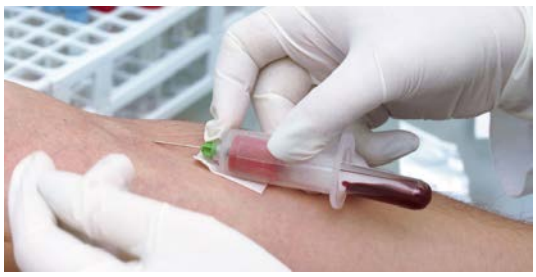
Editor & Layout:
Silke Gloaguen

by an International Prognostic Scoring System (IPSS). EPOANE 3021 data were presented at the 21 Annual Congress of the European Hematology Association (EHA) in 2016. Janssen have data exclusivity for one year.

“This announcement is extremely welcome, as there have been no erythropoiesis stimulating agents approved to treat anaemia in patients with MDS until now, despite the fact that it contributes significantly to their symptoms,” said Pierre Fenaux, M.D., PhD., principal investigator of EPOANE 3021, and Professor of Hematology, Hôpital St Louis/Université, Paris, France.

“We are pleased with the outcome of the MRP which brings us one step closer to offering a new treatment option to patients with MDS-related anaemia throughout Europe.



Anaemia – a frequent symptom of low-risk MDS patients

This approval is a testament to our long-standing commitment to patients living with cancer,” said Dr Catherine
Taylor, Haematology Therapeutic Area Lead, Janssen Europe, the Middle East and Africa
(EMEA).

Author: Silke Gloaguen

Source:
http://www.businesswire.com/news/home/20170324005186/en/EPREX%C2%AE-epoetin-alfa-Marketing-Authorisation-Extended-Include

Deep-phenotyping unravels Treg-subsets as predictive biomarkers in immune-mediated bone marrow failure syndrome

Idiopathic aplastic anaemia (AA) is an immune-mediated and serious form of bone marrow failure. The majority of these patients respond to immune-suppressive therapy. Akin to other autoimmune diseases, regulatory T-cells (Tregs) are reduced in number and function in AA. The importance of Tregs in the pathophysiology of autoimmune diseases is well established, however, the definition and significance of Treg subpopulations is less clear. Identification of Treg subsets is challenging in autoimmune diseases as the number of Tregs is usually low and Tregs may express aberrant markers, and gating strategies for Treg subpopulations are often subjective. Biomarkers that, first, identify AA patients from HDs and, second, identify at time of diagnosis who are less likely to respond to IST, have as yet not been identified. There is an unmet need for more robust predictive factors for response to IST at time of diagnosis of AA. Known predictive factors for response to IST include less severe disease, young age, and absolute reticulocyte and lymphocyte counts of ≥ 25 and ≥ 1.0 x 109/l, respectively. Short telomeres in children, but not in adults, also predict response to IST.

It is now possible to comprehensively characterise rare, complex populations of cells with minimal bias using mass-cytometry (CyTOF) to measure the expression level of more than 40 parameters at the single cell level. In current study, by using this multidimensional phenotyping and unbiased approach, two distinct Treg subpopulations were characterized in HDs and AA patients and the changes in these subsets predicted response to IST at diagnosis of AA. We sorted these cells based on their immunological markers and confirmed their dissimilar TCR, gene expression signatures and function. Our analytical strategy eliminated the unavoidable subjectivity of Treg sub- >>>

population definition based on two-dimensional gating without unnecessary over-clustering.

Within the CD25hi, FOXP3hi and CD127lo Treg population, AA Tregs expressed CD27hi, CD45RAlo, CD45ROhi, CD95hi, CD7lo, CD28hi, CCR4hi compared to the total CD4+ T-cell. We have identified two well-defined subpopulations within this Treg population, ('Treg A and B',). While total Treg numbers were reduced in AA, Treg A was significantly higher in AA patients compared to HDs. In contrast, the number of Treg B subpopulation was significantly lower in AA patients compared to HDs (figure 1). Subpopulation B was characterised by a lower expression of CD45RA, CD7, CD27 and higher expression of CCR4, CCR6, CD25, CD28, CD45RO, CD95, CXCR3, FOXP3 and HLA-DR. The most significantly different markers were CD95, CCR4 and CD45RO. The identified Treg subpopulations were compared to established Treg subpopulation as previously defined by Miyara et al based on relative expression of FOXP3 and CD45RA known as populations I, II and III. Treg I and II are considered the most suppressive Tregs. While Treg A and B overlap with Treg subpopulations I and II respectively, our approach demarcates those Treg III cells which are closer to Tregs and combine them with subpopulation A or B based on their phenotype and eliminate cells which are closer to conventional T cells (Tcon) and less likely to be regulatory.

