Final Report of the Trial AMLSG 21-13

Title	Randomized Phase III Study of Intensive Chemotherapy with or without Dasatinib (Sprycel™) in Adult Patients with Newly Diagnosed Core-Binding Factor Acute Myeloid Leukemia (CBF-AML)
Project Code	AMLSG 21-13
Active Substances/Finished Products	Dasatinib (Sprycel™)
Protocol Number	Version 1.4
Positive initial Vote of the Ethics Committee	14.07.2014
Termination of the Trial	19.02.2024
Sponsor	University Hospital of Ulm, represented by the Chairman of the Board
EudraCT Number	2013-003117-18

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2. Name of Finished Product

Dasatinib (marketed product name: Sprycel™)

3. Name of Active Substance

Dasatinib

4. Individual Study Table

Not applicable

5. Title of Study

Randomized Phase III Study of Intensive Chemotherapy with or without Dasatinib (Sprycel™) in Adult Patients with Newly Diagnosed Core-Binding Factor Acute Myeloid Leukemia (CBF-AML)

Initial approved version of study protocol:
Protocol version V1.1 (Dated: 15.04.2014)

Amendments of the protocol:
Protocol version V1.2 (Dated: 23.06.2015)
Protocol version V1.3 (Dated: 15.06.2016)
Protocol version V1.4 (Dated: 19.03.2019)

This report refers to the current version of study protocol:
Protocol version V1.4 (Dated: 19.03.2019)

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8. Publication reference

Study results have not been published so far.

9. Studied period

First patient in: 29.08.2014

Last patient last visit: 19.02.2024

Recruitment was not interrupted during the study.

10. Phase of Development

Phase III

11. Objectives

Primary Efficacy Objective

- To assess event-free survival (EFS) after intensive induction (daunorubicin and cytarabine) and consolidation (high-dose cytarabine) chemotherapy with or without dasatinib in patients with CBF-AML

Secondary Efficacy Objectives

- To assess the interaction between type of CBF-AML [t(8;21) versus inv(16)] and randomization accordingly on all survival endpoints
- To assess cumulative incidence of relapse (CIR) and death (CID)
- To assess relapse-free (RFS) and overall survival (OS)
- To assess outcome according to *KIT* mutational status
- To assess pharmacodynamic inhibition of KIT
- To assess toxicity

12. Methodology

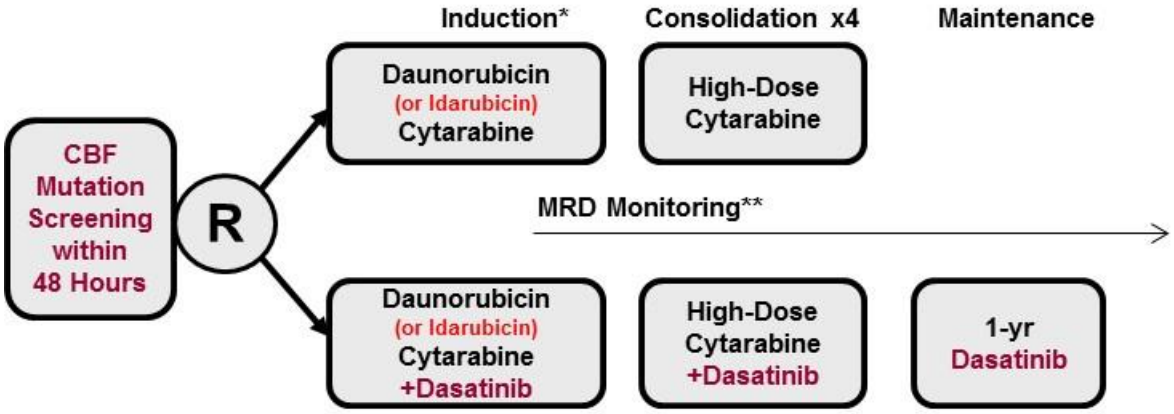
Study Design

Randomized Phase-III, two-arm, open-label, multi-center study in adult patients with newly diagnosed CBF-AML as defined in inclusion/exclusion criteria.

Overall, at the participating AMLSG study centers a total sample size of 202 evaluable patients was recruited.

Treatment

Figure 1: Treatment plan - overview



* Optional 2nd induction cycle (dose-reduced) in patients achieving a partial remission (PR) only after 1st induction cycle
** Patients with molecular disease persistence or molecular relapse are eligible for hematopoietic stem cell transplantation

Standard arm:

<u>Induction therapy</u>:

Patients received induction chemotherapy with daunorubicin 60 mg/m^2/day administered on days 1-3 and cytarabine 200 mg/m^2/day administered by continuous IV infusion (CIVI) on days 1-7. No dose reduction was planned in elderly (>60 years) patients. Response assessment including bone marrow evaluation was performed between day 21 and 28.

In case daunorubicin was not available in the center due to supply shortage, idarubicin could be used instead of daunorubicin:

- Idarubicin 12 mg/m^2/day by intravenous push (IVP) on days 1,3,5 (total dose 36 mg/m^2). No dose reduction is foreseen in elderly (>60 years) patients.
- Cytarabine 200 mg/m^2/day by CIVI on days 1-7 (total dose 1400 mg/m^2).

Optional second induction cycle:

Patients achieving PR only at the end of cycle 1 received a second induction cycle with daunorubicin 50 mg/m^2/day administered on days 1-3 and cytarabine 200 mg/m^2/day administered by cont. IV infusion daily on days 1-5. No dose reduction was planned in elderly (>60 years) patients. Bone marrow evaluation was done between day 21 and 28.

In patients who received idarubicin within the 1st induction cycle cycle idarubicin had to be used also for the dose reduced 2nd induction cycle:

- Idarubicin 10 mg/m^2/day by IVP on days 1 and 3 (total dose 20 mg/m^2). No dose reduction is foreseen in elderly (>60 years) patients.
- Cytarabine 200 mg/m^2/day by CIVI on days 1-5 (total dose 1000 mg/m^2).

Consolidation therapy:
Patients achieving CR or CRi at the end of cycle 1 (or 2) received 4 cycles of consolidation therapy. Consolidation therapy consisted of high-dose cytarabine (HDAC) 3 g/m^2 (>60 years: 1 g/m^2) q12h, days 1-3 administered intravenously over three hours. Bone marrow evaluation was to be done between day 29 and 35 of each cycle. Cycles 2-4 should have begun between day 29 and 35 after start of the previous cycle, following hematologic recovery (ANC ≥1,000/µL, platelet count ≥100,000/µL) and resolution of non-hematologic toxicities to grade ≤1; the start of the next cycle should have been postponed until the above criteria are met.

Follow-up period:
There was no maintenance therapy in the standard arm. Patients were closely followed, in particular for molecular disease persistence or molecular relapse.

Investigational arm:

Induction therapy:
Patients received induction therapy with daunorubicin 60 mg/m^2/day administered on days 1-3 and cytarabine 200 mg/m^2/day administered by CIVI on days 1-7. No dose reduction was planned in elderly (>60 years) patients. Patients received dasatinib 100 mg once daily (QD) on days 8-21. Bone marrow evaluation was done between day 21 and 28.

