

# Characteristics and outcome of patients with acute myeloid leukemia and trisomy 4

Sabine Kayser,<sup>1,2</sup> David Martínez-Cuadrón,<sup>3,4</sup> Maher Hanoun,<sup>5</sup> Friedrich Stölzel,<sup>6</sup> Cristina Gil,<sup>7</sup> H. Christian Reinhardt,<sup>5</sup> Eliana Aguiar,<sup>8</sup> Kerstin Schäfer-Eckart,<sup>9</sup> Juan Miguel Bergua Burgues,<sup>10</sup> Björn Steffen,<sup>11</sup> Teresa Bernal,<sup>12</sup> Stefan W. Krause,<sup>13</sup> Rosalía Ríaza,<sup>14</sup> Christoph Schliemann,<sup>15</sup> Jose Cervera,<sup>3,4</sup> Martin Kaufmann,<sup>16</sup> Laura Torres-Miñana,<sup>3,4</sup> Mathias Hänel,<sup>17</sup> Evelyn Acuña-Cruz,<sup>3,4</sup> Edgar Jost,<sup>18</sup> Jesus Lorenzo Algarra,<sup>19</sup> Martina Crysandt,<sup>18</sup> Lars Fransecky,<sup>20</sup> Javier Cornago-Navascues,<sup>21</sup> Sabrina Kraus,<sup>22</sup> Joaquin Martinez-Lopez,<sup>23</sup> Hermann Einsele,<sup>22</sup> Dirk Niemann,<sup>24</sup> Andreas Neubauer,<sup>25</sup> Ruth Seggewiss-Bernhardt,<sup>26</sup> Sebastian Scholl,<sup>27</sup> Stefan A. Klein,<sup>28</sup> Christoph Schmid,<sup>29</sup> Markus Schaich,<sup>30</sup> Martin Schmidt-Hieber,<sup>31</sup> Sven Zukunft,<sup>6</sup> Anthony D. Ho,<sup>32</sup> Uwe Platzbecker,<sup>1</sup> Claudia D. Baldus,<sup>20</sup> Carsten Müller-Tidow,<sup>32</sup> Christian Thiede,<sup>6</sup> Martin Bornhäuser,<sup>6</sup> Hubert Serve,<sup>11</sup> Mark J. Levis,<sup>33</sup> Pau Montesinos,<sup>3,4</sup> Christoph Röllig<sup>6</sup> and Richard F. Schlenk<sup>2,32,34</sup>

**Correspondence:** S. Kayser  
s.kayser@dkfz-heidelberg.de

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<sup>1</sup>Medical Clinic and Policlinic I, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; <sup>2</sup>NCT Trial Center, National Center of Tumor Diseases, German Cancer Research Center (DKFZ), Heidelberg, Germany; <sup>3</sup>Hematology Department, Hospital Universitari i Politècnic, La Fe, València, Spain; <sup>4</sup>CIBERONC, Instituto Carlos III, Madrid, Spain; <sup>5</sup>Department of Hematology and Stem Cell Transplantation, University Hospital Essen, Essen, Germany; <sup>6</sup>Department of Medicine I, University Hospital Carl-Gustav-Carus, Dresden, Dresden, Germany; <sup>7</sup>Hospital General, Alicante, Spain; <sup>8</sup>Clinical Haematology Department, Centro Hospitalar São João, Oporto, Portugal; <sup>9</sup>Department of Internal Medicine 5, Paracelsus Medical Private University Nürnberg, Nürnberg, Germany; <sup>10</sup>Hematology Department, Hospital San Pedro de Alcántara, Cáceres, Spain; <sup>11</sup>Department of Internal Medicine II, University Hospital of Frankfurt Main, Frankfurt Main, Germany; <sup>12</sup>Hospital Central de Asturias, Oviedo, Spain; <sup>13</sup>Department of Internal Medicine 5 – Hematology/Oncology, University Hospital of Erlangen, Erlangen, Germany; <sup>14</sup>Hematology Department, Hospital Universitario Severo Ochoa, Madrid, Spain; <sup>15</sup>University Hospital Muenster, Muenster, Germany; <sup>16</sup>Robert Bosch Hospital Stuttgart, Stuttgart, Germany; <sup>17</sup>Klinikum Chemnitz, Chemnitz, Germany; <sup>18</sup>Department of Hematology, Oncology, Hemostaseology, and Stem Cell Transplantation, Faculty of Medicine, University Hospital RWTH Aachen, Aachen, Germany; <sup>19</sup>Hospital General de Albacete, Albacete, Spain; <sup>20</sup>Department of Internal Medicine II, University Hospital of Kiel, Kiel, Germany; <sup>21</sup>Fundación Jiménez Díaz, Madrid, Spain; <sup>22</sup>Universitätsklinikum Würzburg, Würzburg, Germany; <sup>23</sup>Hospital 12 de Octubre, Complutense University, CNIO, Madrid, Spain; <sup>24</sup>Gemeinschaftsklinikum Mittelrhein gGmbH, Koblenz, Germany; <sup>25</sup>Philipps University Marburg, and University Hospital Giessen and Marburg, Marburg, Germany; <sup>26</sup>Medizinische Klinik V, Sozialstiftung Bamberg, Bamberg, Germany; <sup>27</sup>Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany; <sup>28</sup>Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany; <sup>29</sup>Department of Hematology and Oncology, Augsburg University Hospital, Augsburg, Germany; <sup>30</sup>Department of Hematology, Oncology and Palliative Care, Rems-Murr-Hospital Winnenden, Winnenden, Germany; <sup>31</sup>Department of Hematology and Oncology, Carl-Thiem-Klinikum, Cottbus, Germany; <sup>32</sup>Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany; <sup>33</sup>Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA and <sup>34</sup>Department of Medical Oncology, National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany.

