

# What can MDS patients expect in the future?

## Views from a patient who attended ASH 2020 Virtual

ASH is the American Society of Hematology, and this society has an annual meeting with the same name, which attracts more than 25,000 hematologists from around the world to what I would call a marketplace for hematology. The event usually involves 2 days with educational sessions for young hematologists and so-called satellite symposia arranged by large companies and patient organizations, such as MDS Foundation. This is followed by three days of the latest research results in hematology. Hematology is a very large group of diseases. A subgroup of this is blood cancers, and MDS is a small subgroup of that.

ASH 2020 was, due to the coronavirus pandemic, very different. It was turned into an all virtual event, which started a day earlier than normal and went on for almost two weeks. A complete report of all the information from AHS 2020 Virtual would quickly become a book - and I think, a very boring one. So I have choose to hear report the following:

- My biggest MDS related takeaway from ASH 2020 Virtual
- My biggest overall takeaway from ASH 2020 Virtual
- The MDS Education Session at this ASH 2020 Virtual
- My selected highlights related to MDS from the scientific sessions

**Caveat:** The viewpoints included here are those of a patient, and not a doctor. Keep that in mind, as you read it. I still hope you get away with more knowledge about the disease you or your relative have, how it is diagnosed, and what treatment is available now and in the future.

### Biggest MDS take away

For many years the only treatment option for high risk MDS patients has been azacitidine, which was approved by both FDA and EMA more than 10 years ago, and unfortunately have turned out to suddenly stop working in many patients. But we don't know why. Hence, I think, it was positive that at Saturday's educational session on MDS Dr. Bart Scoot said for higher risk MDS patients not eligible for hematopoietic stem cell transplant the first line treatment should be considered participation in an MDS clinical trial. But close to all MDS clinical trials of new treatments are not offered in my country.

### Biggest overall take away

Beta-thalassemia and sickle cell disease are two blood diseases, which one usually lives with from birth to death and which normally require regular blood transfusions. At the Sunday plenary session Dr. Haydar Frangoul presented results from two clinical trials THAL-111 and Climb SDC-121 in respectively beta-thalassemia patients and sickle cell disease patients, who after treatment with a new drug called CTX001 to a large degree became transfusion independent and remained that until the data cut-off date for the ASH meeting. The treatment with CTX001 uses a technology for modifying genes called CRISPR-CAS9, the inventors of which last year received a [nobel prize in medicine](#) (click link to read more about CRISPR-CAS9). CTX001 modifies a gene in CD34+ cells, which is roughly 20% of the murine (mouse?) hematopoietic stem cells. Such cells are also used in hematopoietic stem cell transplantation, in which they reduce the graft versus host disease. At the time of the ASH 2020 Virtual meeting the two trials had involved respectively 7 and 3 patients. But with exciting results!

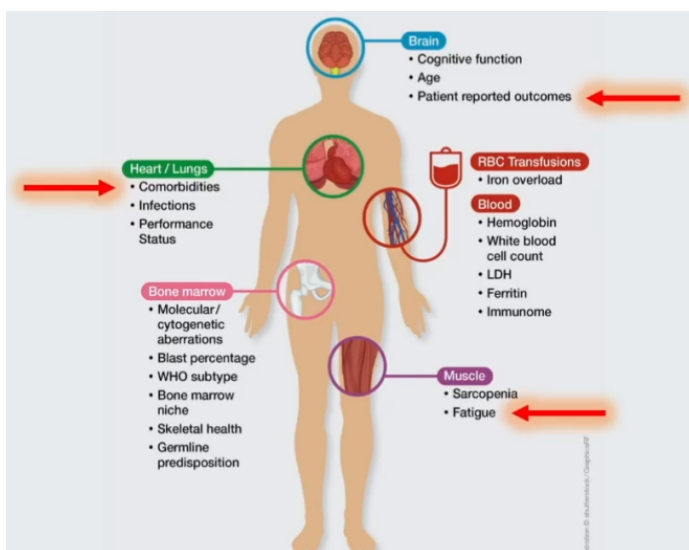
# MDS: What we have and what we want

The purpose of an educational session at ASH or EHA, the European equivalent of ASH, is to train junior doctors to become better educated in the diagnosis and treatment of MDS. A typical MDS education event has three parts: 1) on diagnosis, 2) on treatment of lower risk MDS, and 3) on treatment of higher risk MDS. At ASH 2020 Virtual the three presentations were pre-recorded. Dr. Uwe Platzbecker from MDS Dresden Klinikum in Germany, who is also one of the key people behind the drug Luspatercept, gave the first talk about diagnosis of MDS, which was titled “How a puzzle may become a map”. He was followed by Dr. Hetty Carraway from the Cleveland Clinic in the USA with a talk about treatment of lower risk MDS patients. Finally Dr. Bart L. Scott from Fred Hutchinson Cancer Center in Seattle, USA talked about treatment or the lack of treatment for higher risk MDS patients. As you read the following, keep in mind that this is a case of doctors talking to doctors about MDS.

## Patient stratification in MDS

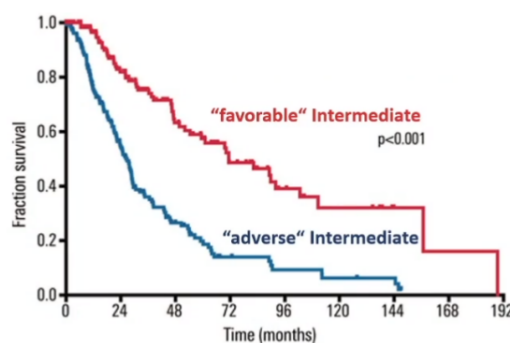
Dr. Platzbecker started his presentation by showing us a map of Germany with their 10 MDS centers. Germany has a population of 80 million people, so that is around 8 million people per MDS center. Denmark - my country - has a population of just 6 million. Until November of 2020 we had 6 MDS centers: Copenhagen, Herlev, Roskilde, Odense, Aarhus and Aalborg. This is around 1 million people per MDS center. That means our centers here in Denmark have a smaller chance of having patient's eligible for a particular clinical trial, and therefore most - if not all - MDS clinical trials bypass Denmark. In my opinion MDS patients would be more likely to be offered participation in a trial if we had just two MDS centers. Clinical trials are crucial to at least higher risk MDS patients, as you will see from Dr. Scott's presentation.

According to Dr. Platzbecker MDS is challenging because of disease diversity, but the majority of MDS patients fortunately have lower risk disease. Diagnosis is based on morphology and cytogenetics. According to [the latest WHO MDS classification](#) (click on link to free reference with definition of MDS subtypes) the adult subtypes of MDS are: MDS-SLD, MDS-RS, MDS-MLD, MDS-EB, MDS-U and MDS del(5q); plus in the latest classification one additional group for children: Refractory cytopenia of childhood (RCC). Although the latest classification is five years old, it is at the moment not used in all currently recruiting clinical trials. Unfortunately the worldwide adaptation of new WHO classifications by doctors, who are not MDS specialists is slow.

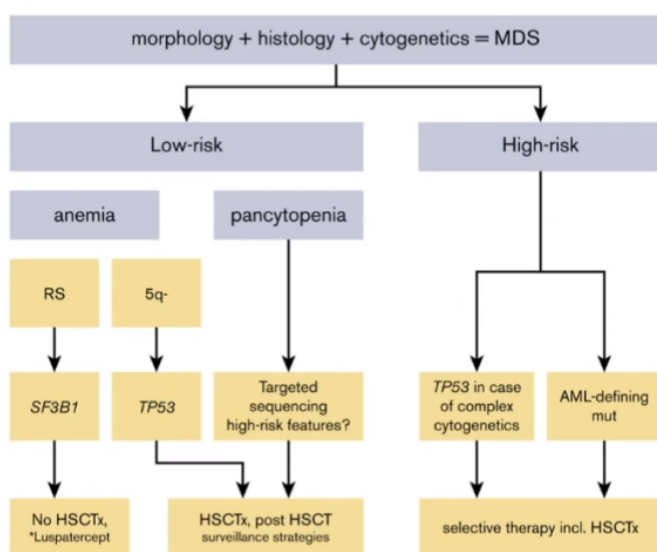


After an MDS patient's disease has been identified by subtype the decision about how to treat the disease requires taking into account the whole patient as seen in the illustration here (Source: ASH Educational Book 2020). In this decision process [Della Porta's MDS-specific comorbidity index](#) (click link for free article about the index) (MDS-CI) could be used. The MDS-CI clearly shows increased risk of death - especially with more than one comorbidity. Currently MDS patients are divided into 5 groups using the revised International Prognostic Scoring System (IPSS-R): Very low risk, low risk, intermediate risk, high risk

and very high risk. The [IPSS-R](#) was published in 2012 (click link to article about it). To quantify other information about the whole patient one could use [FACIT-Fatigue scores](#) and the [MDS specific frailty scale](#) that have recently been published. However, currently the [IPSS-R](#) is the standard for stratification of MDS patients. But data published two years ago clearly indicates that the [intermediate group](#) can be divided into favorable and adverse, as seen in figure here. Other studies by [Greenberg et.al](#) show that age at time of diagnosis also matters. So a revision of IPSS-R seems warranted.



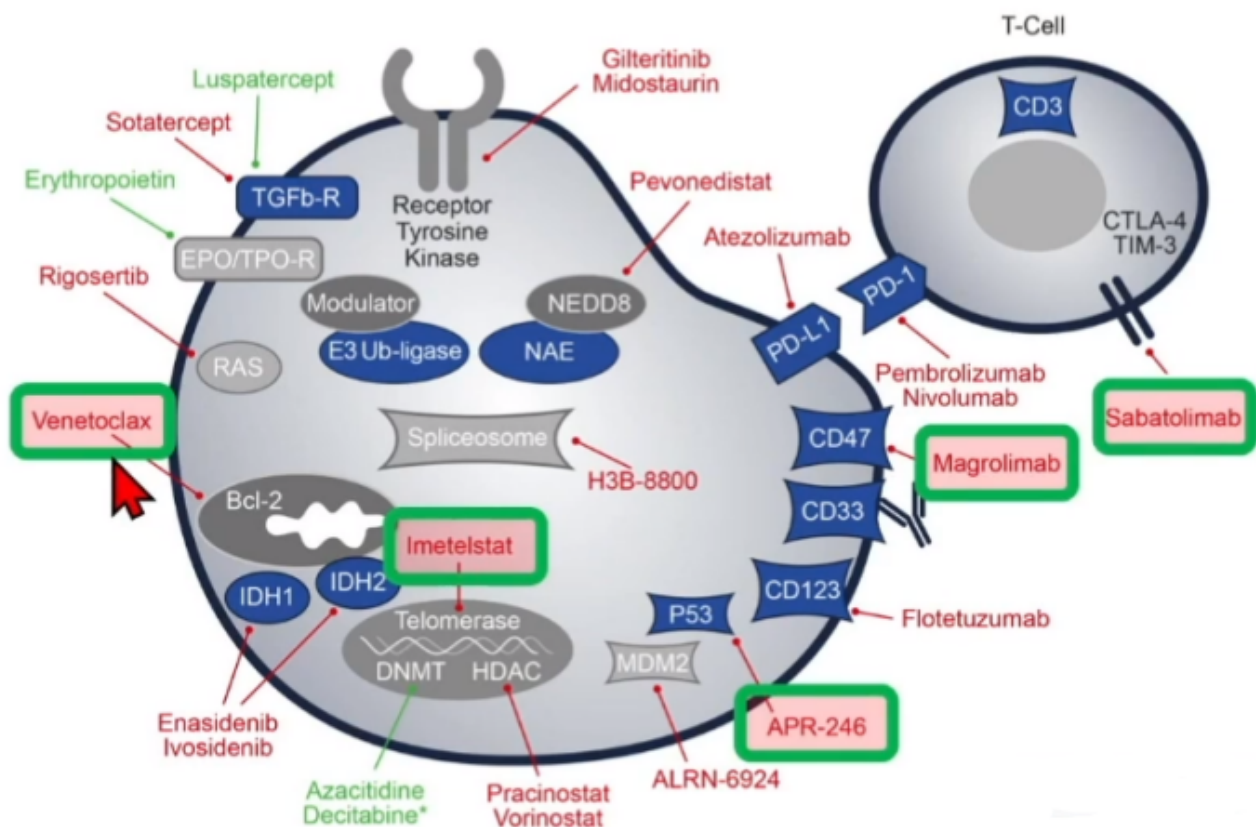
But what about mutations? Do they matter? Mutations are changes in specific genes in the MDS cells of a patient. A study has shown that an SF3B1 mutation is positive news for patients with MDS-RS. But what mutations matters most for [IPSS low and intermediate-1 MDS patients](#) - like me, appear to be mutations in TP53, EZH2, ETV6, RUNX1 or ASXL1, which have a negative influence on survival (luckily I have none of these), and it also seems to matter how [many mutations](#) a patient has. Finally the [amount](#) of a mutation, i.e. what percentage of the MDS cells carry the mutation, also matters. Hence, in my view a revision to the IPSS-R to incorporate information about age and at least mutations, but properly also comorbidities is urgently called for. A group of leading MDS experts are working on this, and maybe the result will be presented at the International Symposium MDS 2021 in Toronto.