In case daunorubicin was not available in the center due to supply shortage idarubicin could be used instead of daunorubicin:

- Idarubicin 12 mg/m^2/day by IVP on days 1,3,5 (total dose 36 mg/m^2). No dose reduction is foreseen in elderly (>60 years) patients.
- Cytarabine 200 mg/m^2/day by CIVI on days 1-7 (total dose 1400 mg/m^2).

Optional second induction cycle:
Patients achieving PR only at the end of cycle 1 received a second induction cycle with daunorubicin 50 mg/m^2/day administered on days 1-3 and cytarabine 200 mg/m^2/day administered by CIVI on days 1-5. No dose reduction was planned in elderly (>60 years) patients. Patients received dasatinib 100 mg QD on days 6-21. Bone marrow evaluation was done between day 21 and 28.

In patients who received idarubicin within the 1st induction cycle cycle, idarubicin had to be used also for the dose reduced 2nd induction cycle:

- Idarubicin 10 mg/m^2/day by IVP on days 1 and 3 (total dose 20 mg/m^2). No dose reduction is foreseen in elderly (>60 yrs) patients.
- Cytarabine 200 mg/m^2/day by CIVI on days 1-5 (total dose 1000 mg/m^2).

Consolidation therapy:
Patients achieving CR or CRi at the end of cycle 1 (or 2) received consolidation therapy for 4 cycles. Consolidation therapy consisted of high-dose cytarabine 3 g/m^2 (>60 years: 1 g/m^2)

q12h, days 1-3 administered intravenously over three hours. Patients received dasatinib 100 mg QD on days 4-28. Bone marrow evaluation was done between day 29 and 35 of each cycle. Cycles 2-4 should have begun between day 29 and 35 after start of the previous cycle, following hematologic recovery (ANC ≥1,000/µL, platelet count ≥100,000/µL) and resolution of non-hematologic toxicities to grade ≦1; the start of the next cycle should have been postponed until the above criteria were met**.**

Maintenance therapy / follow-up:

Patients completing consolidation therapy continued to receive single agent dasatinib 100 mg QD for one year (or until relapse). Patients were closely followed, in particular for molecular disease persistence or molecular relapse. Maintenance therapy with dasatinib might directly follow the last cycle of consolidation (without interrupting dasatinib); day 1 of maintenance then corresponded to day 29 of last consolidation therapy; maintenance therapy should have been started only after hematologic recovery (ANC ≥1,000/µL, platelet count ≥100,000/µL) and documentation of CR or CRi after last consolidation. Patients who were unable to complete four courses of HDAC consolidation because of toxicity were still eligible for maintenance therapy.

13. Number of patients (planned and analyzed)

Number of patients planned: 203

Number of patients recruited: 204

Number of patients analyzed:

- Intention-to-treat (ITT) population: 202
- Per-protocol (PP) population: 178
- Safety population: 200

14. Diagnosis and main criteria for inclusion/exclusion

Diagnosis: Acute Myeloid Leukemia

Inclusion Criteria:

1. CBF-AML with molecular diagnosis of *RUNX1-RUNX1T1* fusion transcript resulting from t(8;21)(q22;q22.1) (or a variant form) or of *CBFB-MYH11* fusion transcript resulting from inv(16)(p13.1q22)/t(16;16)(p13.1;q22) as assessed in one of the central AMLSG reference laboratories (Ulm or Hannover)
2. Age ≥ 18 years; no upper age limit
3. No prior chemotherapy for leukemia except hydroxyurea for up to 5 days during the diagnostic screening phase
4. Non-pregnant and non-nursing. Due to the unknown teratogenic potential of dasatinib in humans, pregnant or nursing patients may not be enrolled. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 72 hours prior to registration. Women of childbearing potential must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control - one highly effective method (e.g., IUD, hormonal, tubal ligation, or partner's vasectomy), and one additional ef-

fective method (e.g., latex condom, diaphragm, or cervical cap) - AT THE SAME TIME, at least four weeks before she begins dasatinib therapy until at least 3 months after last dasatinib administration. “Women of childbearing potential” is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months.

5. Men must agree not to father a child and must use a latex condom during any sexual contact with women of childbearing potential while taking dasatinib and for 3 months after therapy is stopped, even if they have undergone a successful vasectomy.
6. Signed written informed consent.

Exclusion Criteria:

1. Performance status WHO >2
2. Pulmonary edema and/or pleural/pericardial effusion within 14 days of day 1. If edema/effusion resolves to CTC Grade ≤1, patients can be treated with dasatinib.
3. Patients with ejection fraction <50% by echocardiography or MUGA within 14 days of day 1
4. Organ insufficiency (creatinine >1.5x upper normal serum level; bilirubin, AST or AP >2.5x upper normal serum level; heart failure NYHA III/IV; severe obstructive or restrictive ventilation disorder)
5. Uncontrolled infection
6. Patients with a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy, if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within one year.
7. Severe neurological or psychiatric disorder interfering with ability of giving an informed consent
8. Known positive for HIV, active HBV, HCV, or Hepatitis A infection
9. Bleeding disorder independent of leukemia
10. No consent for registration, storage and processing of the individual disease-characteristics and course as well as information of the family physician and/or other physicians involved in the treatment of the patient about study participation.
11. No consent for biobanking.

15. Test product, dose and mode of administration, batch number

The Investigational Product (IMP) in this study was dasatinib (Sprycel™).

Dasatinib was provided as tablets of 50 mg and 20 mg. Each kit contained 60 tablets.

The drug was administered orally in a dose of 100 mg (two 50 mg tablets) one a day on days 8-21 in induction cycle 1, on days 6-21 in induction cycle 2 (optional) and on days 4-28 in the consolidation cycles 1-4. Tablets of 20 mg were used for dose reduction.

Dasatinib was supplied by Bristol Myers Squibb, who was responsible for the labeling of the study drug according to legal requirements. Study drug for individual patients was shipped Bristol Myers Squibb to the pharmacy at the university hospital Ulm and was sent to each study site after order for each patient and each cycle separately.

The following batch numbers were used:

4E79310
4C87895
4K81248
4L77077
AAD6843
AAF3707
AAK8166
AAK2465
AAM2166
AAK2465
AAM1873
AAM1873
AAP5901
AAT3666
AAT9469
AAT3666
AAY1021
AAZ6709
AAW3989
ABC1579
ABJ2321
ABK6756
ABL4767
ABQ9389
ABQ8622
ABU2715

16. Duration of treatment

The estimated treatment duration of an individual patient in case of on cycle of induction therapy and 4 cycles of consolidation therapy was about 6 months (in case of two induction cycles: 7 months). Patients in the investigational arm additionally received 12 months of maintenance therapy, so for these patients maximum treatment duration was 18 to 19 months. Follow-up period was planned until 3.25 years after last patient in.

17. Reference therapy, dose and mode of administration, batch number

Not applicable.

18. Criteria for evaluation: Efficacy, Safety

The frequency and timing of efficacy and safety measurements were defined in the study protocol.

