MDS Newsletter

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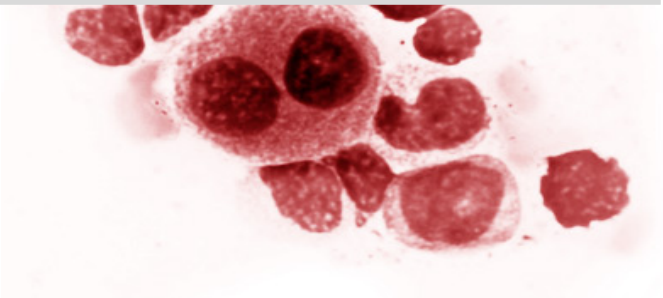

Motivation und Mission

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

9th MDS Colloquium featuring the 5th annual EMSCO meeting on the 27th and 28th October 2017 in Berlin

For the 9th time speakers and guests were gathering in Berlin on the 27th and 28th October 2017 to discuss the latest developments in MDS and AML. This year, for the first time, efforts were bundled and the colloquium featured the 5th annual EMSCO meeting. This way, synergies were created and the speakers and delegates took the opportunity on day 1 to talk about ongoing and future EMSCO projects. In an EMSCO think tank proposals for new common trials were presented and discussed and we hope to be able to launch these projects in the near future through the platform.
The first (plenary) session of the colloquium at the end of day 1 recapitulated how the notions of MDS and AML have

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Snapshot of participants at the 9th MDS Colloquium

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changed through history and captured the role of genomic advanced in the diagnosis of these diseases. Day 2 presented sections on pathophysiology, prognosis, current therapeutic standards as well as new targets in MDS and AML. After each session, panel discussions were held so that the auditorium had the opportunity to lively interact with the speakers on the presented topics.

Audience at the 9th MDS Colloquium

Overall about 130 participants from all over Europe attended the Colloquium and we are very much looking forward to the next edition.

A warm thank you for the successful outcome of the event goes to all organizers, speakers and participants.

The 9th MDS Colloquium featuring the 5th annual EMSCO meeting was supported by:

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Individual outcome prediction for myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia from MDS after allogeneic hematopoietic cell transplantation

Authors: ***Michael Heuser, Razif Gabdoulline, Felicitas Thol***

Many factors influence treatment outcome of MDS and AML patients after allogeneic hematopoietic cell transplantation (alloHCT), but currently there is no tool available to integrate all prognostic information into an individual risk score. We therefore developed an online tool for outcome prediction after alloHCT that integrates molecular, cytogenetic, patient- and transplantation-associated risk factors (https://webext.mh-hannover.de/mdsallo/).(1)

This prediction tool requires 13 parameters: age, patient sex, diagnosis (MDS vs secondary AML after MDS), IPSS-R cytogenetic risk (very good/good/intermediate vs poor/very poor), remission status before alloHCT (complete remission/untreated MDS vs treated but not in CR), donor sex, hematopoietic cell transplantation comorbidity index (HCT-CI) (0-2 vs 3 or higher), complex karyotype and/or TP53 mutation, and mutation status of NRAS, U2AF1, IDH1, IDH2 and EZH2 (Figure 1). Nine of these parameters are required to predict OS, seven to predict cumulative incidence of relapse (CIR) and five to predict non-relapse mortality (NRM). The individual outcome is also calculated if some of the parameters are missing. The model therefore requires a cytogenetic analysis and molecular information that can be obtained by Sanger sequencing, and does not necessarily require a panel analysis by next-generation sequencing.

Our model shows high reproducibility by internal cross validation, but will need further external validation before it can be applied in daily clinical practice. Our prediction tool shows the contribution of relapse and non-relapse mortality to the overall survival (OS) probability, compares the individual survival prediction with the survival of our transplantation cohort, and compares the predicted survival with the age- and sex-matched survival probability of the normal population (Figure 2). Thus, our prediction model provides additional and more detailed information for the individual patient than previous risk models.(2-4) Our comprehensive risk model may also be used to define patient cohorts for specific trial interventions in future prospective trials and to establish comparability of patient populations between trials.