Dr. Platzbecker has published the attempt shown here on including mutations in MDS treatment decision making in [Blood Advances 2020](#). The message seems clear, that a patient can have low risk disease according to IPSS or IPSS-R, but the absence or presence of mutations such as SF3B1 with ring sideroblast or TP53 should lead to early consideration of HSCT. (Note that the diagram is not complete. I have low risk MDS and anemia, but not ring sideroblasts (RS) or the 5q- mutation. No treatment for me!)

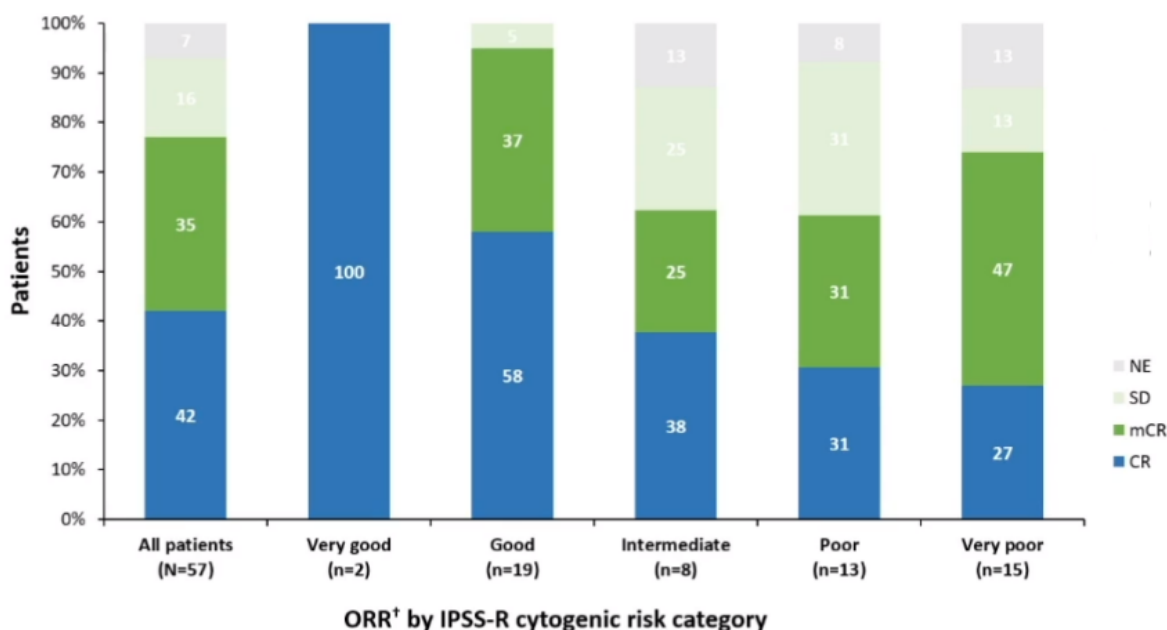
Since the first drug aimed at treating MDS was approved by the FDA in 2007 much has happened, and the treatment landscape is

currently changing if not every month, then at least every year with reports on many investigational drugs at both major hematological events EHA and ASH - the annual congresses of respective the European Hematology Association and the American Society of Hematology. The current diagram for approved drugs and drugs under investigation and where they attack the sick MDS cells is shown in the diagram below, where approved drugs are shown with a green border around the drug name and drugs under investigation in clinical trials are shown with a red border. The figure also indicates which genes the different drugs are aiming at.



A very encouraging result of combining venetoclax and azacitidine was presented at EHA in 2020 with a good response shown in all groups of IPSS-R MDS patients, complete response (CR, blue) ranging from 27% in very poor IPSS-R cytogenetic category to 100% in very good, and marrow complete remission (mCR, green) between 25% (intermediate) and 47% (very poor) - see figure Venetoclax plus azacitidine: efficacy and karyotype.

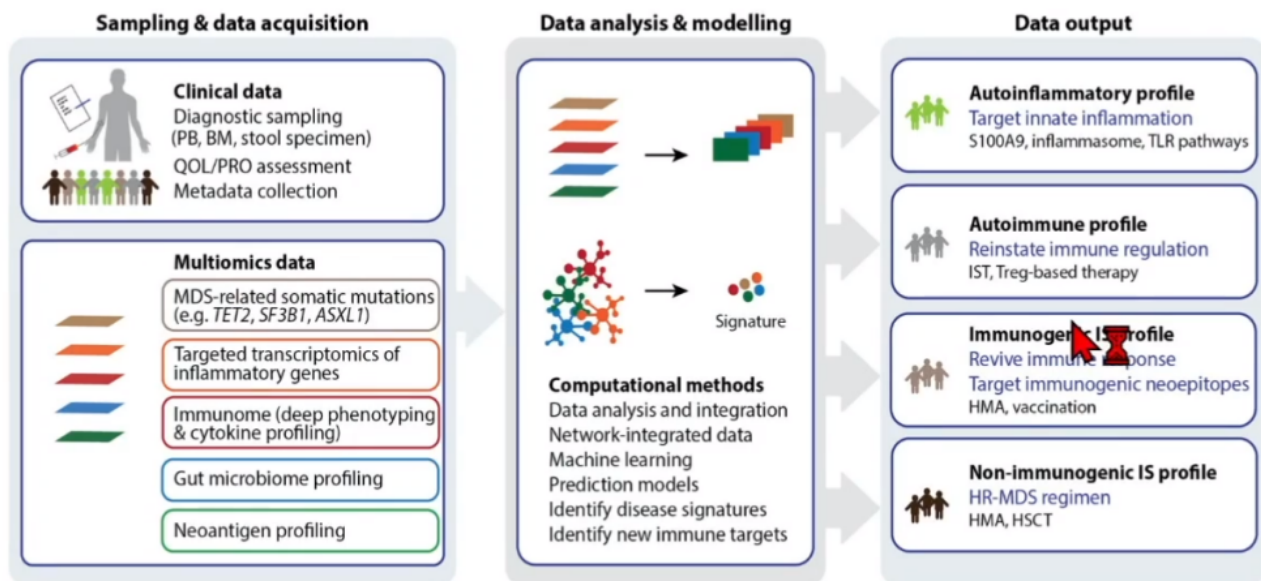
## Venetoclax + azacitidine: Efficacy and karyotype



Towards the end of the presentation, Dr. Platzbecker talked about the use of Artificial Intelligence (AI) in connection with stratification of MDS patients and selection of personalized treatment, and presented the following technical overview of the input data (clinical data about the patient and



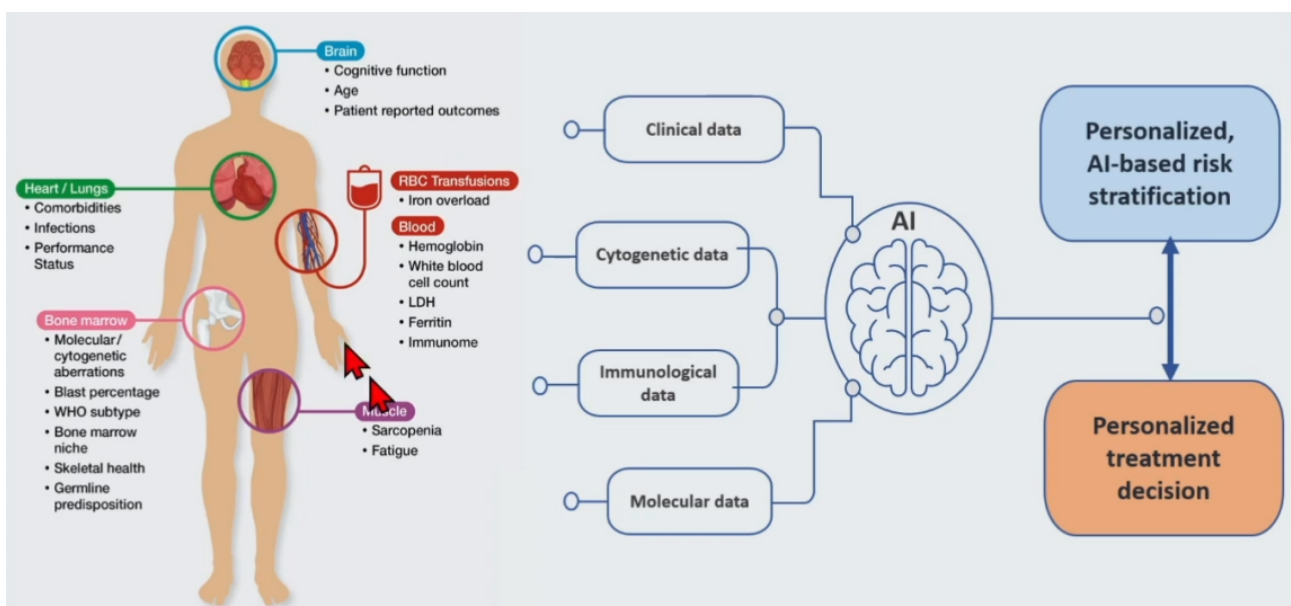
multiomics next generation sequencing data), the computation methods needed for modeling and data analysis, and the output of treatment suggestions. This figure gives a hint at MDS diagnosis in the future.



Dr. Platzbecker said in conclusion that,

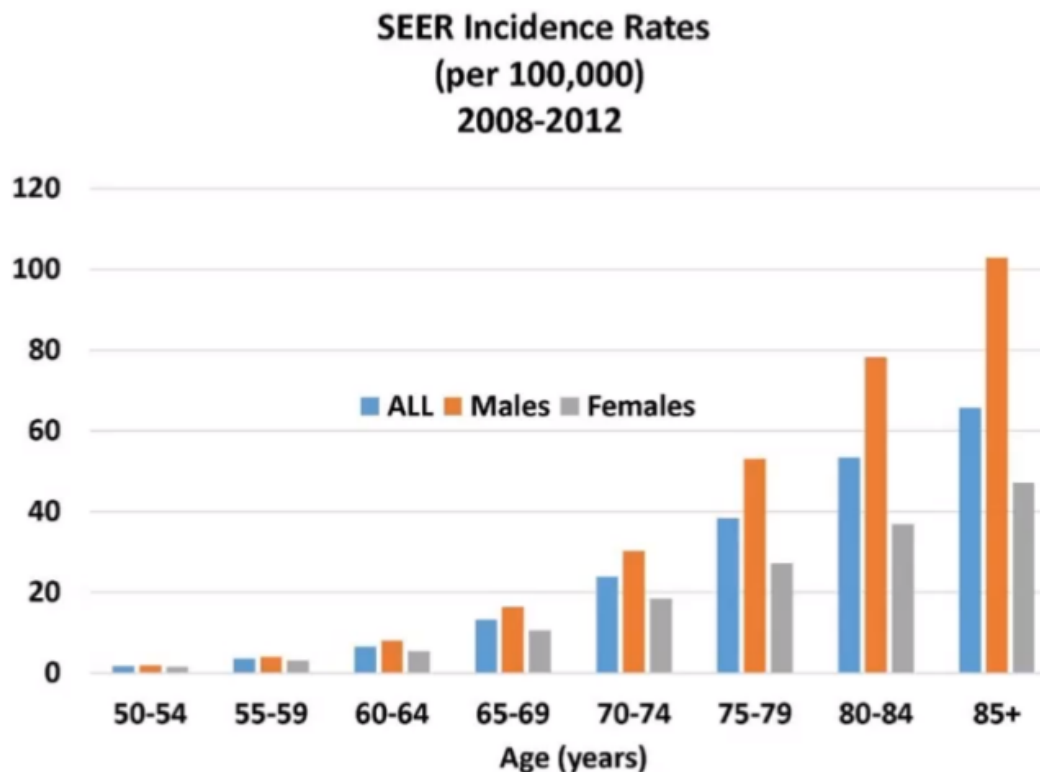
- Current MDS prognostic systems are only an approximation in personal risk stratification.
- Putting the information together will require the integration of complex molecular and immunological interactions with clinical variables.
- **An AI-based next generation classification and prognosis system for MDS patients with integration of comprehensive immunological, genomic and clinical information will push patient stratification to the next level.**

and presented the following schematic of such a system:



## Therapy for lower risk MDS

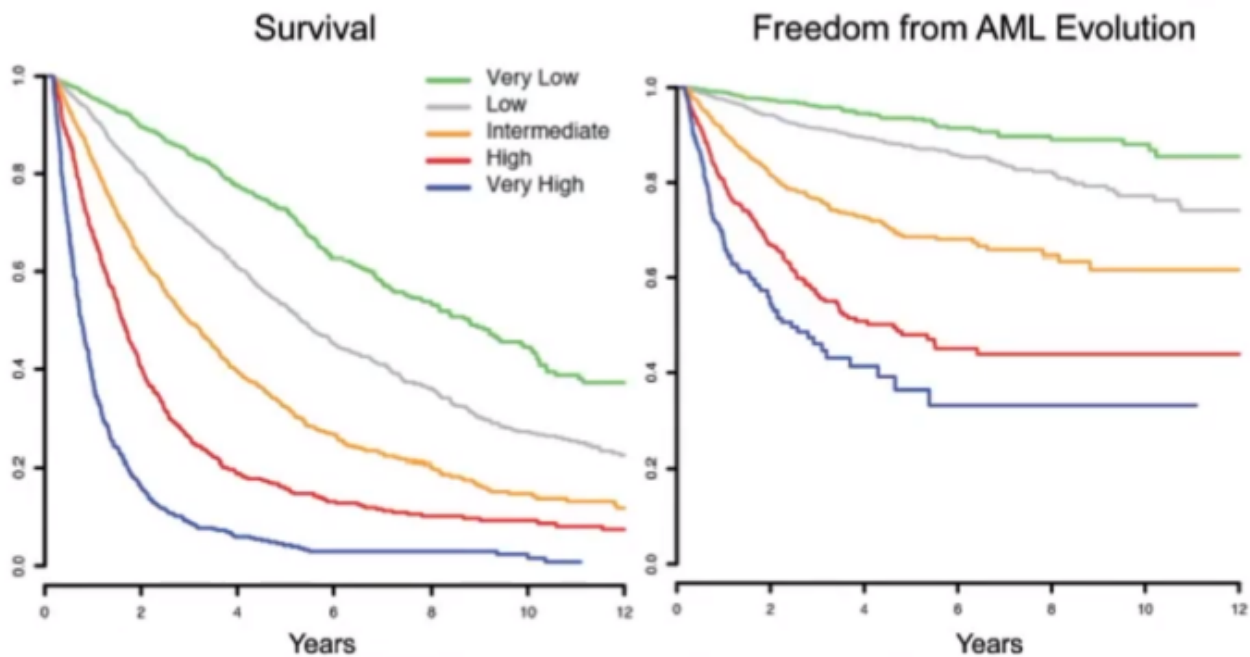
Dr. Hetty Carraway from the Cleveland Clinic talked about treatment of low risk MDS patients. She started by establishing that MDS is a disease of the elderly and as we live longer the disease becomes more prevalent in males and in females at least based on the SEER data shown below. Only one out of three MDS patients experiencing disease progresses to AML.