When AA patients were stratified into IST-responders and non-responders, while the overall frequency of Treg B was lower in both responder and non-responding patients at time of diagnosis compare to HDs (48.8%±6.1 & 28.9%±2.7 v 72.2%±6.7, p=0.005, p<0.0001), non-responders had significantly higher Treg A and lower Treg B cells compared to responders (63.5%±4.5 v 38.8%±5.0, p<0.005 for Treg A, 28.9%±2.7 v 48.8%±6.1, p<0.05 for Treg B).

Following IST response, the frequency of population A was significantly reduced in responders (from 38.8%±5.0 to 19.2%±2.4, p<0.01), but not significant in non-responder patients. Treg B frequency was significantly higher in responders compared to non-responders (59.9%±3.4 v 21.8%±4.3, p<0.0001) and closer to HDs.

To assess function of the Treg subpopulations, HD CD4+ Tregs were sorted based on CD25, CD127 and CD95 expression, that showed highest expression differences between subpopulation A and B on viSNE clusters, excluding intracellular markers to avoid fixation and permeabilisation of the cells. Tregs B were significantly more functional compared to subpopulation A, in suppression of both IFN-γ and TNF-α secretion by T conventional (p<0.05).

Genomic DNA from sorted Tregs A and B was used for T-cell receptor (TCR) Vß chain complementarity determining regions (CDR3) high-throughput sequencing and showed overlap between Treg A, B and Tcon was small suggesting these subpopulations were distinct.

Whole gene expression profile (GEP) data showed both Treg A and Treg B had different GEP compared to Tcon. Nevertheless, when principle component analysis (PCA) was performed, Treg B and Tcon had the highest difference while Treg A subpopulation showed a transcriptional profile in between Treg B and Tcon.

Comparing GEPs of Treg subpopulations to Tcon, using the human Treg's gene-signature, 27, showed both Treg A and B subpopulations were significantly enriched in genes up-regulated in human Tregs including: IL-2RA, FOXP3, IKZF2, TIGIT and CTLA4 (FDR<0.0001 for both Treg subpopulations compared to Tcon.

Gene set enrichment (GSEA) functional analysis22 highlighted several genesets as significantly overexpressed in Treg B subpopulation including: G2M checkpoint (FDR<0.0001), mitosis (FDR=0.015), M phase of mitotic cell-cycle (FDR=0.018) IL2-STAT5 signaling (FDR=0.023) and immune response genes (FDR=0.032). Expression of mRNA encoding proteins involved in mitosis, DNA replication and other

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proliferation functions suggest that the Treg B subpopulation is more likely to be proliferating, primed to proliferate or they have recently exited the cell-cycle.

To explore the potential therapeutic application of expanded Tregs in the treatment of AA, we examined the characteristics and in vitro expandability of the Treg subpopulations in depth. Both AA and HDs Tregs were sensitive to IL-2 as assessed by STAT5 phosphorylation. The expansion rate of AA Tregs (three of them from IST non-responders) was not different from HDs after 4 weeks culture. Expanded Tregs were functional in both autologous and allogeneic settings, and TSDR (Treg-specific demethylated region) of expanded Tregs indicated a stable phenotype.

In summary, we have shown for the first time that a novel strategy for multidimensional deep-phenotyping can reliably identify an immune signature for AA based on Treg subpopulations. This approach also identifies an immune signature that predicts for response to IST at time of diagnosis of AA, and which may allow a more patient specific approach to future treatment decision-making in SAA (figure 2). Our findings also pave the way for future novel therapeutic approaches such as expanded autologous Tregs and low dose interleukin-2 in AA.

This is a summary of the original publication: Blood. 2016 Sep 1;128(9):1193-205. doi: 10.1182/blood-2016-03-703702.