## Abstract

We retrospectively studied 125 patients with acute myeloid leukemia and trisomy 4 (median age at diagnosis, 58 years; range, 16–77 years) treated between 2000 and 2019 within a multicenter study. Trisomy 4 was the sole abnormality in 28 (22%) patients and additional abnormalities were present in 97 (78%) patients. Twenty-two (22%) and 15 (15%) of 101 tested patients harbored *NPM1* and *FLT3*-ITD mutations. Two (3%) of 72 tested patients had double *CEBPA* mutations. Data on response to intensive anthracycline-based induction therapy were available for 119 patients. Complete remission was achieved in 67% (n=80) and the early death rate was 5% (n=6). Notably, patients with trisomy 4 as sole abnormality had

a complete remission rate of 89%. Allogeneic hematopoietic cell transplantation was performed in 40 (34%) patients, of whom 19 were transplanted in first complete remission. The median follow-up of the intensively treated cohort was 5.76 years (95% confidence interval [95% CI]: 2.99–7.61 years). The 5-year overall survival and relapse-free survival rates were 30% (95% CI: 22–41%) and 27% (95% CI: 18–41%), respectively. An Andersen–Gill regression model on overall survival revealed that favorable-risk according to the European LeukemiaNet classification (hazard ratio [HR]=0.34;  $P=0.006$ ) and trisomy 4 as sole abnormality (HR=0.41;  $P=0.01$ ) were favorable factors, whereas age with a difference of 10 years (HR=1.15;  $P=0.11$ ), female gender (HR=0.74;  $P=0.20$ ) and allogeneic hematopoietic cell transplantation (HR=0.64;  $P=0.14$ ) did not have an significant impact. In our cohort, patients with trisomy 4 as their sole abnormality had a high complete remission rate and favorable clinical outcome. Allogeneic hematopoietic cell transplantation did not seem to improve overall survival.

## Introduction

Trisomy 4 is a recurrent but very rare cytogenetic abnormality reported in patients with acute myeloid leukemia (AML).<sup>1,2</sup> In a large analysis on 5,876 younger adult AML patients treated in United Kingdom Medical Research Council trials, only 70 (1%) harbored trisomy 4.<sup>2</sup> The prognostic significance of this abnormality in AML patients is not clear. Informed clinical decision-making in situations in which cytogenetic analysis shows rare cytogenetic abnormalities has been hampered by a lack of consensus regarding the likely outcome of such patients. According to the National Comprehensive Cancer Network guidelines<sup>3</sup> as well as the European LeukemiaNet (ELN) recommendations<sup>4</sup> AML patients with trisomy 4 in the absence of further abnormalities would be assigned to the intermediate-risk group. However, this risk group comprises a rather large and heterogeneous set of abnormalities, leaving the impact of this particular abnormality on outcome unclear. Apart from the benefit of achieving greater consensus in cytogenetic classification, establishing the outcome associated with rare cytogenetic abnormalities is important, particularly given the results of a meta-analysis that has suggested that a relapse risk in excess of 35% can provide a useful working threshold to identify patients in whom allogeneic hematopoietic stem cell transplantation (HSCT) may confer a survival benefit.<sup>5</sup>

The prognosis of AML patients with trisomy 4 is controversial. While data from some cohort analyses suggest that their outcome is comparable to that of AML patients with normal cytogenetics,<sup>2,6</sup> others suggest a poorer outcome<sup>7</sup> compared to that of patients with intermediate-risk cytogenetics.<sup>8</sup> While the rate of complete remission after intensive anthracycline and cytarabine-based combination chemotherapy was comparable to that of patients with normal cytogenetics (87% vs. 90%;  $P=0.3$ ) and the 10-year cumulative incidence of relapse rate was almost identical (49% vs. 54%;  $P=0.7$ ), the 10-year overall survival rate was lower (16% vs. 38%;  $P=0.2$ ).<sup>2</sup> Allogeneic HSCT may improve survival if performed early in first complete remission. However, neither prospective clinical

nor larger retrospective cohort studies are available to support these results.