We looked specifically at the contribution of molecular risk factors to our OS model (NRAS, TP53 mutation/complex karyotype, U2AF1, IDH2). Adding these molecular markers to a model without molecular information for example reclassified 41% of the patients in the intermediate risk group to a more favorable risk group and 5% of the intermediate risk patients to a higher risk group. This reclassification resulted in a significant stratification of survival probabilities as shown in Figure 3 (the black line indicates the survival of the intermediate risk group according to the risk model without molecular information). The addition of molecular risk factors to the model resulted in a 16-fold and 148-fold reduced probability that prognostic information is lost for prediction of OS and CIR, respectively.

Complex karyotype was a strong predictor for OS besides IPSS-R cytogenetic risk and therefore was included in addition to IPSS-R cytogenetics. Previous studies have already shown the strong prognostic impact of complex cytogenetics especially in the transplantation setting.(5, 6) While Bejar et al. found a stronger effect of mutated TP53 compared to complex cytogenetics,(6) in our analysis these two parameters alone or in combination had a similarly poor prognostic effect and therefore were combined into one risk factor. Complex karyotype/TP53 and mutated NRAS were also predictive for CIR, suggesting that these aberrations are drivers of relapse and may confer treatment resistance.

The poor prognostic impact of mutated TP53 is consistent among the two previously published studies on molecular

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predictors of outcome after alloHCT and our analysis.(6, 7) The negative prognostic impact of TP53 and RAS mutations found in our study was also described in a recent study of 1514 patients with MDS receiving alloHCT and supports the validity of our results.(8) However, survival differences among TET2 and DNMT3A mutated and wildtype patients were only seen in the study by Bejar et al. but not our or other studies.(1, 6-8) The prognostic effect of ASXL1 and RUNX1 mutations in the study by Della Porta et al. and the effect of U2AF1 and IDH2 in our study was not replicated by other studies. These discrepancies may be due to different patient populations: MDS/sAML patients were not included in the study by Bejar et al., constituted 32% of all patients in the study by Della Porta et al. and 53% in our study. The discrepancies may be also due to competing risk factors that were included in our model but not in the other models like comorbidities and transplantation associated risk factors.

Patients without any of our nine risk factors for OS have a base hazard of 27%, i.e. 27% of the mortality risk is not captured by any of our markers yet. When more patients become available, rare mutations will be found in large enough patient subgroups and may become prognostically relevant. In addition, immunologic parameters may be defined that explain some of this risk.(9) Our model can then be easily adapted to larger patient numbers.

In summary, we propose a comprehensive risk model integrating patient- and transplantation-related, cytogenetic and molecular information into one prediction tool, which provides personalized predictions of outcome. After external validation our tool will help to inform physician and patient about the specific risk associated with alloHCT and may be helpful to stratify patients to address specific questions in prospective clinical trials.

Figure 1: Screenshot of our MDSallo online calculator that can be used to determine the individual prognosis of MDS and sAML patients for OS, CIR and NRM after alloHCT (https://webext.mh-hannover.de/mdsallo/).(1):