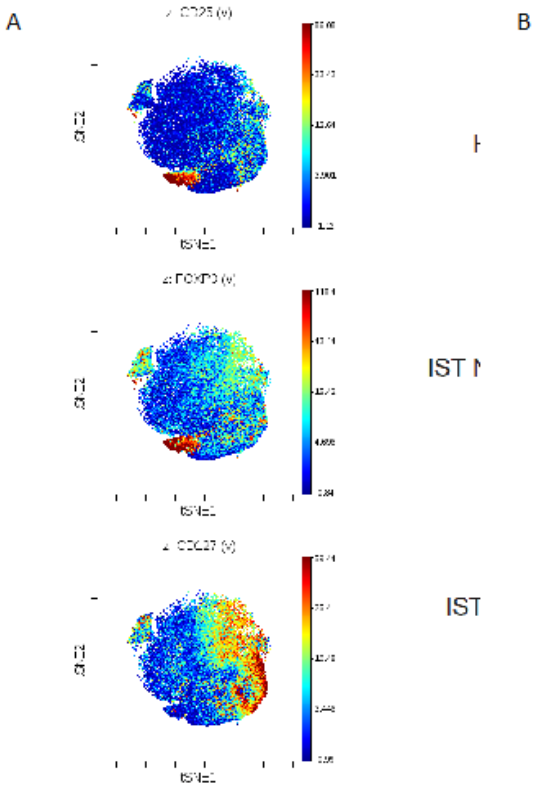

Figure 1: Mass cytometry (CyTOF) of CD4+ T cells in AA and HDs: (A) After initial gating for CD3+, CD4+, and CD8− T cells, the gated cells were clustered using viSNE (Cytobank). Treg populations were identified based on high expression of CD25 and FOXP3 and low expression of CD127. (B) The density plot of viSNE plots revealed 2 subpopulations within Tregs, designated as Treg A and B (arrows). The frequencies of Treg A and B were different between HD and AA patients. Patients who did not respond to IST (IST NR) had a higher number of Treg A at the time of diagnosis compared with responder patients (IST R) and HDs. The viSNE plots (right) are an overlay of Tregs' contour plots colored by density and CD4+ T cells uncolored contour plots.

Adopted from Kordasti et al. Blood 2016;128:1193-1205

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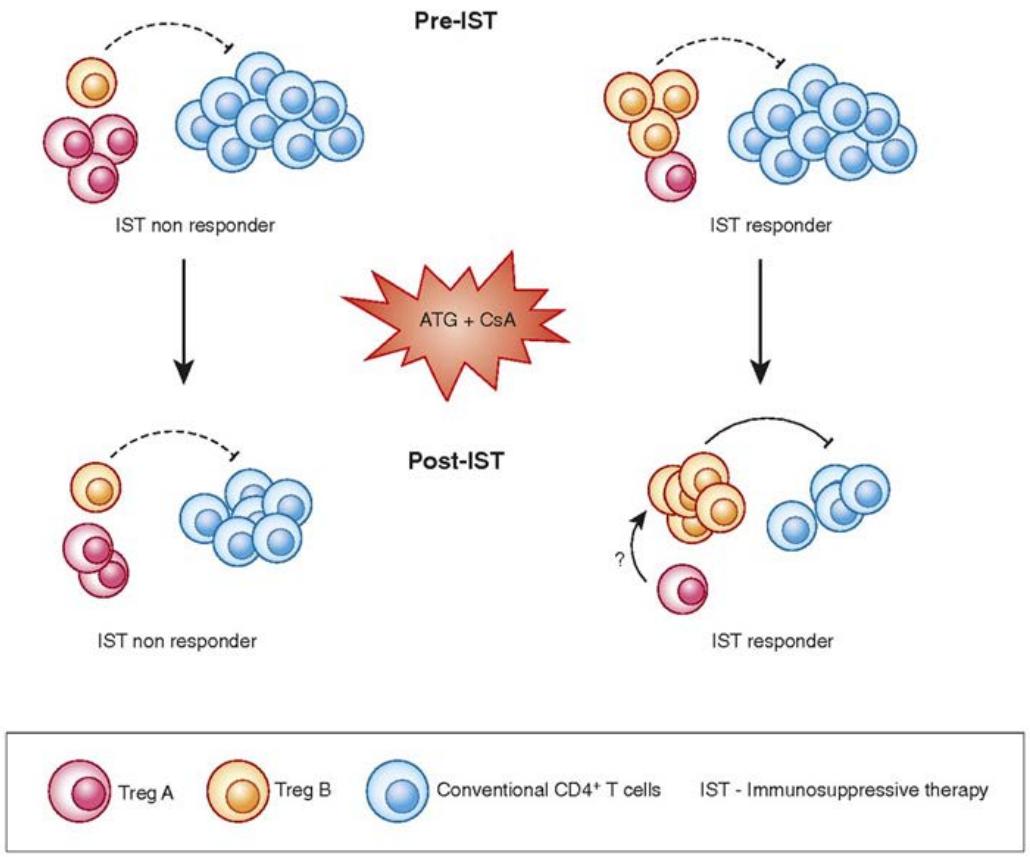