Lower risk MDS is characterised by dysplasia in one or more of the three main cell lines in the blood - red blood cells, white blood cells and platelets, a low marrow blast percentage, moderate cytopenias in one or more blood cell lines, and - according to Dr. Carraway - relatively good risk karyotype and molecular abnormalities. I tend to disagree with the latter, as several studies - some cited by Dr. Platzbecker - have shown that some molecular abnormalities (mutations) make a low risk patient look more like an intermediate (IPSS-R) or intermediate-2 (IPSS) patient.

Dr. Carraway also classifies lower risk MDS as patients with IPSS score less than or equal to 1 or IPSS-R scores less than or equal to 3.5, and states that the IPSS or IPSS-R score should be supplemented by next-generation sequencing for MDS specific mutations before a decision about treatment. Dr. Carraway further says that all MDS patients get supportive care, and should be considered for enrollment in clinical trials. This in my view means a huge need for cross-border access to clinical trials, as many MDS patients live in countries or areas of countries with no, very limited or very difficult (travel) access to clinical trials.

For survival and freedom from progression to AML, Dr. Carraway cited [Greenberg et.al \(2012\)](#) and [Hellström-Lindbeg et.al \(2020\)](#) for the data shown in the following figure:



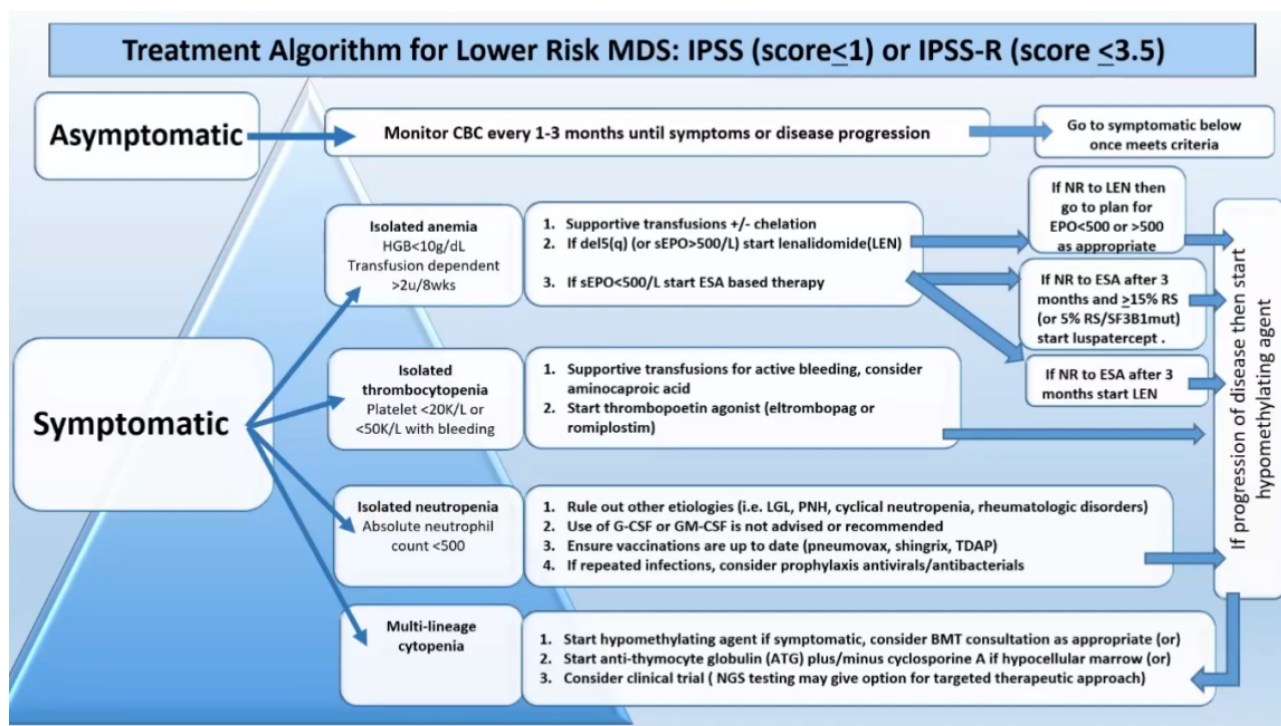
I very much appreciate the positive words in the titles of these two graphs: survival and freedom. Messages such as the ones contained in these graphs, when communicated to patients should emphasize the positive.

Dr. Carraway stated the goal of treatment of lower risk MDS is:

- Supportive care by decreasing symptoms impacting quality of life
  - Transfusion support (RBC, platelet, etc)
  - Chelation treatment to prevent iron overload leading to organ failure
- Improve hematopoiesis and function
  - Growth factor treatment (e.g. Aranesp with/without Neupogen)
  - Decrease infections by treating neutropenia
  - Decrease transfusion burden
- Lower risk of transformation to AML
- Cure

A cure is in my view currently eutopia, since the only potential cure is a HSCT, which has several unpleasant elements, such as death before engraftment, death from GVHD after engraftment, prolonged GVHD, and life long medication post HSCT. The medical literature shows survival historically below 50%, however recent data on HSCT of MDS patients at Rigshospitalet, Denmark suggest three year survival can be as high as +75% even in a population including men above 70 years and with comorbidities.

Dr. Carraway presented the following decision tree for choice of treatment for lower risk MDS patients:



After describing treatment with Erythropoiesis-stimulating agents (ESAs), Dr. Carraway discusses results from a study of Lenalidomide - a product very similar to thalidomide, known for causing severe birth defects in the late fifties and early sixties - to MDS patients with del(5q) with or without ring sideroblast. However, the response was clearly better in the group with ring sideroblast. Earlier this year a new drug Luspatercept was approved by both FDA and EMA for MDS patients with ring sideroblasts.

As far as I know a comparison of lenalidomide and luspatercept from a patients perspective, i.e. with focus on patient reported quality of life has not been performed yet, and could help deciding which of these two drugs to give MDS del(5q) patients with ring sideroblasts.

Other treatment options for some lower risk MDS patients are Anti-Thymocyte Globulin (ATG). Clinical trials are ongoing in using low dose azacitidine in lower risk MDS patients, who respond to ESAs. Some emerging therapies in lower risk MDS patients are listed in the table on the next page. Both Roxadustat and Imetelstat are in phase 3 trials for lower risk MDS patients without del(5q) and have reported good preliminary results.

Several other drug trials also report encouraging results, although they are aimed at MDS patients with higher risk disease, such as APR-246 for patients with a TP53 mutation or Ivosidenib for patients with an IDH2 mutation.

I wonder if the short duration of response of 18-24 months to ESAs, cited by Dr. Carraway, is due to incorrect classification of some IPSS-R intermediate patients, as referenced by Dr. Platzbecker? I live in Denmark and have met MDS patients with a much longer response to ESAs.

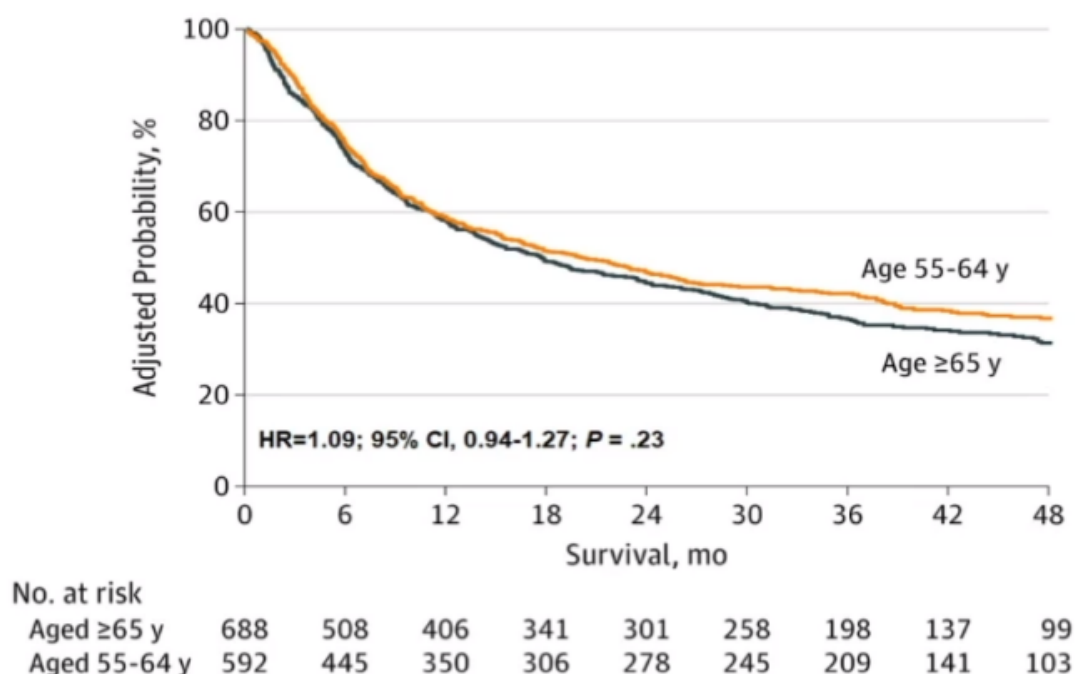


Agent	Mechanism of Action	Route	Patient Population	Single or Combination	Response Rate
Roxadustat	Hypoxia inducible factor (HIF) inhibitor	PO	LR-MDS (non-del 5q) with low Transfusion burden (TB), sEPO <400 U/L	Phase 3 Study ongoing Roxa versus Placebo	Dose finding Cohort results: N=24 HI-E=54%, TI=38% Higher dose TI=78%
Imetelstat	Telomerase inhibitor	IV	LR-MDS (non-del 5q) with high TB and ESA failure	Phase 2/3 IMERGE Study	HI-E=68%, TI for 8wks=42% CR=13%, CRi=10%; myelosupprsn
H3B-8800	Spliceosomal inhibitor	PO	LR-MDS with spliceosomal mutations	Phase 1	HI=14%, no CR/PR PD studies/dose dept splice modltn
APR-246	TP53 modifier	IV	Treatment naïve HR-MDS/AML with TP53m	Phase 2: Combined w/ HMT	RR+75-87%, CR=55% in P2 w/ HMT
Ivosidenib	IDH1 inhibitor	PO	R/R MDS with IDH1m (N=12)	Phase 1 single agent	CR=5/12 and RR=11/12
FT-2102	IDH1 inhibitor	PO	MDS and AML (N=36)	Phase 1 and 2 Single agent +/- HMT	CR/CRi=38% single (N=16) CR=27% combo w/ HMT
Enasidenib	IDH2 inhibitor	PO	R/R MDS with IDH2m (N=17)	Single or combined	1/17=CR and 10/17=RR

## Existing Agents, Novel Agents or Transplantation for High Risk MDS

Dr. Bart Scott from Fred Hutchinson Cancer Research Center started the Q&A by stating that first line treatment for higher risk MDS patients should be enrolling them in a clinical trial. Adding that the statement probably meant he would never again be invited to talk at an ASH Education Session, to which Dr. Platzbecker replied that he would still be welcome in Germany.