## Methods

### Patients and treatment

Information on 125 adult patients with AML and trisomy 4 diagnosed between 2000 and 2019 (2000–2010,  $n=48$ ; after 2010,  $n=77$ ) was collected within a large, multicenter international cohort (Study Alliance Leukemia [SAL],  $n=82$ ; Programa Español de Tratamientos en Hematología [PETHEMA],  $n=40$ ; Johns Hopkins University, Baltimore,  $n=3$ ). Detailed case report forms (including information on baseline characteristics, chemotherapy, allogeneic HSCT, response, and survival) were collected from all participating centers. Inclusion criteria were adult AML patients with trisomy 4 and all patients who fulfilled these criteria were included by the participating groups/institutions. The diagnosis of AML was based on French-American-British Cooperative Group criteria,<sup>9</sup> and, after 2003, on revised International Working Group criteria.<sup>10</sup> Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.<sup>11</sup> A complex karyotype was defined according to the 2017 ELN classification.<sup>4</sup> *FLT3* mutation screening for internal tandem duplications (ITD) and point mutations within the tyrosine kinase domain was carried out at each institution as previously described.<sup>12,13</sup> Data collection and analysis were approved by the institutional review boards of the participating centers.

### Treatment

Of the 125 patients, 119 (95%) received intensive induction treatment either within clinical trials ( $n=46$ ) or according to local institutional standards ( $n=73$ ). Treatment protocols for patients treated within the SAL ( $n=82$ ) included AML60+ ( $n=4$ ),<sup>14</sup> AML96 ( $n=12$ ),<sup>15</sup> AML2003 ( $n=21$ ),<sup>16</sup> and SORAML ( $n=2$ ).<sup>17</sup> Additionally, 43 patients were included within the prospective SAL registry (NCT03188874). All patients from PETHEMA ( $n=40$ ) were

included within the PETHEMA AML registry (NCT02607059).<sup>18</sup> The treatment protocols for patients treated within the PETHEMA included LMA2007 (n=1; NCT01041040), LMA2010 (n=3; NCT01296178), LMA2017 (n=1), as well as the CALGB/Ratify trial (n=1).<sup>19</sup> One patient from Johns Hopkins was included in a clinical trial and treated with ivosidenib,<sup>20</sup> the other two patients were treated according to local institutional standards.

Induction therapy for the 73 patients treated according to local institutional standards consisted of the anthracycline/cytarabine-based “7+3” regimen (n=66) or comparable intensive treatment (n=7). One of the 73 patients was treated with the “7+3” regimen in combination with gemtuzumab ozogamicin.

Six (5%) of the 125 patients were treated non-intensively. Of those, three received azacitidine therapy, one ivosidenib and two patients were managed with best supportive care. Response was assessed according to International Working Group recommendations.<sup>10</sup> All clinical studies were approved by the institutional review boards of the participating centers. All patients provided written informed consent to participation in one of the treatment trials or to therapy according to local standards.

### Statistical analyses

Survival endpoints, including overall survival, relapse-free survival, cumulative incidence of relapse and cumulative incidence of death in complete remission, were defined according to the revised recommendations of the International Working Group.<sup>10</sup> Comparisons of patients' characteristics were performed with the Kruskal-Wallis rank sum test for continuous variables and the Fisher exact test for categorical variables. To identify prognostic variables with respect to response to induction therapy a logistic regression model was used. Variables included ELN favorable-risk category, gender, trisomy 4 as sole abnormality, and age. The median follow-up time was computed using the reverse Kaplan-Meier estimate.<sup>21</sup> The Kaplan-Meier method was used to estimate the distribution of relapse-free survival and overall survival.<sup>22</sup> Confidence interval (CI) estimations for survival curves were based on the cumulative hazard function using the Greenwood formula for variance estimation. Log-rank tests were employed to compare survival curves between groups. Cumulative incidences of relapse and death and their standard errors were computed according to the method described by Gray<sup>23</sup> and included only patients attaining complete remission. The effect of allogeneic HSCT (including all transplanted patients) on overall survival as a time-dependent intervening event was tested in a multivariable Andersen-Gill model.<sup>24</sup> Variables included in the model were ELN favorable-risk, gender, trisomy 4 as sole abnormality, age with a difference of 10 years as well as allogeneic HSCT. All statistical analyses were performed with the statistical

software environment R, version 3.3.1, using the R packages *prolim*, version 1.5.7, and *survival*, version 2.39-5.<sup>25</sup>

## Results

### Study cohort

Demographic and clinical data were collected from 125 patients diagnosed with AML and trisomy 4 between 2000 and 2019. Their median age was 58 years (range, 16-77 years) and 62 patients (50%) were female. Most of the patients had *de novo* AML (79%). The baseline characteristics of the study cohort are summarized in Table 1.