Efficacy Measurements

Efficacy assessments were done after each induction and consolidation cycle and 3-monthly during maintenance therapy. They were based on analysis of full blood count, bone marrow aspirate or bone marrow histology and, for patients with extramedullary disease, on clinical examination and/or tumor imaging.

The response to treatment was evaluated by using standard criteria defined by the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (see Appendix A). The response at every assessment time was recorded for every patient.

Primary Efficacy Variable

The primary efficacy variable for this trial was event-free survival (EFS); an event was defined as refractory disease, death by any cause, hematologic relapse, molecular persistence or molecular relapse

Secondary Efficacy Variables

Secondary efficacy variables assessed for this trial were:

- The interaction between type of CBF-AML [t(8;21) *versus* inv(16)] and randomization accordingly on all survival endpoints
- Cumulative incidence of relapse (CIR) and death (CID)
- Relapse-free (RFS) and overall survival (OS)
- Outcome according to *KIT* mutational status
- Pharmacodynamic inhibition of KIT assessed by the KIT plasma inhibitory assay (PIA)
- Toxicity

Safety Measurements

Safety endpoints in this study were:

- Rate of early deaths and hypoplastic deaths (ED/HD)

-Type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), timing and relatedness of non-hematologic toxicity observed during different treatment cycles.

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, Chest X Ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the eCRF.

19. Statistical methods

The primary endpoint of the study was event-free survival; an event was defined as one of the following:

- Refractory disease, defined as failure to achieve at least a PR after the first induction cycle and CR or CRi after an optional second induction cycle
- Death by any cause
- Hematologic Relapse
- Molecular persistence
- Molecular relapse.

The primary endpoint was analysed with a stratified log-rank test. In order to evaluate the robustness of the primary endpoint analysis of EFS, additional stratified log rank tests and stratified Cox regression models as well as sub group analyses were performed.

All statistical tests used age (18-60 years vs. >60 years) and type of CBF-AML (t(8;21) vs. inv(16)) as stratification factors to account for the stratified randomisation. In addition to the test results, the estimates for the hazard ratio (HR) are provided, including 95% CIs.

For EFS Kaplan-Meier (KM) estimates for the rates at 12, 24, 36 and 48 months with corresponding 2-sided 95% CIs as well as median survival times were calculated. For EFS, the number and percentage of subjects who had induction failure, death by any cause, hematolocic relapse, molecular persistence or molecular relapse and who were censored was reported.

Furthermore, a multivariate Cox proportional hazards model was fitted for EFS using the following variables as covariates: age, gender, ECOG performance status, AML type, CBF type, mutational status of *FLT3*-ITD, *FLT3*-TKD and KIT, white blood count at diagnosis as well as minimal residual disease status as time-dependent covariable.

Secondary endpoints were analysed in an exploratory manner. They were analysed using appropriated univariable and multivariable methods to estimate the effect sizes of potentially relevant factors including mutation markers.

For OS and RFS, similar analyses as described for EFS were performed.

The cumulative incidences CIR and CID were estimated at 12, 24, 36 and 48 months, along with the 95% CI using the method of Aalen-Johansen. As multivariable analyses, cause-specific Cox regression models were adjusted for the potential prognostic covariates as with the EFS main analysis described above.

The amount of missing explanatory and response data was documented, including the proportion of missing values for each variable being analysed and missing value imputation was used.

Adverse event (AE) data were summarized overall and by treatment arm for each cycle of the induction and consolidation treatment separately. All AEs occurring after randomization are presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (version 26.1). The severity of AEs was graded according to the NCI CTCAE version 4.03. When summarizing the number and percentage of patients, patients with multiple occurrences of the same adverse event were counted once, and only the maximum severity level is presented in the severity summaries.

All grade ≥ 3 AEs are tabulated by SOC and PT using frequency counts and percentages (i.e., number and percentage of patients with an event) for each treatment arm and for all patients together. The same information is also provided for all grade 1, 2, 3 and 4-5 toxicities separately. The proportion of patients developing any grade ≥ 3 AE across treatment arms was compared using Barnard's exact test (Barnard 1945, 1947).

Summary statistics regarding serious adverse events (SAEs) were provided separately for each treatment cycle by treatment arm as well as for all patients together based on the safety population for the respective treatment cycle. Descriptive summaries of patients with serious adverse events, patients who withdrew from study treatment because of adverse events, and patients who died during study treatment were also provided.

Cumulative incidence curve of the time (from registration) to the occurrence of the first SAE was presented, where going off protocol treatment without an SAE was considered as a competing risk.

Regarding mortality, the total number of deaths and a by-subject listing of patients who died together with the cause of death was presented.

The following data on hematopoietic recovery were analysed for each cycle of induction and of consolidation chemotherapy treatment, overall and by treatment arm:

- Cumulative incidence curve for time to ANC recovery ≥ 0.5×109/L and 1.5×109/L
- Cumulative incidence curve for time to WBC recovery ≥ 1.0×109/L
- Cumulative incidence curve for time to platelet recovery ≥ 50×109/L and 100×109/L

In the analysis of ANC, WBC and platelet recovery, patients who start next treatment without recovery were censored at the date of start of next treatment or, in case no further treatment is given, at the date of last contact. Deaths without recovery were considered as competing events.

20. Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

20.1 Efficacy Results

Regarding the primary endpoint EFS, no statistically significant difference between the two treatment arms was detected.

In total, 114 events were observed (60 events in the standard arm and 54 events in the investigational arm). EFS of the whole cohort was 42% at 4 years. EFS rates were comparable between the treatment arms with 44% in the investigational arm and 41% in the standard arm. There was no statistically significant difference in the EFS times according to the stratified logrank test (p=0.66). Also, within the subgroup analyses according to age group, CBF-AML type and *KIT* mutation status no significant difference in EFS times could be detected.

Multivariate models supported this result. Negative prognostic effects were detected for higher white blood cell count (HR for log10 increase 2.01; p<.001), presence of a *KIT* mutation (HR 1.96; p=0.002), and in trend for molecular MRD persistence (HR 1.66; p=0.052*)*.

When analyzing the PP population, EFS rates in this cohort were numerically higher in the investigational arm (48%) than in the standard arm (42%). However, this difference between the treatment arms was not statistically significant according to the stratified logrank test (p=0.48).

Utilizing an alternative definition of EFS without the events based on MRD (molecular persistence / molecular relapse) did not reveal a significant treatment effect as well (stratified logrank test: p=0.76).

Results of the secondary efficacy variables are summarized as follows:

Overall, 49 (24%) patients died within the study, 26 (25%) patients in the standard arm and 23 (23%) patients in the investigational arm. The OS rate of the whole cohort was 77% at 4 years with 76% in the standard arm and 78% in the investigational arm. There was no statistically significant difference in the (OS) times of the two treatment arms according to the stratified logrank test (p=0.79). Also, within the subgroup analyses according to age group, CBF-AML type and *KIT* mutation status, no significant difference in OS times could be detected.