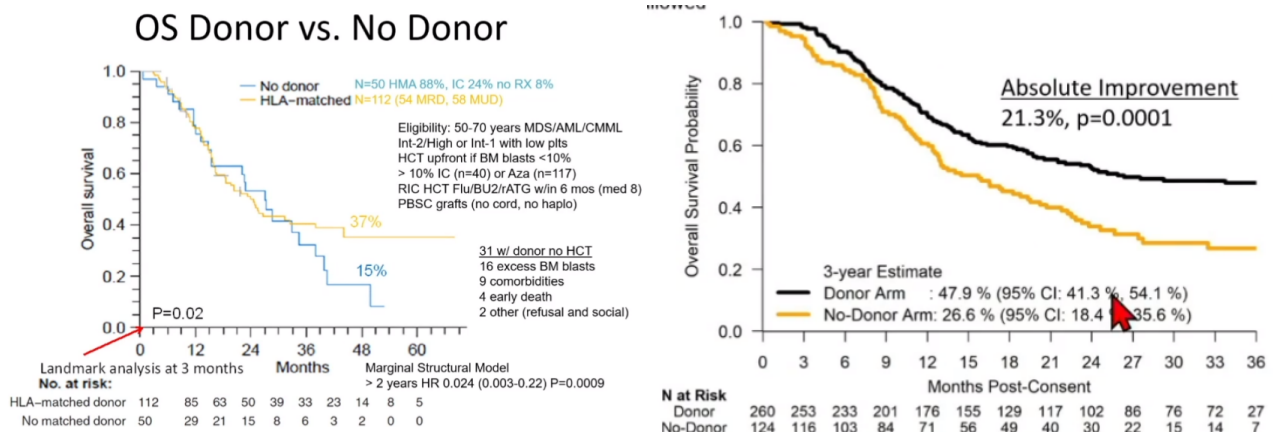
Dr. Scott started his presentation by showing a graph below comparing survival for patients transplanted at age above 65 with patients transplanted with an age between 55 and 64, that indicated no difference between the two age groups. So age alone should not decide if a patient is eligible for a transplant or not.



Dr. Atallah found that MDS patients undergoing a HSCT at age greater than 65 years had similar survival as patients between 55 years and 64 years. I can add that the experience at Rigshospitalet in Denmark after introducing a new conditioning regimen for MDS patients in 2017 was that age based on date of birth was not relevant for HSCT outcome and very preliminary data

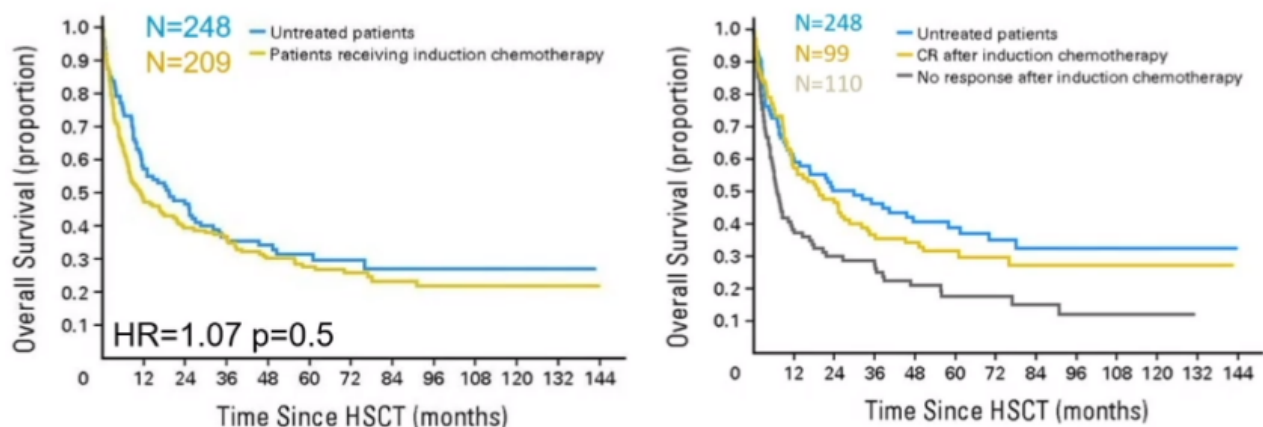
show one year survival above 90% and 3 year survival above 75% (information communicated by leading MDS and transplant doctors at local Danish meetings for MDS patients).

The second question raised by Dr. Scott was if HSCT improved survival. The left graph by [Robin et.al \(2015\)](#) shows that if the patient gets through the first 2-3 years after a HSCT, then there is an advantage. The right graph is a more recent analysis by [Nakamura et.al](#) presented at ASH 2020. The key question is whether a suitable donor can be found. Currently finding a donor is easier for Europeans and white Americans.

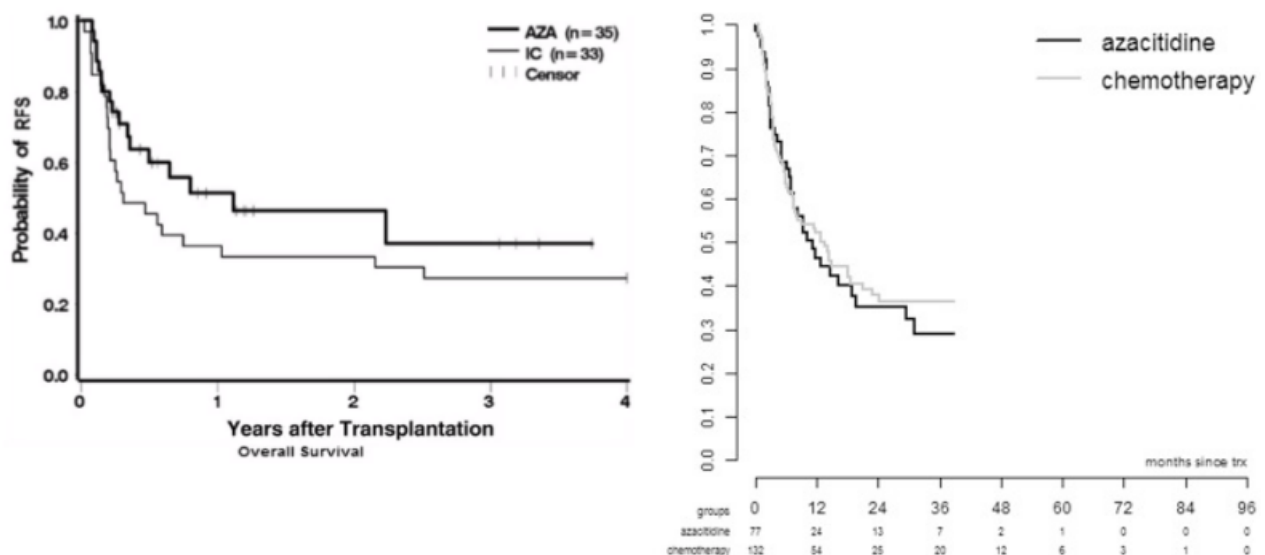


However, I think the first years after a transplant can be a rough ride, and hence more data especially from the Nordic transplant experience for MDS patients in the past 4-5 years is needed in order to properly advise MDS patients about the advantage of HSCT. Hopefully, we will soon see such data.

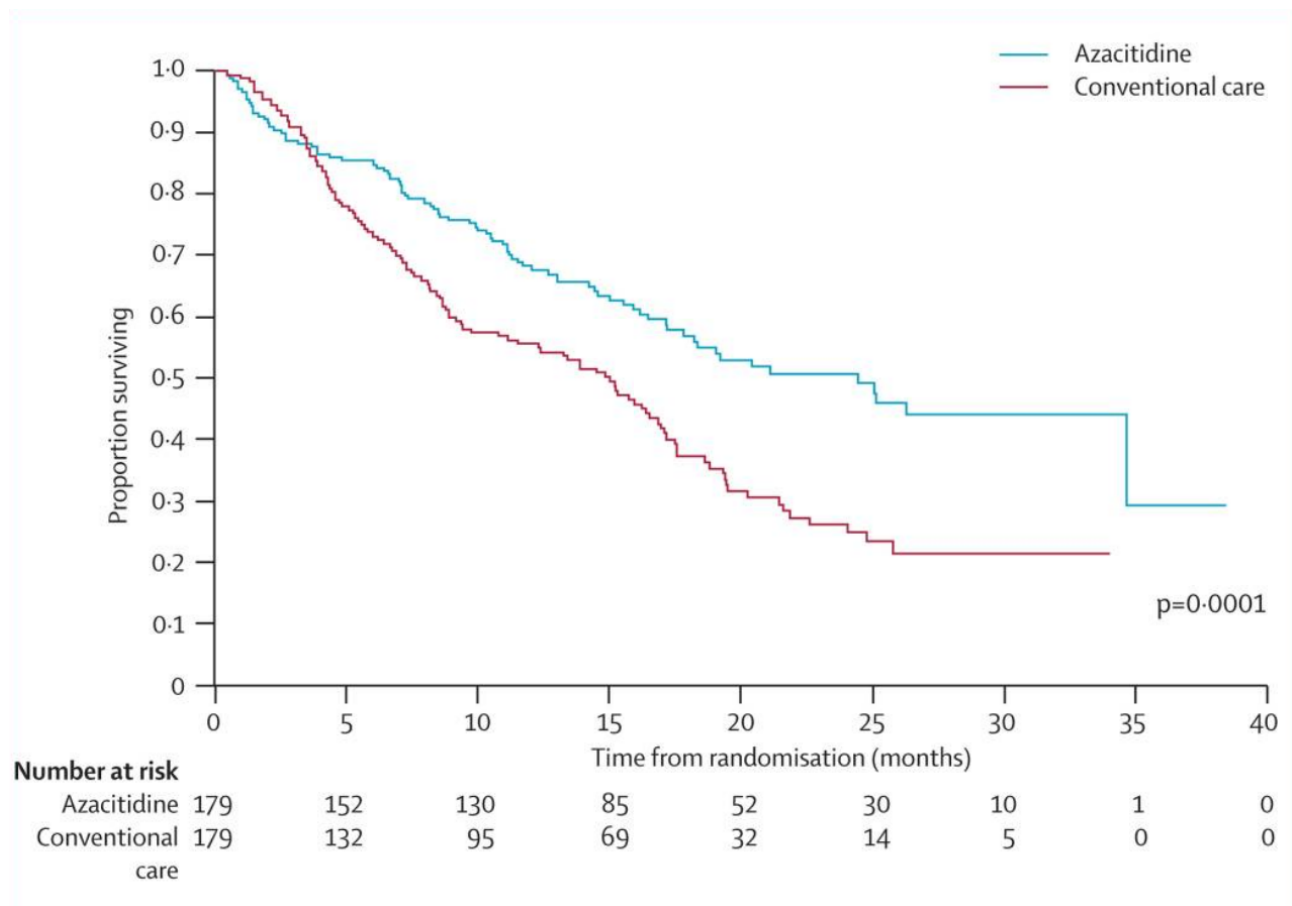
Dr. Scott continued by showing data on the influence of pre-treatment with either hypomethylating agents (HMAs) or induction chemotherapy (CT) before HSCT. Data from [Alessandrino et.al \(2013\)](#) indicate no survival advantage for patients pre-treated with induction chemotherapy compared to untreated patient's (left graph).



However, further analysis of the data indicates (right graph) that patients with a complete response (CR) to CT fared better after HSCT. As far as HMA versus IC based on [Gerds et.al \(2012\)](#) patients pre-treated with azacytidine have slightly better relapse free survival (RFS) than those pre-treated with induction chemotherapy, but later data by [Potter et.al \(2016\)](#) show no difference.



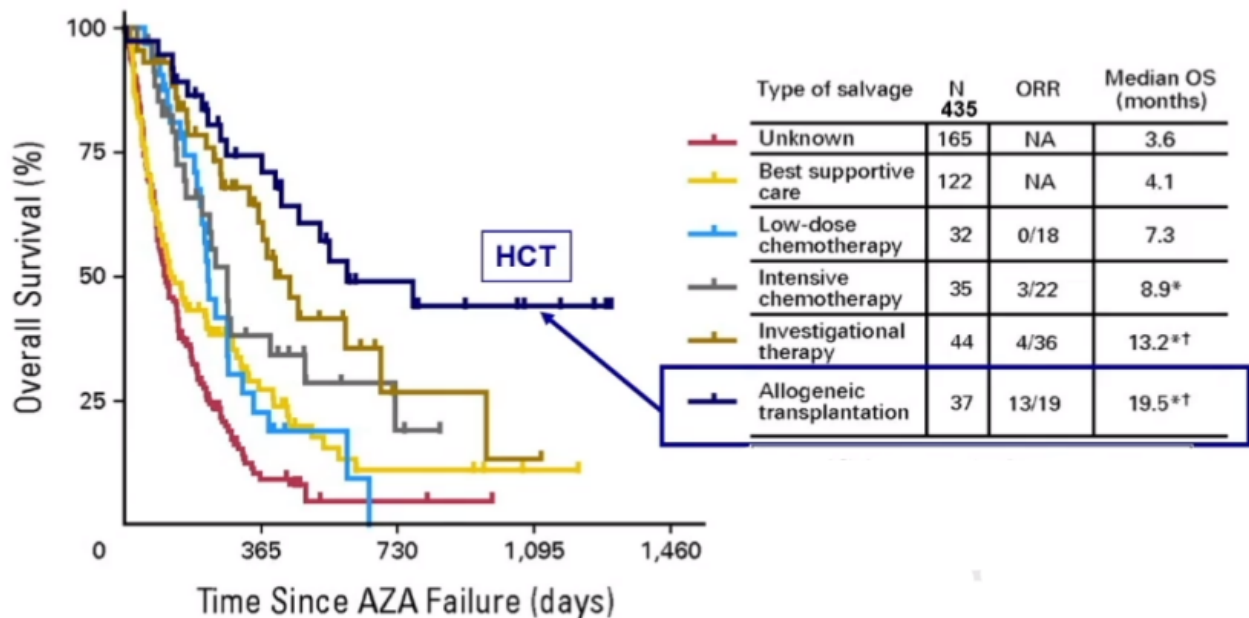
The phase 3 results from the azacytidine trial published by Fenaux et.a (2009) showed the impressive effect in higher risk MDS patients, as seen in the graph below. However, in the clinic doctors started to see the effect of AZA disappearing after a rather short period compared with results from the trial, with some patients losing effect within a year.