**Table 1.** Baseline characteristics of patients with acute myeloid leukemia and trisomy 4.

|                                  | Number<br>(total=125) | %                  |
|----------------------------------|-----------------------|--------------------|
| Female gender                    | 62                    | 50                 |
| Median age                       | 58 years              | range, 16-77 years |
| Type of AML                      |                       |                    |
| <i>De novo</i>                   | 99                    | 79                 |
| Secondary AML                    | 15                    | 12                 |
| Therapy-related AML              | 8                     | 6                  |
| Missing                          | 3                     | 2                  |
| ECOG PS                          |                       |                    |
| 0                                | 36                    | 29                 |
| 1                                | 59                    | 47                 |
| 2                                | 19                    | 15                 |
| Missing                          | 11                    | 9                  |
| Cytogenetics                     |                       |                    |
| Sole trisomy 4                   | 28                    | 22                 |
| Additional abnormalities         | 97                    | 78                 |
| ≥3 abnormalities                 | 68                    |                    |
| Autosomal monosomies             | 20                    |                    |
| Monosomal karyotype <sup>#</sup> | 18                    |                    |
| Trisomy 4 & trisomy 8            | 43                    |                    |
| Trisomies only                   | 23                    |                    |
| t(8;21) or inv(16)               | 10                    |                    |
| Molecular genetics*              |                       |                    |
| <i>NPM1</i> mutated              | 22                    | 22                 |
| <i>FLT3</i> -ITD positive        | 15                    | 15                 |
| <i>CEBPA</i> double mutated      | 2                     | 3                  |
| ELN risk group                   |                       |                    |
| Favorable                        | 27                    | 22                 |
| Intermediate                     | 29                    | 24                 |
| Unfavorable                      | 66                    | 54                 |
|                                  | <b>Value</b>          | <b>Range</b>       |
| Median WBC x10 <sup>9</sup> /L   | 4.8                   | 0.4-255            |
| Platelets x10 <sup>9</sup> /L    | 47                    | 2-330              |
| Hemoglobin, g/dL                 | 9.1                   | 4.9-16.6           |
| Median BM blasts                 | 77                    | 1-100              |

Results may not add up to 100 due to rounding. <sup>#</sup>According to Breems et al.<sup>34</sup> \*Available for 101 (80%) patients. AML: acute myeloid leukemia; BM: bone marrow; ECOG PS: Eastern Cooperative Oncology Group performance status; ELN: European LeukemiaNet; *FLT3*: *fms-related tyrosine kinase 3*; ITD: internal tandem duplication; WBC: white blood cell count.

### Cytogenetic and molecular analyses

According to cytogenetic analysis, trisomy 4 was the sole abnormality in 28 (22%) patients, whereas additional abnormalities were present in a non-complex karyotype in 29 (22.5%) patients, and in a complex karyotype in 68 (54.5%) patients. The most frequent additional abnormality was trisomy 8 (n=43, 34.5%), karyotypes characterized by trisomies only (n=23, 18.5%) and t(8;21) or inv(16) (core binding factor; n=10, 8%). A total of 101 patients (80%) underwent testing for *NPM1* and *FLT3*-ITD mutations. Of those, 22 (22%) and 15 (15%) harbored *NPM1* and *FLT3*-ITD mutations, respectively. The *FLT3*-ITD allelic ratio was available for 12 (79%) of the ITD-positive patients and the median ratio was 0.66 (range, 0.01-1.43). Three (10%) of 29 patients with available data also harbored a *FLT3*-tyrosine kinase domain mutation. Two (3%) of 72 analyzed patients had double *CEBPA* mutations (Table 1). *KIT* mutational status was available for two of the ten patients with core binding factor leukemia; both were *KIT* wild-type. Next-generation sequencing data were available for a small subset of patients (12%, n=15/125). The gene panel included the following genes: *ASXL1*, *ATRX*, *BCOR*, *BCORL1*, *CBL*, *CDKN2*, *CSF3R*, *CUX1*, *DNMT3A*, *FBXW7*, *GATA1*, *GATA2*, *IDH1*, *IDH2*, *IKZF*, *JAK2*, *KDM6A*, *KIT*, *KRAS*, *NOTCH1*, *NRAS*, *PDGFRA*, *PHF6*, *PTPN11*, *RAD21*, *RUNX1*, *SF3B1*, *SMC1A*, *SMC3*, *STAG2*, *TET2*, *TP53*, *U2AF1*, *WT1*, *ZRSR2*, *BRAF*, *CALR*, *CBL*, *ETV6*, *GNAS*, *HRAS*, *MPL*, *MYD88*, *PTEN*, *SETBP1* and *SFRS2*. When we grouped the mutations according to their function, the identified gene mutations were found in all functional groups. However, the mutational profile was dominated by mutations in methylation-related genes (n=15; *DNMT3A*, n=4; *IDH1/2*, n=2, each; *TET2*, n=7), transcription factors (*RUNX1*, n=4), chromatin remodeling (*ASXL1*, n=2), RAS pathway (*KRAS*, n=1; *NRAS*, n=2) and tumor suppressors (n=3; *WT1*, *TP53* and *PHF6*, n=1, each). Single mutations were found in *EZH2*, *FBXW7*, *KDM6A*, *U2AF1* and *ZRSR2*. None of the other genes was mutated.