Multivariate analysis supported this result. There were no significant prognostic effects and covariates, only a trend for a negative effect on OS (=higher risk of death) was observed for presence of *KIT* mutation (HR 1.76; p=0.086).

When analyzing the PP population, OS rates in this cohort were 79% in the investigational arm and 76% in the standard arm (stratified logrank test: p=0.76).

Regarding the secondary endpoint relapse-free survival (RFS), 101 (53%) patients had RFS events (relapse or death in CR/CRi) with a higher rate of events in the standard arm (57%) than in the investigational arm (49%). The RFS rate of the whole cohort was 45% at 4 years with 42% in the standard arm and 49% in the investigational arm. This difference between the two treatment arms was not statistically significant according to the stratified logrank test (p=0.31). Also, within the subgroup analyses according to age group, CBF-AML type and *KIT* mutation status, no statistically significant difference in RFS times could be detected.

In multivariate analysis, negative prognostic effects on RFS were detected for higher white blood cell count (HR for log10 increase 2.21; p<.001), presence of a *KIT* mutation (HR 2.15;

p<.001), and presence of CBF-AML type t(8;21) (HR 1.58; p=0.048). A negative trend was observed for MRD positivity (HR 1.62; p=0.069).

Analysis of the PP population revealed a RFS of 52% in the investigational arm and 43% in the standard arm, but the stratified logrank test was not significant (p=0.23).

Analyses of CIR and CID were based on 189 patients with achievement of CR/CRi by end of induction therapy. Overall, 90 patients relapsed and 11 patients died in CR/CRi. Cumulative incidences of relapse and death in CR/CRi after 4 years were 50% and 5% (Figure 23 and Tables 38/39), respectively, with a slightly lower CIR in the investigational arm compared to the standard arm (47% vs. 52%). CIR and CID were compared between the treatment arms using stratified Gray's test. The resulting p-value of the stratified Gray's test for CIR was 0.37 and for CID it was 0.96 (p-values vor unstratified Gray's test were 0.29 for CIR and 0.92 for CID).

Also, within the subgroup analyses according to age group, CBF-AML type and *KIT* mutation status, no statistically significant difference in CIR and CID could be detected.

To assess whether the therapeutic effect of dasatinib on the survival endpoints (EFS, OS, RFS) differs between CBF-AML types, an interaction test was performed. For all survial endpoints, no significant results for the interaction effect could be detected.

20.2 Safety Results

During induction cycles, there was no major difference between the two treatment arms regarding hematological recovery of neutrophils, white blood count and platelets. However, during consolidation cycles hematological recovery of neutrophils and platelets was slightly prolonged in the standard arm compared to the investigational arm indicated by higher recovery rates of neutrophils ≥1.5 G/l as well as platelets ≥50 G/l and ≥100 G/l in the investigational arm.

Overall and in both treatment arms, AEs occurred most frequently in the SOCs of blood and lymphatic system disorders (96%), investigations (96%) and gastrointestinal disorders (92%). Other frequent affected SOCs were infections and infestations (89%) and general disorders and administration site conditions (87%). In general, both arms were comparable with regards to the affected SOCs. Regarding the affected SOCS, renal and urinary disorders, cardiac disorders and hepatobiliary disorders were more frequently observed in the investigational arm with 47%, 31% and 8% compared to the standard arm with 39%, 22% and 3%, respectively. Musculoskeletal and connective tissue disorders were more frequently observed in the standard arm (45%) compared to the investigational arm (32%). With regard to the induction and consolidation cycles, the most frequently affected SOCs were blood and lymphatic system disorders and investigations (≥90% of patients). During maintenance therapy, investigations (65%), general disorders and administration site effects (63%) and blood and lymphatic system disorders (63%) were the most frequently affected SOCs.

The most frequently reported adverse event ≥ CTCAE grade 3 overall was thrombocytopenia (platelet count decreased) (92%). Other frequently occurring adverse events were anemia (88%), white blood cell count decreased (85%), neutrophil count decreased (67%) and febrile neutropenia (44%). Decrease in platelet counts, hemoglobin and white blood cells were the most frequent AEs during all treatment cycles and in both treatment arms.

Comparisons between the two treatment arms were performed by Barnard's exact test for 2x2 tables for the overall study period and separately for each individual treatment cycle. The following major differences were identified: Overall, white blood count decreased ≥ CTCAE

grade 3 was significantly increased in the standard arm (91%) compared to the investigational arm (79%) (p=0.02). In the investigational arm, colitis occurred more frequently (8% vs. 1%, p=0.02) as well as acute kidney injury (4% vs. 0%, p=0.04) and atrial fibrillation (4% vs. 0%, p=0.04). In the first induction cycle, allergic reaction was significantly increased in the investigational arm compared to the standard arm (4% vs. 0%, p=0.03). Frequency of increased C-reactive protein was increased in the investigational arm compared to the standard arm in the third consolidation cycle (9% vs. 1%, p=0.01), as well as nausea (5% vs. 0%, p=0.04).

There were 10 (5%) deaths reported during study treatment. Five patients died due to infections (sepsis (n=3), bronchial pneumonia (n=1) and SARS Cov-2 infection (n=1)), three patients died due to multi-organ failure / death of unknown origin and two patients died due to respiratory disorders (ARDS and pneumonia). Patients who died during study treatment were between 22 and 74 years old. Most of them (60%) were younger patients (≤60 years of age).

Rates of on-study deaths were equal between the two treatment arms. Overall, most of the on-study deaths occurred during induction cycle 1 (60%). Forty percent of deaths occurred during consolidation therapy. There was no difference between the two treatment arms.

Five of the on-study deaths during induction cycle 1 were early/hypoplastic deaths (ED/HDs). Rate of ED/HD between treatment arms was comparable with 2% and 3%, respectively.

Overall, 99 patients had serious adverse events, whereby the incidence of SAEs was higher in the investigational arm (64%) compared to the standard arm (36%). The most frequent SAEs occurring during the whole treatment period and also within the individual treatment cycles were pneumonia/pneumonitis, sepsis, febrile neutropenia and pyrexia. This was true for both treatment arms, however, incidence of these events was higher in the investigational arm compared to the standard arm.

The number of patients with SAEs assessed to be related to cytarabine was comparable between the treatment arms (26%), more patients had SAEs assessed to be related to daunorubicin in the investigational arm (12%) than in the standard arm (5%). Forty-one (41%) patients had SAEs assessed to be related to dasatinib.

Thirty-one adverse events led to premature termination of study treatment; more patients terminated study treatment due to an AE in the investigational arm (27%) than in the standard arm (4%).

There were a total of 24 (12%) patients with adverse events of special interest. The majority of patients (n=15) were in the investigational arm, compared to 9 patients in the standard arm. Most of the AESIs were related to lack of efficacy due to molecular persistence or molecular relapse (84%), five cases of overdose of study drugs were reported.