Dr. Scott compared other drugs approved for use in MDS by either FDA and / or EMA. Decitabine has been approved by the FDA for use in MDS, but failed to get approval in MDS by the EMA - see e.g. study by [Lübbert et.al \(2011\)](#), which showed no effect on OS and limited effect on progression free survival (PFS). An oral formulation of decitabine which include some cedazuridine have been shown to be equivalent to IV decitabine in the ASCERTAIN trial - see [Garcia-Manero et.al \(2020\)](#).

Results of a number of combination treatments with preliminary results presented at ASH 2020 were mentioned by Dr. Scott: Venetoclax and Azacytidine, Magrolimab and Azacytidine, APR-246 and Azacytidine, Pevonedistat and Azacytidine. More information about these are included in the section about encouraging new drugs.

The big question currently with higher risk MDS patients is what to do after HMA failure. There is as seen in the following graph no good options. Essentially, as you can see in the table there are two options for this group of patients: HSCT or clinical trial. Even with these the median OS is between 1 and 2 years.



Dr. Scott ended his presentation by talking about the STOP MDS Trial, which feature these simple inclusion and exclusion criteria:

#### Inclusion Criteria

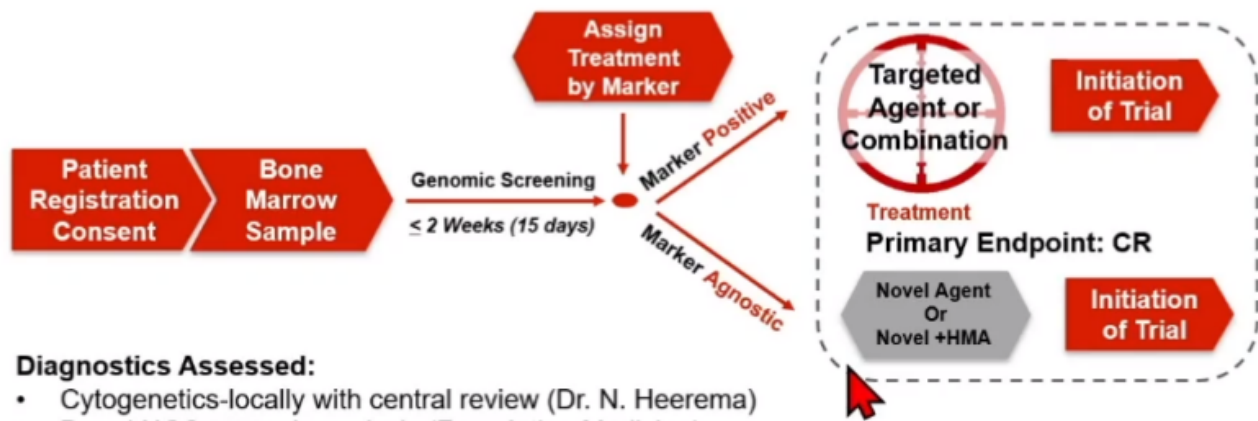
- Age 18 years or > at time of diagnosis
- Ability to give informed consent
- Group A: untreated intermediate, high, or very high risk MDS (IPSS-R)
- Group B: R/R MDS of any IPSS-R classification after a HMA treatment

#### Exclusion Criteria

- Group A: very low or low-risk MDS (IPSS-R)
- Group A: known sole 5q deletion karyotypes
- DIC with active bleeding or signs of thrombosis
- Features that impair compliance with study treatment and follow-up
- Pregnant or lactating females

and the following study design with cytogenetics evaluated locally at participating institutions, but reviewed centrally by [Dr. N. Heerema](#), Department of Pathology, Ohio State University and with a broad Next Generation Sequencing (NGS) genomic analysis by [Foundation Medicine](#):

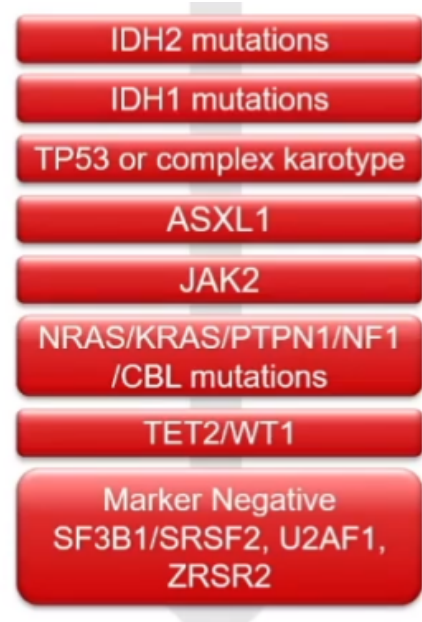




and with treatment assigned using this schema;

### Assignment based on:

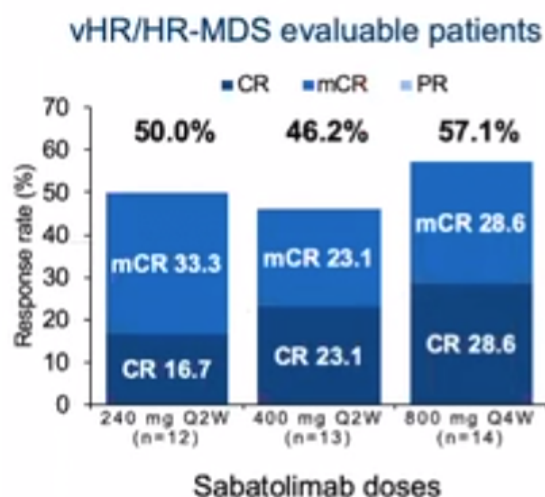
- **Best option for patient (curability) – top to bottom**
- Dominant clone at VAF > .3
- If no dominant clone at VAF > .3, go to .2
- If no dominant clone at VAF > 0.2, then top to bottom for assignment



An investigational new drug application (IND) was submitted on November 6th, 2020 with one master protocol and 3 sub-protocols, and the first patient in (FPI) was expected in February, 2021. Additional studies to be added during 2nd quarter 2021. VAF is an abbreviation for Variant Allele Frequency – a measure of how often a mutation appears in a gene. I certainly look forward to hearing more about this trial focused on high risk and very high risk MDS at future congresses.

## Encouraging drugs in clinical trial posters

[Sabatolimab](#) (click on link for Novartis video showing how this drug works. The website also has a comic strip with more detailed information), which formerly was known as [MBG453](#), is an experimental TIM-3 monoclonal antibody. TIM-3 is an abbreviation for T-cell immunoglobulin and mucin domain 3, a checkpoint receptor expressed by a wide variety of immune cells as well as leukemic stem cells. A monoclonal antibody is an antibody made by cloning a unique white blood cell. TIM-3 is a [promising target in cancer immunotherapy](#) (click link for publication about this).



Dr. Andrew H. Wei from Monash University in Australia presented a [poster](#) (click link to read abstract) about safety and efficacy of sabatolimab in different patient populations. In the figure the complete response (CR) and marrow complete response (mCR) in patients with either very high risk or high risk MDS according to the IPSS-R is shown for different drug doses, i.e. 240 mg every two weeks, 400 mg every two weeks or 800 mg every four weeks. The duration of the study was just less than a year, and with quite encouraging responses in these very difficult to treat patients. Based on the results of this phase 1 study a phase 2 study called [STIMULUS](#) (click link to clinicaltrials.gov) is ongoing with three parts MDS1 (phase 2, under evaluation), MDS2 (phase 3, recruiting), and AML1 (recruiting) using the 400 mg every two weeks and 800 mg every four week dosing regimens for sabatolimab. Read the abstract by Amer M Zeidan about STIMULUS [here](#).

Explore the other posters presented at ASH 2020 Virtual by clicking on the abstract numbers in table 1. The link opens the poster abstract. A search in the online program for just MDS posters give 314 hits, so the ones below are just the sample, which I found worth looking closer at. You can explore all 314 MDS related posters in the online program for ASH 2020 [here](#).

Normally at an in-person event you have only a couple of hours at the end of a busy conference day to explore many hundreds of posters. At this the 2020 ASH Virtual the physical poster usually with a huge amount of information was replaced with a pre-recorded presentation with at the most 10 slides, and you had access to this for several weeks. So I definitely see advantages to the virtual conference format.

Table 1 MDS related poster I looked at during ASH 2020 Virtual. The abstract # contains a link to the poster abstract, and copies of most poster presentations are on file. Drug names in this table contain links to [chemocare.com](#). Retro betyder retrospective studies.

MDS - Myelodysplastic Syndromes LR MDS - Low Risk MDS HR MDS - High Risk MDS AML - Acute Myeloid Leukemia OS - Overall Survival PFS - Progression Free Survival IPSS - International Prognostic Scoring System IPSS-R - IPSS Revised	GVHD - Graft Versus Host Disease MRD - Minimal Residual Disease HSCT - Hematopoietic Stem Cell Transplant WGS - Whole Genome Sequencing PROM - Patient Reported Outcomes Measures CR - Complete Remission mCR - Marrow Complete Remission HMA - Hypomethylating Agent NCCN - National Comprehensive Cancer Network
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Abstract #	Phase	Type	Disease	Remarks
<a href="#">1042</a>	1a/b	Dose escalation study of the <a href="#">MYC</a> repressor <a href="#">APTO-253</a>	Relapsed or refractory AML or HR MDS	No PROM, study ongoing and no OS or PFS data.
<a href="#">2203</a>	2	Double immune checkpoint inhibitor blockade with <a href="#">Nivolumab</a> and <a href="#">Ipilimumab</a> with or without <a href="#">Azacitidine</a>	HR MDS frontline or after HMA failure	CR 67% in frontline and 37% after HMA failure. Need a randomized trial.
<a href="#">2180</a>		WGS versus 12 gene panel recommended by NCCN	MDS	More learning needed to take advantage of WGS.
<a href="#">2179</a>	Retro	Identify genetically defined disease subtypes	LR MDS	Better treatment decisions in LR MDS
<a href="#">2438</a>	Retro	Change in IPSS-R between diagnosis and transplant	MDS	No influence on HSCT outcome.
<a href="#">2338</a>	1	Donor-derived t-cells specific for prevention of relapse and infection after HSCT	AML and HR MDS	7 of 20 patients enrolled, 2 died and one has chronic GVHD. Ongoing trial.
<a href="#">2197</a>	Retro	Iron saturation versus ferritin as measure of iron overload	LR MDS	Weak correlation between ferritin and iron saturation.
<a href="#">1905</a>	2	Genetic abnormalities and MRD negativity	HR MDS and AML	Genetic abnormalities have no impact on MRD negativity.
<a href="#">2427</a>	Retro	Survival of AML and MDS patients after HSCT	AML and HR MDS	Significant improvement since 2004.
<a href="#">2403</a>	Retro	Predict relapse from blood samples using PCR for patient specific biomarkers	MDS patients after HSCT	Power to predict established. Study of prediction starts in 2021.
<a href="#">2193</a>	Retro	Red blood cell transfusion burden in MDS-RS	MDS-RS	Demonstrate the need of MDS-RS for luspatercept.
<a href="#">2192</a>	1	Safe dose and effect of sabatolimab	AML and high risk MDS	Safe dose established for <a href="#">STIMULUS</a> trial.
<a href="#">2374</a>	Retro	Epstein-Barr-Virus (EBV) infection after T-cell depletion and HSCT	AML and high risk MDS	Nothing about how to cope with this.
<a href="#">2198</a>	3	<a href="#">Luspatercept</a> vs <a href="#">Epoetin Alfa</a> in treatment naive MDS	Very low, low or intermediate MDS after IPSS-R	Recruiting <a href="#">COMMANDS</a> trial..
<a href="#">1948</a>	2	PFS and OS with reduced dose <a href="#">Azacitidine</a> for 5 days SC each 4 week cycle	AML after MDS or HR MDS	This was an observational study only.
<a href="#">1286</a>	Retro	Improved prognosis with IPSS-R plus NGS on panel and regular hemoglobin measurements	MDS	Good idea, another panel could give better results.

# Gene Sequencing - what to do and when to do it?

Gene Sequencing is a technology that has the potential to give doctors more information about your MDS disease. However, this technology may also reveal information that many of us would rather be without, such as whether we carry mutations indicating that we have gene mutations associated with a genetic disease, i.e. an inherited disease that no one in the family have talked about. So if you say yes to having a gene sequencing performed on a blood or bone marrow sample, then the results could have implications beyond yourself. I agreed to a gene sequencing analysis, and the result showed my MDS cells were missing a Y chromosome. That was lucky, since that is a good mutation to have as an MDS patient. Contrary to e.g. at TP53 mutation.

With the recently identified diseases idiopathic cytopenia of undetermined significance (ICUS), clonal cytopenia of undetermined significance (CCUS) and clonal hematopoiesis of indeterminate potential (CHIP), all of which may progress to MDS and beyond, your treatment center properly is increasingly using next generation sequencing to discover how likely your ICUS, CCUS or CHIP is to progress to MDS and AML. At the Danish hospital [Rigshospitalet](#) next generation sequencing is already standard in connection with diagnosis of MDS.

This increased interest in next generation sequencing at the clinic also leads to an increased number of presentations about the use of next generation sequencing at hematological conferences, such as ASH. And last year's virtual ASH was no exception. However, from a patient perspective improvements in MDS disease treatment and understanding is properly more important, so let us first take a closer look at those parts of the ASH 2020 program.