### Response to induction therapy

Data on response to intensive induction therapy were available for all 119 patients. Eighty (67%) achieved a complete remission after induction therapy. Early death occurred in six (5%) patients.

Six patients were treated less intensively because of higher age (median; 67.5 years; range, 31-77 years) or comorbidities. Among these patients, only one achieved a complete remission, after 85 days of ivosidenib treatment. The patient is in an ongoing complete remission which has lasted more than 4 years so far. Cytogenetically, the patient had trisomy 4 as well as deletion of the long arm of chromosome 7. Molecularly, *IDH1* and *NPM1* mutations were detected.

All other patients died early (median, 2.4 months; range, 0.03-7.7 months).

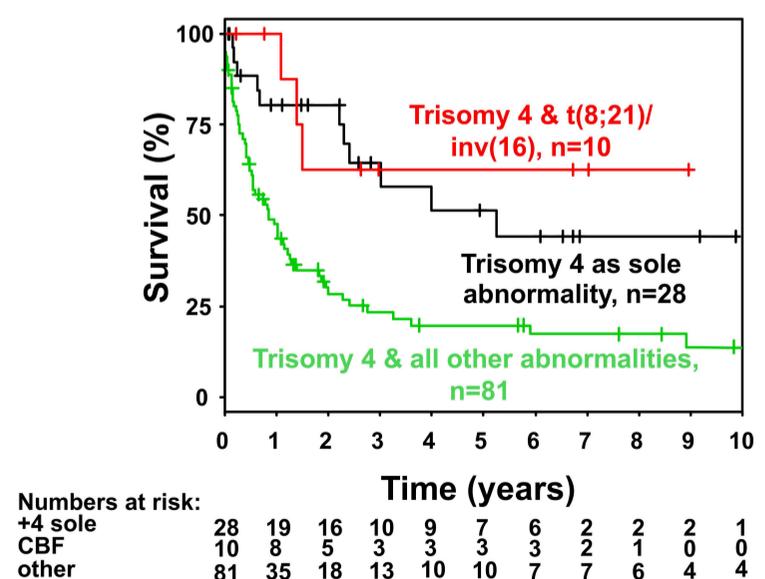
Notably, patients with trisomy 4 as sole abnormality had a complete remission rate of 89% (n=25/28) and those with trisomy 4 in combination with t(8;21) or inv(16) of 100% (n=10/10).

There was no difference in the complete remission rate between *FLT3*-ITD-positive (71%) and *FLT3*-wildtype (68%) patients ( $P=0.99$ ). Univariable analysis revealed that trisomy 4 as sole abnormality (odds ratio [OR]=5.39;  $P=0.005$ ) and *NPM1* (OR=11.46;  $P=0.003$ ) were favorable factors. A logistic regression model revealed that female gender (OR=2.60;  $P=0.03$ ) and ELN favorable-risk (OR=12.84;  $P=0.02$ ) were favorable factors and trisomy 4 as sole abnormality showed a tendency (OR=3.27;  $P=0.08$ ) to be favorable.

### Further therapy including intensive consolidation and allogeneic hematopoietic stem cell transplantation

Sixty-one (76%) of eighty intensively treated patients in first complete remission received intensive consolidation chemotherapy consisting of high-dose cytarabine with or without additional chemotherapy. Nineteen (14%) patients proceeded to allogeneic HSCT in first complete remission with eight of the transplanted patients receiving consolidation chemotherapy prior to transplantation. There was no difference in baseline characteristics between patients proceeding to allogeneic HSCT in first complete remission and patients receiving consolidation chemotherapy, such as median white blood cell count ( $P=0.42$ ), median age ( $P=0.08$ ), *NPM1* mutations ( $P=0.99$ ), *FLT3*-ITD ( $P=0.71$ ) and ELN-risk classification ( $P=0.60$ ).