Figure 2: AA patients with higher number of Treg B cells before IST are more likely to respond to therapy. Following response to IST, responder patients have a higher number of Treg B cells compared with nonresponders. Treg B cells are enriched with cell-cycle–related proteins and are more likely to enter the cell cycle compared with Treg A sub-populations. In vitro expanded Tregs are also phenotypically closer to Treg B than Treg A. Tcon, conventional CD4+ T cells.

Adopted from Kordasti et al. Blood 2016;128:1193-1205

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EMSCO MDS-App

Enhancing the quality of cancer care throughout Europe is essential for improving cancer survival rates. High quality clinical research will make an important contribution to this goal. Myelodysplastic syndromes (MDS) are relatively rare diseases frequently progressing to acute myeloid leukemia (AML). Clinical research in MDS accelerated in recent years with numerous trials open worldwide, including a significant proportion in Europe. These efforts are based on an ever more detailed understanding of the disease mechanisms, based on cytogenetic findings and the relevance of specific mutations or the identification of new pathogenic mechanisms. Current and upcoming clinical research reflects this evolution and trial designs must meet the requirements of increased disease complexity by incorporating more complex stratifications, smaller subgroups and by targeting specific patient groups with tailored therapy options.

For treating physicians, especially those not practicing in academic institution, gaining and maintaining an overview on the clinical trial landscape in MDS can be a challenge. Thus, it is to be assumed that a big proportion of patients are missing the opportunity to be enrolled in suitable clinical trials.

Based on these considerations the idea for an easy-to-use tool primarily offering support for the identification of clinical trials was born within the EMSCO platform. This initial idea has quickly developed into the wish of offering a more comprehensive application for mobile devices integrating essential features for physicians treating MDS.

Prof. Platzbecker and his team at the University Hospital in Dresden, Germany, and several members of German speaking national MDS groups have worked out the concept for this app, which, for a start, has been designed for the German speaking market and in German language. The app has now successfully been completed and can be downloaded under the name “MDS Center” in the Apple App Store (iOS) as well as in Google Play (Android).

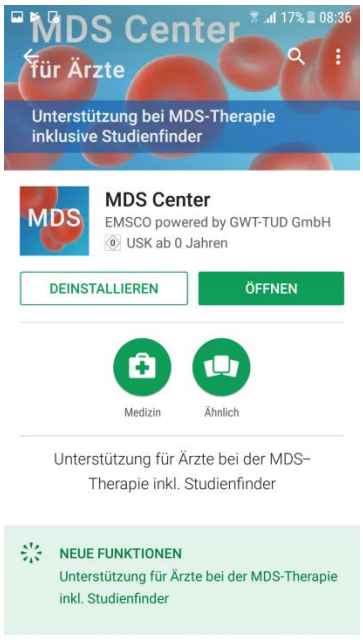
In the following we provide a summary of the tools offered by the app and we hope to be able to expand this project to the rest of Europe in the future by developing an English version in the near future.

Overview:

For easy identification you find below how the app presents in the two stores:

App Store:

Google Play:



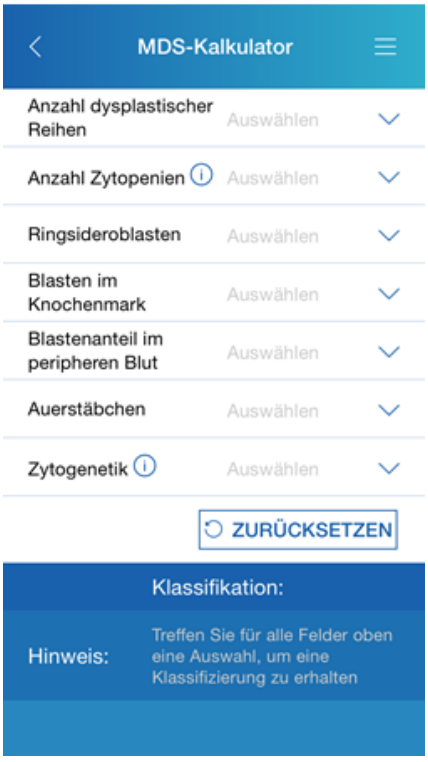
In terms of structure the app has five leading themes, which are:

- Individual calculator and tables for the WHO classification
- Calculator for IPSS and IPSS-R scores
- Therapy algorithm to identify treatment options and clinical trials for a given patient
- Clinical trial finder
- Knowledge

WHO calculator:

We have programmed a calculation tool for the WHO classification. It is based on the 2016 classification and provides individual results for a given patient by guiding the physician through the different parameters. In order to provide values for the alternative classifications as well we have included a conversion table showing corresponding classifications between WHO 2016, WHO 2008 and FAB. Also, the classifications are provided in the form of tables for a quick overview.

Calculator for WHO 2016:

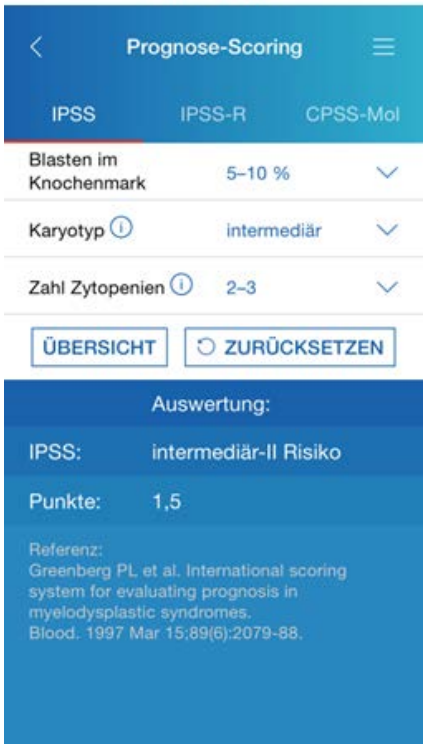


Conversion table:

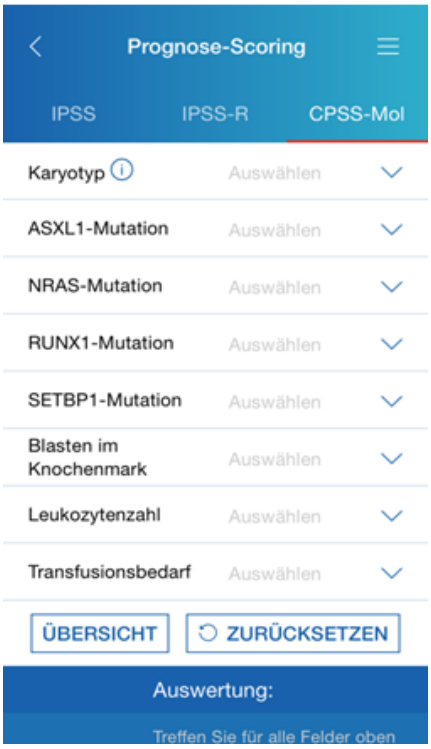
Prognostic scores:

Calculators for the determination of IPSS, IPSS-R and CPSS-mol scores have been programmed. zur Bestimmung des IPSS, IPSS-R und CPSS-Mol, inkl. Übersichten zum Nachschlagen. In terms of results the denomination of the risk categories as well as the corresponding scores are provided.

IPSS calculator:



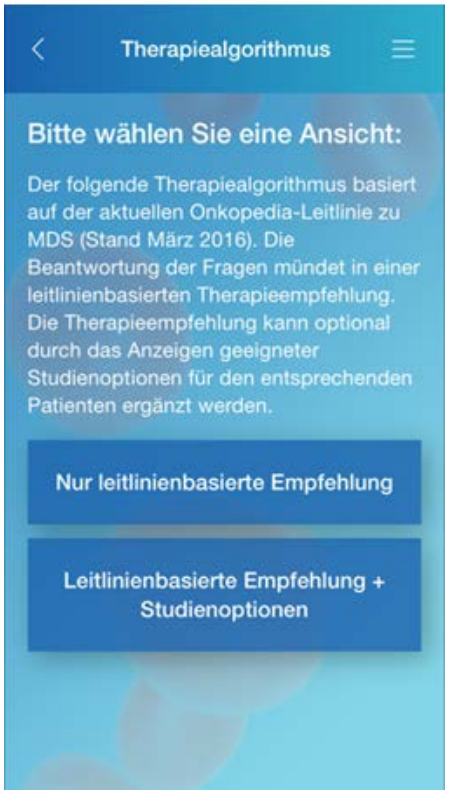
CPSS-Mol calculator:



Therapy algorithm:

The app provides the user with an interactive therapy algorithm for MDS and CMML. The tool guides the physician step-by-step through the currently relevant guidelines and results in the corresponding treatment recommendation for a given patient presenting with the clinical parameters having been fed in the algorithm. Besides the treatment recommendation according to guidelines the therapy algorithm offers the possibility to indicate clinical trials covering the given criteria.

Start page therapy algorithm:



Therapy recommendation incl. study options based on the the parameters chosen in the step-by-step algorithm:

Clinical trial finder:

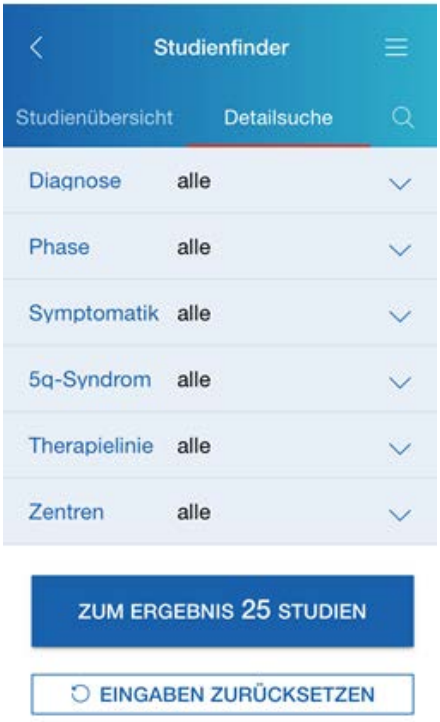
The clinical trial finder has been designed in order to offer an uncomplicated research tool for the identification of currently running clinical trials in the field of MDS and CMML in Germany, Austria and Switzerland. On one hand, a summary page provides an overview on all listed trials. On the other hand, an algorithm, which is connected with a study database designed and maintained by the team, allows a detailed search based on various parameters (see list below). Additionally a free search field where study names or keywords can be inserted has been programmed. The study database behind the algorithm can be updated any time without the need for loading an updated version of the app.

For every listed trial the following parameters are documented in the database:

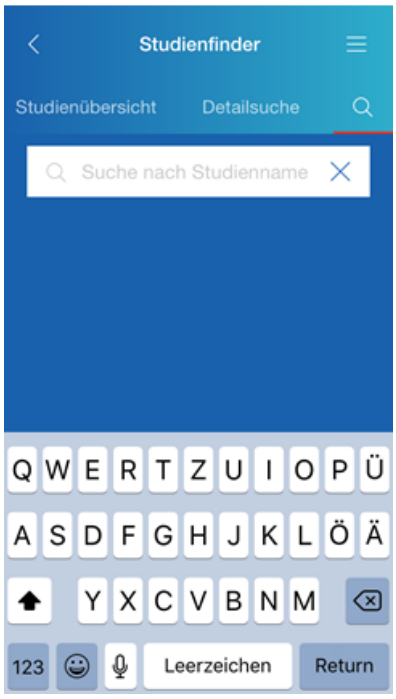
- Full title of the trial
- Short title / acronym
- Patient profile
- Diagnosis
- Tested product(s)
- Line of therapy
- Type of study (interventional / non-interventional)
- Phase
- Inclusion and exclusion criteria
- Participating sites
- Sponsor
- Link in clinicaltrials.gov

Study overview by themes:

Detailed search:



Keyword search:

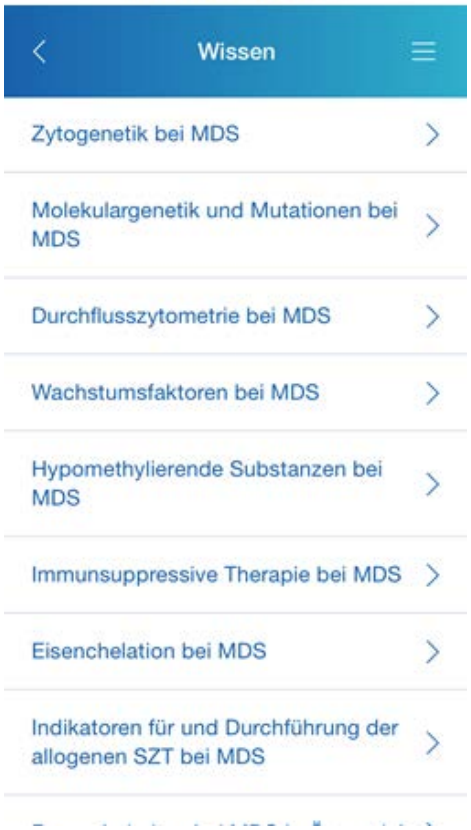


Knowledge:

In the „knowledge“ part of the app MDS experts from Germany, Austria and Switzerland have provided summaries on specific themes around MDS and associated scientific topics. The following themes are covered:

- Cytogenetics
- Molecular genetics and mutations
- Flow cytometry
- Growth factors
- Hypomethylating agents
- Immunosuppressive therapy
- Iron chelation
- Stem cell transplantation
- Particularities in Austria
- Particularities in Switzerland

Overview themes:



Example of topic presentation – iron chelation:

We would like to thank all contributors for their efforts and hard work on this projekt, namely Prof. Uwe Platzbecker and Dr. Katja Sockel for the development of the idea, the concept and their continuous medical and scientific advice; Prof. Aristoteles Giagounidis, Dr. Nicolas Bonadies, Prof. Arnold Ganser, Prof. Michael Heuser, Prof. Guido Kobbe, Prof. orbert Gattermann, Prof. Ulrich Germing, Prof. Katharina Götze, Prof. Detlef Haase, Prof. Wolf-Karsten Hofmann, Dr. Uta Oelschlägel, Prof. Jakob Passweg, Prof. Michael Pfeilstöcker for their kind contribution to the knowledge section and Michaela Morkel & team of interActive Systems in Berlin for the great technical collaboration and always prompt reactivity.

This project would not have been realised without unrestricted support from Novartis for which a big thank you goes to the company and the involved staff.

16th Annual D-A-CH MDS Meeting in Düsseldorf on the 13th Sept. 2017

On the 13th of September 2017 the 16th annual D-A-CH MDS Meeting took place in Düsseldorf hosted by Prof. Ulrich Germing. The purpose of this yearly reunion is to foster and further expand collaborative projects between the three countries and to discuss current and potential future projects initiated in this cross-border context.

As every year, about 50 collaborators gathered in Düsseldorf to exchange ideas. During the first part of the day, various common initiatives presented an overview regarding their current status, the current biobanking update was discussed and new initiatives evaluated.

Following this general part of the meeting, register projects were presented and various talks provided an overview on prognostic issues for MDS.

The second part of the meeting was filled with scientific contributions on genetics, diagnosis and molecular studies. Detlef Haase, Christina Ganster and Julie Schanz from Göttingen for instance presented results of recent cytogenetic studies and provided an overview on a new initiative on trisomy 8.

In the diagnostics part, Guntram Büsche from Hannover Medical School talked about erythropoietic islands in MDS with del(5q), Stefani Parmentier from Winnenden presented data on dysplasia in healthy subjects and Karl Sotlar (Salzburg) provided a focus on histopathology.

In the molecular session various topics were addressed, including an update on HbF in MDS by Michael Lübbert (Freiburg), a presentation of new data on MSC in MDS by Thomas Schröder from Düsseldorf and a talk on the role of the bone marrow niche and clonal evolution in MDS as a preclinical model for myeloid neoplasms, which was given by Daniel Nowak (Mannheim).

Prof. Germing is now looking forward to another productive year of the group ahead and to welcoming the D-A-CH members again in September 2018.

Author: Silke Gloaguen

The 16th MDS D-A-CH Meeting was supported by:

Celgene
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CHUGAI
NOVARTIS
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PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Upcoming events

Annual Meeting of the DGHO, OeGHO, SGMO and SGH
29 September - 3 October 2017 - Stuttgart, Germany

9th MDS Colloquium featuring the 5th Annual EMSCO Meeting
27-28 October 2017 - Berlin, Germany

59th ASH Annual Meeting
9-12 December 2017 - Atlanta, USA

7th MDS Forum
13-14 April 2018 - Dresden, Germany

International Conference on Myelodysplastic Syndromes (ESH)
26-28 April 2018 - Mandelieu, France