## Improvements in disease diagnosis and treatment

The relevant parts of the programme are sessions called "Myelodysplastic Syndromes - Basic and Translational Studies" on understanding the disease, and two sessions called "Myelodysplastic Syndromes - Clinical Studies". The first of these subtitled "[Personalized Clinical-Decision Tools and treatment of lower risk MDS](#)" and the second subtitled "[Treatment of Higher Risk Myelodysplastic syndromes](#)" (links to programs of each session).

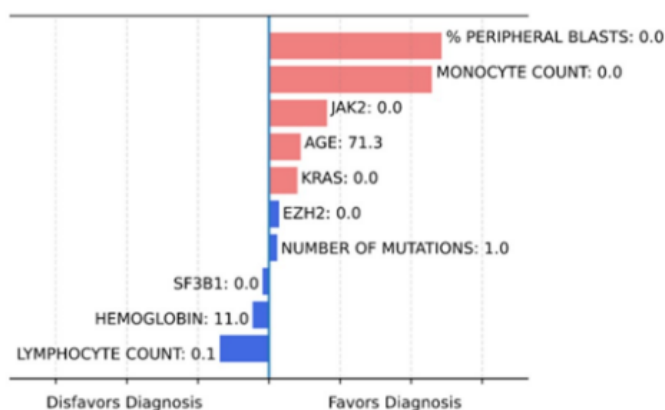
The presentations related to personalized clinical-decision tools and treatment of lower risk MDS are (links to authors twitter account and abstract):

- TREATMENT [Maria Diez-Campelo](#) "[Phase 3 Study of Lenalidomide \(LEN\) Vs Placebo in Non-Transfusion Dependent \(TD\) Low Risk Del\(5q\) MDS Patients - Interim Analysis of the European Sintra-REV Trial](#)". The interim analysis confirmed that low dose LEN (5 mg) in anemic non-transfusion dependent (non-TD) low risk MDS del(5q) patients prolongs the period of time to TD, improves Hemoglobin levels and induces clonal responses (70% complete cytogenetic response), but longer follow up required to asses the benefit of early treatment with [Lenalidomide](#).
- TREATMENT [Soo Park](#) "[DNA Methylation Analysis before and during Treatment with Azacitidine Plus Pevonedistat or Azacitidine Alone in Patients with MDS, CMML, and AML Previously Untreated with Hypomethylating Agents](#)". DNA methylation patterns early in the course of hypomethylating agent (HMA) treatment correlate with eventual response, with complete response associated with the greatest degree of demethylation. Ongoing work on DNA methylation signatures that may predict response to HMA.
- DIAGNOSIS [Constance Baer](#) "[The Potential of Molecular Genetic Analysis for Diagnostic and Prognostic Decision Making in Clonal Cytopenia of Undetermined Significance \(CCUS\) and MDS – a Study on 576 Patients](#)". The results suggest that molecular genetic markers should be recognized as presumptive evidence of MDS and allow the diagnoses to be



based on three things: morphology, cytogenetics and molecular genetics, and furthermore in two thirds of MDS patients and one third of CCUS patients mutations could be identified that allow personalized treatment based on molecular genetics.

- [Lin-Pierre Zhao](#) “[MDS/CMML with TET2 or IDH mutation Are Associated with Systemic Inflammatory and Autoimmune Diseases \(SIAD\) and T Cell Dysregulation](#)”. This study finds a correlation between mutation in the genes *TET2* and *IDH*, T lymphocyte imbalance and association with Systemic Inflammatory and Autoimmune Diseases (SIAD) in MDS and CMML, but the functional role of T lymphocytes is not clear and in my opinion needs further work to be usable in the clinic.
- DIAGNOSIS Johannes B Goll “[Targeted Sequencing of 7 Genes Can Help Reduce Pathologic Misclassification of MDS](#)”. In a setup with both local and central pathology review of MDS diagnosis it was attempted to amount of mutation (VAF - variable allele frequency) in the 7 genes *TP53*, *SF3B1*, *U2AF1*, *ASXL1*, *TET2*, *STAG2*, and *SRSF2* to re-classify diagnosis. It is claimed that complementing pathology review with targeted gene sequencing improves diagnosis. However, I don't believe the data are convincing enough to warrant implementation of this approach in the clinic.
- DIAGNOSIS [Nathan Radakovich](#) “[Personalized Clinical-Decision Tool to Improve the Diagnostic Accuracy of Myelodysplastic Syndromes](#)”. A machine learning model for diagnosis of ICUS, CCUS, MDS, MDS/MPN, MPN and CMML was developed using data from a US and Italian institution based in order of importance data on mutations/sample, peripheral blast percentage, absolute monocyte (AMC), *JAK2* status, Hemoglobin, basophil count, age, eosinophil count, absolute lymphocyte count (ALC), white blood count (WBC), *EZH2* status, absolute neutrophil count (ANC), *KRAS* and *SF3B1* status, platelets, and gender. For each patient the software provided a diagram showing which factors favored or disfavored a diagnosis. An example for a MDS patient is shown here with zero peripheral blast, zero monocyte count, no *JAK2* mutation, age in 70s, and no *KRAS* mutation favors a MDS diagnosis, while lymphocyte count of 0.1, hemoglobin of 11.0 and no *SF3B1* mutation disfavors a MDS diagnosis. The model achieved an accuracy of 93% on a German dataset not used in the modelling. Don't view this ML model as a replacement for your doctor, but rather as a potential assistant to the doctor, so he/she can make better informed decisions on diagnosis of hematological malignancies. Even if you are the first MDS patient he sees!



age in 70s, and no *KRAS* mutation favors a MDS diagnosis, while lymphocyte count of 0.1, hemoglobin of 11.0 and no *SF3B1* mutation disfavors a MDS diagnosis. The model achieved an accuracy of 93% on a German dataset not used in the modelling. Don't view this ML model as a replacement for your doctor, but rather as a potential assistant to the doctor, so he/she can make better informed decisions on diagnosis of hematological malignancies. Even if you are the first MDS patient he sees!

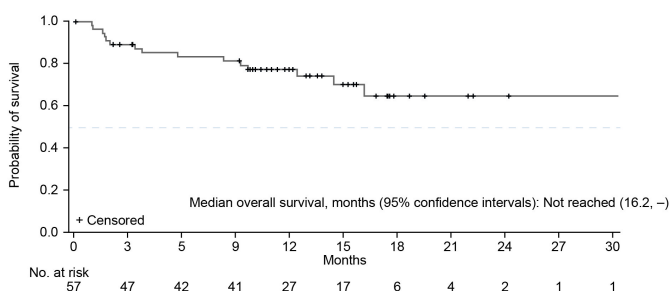
My two favorite presentations are Constance Baer's idea of identifying personalized treatment for MDS, but more work is needed before it can be implemented in the clinic, and Nathan Radakovich's machine learning model which attempts to include many types of data, as suggested by Dr. Platzbecker in his final remarks in the MDS Educational Session.

The presentations related to treatment of higher risk MDS are (links to authors twitter account and abstract):

- [Mikkael A. Sekeres](#) “[Efficacy and Safety of Pevonedistat Plus Azacitidine Vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes \(MDS\) from Study P-2001](#)”

([NCT02610777](#)). In phase 2 trial patients with higher-risk MDS, the combination treatment gave longer event free survival (EFS) and a higher rate of complete response than azacytidine alone, as well as a longer duration of response and later progression to AML. A phase 3 trial [NCT03268954](#) is ongoing.

- [Raphael Itzykson](#) “[Decitabine Versus Hydroxyurea for Advanced Proliferative CMML: Results of the Emsco Randomized Phase 3 Dakota Trial](#)”. No MDS patients in this phase 2 trial, but CMML patients treated with Decitabine did not show an overall (OS) or event-free survival (EFS) advantage over Hydroxyurea. However, one third of Hydroxyurea treated patients subsequently received treatment with hypomethylating agents and more Decitabine treated patients achieved a response and were bridged to Hematological Stem Cell Transplant (HSCT). Treatment of advanced proliferative CMML remains an unmet medical need.
- [Nathan Radakovich](#) “[Multicenter Validation of a Personalized Model to Predict Hypomethylating Agent Response in Myelodysplastic Syndromes \(MDS\)](#)”. An externally validated personalized prediction model that uses changes in blood counts during the initial 3 cycles of hypomethylating agent therapy and can predict response or resistance to treatment with high accuracy was developed. Important variables for prediction of response were improvements in hemoglobin from baseline between days 21-30 of therapy, improvement in platelets between days 51 and 60, changes in monocyte % between days 41 and 50, and changes in average size of red blood cells (MCV) and measurement of the range in the volume and size of your red blood cells (RDW) between days 31 and 60. This is good news for high risk MDS patients, who with this model after just 3 months can know if the treatment will work or not, i.e. a reduced treatment burden. However, we still don't know how long the response duration will be.
- [Jacqueline S. Garcia](#) “[Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study](#)”. The combination treatment demonstrated promising efficacy, including response durability, and an acceptable safety profile for patients with higher risk MDS, and also maintained physical functioning and showed clinically meaningful improvement in dyspnea and fatigue throughout the first 48 weeks. This combination treatment has shown good response in elderly (> 70 year) AML patients, and hopefully those results can be repeated in the high risk MDS patient population. The graph shows significant improvement in survival even after 2½ years of treatment compared with other options for these difficult to treat high risk MDS patients.



- [Andrew M. Brunner](#) “[Efficacy and Safety of Sabatolimab \(MBG453\) in Combination with Hypomethylating Agents \(HMAs\) in Patients with Acute Myeloid Leukemia \(AML\) and High-Risk Myelodysplastic Syndrome \(HR-MDS\): Updated Results from a Phase 1b Study](#)”. Sabatolimab in combination with HMA is well tolerated (in my view, that is doctors talk meaning that none died) in patients with HR-MDS and continues to show promising antileukemic activity and durability of response. We need to wait for results from ongoing and coming phase 2 and 3 trials to see if this drug will be generally available in the clinic.
- [Uwe Platzbecker](#) “[Treatment with Imetelstat Provides Durable Transfusion Independence \(TI\) in Heavily Transfused Non-Del\(5q\) Lower Risk MDS \(LR-MDS\) Relapsed/Refractory \(R/R\) to Erythropoiesis Stimulating Agents \(ESAs\)](#)”. This presentation properly should have

been in the other clinical session as it is focused on lower risk MDS patients with a large transfusion burden, e.g. patients who don't respond to ESAs, such as [Aranesp](#). Imetelstat treatment gave 42% of these patients transfusion independence (TI) after just 8 weeks with a median duration of 20 months, and TI in 29% of patients lasting more than a year. Furthermore 68% of patient's showed hematological improvements with a median duration of 21 months. The evaluation of Imetelstat continues in the ongoing [phase 3 IMerge trial](#). A major benefit of transfusion independence is avoidance of iron chelation treatment to remove excess iron from the body and avoid organ failures.

My two favorites here are Nathan Radakovich's model for predicting response to HMAs and Jacqueline S. Garcia's combination of venetoclax and azacytidine. I look forward to more HMA response prediction models being developed possibly also involving endurance of response, although that will properly be more difficult to achieve. As far as prolonged survival for higher risk MDS patients the combination of venetoclax and azacitidine appear to be the best option at this moment in time.

## Better understanding of MDS disease development

Presentations about new research results about understanding the MDS group of diseases are found in sessions titled "Myelodysplastic Syndromes - Basic and Translational Studies" - both oral and poster sessions, as well as sessions on epigenetics or new therapeutics. Most of these results do not immediately have implications on disease diagnosis and treatment.

- Thomas Laframboise "[Characterization of the Blood and Bone Marrow Microbiome of MDS Patients and Associations with Clinical Features](#)". As next generation sequencing becomes cheaper the researcher finds more things to sequence in order to better understand a particular disease. This study is a step in that direction which expands analysis to the environment the MDS cells live in within the bone marrow. Epigenetists have long suspected that environment to be important, and when they attempt to grow a patient's MDS cells in mice they also transfer a part of this environment to the mice, so the cells feel more at home and grow better. This can potentially lead to personalized medicine for a particular patient.
- Yang Mei "[Deficiency Reverses Leukemic Transformation in an MDS Mouse Model](#)". This is an example of a mice study to find new targets for drugs in specific MDS patient groups. The researchers demonstrated depletion of interleukin-6 (IL-6), which is a proinflammatory cytokine, could in mice revert an MDS leukemic transformation. This indicates IL-6 could be a drug target in high risk MDS. Once a target is identified a drug needs to be designed or discovered to target and bind to it. Then the effect has to be demonstrated in animal studies, and if these results are positive in a series of clinical trials. This is indeed very futuristic.
- David B. Beck "[Somatic Mutations in a Single Residue of UBA1 Cause Vexas, a Severe Adult-Onset Rheumatic Disease Associated with Myeloid Dysplasia](#)". A novel disease called VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), which connects seemingly unrelated adult-onset inflammatory and hematologic diseases was defined, and UBA1 mutations identified as a cause. This discovery could potentially have implications for classification, prognosis, and treatment of patients. It is relevant because many of the patients investigated developed MDS.
- Monika M Kutyna "[Therapy-Related Myeloid Neoplasm Has a Distinct Pro-Inflammatory Bone Marrow Microenvironment and Delayed DNA Damage Repair](#)". This work is concerned with therapy caused myeloid malignancies, such as secondary MDS or therapy related MDS, and understanding the damage induced by therapy to the bone

microenvironment and how this damage impacts malignant or normal haematopoiesis. The conclusion is that prior chemotherapy or radiation therapy leads to long-term irreversible damage to the bone marrow microenvironment.