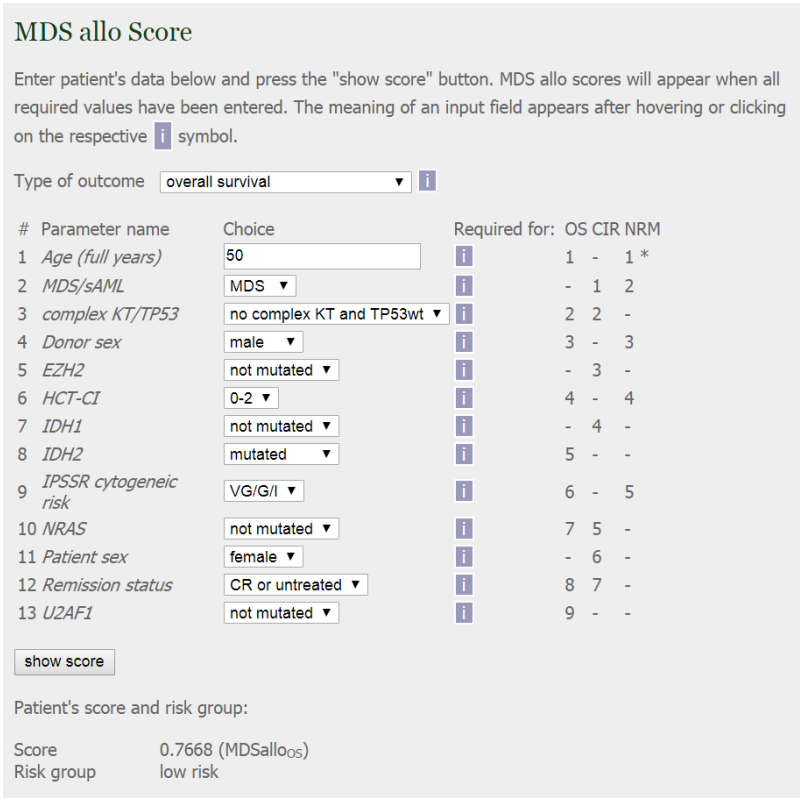
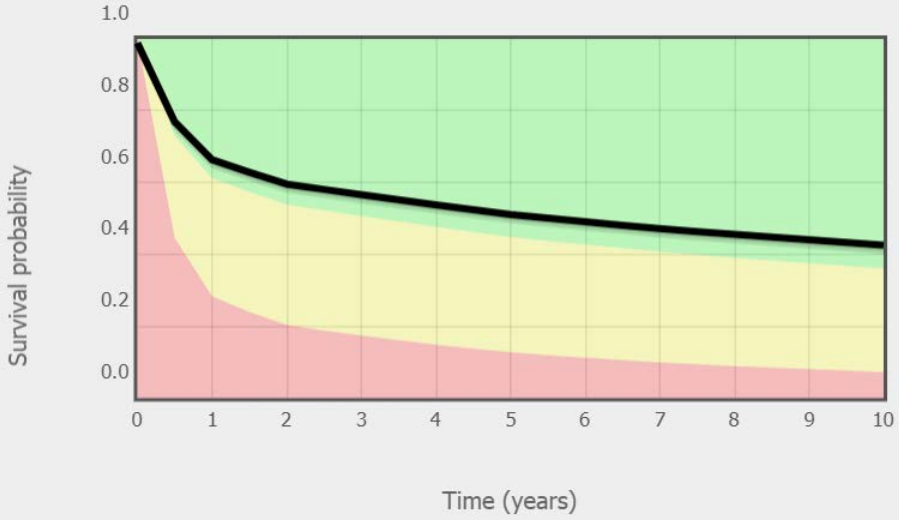


Figure 2: Screenshot of the survival probability of the patient shown in figure 1:

Patient's survival probability / cumulative incidences during 10 years. The coloured areas representing the survival probabilities of low (green), intermediate (yellow) and high (red) risk patients in our training cohort are provided for comparison of the personalized prediction (black line).

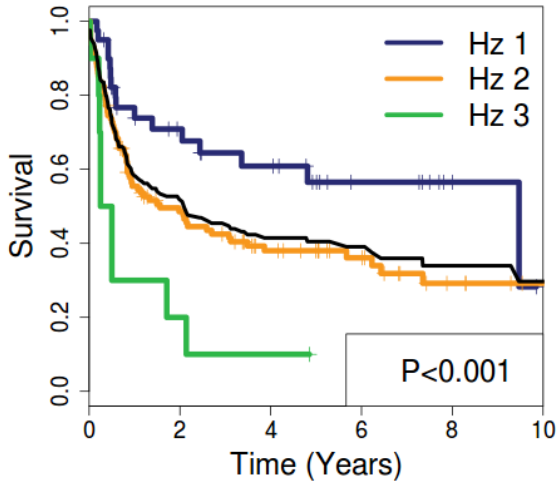


Patient's survival probability as compared to that of the age and sex matched normal population of Germany (year 2010):

after 0.0 years: 1.0000 vs 1.0000
after 1.0 years: 0.6634 vs 0.9981
after 2.0 years: 0.5957 vs 0.9959
after 3.0 years: 0.5661 vs 0.9936
after 4.0 years: 0.5519 vs 0.9910
after 5.0 years: 0.5112 vs 0.9882