Among the patients consolidated with chemotherapy, relapses occurred in 35 and seven died of a treatment-related cause after consolidation. In patients consolidated with allogeneic HSCT in first complete remission, ten patients relapsed and most of them died shortly



**Figure 1. Kaplan-Meier plot of overall survival in intensively treated patients according to cytogenetic abnormality.** +4 sole: trisomy 4 as sole cytogenetic abnormality; CBF: core binding factor.

thereafter (median, 3.3 months; range, 0-96.2 months). Only two patients survived beyond 1 year after relapse due to either a second allogeneic HSCT (n=1, survival after relapse, 96.2 months) or repetitive cycles of lenalidomide and azacitidine (n=1; survival after relapse, 25.7 months). Among those relapsing after chemotherapy, allogeneic HSCT was performed in 21 patients.

### Characteristics of patients undergoing allogeneic hematopoietic stem cell transplantation

Allogeneic HSCT was performed in 40 (32%) patients, of whom 19 were transplanted in first complete remission after induction therapy. Nine patients achieved complete remission after salvage chemotherapy and went on to allogeneic HSCT; another 12 patients underwent allogeneic HSCT with active disease. Twelve patients received myeloablative conditioning and 24 patients reduced-intensity conditioning (data were missing for 4 patients). The type of donor was matched related in eight cases, matched unrelated in 31 cases, and unknown in one of the 40 patients.

### Relapse-free and overall survival

The median survival of the non-intensively treated patients was 0.33 years. Only one patient treated with ivosidenib survived more than 4 years. The median follow-up of the intensively treated cohort was 5.76 years (95% CI: 2.99-7.61 years). Five-year overall survival and relapse-free survival were 30% (95% CI: 22-41%) and 27% (95% CI: 18-41%), respectively.

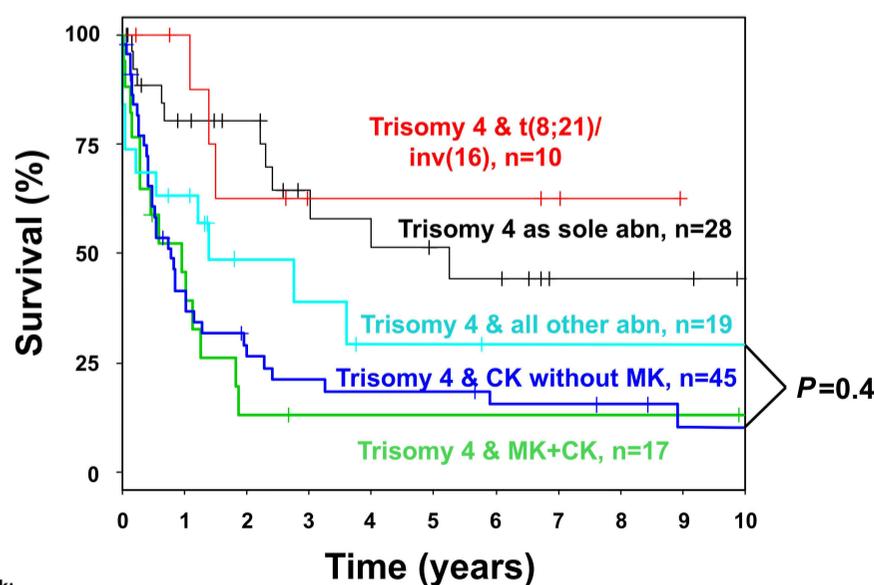
Overall survival rates were significantly higher in patients with core binding factor leukemia or patients with trisomy 4 as a sole abnormality as compared to those with trisomy 4 and all other abnormalities (Figure 1) ( $P < 0.001$ ). There was no difference between overall survival rates in patients with a complex karyotype, a complex karyotype

without monosomal karyotype or monosomal karyotype (Figure 2) ( $P = 0.4$ ). An Andersen-Gill model including allogeneic HSCT as a time-dependent covariable revealed ELN favorable-risk class (hazard ratio [HR]=0.34;  $P = 0.006$ ) and trisomy 4 as sole abnormality (HR=0.41;  $P = 0.01$ ) as favorable factors, whereas age with a difference of 10 years (HR=1.15;  $P = 0.11$ ), female sex (HR=0.74;  $P = 0.20$ ) and allogeneic HSCT (HR=0.64;  $P = 0.14$ ) had no significant impact. There was no difference in overall survival measured from the date of allogeneic HSCT if the patients proceeded to the transplant in first complete remission (n=19) or with active disease (n=21;  $P = 0.60$ ) (Figure 3). In patients achieving a first complete remission, the 5-year relapse-free survival was 19% (95% CI: 4-90%) for those patients proceeding to allogeneic HSCT (n=19) as compared to 28% (95% CI: 18-42%) for those who received consolidation chemotherapy (n=61).