- Hideki Makishima "[Clinical Impacts of Germline DDX41 Mutations on Myeloid Neoplasms](#)". This research used next generation sequencing to investigate inherited mutations in MDS with a focus on DDX41 somatic and germline mutations. Somatic mutations occur in a single cell, and cannot be inherited, but can be replicated in the individual. Germline mutations are found in all cells of an individual and can be passed on to children, i.e. inherited. The germline mutations in DDX41 showed conspicuous ethnic diversity from country to country and from continent to continent. *DDX41* has been identified as a causative gene for late-onset familial MDS.
- Timothy M Chlon "[The Inherited MDS Gene DDX41 Is Essential for Ribosomal RNA Processing through Regulation of Snorna Biogenesis](#)". This work is based on the fact that germline mutations in the gene DDX41 cause inherited susceptibility to Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML), but with an on average 10 year earlier disease onset. To investigate the role of the mutations in disease development a mice model was created and it was found that DDX41 is essential for the viability and function of hematopoietic stem and progenitor cells (HSPCs) and that some mutations make DDX41 inactive. The findings provide mechanistic insight into the protein translation defect observed in DDX41-deficient cells and hint at the basis of ineffective hematopoiesis in MDS patients with DDX41 mutations - common in inherited MDS.
- Rashmi Kanagal-Shamanna "[SF3B1-Mutant Myelodysplastic Syndrome with Ringed Sideroblasts \(MDS-RS\) at the Single-Cell Level](#)". The biological mechanisms of abnormal erythroid differentiation in MDS with ringed sideroblasts (MDS-RS) and *SF3B1* mutations are largely unknown, which delay the design of second-line treatments for patients who have failed hypomethylating agent (HMA) therapy. This work shows using advanced next generation sequencing technology how *SF3B1* mutations molecularly affect distinct stages of erythropoiesis and have implications for developing approaches that achieve lasting hematological remission in patients with MDS-RS.
- Tanzir Ahmed "[Mutant TRP53-R172H Has Gain-of-Function or Dominant-Negative Effects in Response to Different Hematopoietic Stressors in Mice](#)". This work is based on *TP53* mutations being quite common (~18%) in patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). However our understanding of the hematopoietic consequences of mutation TP53-R175H, one of the most common mutations in MDS, is incomplete including its response to chemotherapy. Studies in exposing mice to radiation or chemotherapy collectively indicate that mutation TRP53-R172H may induce a gain-of-function or a dominant-negative effect depending on which hematopoietic stressor it is exposed to. In my view these results could have implications for patients with secondary MDS and their prior treatment exposure.
- Carmelo Gurnari "[The Genomic Landscape of Myeloid Neoplasms Evolved from AA/PNH](#)". See discussion below.
- Andrew J Menssen "[Signaling Gene Mutations Are Characterized By Diverse Patterns of Expansion and Contraction during Progression from MDS to Secondary AML](#)". See discussion below.
- Giulia Biancon "[High-Resolution Binding Atlas of U2AF1 Mutants Uncovers New Complexity in Splicing Alterations and Kinetics in Myeloid Malignancies](#)". This work used advanced next generation sequencing to look for novel molecular mechanisms of pathogenic U2AF1 mutations in the context of myeloid malignancies, which may provide a



basis for development of effective U2AF1 directed therapeutics some time in the distant future.

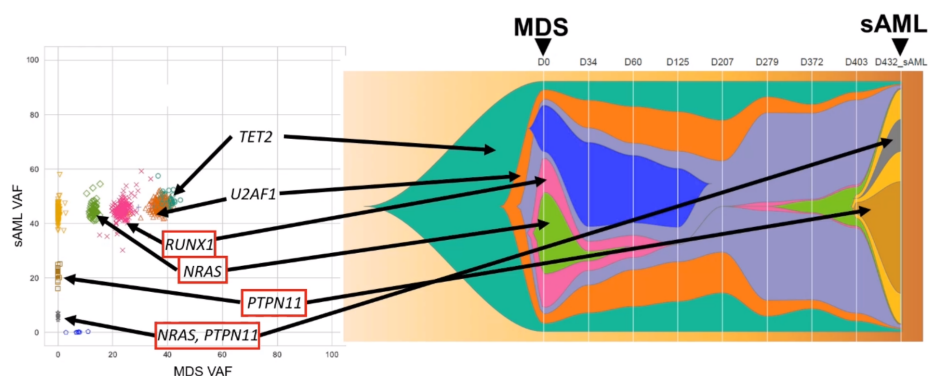
- Courtnee Clough “[Coordinated Mis-Splicing of Multiple Mitochondrial Iron Metabolism Genes Causes Ring Sideroblast Formation in SF3B1-Mutant MDS](#)”. See discussion below.

Some are very technical and require significant knowledge about biology and next generation sequencing to understand. So here I will limit the detailed coverage to a few studies, which I found particularly interesting.

## Genomic mutations in MDS progressing to sAML

This work presented by Dr. Andrew Menssen concerning the evolution of MDS to sAML, and was titled “[Signaling Gene Mutations Are Characterized By Diverse Patterns of Expansion and Contraction during Progression from MDS to Secondary AML](#)”. Dr. Menssen started with picturing the clonal evolution of MDS and its progression to AML. Today the difference between MDS and AML has been arbitrarily set at 20% blasts in the bone marrow. In older days, i.e. before the year 2000 it was equally arbitrarily set at 30% blast. I sincerely hope that the MDS community soon will use a better tool to distinguish between MDS and AML than blast percentage. A decade ago I knew an American MDS patient, whose blast percentage occasionally shot up in the thirties, and with sometimes more than 5% difference between two types of measurements. Read more about this issue in Dr. Michael Heuser’s guest editorial “High risk MDS and AML: One or two diseases?” in [MDS News volume 25 Issue 1](#) (link opens issue as PDF).

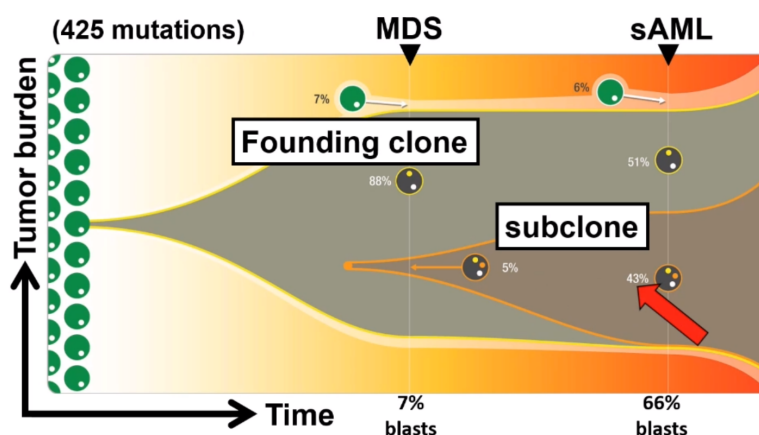
Dr. Menssen explained that mutations in signaling - e.g. receptor tyrosine kinases - and transcription factor genes are more common in secondary AML than MDS, which could indicate a role in disease progression. In order to better understand a possible role, paired samples from the same



patient from the MDS phase of the disease and from the sAML phase of the disease are needed to possibly define markers for MDS progression. Dr. Menssen therefore analyzed paired samples from 44 MDS patients who had progressed to sAML. The above graph of sAML VAF versus MDS VAF indicates that some mutations don’t appear until disease progression, such as PTPN11 or NRAS, that both have 0 MDS VAF.

VAF is an abbreviation for Variant Allele Frequency - read more about this in “[Current practices and guidelines for clinical next-generation sequencing oncology testing](#)”. Others such as RUNX1 and NRAS appear to present in MDS and then disappear only to come back as the disease progresses.

Further analysis showed that transcription factor gene mutations occur before signaling gene mutations,



and multiple signaling gene mutations rarely occurred in the same cell. This according to Dr. Menssen indicates that signaling gene mutations are redundant or detrimental to leukemia cells. Unfortunately the clonal evolution is not the same across the patient cohort analyzed in this study as illustrated in the above graph. Signaling gene mutations are mutations that lead to unrestricted cell growth, and transcription factor gene mutations work to turn certain genes on and off.

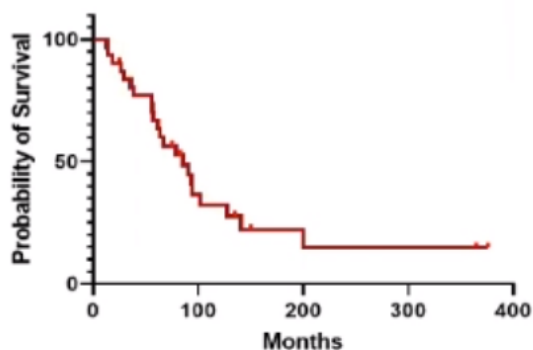
Dr. Menssen concluded that signaling gene mutations are present in nearly half of the MDS patients who progress to sAML, and suggest that signaling genes are a driver of MDS progression to sAML. These signaling gene mutations could be a possible biomarker for progression of MDS to sAML.

% of Patients	MDS	sAML	
20 (45%)	-	- *	Negative
5 (11%)	-	+	Acquired
6 (14%)	+	+	Expand
2 (5%)	+	- *	Collapse
4 (9%)	+	+	Hybrid
7 (16%)	+	+	Switch

## Genomic landscape in AA/PNH progression to MDS/AML

Dr. Carmelo Gurnari talked about secondary Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) coming from Aplastic Anemia (AA) or Paroxysmal Nocturnal Hemoglobinuria (PNH) under the title "[The Genomic Landscape of Myeloid Neoplasms Evolved from AA / PNH](#)".

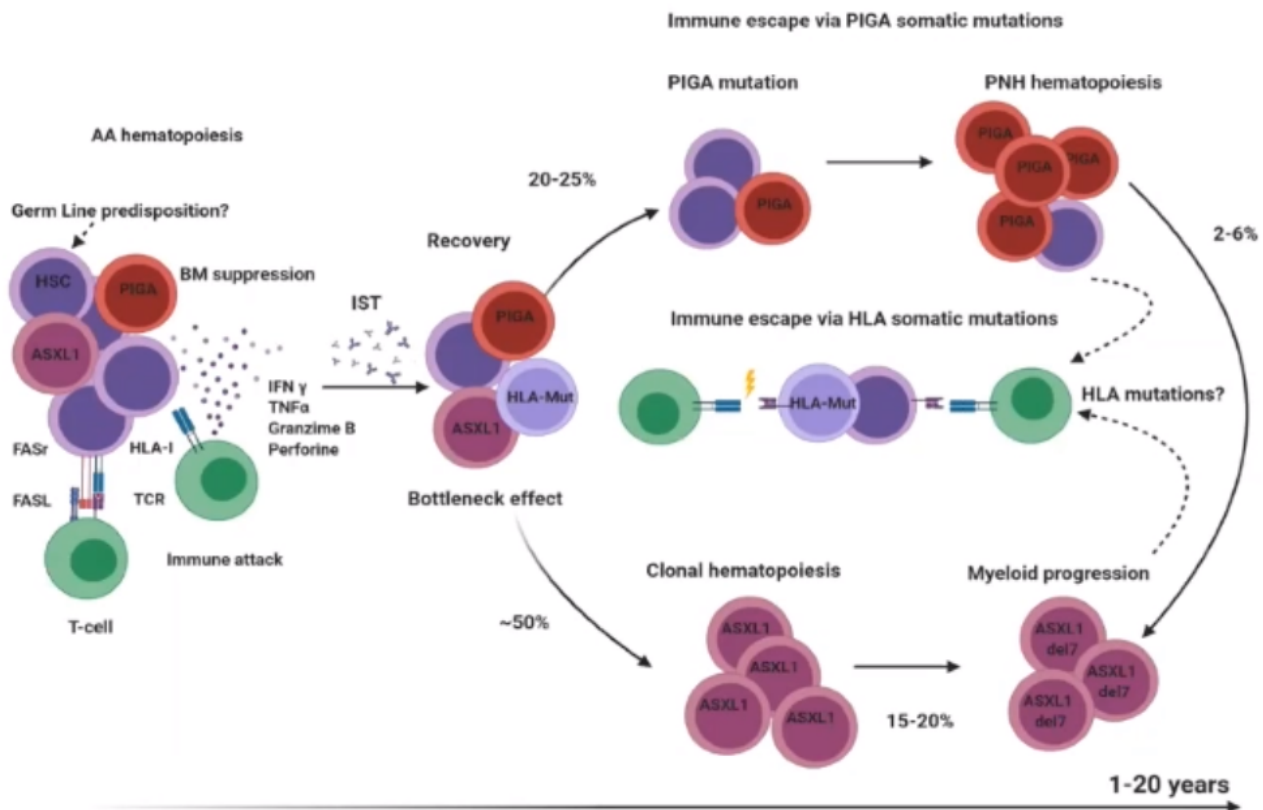
Dr. Cunrnari said that 15-20% of aplastic anemia patients over 10 years develop secondary MDS or AML with poor survival, as seen here. However, even after 25 years the probability of progression is only 25%.