* these numbers indicate which parameters are required for OS, CIR or NRM models, respectively

Figure 3: Importance of molecular mutations in our comprehensive risk model. Overall survival of patients belonging to the intermediate risk group of the risk model without mutations (black line) was reclassified into 3 significantly different risk groups (Hz 1-3) by the comprehensive risk model with mutations:



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Planned proposal for a revision of the IWG 2006 response criteria for hematological improvement in myelodysplastic syndromes (MDS) in the context of clinical trials

The heterogeneity of myelodysplastic syndromes (MDS) makes evaluating patients' response to treatment challenging. In 2006, an International Working Group (IWG) proposed a revision to previously published standardized response criteria (IWG 2000) for uniformly evaluating clinical responses in MDS. These IWG 2006 criteria have been used in many clinical trials in MDS, but sometime have proved to be a challenging tool.

In 2015, a group of clinicians, including the EMSCO founders Pierre Fenaux from Paris and Uwe Platzbecker from Dresden, first gathered to discuss a potential revision of these criteria. After some initial meetings and an extension of the review board, the proposal is now in a final phase.

The proposal will provide rationale for modifications of the currently used recommendations (IWG 2006), mainly for "hematological improvement" criteria used for lower risk MDS. These suggestions are based on recent practical and reported experience in clinical trials and most of them relate to erythroid response assessment, which will be refined in an overall more stringent manner. Two major proposed changes are the differentiation between "procedures" and "criteria" for hematologic improvement-erythroid (HI-E) assessment and a new categorization of transfusion burden.

The report will be proposed in the course of 2018 by the following group of authors:

P. Fenaux, V. Santini, L. Adès, A.A. van de Loosdrecht, A. Giagounidis, M. Sekeres, E. Hellström-Lindberg, D. Bowen, U. Germing, T de Witte, G. Garcia-Manero, L. Malcovati, D. Steensma and U. Platzbecker

Author: Silke Gloaguen

The BERGAMO trial

A phase II study evaluating the efficacy and safety of BGB324 in patients with MDS or AML failing standard of care therapy

Background:

Novel treatment options in patients with MDS or AML are urgently needed. Treatment has not changed significantly over the past decades and survival is still dismal, especially in elderly patients not capable for allogeneic stem cell transplantation and failing first line treatment with hypomethylating agents.

BGB324 is a potent selective small molecule inhibitor of Axl, a surface membrane protein kinase receptor. Signaling through Axl seems to stimulate a number of pro-survival pathways, some of which are mediated by AKT phosphorylation and up-regulation of the epithelial receptor kinase pathway. Furthermore, Axl enables malignant cells to develop resistance to conventional chemotherapies. It has been shown that Axl is overexpressed on leukemic cells of both AML and MDS patients, especially in the CD34+ compartment.