20.3 Conclusion

Discussion

Acute myeloid leukemia (AML) with t(8;21)(q22;q22.1)/ *RUNX1*::*RUNX1T1* and AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ *CBFB*::*MYH11* are recognized as disease entities within both current AML classification systems, the International Consensus Classification (ICC), and the 5th Edition of the World Health Organization (WHO). Both leukemias are commonly designated as "core-binding factor" AML (CBF-AML) because these chromosome abnormalities result in abnormal fusions involving genes of the CBF complex. Both types of leukemia have previously been shown to harbor co-mutations in the receptor tyorise kinase (TKI) gene *KIT* in about one-third of cases. Moreover, irrespective of the presence of a *KIT* co-mutation, in gene expression analyses CBF-AML have been shown to exhibit higher *KIT* expression compared to other subtypes of AML. These observations on the genetic landscape of CBF-AML were the basis to evaluate the concept of KIT inhibition using a TKI in combination with standard of care intensive treatment in patients with CBF-AML eligible for intensive chemotherapy.For this trial, we selected the TKI dasatinib. Dasatinib is an ATP-competitive, dual SRC/ABL inhibitor. There is extensive experience with the TKI in the treatment of chronic myeloid leukemia (CML), also with regard to the safety profile. In phase I-III clinical trials evaluating dasatinib in imatinib-resistant CML, the drug was safe, well tolerated and effective. In 2006, dasatinib (Sprycel®) was approved by FDA and EMA for the treatment of CML resistant or intolerant to treatment with imatinib, and in 2010 dasatinib was approved for first-line therapy of CML. Of note, dasatinib has also been demonstrated to have potency against both mutated and wildtype *KIT* (Schittenhelm et al. 2006). Based on the molecular profile of CBF-AML and the high activity of dasatinib against wildtype and mutant KIT, the compound appeared attractive for the treatment of patients with CBF-AML.

Two previous single-arm phase 1b/2a studies, one conducted by our group (AMLSG; n=89 patients; Paschka et al. 2018) and one by the US Cancer and Leukemia Group B (CALGB; n=89 patients; Marcucci et al. 2020) evaluated dasatinib in combination with intensive chemotherapy in 89 patients with CBF-AML. In both trials, the addition of dasatinib to intensive chemotherapy was safe, and outcome of patients was favorable. Results from single-arm trials are limited by patient selection and lack of an appropriate control group, therefore no firm conclusions could be drawn from the two studies.

The data from the two trials prompted the initiation of the current AMLSG 21-13 trial which evaluated dasatinib in a randomized, open-label phase 3 trial. Primary endpoint was event-free survival (EFS); an event was defined as one of the following: refractory disease after induction therapy, death by any cause, hematologic relapse, molecular persistence, and molecular relapse. Secondary endpoints included overall survival (OS), relapse-free survival (RFS), and cumulative incidence of relapse (CIR) and death (CID). Between August 2014 and February 2021, 204 patients were recruited. 103 patients were assigned to the standard arm, 101 patients to the investigational arm with dasatinib.

The trial failed to reach the primary endpoint, a significant improvement of EFS. There was no statistically significant difference in the EFS times according to the stratified logrank test (HR 0.92, 95%-CI 0.63, 1.33; p=0.66). 4-year EFS rates were comparable between treatment arms with 44% in the investigational arm and 41% in the standard arm. Also, within subgroup

analyses according to age group, CBF-AML type, and *KIT* mutation status no significant difference in EFS times could be detected. Multivariate models supported these results. Negative prognostic effects were detected for higher white blood cell count (HR for log10 increase 2.01; p<.001), presence of a *KIT* mutation (HR 1.96; p=0.002), and in trend for molecular MRD positivity persistence (HR 1.66; p=0.052).

Similarly, there was no difference between treatment arms with regard to the secondary endpoints. There was no statistically significant difference in the overall survival (OS) times between the two treatment arms according to the stratified logrank test (p=0.79). The 4-year OS rates were 76% in the standard arm and 78% in the investigational arm. The 4-year RFS rates were 42% in the standard arm and 49% in the investigational arm. This difference between the two treatment arms was not statistically significant according to the stratified logrank test (p=0.31). CIR and CID were compared between the treatment arms using stratified Gray's test. The resulting p-value of the stratified Gray's test for CIR was 0.37 and for CID it was 0.96 (p-values vor unstratified Gray's test were 0.29 for CIR and 0.92 for CID). To assess whether the therapeutic effect of dasatinib on the survival endpoints (EFS, OS, RFS) differs between CBF-AML types, an interaction test was performed. For all survial endpoints, no significant results for the interaction effect could be detected.

With regard to safety, the most frequently reported adverse events ≥ CTCAE grade 3 overall were thrombocytopenia (platelet count decreased) (92%), anemia (88%), white blood cell count decreased (85%), neutrophil count decreased (67%), and febrile neutropenia (44%). Decrease in platelet counts, hemoglobin and white blood cells were the most frequent AEs during all treatment cycles and in both treatment arms. These rates of hematologic adverse events and of febrile neutropenia are seen in virtually all studies of intensive chemotherapy protocols in acute leukemia.

The following major differences were identified between treatment arms: In the investigational arm, colitis occurred more frequently (8% vs. 1%, p=0.02) as well as acute kidney injury (4% vs. 0%, p=0.04) and atrial fibrillation (4% vs. 0%, p=0.04). In the first induction cycle, allergic reaction was significantly increased in the investigational arm compared to the standard arm (4% vs. 0%, p=0.03). Frequency of increased C-reactive protein was increased in the investigational arm compared to the standard arm in the third consolidation cycle (9% vs. 1%, p=0.01), as well as nausea (5% vs. 0%, p=0.04). White blood count decreased ≥ CTCAE grade 3 was increased in the standard arm (91%) compared to the investigational arm (79%) (p=0.02). Colitis is a known but rare adverse event in single-agent dasatinib treatment (https://packageinserts.bms. com/ pi/pi_sprycel.pdf); combining dasatinib with intensive chemotherapy may potentially enhance incidence and severity due to the cytotoxic effects of anthracyclines and cytarabine on the colonic mucosa. Similarly, cardiac arrhythmias have been observed during single-agent dasatinib treatment.

Overall, 99 patients had serious adverse events (SAE), whereby the incidence of SAEs was higher in the investigational arm (64%) compared to the standard arm (36%). The most frequent SAEs occurring during the whole treatment period and also within the individual treatment cycles were pneumonia/pneumonitis, sepsis, febrile neutropenia and pyrexia. This was true for both treatment arms, however, incidence of these events was higher in the investigational arm compared to the standard arm. The number of patients with SAEs assessed to be

related to cytarabine was comparable between the treatment arms (26%), more patients had SAEs assessed to be related to daunorubicin in the investigational arm (12%) than in the standard arm (5%). Forty-one (41%) patients had SAEs assessed to be related to dasatinib.

Thirty-one adverse events led to premature termination of study treatment; more patients terminated study treatment due to an AE in the investigational arm (27%) than in the standard arm (4%), however, many terminations on the investigational arm occurred during the maintenance phase which was not included in the standard arm.