Dr. Gurnari described a study comparing the genomic landscape of a large group (654) of patients with primary MDS or AML with a small group (22) of patients who had progressed to MDS or AML from AA, and found large differences in chromosome 7 mutations between primary MDS or AML and secondary MDS or AML after progression from AA.

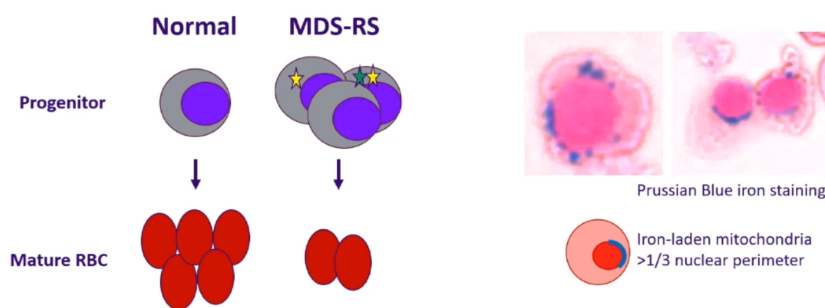
MDS evolution in inherited bone marrow failure syndromes suggests that germline alterations can be predisposing. This work studies the molecular landscape of MDS or AML arising from Aplastic Anemia by looking at germline alterations first in *NF1*, *CBLC*, *SBDS*, and *SAMD9L*, and then in *BRCA2*, *FANCI*, *FANCD2*. Followed by investigation of cytogenetic abnormalities. And finally somatic mutations were investigated with an average of more than four mutations in each patient. Mutations in *ASXL1* and *SETBP1* were more common in patients who had progressed, while mutations in *TET2* and *TP53* were less common than in de novo MDS (or AML).

Dr. Gurnari also analyzed the evolution of the mutations, which showed a significant increase in Clonal Hematopoiesis of Indeterminate Potential (CHIP) related mutations. However, more long term follow up data are needed to identify risk factors. The above picture shows evolution from AA to PNH and myeloid malignancies. Notice that this is a slow process. The time scale at the bottom covers 20 years.



## Cause of Ring Sideroblast Formation in SF3B1-mutant MDS

Dr. Courtnee Clough talked about ring sideroblast formation under the title “[Coordinated Mis-Splicing of Multiple Mitochondrial Iron Metabolism Genes Causes Ring Sideroblast Formation in SF3B1-Mutant MDS](#)”. The basic concepts are that splicing is the process by which introns, the noncoding regions of genes, are excised out of the primary messenger RNA transcript (mRNA), and alternative splicing is a process that enables mRNA to direct synthesis of different protein variants. Aberrant splicing generates novel transcripts not found in normal cells. For example heterozygous gain-of-function mutations in the spliceosome factor SF3B1 is present in ~25% of myelodysplastic syndrome (MDS) patients, but in ~80% of MDS patients with ring sideroblasts (MDS-RS) suggesting a causal connection between mutant SF3B1 and ring sideroblasts (RS), erythroid precursors with iron-laden mitochondria. That is in MDS-RS the SF3B1 mutation has a high mutation frequency compared to other hematologic cancers such as Chronic Myelomonocytic Leukemia, MDS (non-RS), sAML, Acute Myeloid Leukemia (AML) and Chronic Myelogenous Leukemia. The authors group created in an induced pluripotent stem cell (a type of pluripotent stem cell derived from adult somatic cells that have been genetically reprogrammed to an embryonic stem (ES) cell-like state through the forced expression of genes and factors important for maintaining the defining properties of ES cells) model that indicated the mutant SF3B1 is sufficient to drive RS formation. The findings confirm the hypothesis that mis-splicing of mitochondrial iron metabolism genes causes RS formation, and furthermore suggest that RS



formation in MDS is a multigenic event caused by coordinated but incomplete mis-splicing of several critical iron metabolism genes (which still have to be identified). This high presence of SF3B1 mutations in MDS-RS suggests a causal connection between SF3B1 mutation and ring

sideroblast (RS). The above figure shows to the left, that in MDS-RS fewer mature red blood cells are generated, and to the right a microscopic picture of a blood smear from an MDS-RS patient, that has been stained with Prussian Blue to the iron containing ring sideroblasts visible.

I wonder if the approach described here could be used to create iPSC models of other MDS disease subtypes. The [Program in Translational Hematology](#) established as a cooperation between University of Copenhagen and Rigshospitalet in Copenhagen, Denmark attempts to create personalized treatments for MDS and AML patients by growing their sick cells in mice models, and then screen for the effect of a large panel of drugs.

## ASH Sunday Plenary Session

The Sunday plenary session featured 6 presentation:

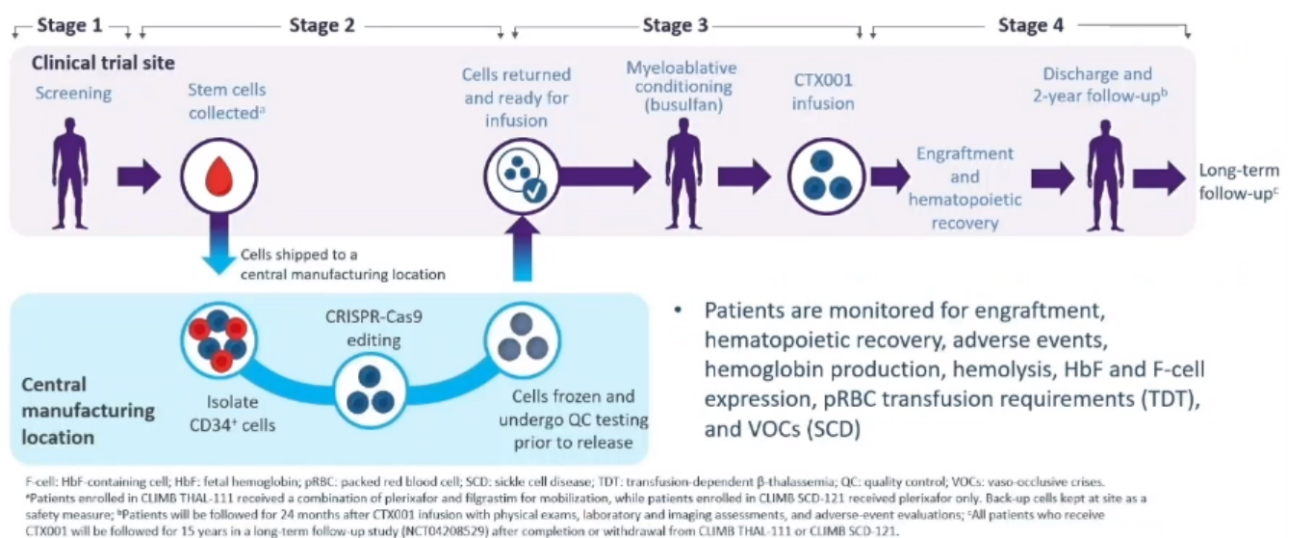
- [“Loss of LBK1/STK11 Facilitates Leukemic Progression of the Myeloproliferative Neoplasms”](#) was the abstract title, which in the presentation given by Dr. Christian Marinacci was re-titled to “STK11/LBK1 is a Tumor Suppressor in the Leukemic Progression of Myeloproliferative Neoplasms”, such polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF) or myelodysplastic syndromes (MDS) progressing to acute myeloid leukemia. This was a mice study with some comparison with data observed in actual patients.
- [“Effects of Tranexamic Acid Prophylaxis on Bleeding Outcomes in Hematologic Malignancy: The a-TREAT Trial”](#) was the abstract title, which in the presentation given by Dr. Terry B. Gernsheimer was re-titled to “The American Trial Using Tranexamic Acid in Thrombocytopenia (A-TREAT)” and by the introducer to “Prevention of Bleeding in Patients with Hematologic Malignancy and Thrombocytopenia”. The conclusion of the trial was that tranexamic acid did not reduce bleeding events.
- [“BCL10 Gain-of-Function Mutations Aberrantly Induce Canonical and Non-Canonical NF-κB Activation and Resistance to Ibrutinib in ABC-DLBCL”](#) was the abstract title, which was also the title of Dr. Min Xia’s presentation.
- [“Safety and Efficacy of CTX001 in Patients with Transfusion-Dependent β-Thalassemia and Sickle Cell Disease: Early Results from the Climb THAL-111 and Climb SCD-121 Studies of Autologous CRISPR-CAS9-Modified CD34+ Hematopoietic Stem and Progenitor Cells”](#) presented by Dr. Haydar Frangoul. *The data from the two trials was very preliminary and based on small numbers of patients. Nonetheless was the transfusion independence spectacular at least to me. CTX001 appears to be a game changer in these groups of patients, who so far have lived with blood transfusions. I cannot stop speculating if a similar potentially curable treatment approach could be possible for other hematologic malignancies which originates from errors in the stem cells.*
- [“Divergent Levels of CD112 and INKA1 Define a Subset of Human Hematopoietic Stem Cells That Resists Regenerative Stress to Preserve Stemness”](#) was the abstract title, and also the title of Dr. Kirsten B. Kaufmann’s presentation. Stemness refers to the ability of



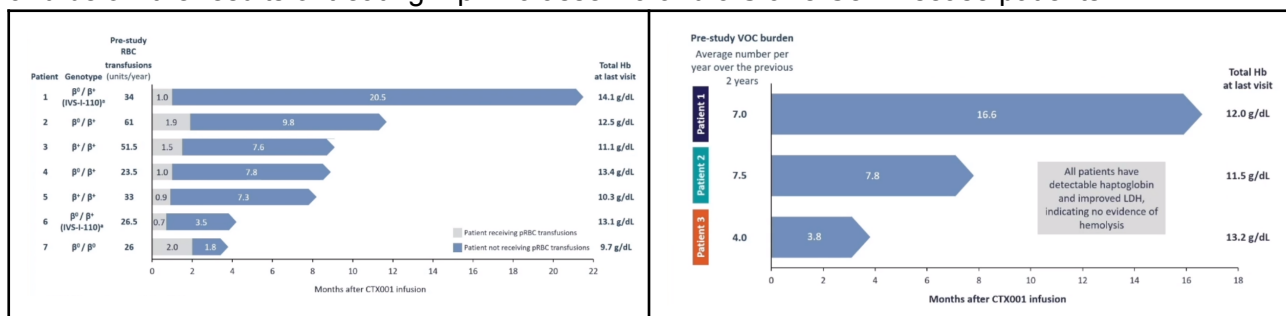
stem cells to replicate themselves and their potential to differentiate into other types of cells. So stemness is a combination of 'self-renewal' and 'differentiation' capabilities. This study was on mice.

- “[Poor Treatment Outcomes of Young \(<60 Years\) African American Patients Diagnosed with Acute Myeloid Leukemia \(Alliance\)](#)” was the abstract title and also the title of Dr. Bhavana Bhatnagar’s presentation. Not surprisingly the African American group had poorer outcomes than a comparable group of White Americans. In Denmark we see such differences between the well educated (with a university degree) and people without anything beyond elementary school in all interactions with the health care system.

I will not go into details about these plenary presentations except for the CTX001 study, which at the time of data cut-off had enrolled 7  $\beta$ -Thalassemia and 3 Sickle Cell Disease patients. The first of the following figures show the treatment procedure:



and below the results of treating 7  $\beta$ -Thalassemia and 3 Sickle Cell Disease patients:



Very nice to see the CRISPR-CAS9 technology finding its way to the clinic in the same year the inventors of the technology received the Nobel Prize in Medicine for their discovery of this technology. This is the ultimate personalized treatment in hematology.

## Conclusion

This ASH 2020 Virtual provided spectacular news about a CRISPR-CAS9 based treatment of  $\beta$ -Thalassemia and Sickle Cell Disease. I think that development will find its way to other hematological diseases, such as MDS, PNH and related diseases in the next 5 years.

Within MDS there is an ongoing trial to expand the use of Luspatercept to more low risk MDS patients, than the initial approval for the RS group. Also there are many promising drugs for higher



risk MDS in different stages of clinical trials. I will especially be following APR-246 and the TIM-3 inhibitors as well as the combination of venetoclax and azacitidine the next little while.

This year's virtual format of the ASH conference allowed you to go back to watch most presentations several times over a 3 week period. I found this much better than cramping all into some very busy 3 days.

*Niels Jensen*

MDS patient and member of LyLe  
Slangerup, 2021-03-29, Updated 2022-03-04.

Thanks to Ashley Donaway for carefully reading this document, and catching all the typos and other errors, I did not see. Properly because English is not my primary language.

PS: I did also attend both the MDS Foundation and AA & MDS International Foundation Satellite Symposia. If you need info about these please contact me at [niels.jensen@mds-and-you.info](mailto:niels.jensen@mds-and-you.info).

A virtual event has some advantages and some drawbacks. One of the advantages was that you can watch many pre-recorded presentations at any time, e.g. presentations from educational sessions or presentations from Fridays Satellite Symposia. You can even watch one event as it happens, and another parallel event later in the day or even next morning. Another advantage was that posters had been replaced with 4-5 minute pre-recorded presentations of each poster available throughout the duration of the meeting, and not just one day or one evening after a busy day running from session to session. Also in the poster area one could easily search for the ones of interest, e.g. those related to MDS.

A major drawback of the virtual event is the missing servings of good coffee and cookies in the exhibition area, which I enjoyed tremendously at the ASH Annual Meeting I attended years ago in San Diego. Luckily Philips Senseo makes excellent single cups of good coffee. However, I did not miss the huge amount of paper I returned from San Diego with.