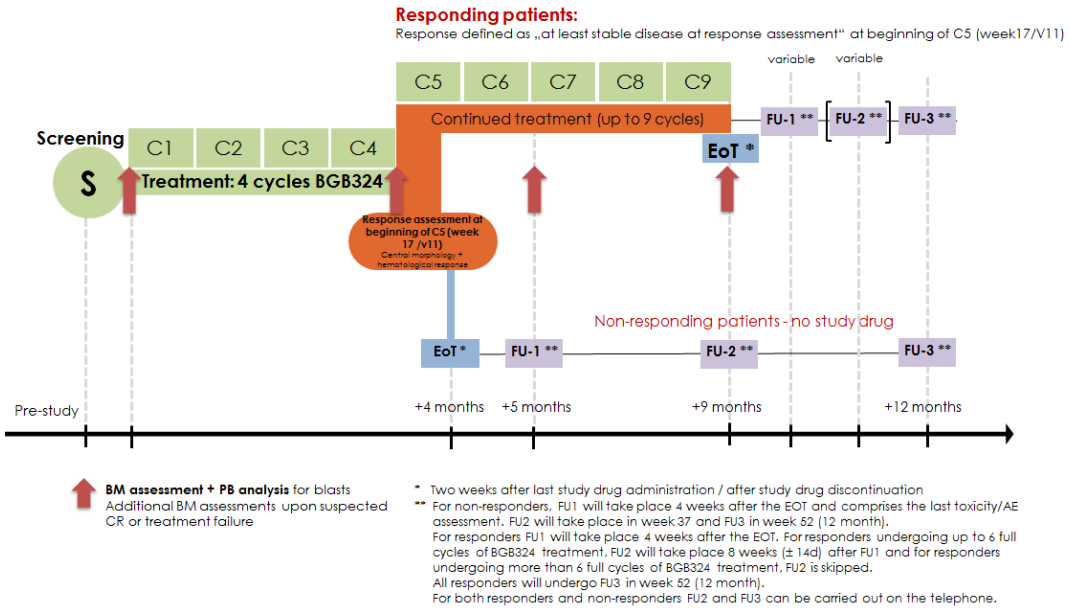
Preliminary studies investigating this pathway by using AML cell lines in combination with Axl inhibitors indicate at least an additive effect when administered with cytarabine. Additionally, there is evidence that Axl inhibition with BGB324 inhibits proliferation of clonal cells derived from patients with MDS. In fact, in a translational research setting, Medyouf et al. have shown that bone marrow derived stromal cells play a critical role in MDS pathogenesis and provide essential support to disease propagating MDS stem cells in vivo [9]. In-depth molecular characterization of patient-derived stromal cells revealed deregulated expression of key stromal factors being involved in inter-cellular communication and cancer progression. Gas6, a high-affinity Axl ligand, was identified to be readily and consistently over-expressed in bone marrow derived stromal cells isolated from MDS patients. Functionally, it was shown that blockade of Gas6/Axl signaling axis by BGB324 significantly impairs MDS growth in an ex-vivo stroma-dependent co-culture setting using patient-derived primary material recently established by Medyouf et al. These effects were especially observed in the CD34+ MDS stem cell compartment. A persistence of this stem cell compartment is expected to underlie drug resistance and/or drive disease progression in MDS. Therefore, we believe that Axl inhibition seems to be a promising approach to improving the currently dismal outcomes in the BERGAMO trial population.

Design & flow:

This is an open-label, single-arm, multicenter, phase II study of BGB324 in subjects suffering from MDS and AML. The trial will involve participating sites from different sites in Europe. 43 subjects will be enrolled in the study. BGB324 will be self-administered orally for an initial treatment period of 4 treatment cycles of 28 days each. After completion of these first 4 cycles, response will be assessed.

Non-responding patients subsequently start a follow-up phase lasting for up to 8 months resulting in a total duration of 12 months. Responding patients will continue treatment with BGB324 for up to additional 5 treatment cycles (up to a total of 9 cycles), followed by a (minimum of) 3 months follow-up. Thus, the individual study duration for a subject will be approx. 12 months.

Flowchart of the BERGAMO trial:



Endpoints:

The primary endpoint of this trial is the overall hematological response rate as assessed after cycle 4.

Secondary endpoints comprise toxicity as measured by NCI CTCAE 4.03, overall survival, progression-free-survival, time to treatment failure, duration of response and best overall response.

Translational program:

In addition to the clinical part of the trial, a comprehensive translational program will be carried out in order to evaluate the role of potential biomarkers in this setting. This comprises immunophenotyping, immunohistochemistry, gene expression analyses as well as investigations on a protein level.

Project status:

Submission for the BERGAMO trial is currently ongoing and we are confident to be able to enroll the first patients by July of this year.

Author: Silke Gloaguen

Upcoming events

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

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

14th Göttingen MDS Workshop
26 May 2018 - Göttingen, Germany

12th Days of the Groupe Francophone des Myélodysplasies (GFM)
31 May - 1 June 2018 - Tours, France

6th Annual EMSCO Meeting
21-22 September 2018 - Amsterdam, Netherlands