There were 10 (5%) deaths reported during study treatment, five each on both treatment arms. Most of the on-study deaths occurred during induction cycle 1 (60%). Five patients died due to infections (sepsis (n=3), bronchial pneumonia (n=1) and SARS CoV-2 infection (n=1)), three patients died due to multi-organ failure / death of unknown origin and two patients died due to respiratory disorders (ARDS and pneumonia).

Overall conclusion

In this randomized, open label, phase 3 trial of intensive chemotherapy with or without dasatinib in patients with CBF-AML, the primary endpoint of improvement of event-free survival was not reached. Similarly, all secondary outcome endpoints were negative. Although overall there was no particular safety signal and on-treatment deaths were distributed equally between the two treatment arms, there was an excess toxicity in the investigational arm, as demonstrated by a higher incidence of SAEs, most frequently pneumonia/ pneumonitis, sepsis, febrile neutropenia, and pyrexia.

Thus, the seemingly favorable outcome data reported in the two previous phase 1a/2 single arm studies evaluating dasatinib in combination with intensive chemotherapy in CBF-AML could not be confirmed in the randomized, phase 3 trial. Whether *KIT* mutations or deregulated expression of *KIT* may not be a suitable therapeutic target in CBF-AML, or whether the multi-kinase inhibitor dasatinib may not be a potent KIT inhibitor *in vivo* remains speculative. Currently, dasatinib is used *off-label* in combination with intensive induction chemotherapy by some clinicians for patients with CBF-AML. Based on the data from this randomized trial, the use of dasatinib for the treatment of patients with CBF-AML cannot be recommended. The addition of the TKI to standard-of-care intensive chemotherapy may even expose the patient to additional toxicity.

21. Date of Report

Date 04.02.2025

Prof. Dr. Hartmut Döhner
Coordinating Investigator

Appendix A: Response Definition

Response Definition:

Response to treatment was evaluated according to the following criteria (modified from the National Cancer Institute/Cancer and Leukemia Group B criteria, Ref: Cheson et al. 2003):

- Complete remission (CR)

Peripheral blood: neutrophils ≥1,000/µl and platelets > 100,000/µl and no leukemic blasts in the peripheral blood smear or by FACS analysis. Maturation of all cell lines and < 5% blasts by morphologic criteria and no Auer rods. Extramedullary involvement: no detectable involvement at any site.

- Complete remission with incomplete neutrophil or platelet recovery (CRi)

All of the above criteria for CR must be met, except that are neutrophils < 1,000/µl or thrombocytes < 100,000/µl in the peripheral blood.

- Partial remission (PR)

All of the above criteria for CR must be met, except that the bone marrow contains ≥ 5% but less than 25% blasts in cases of pretreatment BM-blasts above 50% or a ≥50% reduction of pretreatment blast count in cases with pretreatment BM-blasts 20-50%), or ≤ 5% blasts in the presence of Auer rods or abnormal morphology.

- Progressive disease (PD)

Patient surviving ≥ 7 days after completion of initial treatment course with increase of blast population in the bone marrow or peripheral blood or aggravation or new development of extramedullary disease or further deterioration or death due to leukemia. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be classified as having ‘symptomatic deterioration’. Every effort should be made to document the objective PD even after discontinuation of treatment.

- Refractory AML

No CR, CRi or PR

- Early death

Death during chemotherapy or within 7 days after completion of chemotherapy.

- Hypoplastic death

Deaths later than 7 days after completion of chemotherapy without regeneration of hematopoiesis, no new chemotherapy.

Appendix B
Background information and study rationale

Introduction

Clinical course of CBF-AML

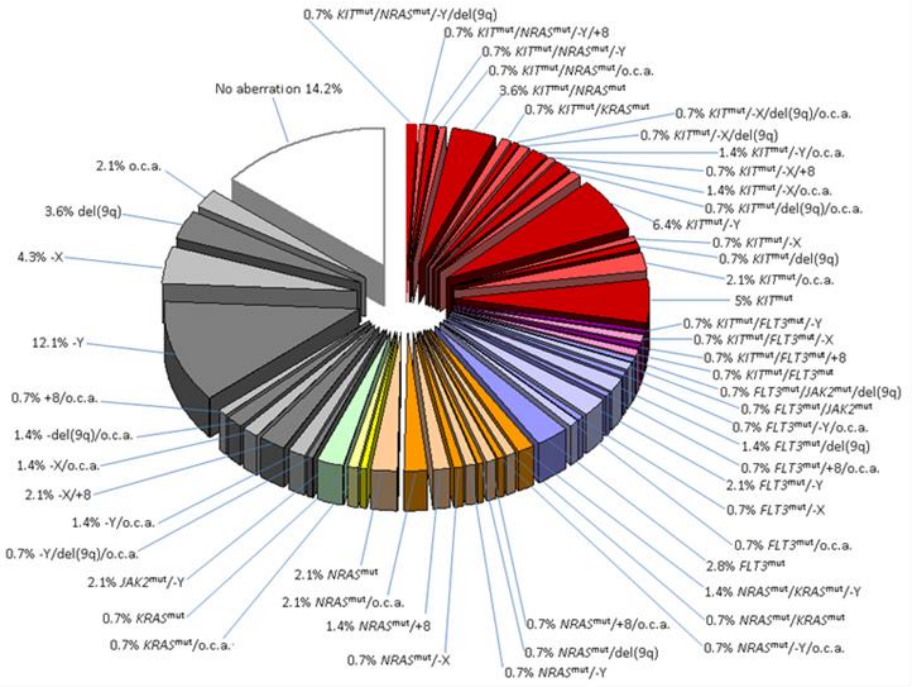
Acute myeloid leukemia (AML) with t(8;21)(q22;q22.1) and with inv(16)(p13.1q22) or the less frequent balanced translocation t(16;16)(p13.1;q22), are recognized by the World Health Organization (WHO) classification as unique entities within the category "AML with recurrent genetic abnormalities" (Swerdlow et al., 2008). Upon detection of these clonal genetic abnormalities the diagnosis of AML can be made regardless of the proportion of bone marrow (BM) blasts. CBF-AMLs are associated with a relatively favorable prognosis, in particular when treated with consolidation regimens containing repetitive cycles of high-dose cytarabine (Bloomfield et al., 1998; Byrd et al., 1999; Byrd et al., 2004; Delaunay et al., 2003; Marcucci et al., 2005; Nguyen et al., 2002; Schlenk et al., 2004; Paschka and Döhner, 2013). Outcome of older patients with CBF-AML is less favorable. In a French study on 147 patients with t(8;21) or inv(16) aged 60 years or older, almost 90% of patients achieved a complete remission (CR) following one to two courses of induction therapy (Prebet et al., 2009). This high CR rate is comparable to what is seen in younger CBF-AML patients indicating that chemosensitivity is retained in older patients. However, the leukemia-free survival (LFS) at 5 years in the French study was only 26%. Of note, the group of patients who received intensive postremission therapy appeared to have a superior LFS compared to those who received maintenance therapy only. When compared with maintenance therapy, the postremission therapy incorporating intermediate- to high-dose cytarabine was in trend associated with a superior LFS (*P*=.08; median LFS 26 *vs* 14 months), which was mainly due to a better LFS in patients with t(8;21) AML, but not in AML patients with inv(16). Overall, only approximately 50% of adult patients with CBF-AML are alive at 5 years.