There was not a significant difference in cumulative incidence of relapse between patients proceeding to allogeneic HSCT and those who were treated with consolidation chemotherapy ( $P = 0.60$ ) (Figure 4). The same was true for cumulative incidence of death ( $P = 0.13$ ) (Figure 4).

## Discussion

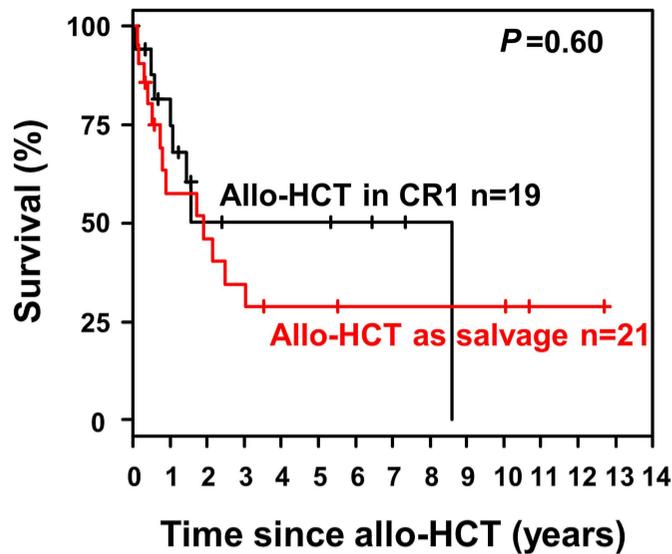
The focus of our study was to characterize adult AML patients with trisomy 4 in an international, multicenter cohort study and compare outcomes according to treatment strategies, with a specific focus on the impact of allogeneic HSCT as compared to conventional chemotherapy on survival. Trisomy 4 is very rare, particularly as a sole abnormality.<sup>6,7,26</sup> Its prognostic relevance has been debated<sup>2,7,8</sup> and its association with outcome remains unclear. We here present the largest cohort of 125 patients with trisomy 4 to date, of whom 119 were treated inten-



Numbers at risk:

|               |    |    |    |    |   |   |   |   |   |   |   |
|---------------|----|----|----|----|---|---|---|---|---|---|---|
| +4 sole       | 28 | 19 | 16 | 10 | 9 | 7 | 6 | 2 | 2 | 2 | 1 |
| CBF           | 10 | 8  | 5  | 3  | 3 | 3 | 3 | 2 | 1 | 0 | 0 |
| CK & MK       | 17 | 7  | 2  | 1  | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| CK without MK | 45 | 17 | 11 | 8  | 7 | 7 | 5 | 5 | 4 | 2 | 2 |
| other         | 19 | 11 | 5  | 4  | 2 | 2 | 1 | 1 | 1 | 1 | 1 |

**Figure 2. Kaplan-Meier plot on overall survival in intensively treated patients according to cytogenetic abnormality including complex karyotype and monosomal karyotype.** +4 sole: trisomy 4 as sole cytogenetic abnormality; CBF: core binding factor; CK: complex karyotype; MK: monosomal karyotype.



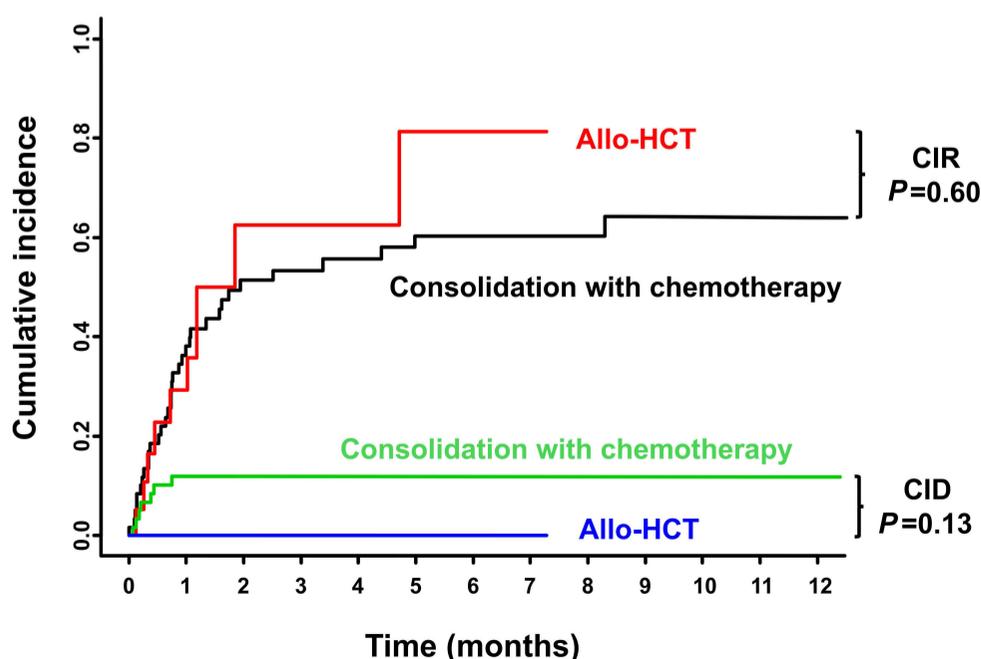
**Figure 3. Overall survival after allogeneic hematopoietic stem cell transplantation according to remission status.** Allo-HCT: allogeneic hematopoietic stem cell transplantation; CR1; first complete remission.