Molecular basis of CBF-AML

At the molecular level, t(8;21) and inv(16) result in the fusion genes *RUNX1-RUNX1T1* and *CBFB-MYH11*, respectively, that lead to the disruption of the CBF complex, a transcription factor complex involved in the regulation of hematopoiesis (Downing, 2003; Fröhling et al., 2005). Full-length *RUNX1-RUNX1T1* and *CBFB-MYH11* fusions are considered as preleukemic conditions in CBF leukemogenesis, but they alone are not sufficient to induce leukemic transformation. The acquisition of additional genetic hits is necessary for the development of a leukemic phenotype. Secondary alterations cooperating with CBF fusion proteins in the process of leukemogenesis are e.g. mutations in genes encoding protein effectors controlling cell proliferation and/or conferring survival advantage to the malignant cells. Genes encoding tyrosine kinases, namely *KIT* (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) and *FLT3* (FMS-like tyrosine kinase), as well as N-and K-RAS guanosine triphosphatases, i.e. *NRAS* (neuroblastoma rat sarcoma viral oncogene homolog) and *KRAS* (Kirsten rat sarcoma viral oncogene homolog), have been identified as frequent secondary mutations in CBF-AML. Indeed, almost 90% of AML with t(8;21) (Figure 1) and more than 90% of AML with inv(16) harbor additional secondary chromosome aberrations and/or mutations affecting *KIT*, *FLT3*, *NRAS*, and *KRAS* (Paschka et al., 2009; Paschka et al., 2013).

This finding is consistent with the model that at least two types of mutations are required, one that leads to impaired differentiation (conferred by the gene fusions) and another that leads to the proliferative advantage (conferred by mutations in receptor tyrosine kinase or *RAS* genes) (Döhner K and Döhner H, 2008). However, data from recent next-generation sequencing studies indicate that additional functional categories of genes are involved in the pathogenesis of AML, including CBF-AML (Cancer Genome Atlas Research Network, 2013).

Figure 2: **Secondary chromosomal abnormalities and gene mutations in 141 AML with t(8;21) treated on AMLSG trials (Paschka and Döhner 2013).**



Mutations and deregulated expression of KIT in CBF-AML

High KIT expression is observed in hematopoietic stem cells (HSCs) (Pittoni et al., 2011). KIT, also designated as CD117, is commonly used as a phenotypic marker for HSCs. The KIT protein is a member of type III tyrosine kinases (RTK), which share a common protein structure consisting of five immunoglobulin-like domains in the extracellular part, a transmembrane domain (TM), an intracellularly located juxtamembrane (JM), and a split kinase domain. Under physiological conditions the monomeric KIT receptor dimerizes following the binding of its specific ligand, the stem cell factor (SCF), then KIT becomes autophosphorylated at key tyrosine sites, and activates downstream signaling pathways including the Ras/ERK, phosphatidylinositol 3-kinase (PI3-K), Src kinases, and JAK/STAT pathways (Pittoni et al., 2011). Both the KIT receptor and SCF are essential for the maintenance of normal hematopoiesis.

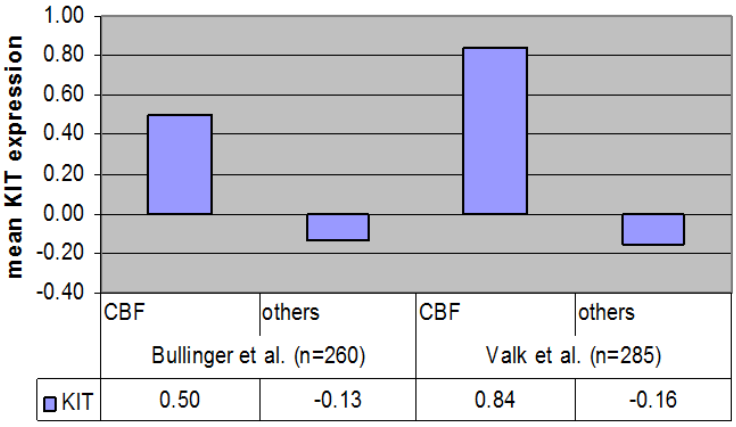
Ligand-independent constitutive KIT activation can be caused by gain-of-function mutations. Such mutations have been detected in various malignancies including mastocytosis, gastrointestinal stromal tumors, distinct type of melanoma, germ cell tumors, and AML. Although within all AML *KIT* mutations represent an infrequent molecular alteration, they can be detected in approximately one third of patients with CBF-AML representing the most frequently mutated RTK in CBF-AML (for review see Paschka and Döhner, 2013). The main muta-

tional clusters in CBF-AML include *KIT* exon 17 encoding the activation loop (A-loop), and exon 8, which encodes a region in the extracellular part of the receptor. Mutations involving TM and JM domains have been only rarely reported in CBF-AML (Cairoli et al., 2006; Corbacioglu et al., 2006; Shimada et al., 2007; Paschka et al., 2013; Kim et al., 2013). *In vitro* as well as mice studies support that mutant *KIT* is a sufficient cooperating second event in the development of CBF-AML. In a cytokine-dependent myeloid cell line (32D) the overexpression of common *KIT* A-loop and JM-mutants induced factor-independent growth, and the retroviral infection of NIH3T3 fibroblast cell line with these *KIT* mutants caused ligand-independent colony formation (Wang et al., 2011). Recent mice studies provided further evidence for mutant *KIT* as sufficient cooperative event in CBF leukemogenesis (Wang et al., 2011; Nick et al., 2012; Zhao et al., 2012). In addition, one mice study implicated that the KIT^{D814V} A-loop mutant (corresponding to human D816V) and a distinct *KIT* exon 8 mutant differ with respect to their transforming abilities (Nick et al., 2012). In this study, the co-expression of *Runx1-Runxt1* and KIT^{D814V} resulted in lethal hematopoietic malignancies of short term latency (2-4 months) in all cases including AML (45%), myeloproliferative neoplasia (35%), and pre-B ALL (20%), whereas only half of the mice that co-expressed *Runx1-Runxt1* and the *KIT* exon 8 mutant developed AML with a latency of 4-5 months within the observation time of one year; of note, AML was the only malignant hematologic phenotype noticed in these animals (Nick et al., 2012).

Retrospective studies have assessed the impact of *KIT* mutations as prognostic marker in t(8;21) and inv(16) AML. While in t(8;21) AML, in several, but not in all studies, *KIT* mutations, and particularly those affecting A-loop, have been associated with unfavorable outcome, the prognostic impact of *KIT* mutations in inv(16) AML is less clear (for review see Paschka and Döhner, 2013). In inv(16) AML the breakpoint variability in the *MYH11* gene results at least in 10 different fusion variants, with type A fusion being found in approximately 90% of the cases. One recent study in adult patients with inv(16) AML reported for the first time that *KIT* mutations at exons 8 and 17 do not occur in patients with non-type A *CBFB–MYH11* fusions (Schwind et al., 2013). In this study, patients with *KIT* mutations had significantly inferior EFS and OS compared to patients with type A *CBFB*-fusion and wildtype *KIT* and patients with non-type A *CBFB*-fusions. In contrast to adult CBF-AML, most pediatric studies did not show prognostic relevance of mutated *KIT*. Although the current data do not support the use of *KIT* mutational status in clinical practice to guide clinical decision making regarding therapeutic interventions, testing for *KIT* mutations as a prognostic marker has already been implemented into the NCCN (National Comprehensive Cancer Network) guidelines (O'Donnell et al., 2012). Indeed, according to the current NCCN guidelines AML with t(8;21) or inv(16) and mutated *KIT* are considered as intermediate-risk and not as favorable-risk AML. In contrast, within the international European LeukemiaNet (ELN) recommendations the assessment of *KIT* mutational status is currently not recommended as part of the initial routine diagnostic work-up and does so far not impact the patient management outside the context of a clinical trial (Döhner et al., 2010).

Global gene expression studies found *KIT* to be highly expressed in CBF-AML independent of its mutation status (Bullinger et al., 2004; Valk et al., 2004) (Figure 3). CBF-AML cases with mutated *KIT* show even higher *KIT* expression than those without *KIT* mutations (Lück et al., 2010).

Figure 3: Comparison of mean *KIT* expression between CBF- and non-CBF-AML using global gene expression profiling (from Bullinger et al., 2004; Valk et al., 2004).



Targeting KIT in CBF-AML

Thus, in CBF-AML there is a good rationale to use tyrosine kinase inhibitors (TKIs) to target both the overexpressed and mutated KIT. *In vitro* studies support the concept showing that exposure to TKIs inhibits growth of cells expressing wildtype *KIT* or various *KIT* mutants (Cammenga et al., 2005; Growney et al., 2005; Schittenhelm et al., 2006; Gleixner et al., 2006; Guerrouahen et al., 2010; Kampa-Schittenhelm et al., 2013; Gleixner et al., 2013). Notably, differential activity of specific TKIs with respect to the particular *KIT* mutations has been observed. The rationale to target *KIT* in the treatment of CBF-AML is further supported by a recent murine study, where leukemic cells co-expressing *RUNX1-RUNX1T1* and the A-Loop *KIT*^{N822K} mutant were injected into sublethally irradiated mice, and the animals were subsequently treated with cytarabine and/or the TKI dasatinib (Wang et al., 2011). The combination of cytarabine with dasatinib significantly prolonged the survival of the animals when compared to the treatment with both agents as single drugs.

In the ClinicalTrials.gov registry of the U.S. National Institutes of Health, the following clinical trials using dasatinib in AML are listed:

NCT 00850382: AMLSG 11-08 trial (see data below 4.3.3; Paschka et al. Leukemia. 2018 Jul;32(7):1621-1630)

NCT 01238211: Combination chemotherapy and dasatinib in treating patients with newly diagnosed acute myeloid leukemia (CALGB; n=61 patients enrolled; Marcucci G, et al. Blood Adv. 2020 Feb 25;4(4):696-705)

NCT 01876953: Dasatinib, cytarabine, and idarubicin in treating patients with high-risk acute myeloid leukemia (City of Hope Medical Center; n=20 patients enrolled; results not yet published)

NCT 00892190: Study of dasatinib and all-*trans* retinoic acid for relapsed/refractory and/or elderly patients with acute myelogenous leukemia (AML) (University of Pittsburgh).

One case report of a patient with t(8;21) and a *KIT*^{N822K} mutation treated with dasatinib has been published. Chevalier et al. (2010) reported on an *in vivo* differentiation of t(8;21)-positive AML blasts to neutrophilic granulocytes induced by treatment with dasatinib. The patient had relapsed three times after standard treatments, including allogeneic blood stem cell transplantation from an HLA-identical sibling. Within a week after starting dasatinib (70

mg BID initially), leukemic regrowth was mitigated, followed by progressive clearing of myeloid blasts and appearance of morphologically unusual neutrophils in the blood. Bone marrow aspirates taken 10 and 30 days after start of dasatinib showed a decrease of blasts from 86% to <10% with high levels of KIT expression and expansion of more mature myelopoiesis and eosinophils, still exhibiting the chromosomal rearrangement as assessed by FISH analysis. This interesting case report provides proof of prolonged *in vivo* differentiation of blasts bearing the t(8;21) to mature neutrophilic granulocytes following treatment with dasatinib that is reminiscent of the effect of all-*trans* retinoic acid in acute promyelocytic leukemia.

Targeting SRC family kinases

The SRC family kinases (SFKs) are activated in human AML cells. Data from a recent study demonstrate that the SFKs LYN, HCK or FGR are overexpressed and activated in AML progenitor cells (Dos Santos et al., 2013). Treatment with the SFK and c-KIT inhibitor dasatinib selectively inhibited human AML stem/progenitor cell growth *in vitro*. Dasatinib markedly increased the elimination of AML stem cells capable of engrafting immunodeficient mice by chemotherapeutic agents. *In vivo* dasatinib treatment enhanced chemotherapy induced targeting of primary murine AML stem cells capable of regenerating leukemia in secondary recipients. The data from this study suggest that enhanced targeting of AML cells by the combination of dasatinib with daunorubicin (DNR) may be related to inhibition of AKT mediated HDM2 phosphorylation, resulting in enhanced p53 activity in AML cells. Thus, targeting SFKs may provide an additional rationale of combining dasatinib and chemotherapy in AML.

Dasatinib

Dasatinib, formerly known as BMS-354825, is an ATP-competitive, dual SRC/ABL inhibitor. Dasatinib can inhibit BCR-ABL activation loop mutations that are found in some chronic myeloid leukemia patients with acquired resistance to imatinib. Some small-molecule SRC/ABL inhibitors also have been demonstrated to have potency against KIT kinase. In a study by Schittenhelm et al. (2006), dasatinib was shown to potently inhibit wildtype (wt) KIT with an IC50 of 5 to 10 nmol/l for inhibition of autophosphorylation and cellular proliferation. Dasatinib also potently inhibited KIT juxtamembrane domain mutations with an IC50 of 1 to 10 nmol/l. Notably, dasatinib is a potent inhibitor of KIT activation loop mutants, with IC50 values for inhibition of autophosphorylation of KIT D816 mutants in the range of 10 to 100 nmol/l. The potency seems to be differentially influenced by various activation loop mutations, i.e., *KIT* D816Y is 10-fold more sensitive to dasatinib that *KIT* D816V/F.

Taken together, based on the molecular profile of CBF-AML and the high activity of dasatinib against wt and mutant KIT, the compound appeared attractive for the treatment of patients with CBF-AML. In the phase I-III clinical trials evaluating dasatinib in imatinib-resistant CML, the drug was safe, well tolerated and effective. In 2006, dasatinib (Sprycel®) was approved by FDA and EMA for the treatment of CML resistant or intolerant to treatment with imatinib, and in 2010 dasatinib was approved for first-line therapy of CML.

Appendix C
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