sively. In line with a previous publication,<sup>6</sup> the complete remission rate was high in our cohort in those patients with trisomy 4 as a sole abnormality. Nevertheless, most patients relapsed, a fate which seems not to have been improved by allogeneic HSCT, suggesting that other treatment approaches are needed to prolong survival. The only factors associated with prolonged survival were ELN favorable-risk classification and trisomy 4 as the sole abnormality, confirming the findings of Chilton *et al.*<sup>6</sup> Secondary chromosome aberrations can be detected in more than three quarters of cases with trisomy 4. The most frequent secondary chromosome aberrations in our cohort were trisomy 8 and in roughly half of the cases a complex karyotype. In contrast to previous reports, we did not observe a high frequency of *FLT3*-ITD<sup>7</sup> or *NPM1* mutations in our cohort.<sup>27</sup> Although *cKIT* is located on chromosome 4q12, mutations in *cKIT* seem to be infrequent in patients with trisomy 4.<sup>7</sup> Nevertheless, we cannot exclude *KIT* overexpression, as a result of chromosomal gain, which may contribute to leukemogenesis in these cases,

particularly in those with trisomy 4 as a sole abnormality. In a small subset of our patients, next-generation sequencing data were available. Regarding the molecular make-up, our data are in line with those of Bhatnagar *et al.*<sup>27</sup> Besides *NPM1* and *FLT3*, the most frequently mutated genes were *TET2*, *RUNX1*, *DNMT3A* and *IDH1/2*. In contrast to us, Bhatnagar *et al.* did not identify any case with an *ASXL1* or *WT1* mutation.<sup>27</sup> To date, however, the pathogenic role of trisomy 4 *per se* in leukemogenesis is still unclear. An association of therapy-related AML and development of AML with trisomy 4 has been suggested,<sup>28</sup> although not confirmed by others.<sup>7,29</sup> We did not observe a high rate of patients with therapy-related AML in our cohort.

Of note, allogeneic HSCT, particularly when performed in first complete remission, resulted in an equally high relapse rate as that of patients receiving consolidation chemotherapy and did not improve outcome in our cohort based on an Andersen-Gill model taking into account the time dependency of allogeneic HSCT. This is in line with our recent findings in a cohort of AML patients characterized by trisomy 19.<sup>30</sup> Nonetheless, this is in contrast to previous reports<sup>31-33</sup> focusing on other trisomies such as +8, +11, +13 and +21 and may indicate that the outcomes of patients with trisomies need to be evaluated individually. However, we would like to emphasize that retrospectively collected data have serious limitations since the factors for allocating patients to allogeneic HSCT, such as co-morbidities, individual assessment of the treating physician, choice of conditioning, and availability of a donor, remain unknown; this limitation also needs to be taken into account when assessing the value of allogeneic HSCT in our series. Additionally, data from multicenter cohort studies potentially introduce biases related to enrollment criteria for those studies, which may have excluded certain populations.

In conclusion, patients with trisomy 4 are very heterogeneous, in particular with respect to cytogenetic and molecular abnormalities. In our cohort, patients with tri-



**Figure 4. Cumulative incidences of relapse and death according to treatment strategy.** These analyses included only patients who attained complete remission. Allo-HCT: allogeneic hematopoietic stem cell transplantation; CIR: cumulative incidence of relapse; CID: cumulative incidence of death.

somy 4 as their sole abnormality as well as those with trisomy 4 in combination with ELN favorable-risk genetics had a high complete remission rate and favorable clinical outcome. Considering the whole cohort, allogeneic HSCT appeared not to improve overall survival. The shortcomings of retrospective cohort studies do, however, need to be taken into account.

### Disclosures

No conflicts of interest to disclose.

### Contributions

SK and RFS were responsible for the concept of this paper, contributed to the literature search data collection, analyzed and interpreted data, and wrote the manuscript. DM-

C, MH, FS, CG, HCR, EA, KS-E, JMBB, BS, TB, SWK, RR, CS, JC, MK, LT-M, MH, EA-C, EJ, JLA, MC, LF, JC-N, SK, JM-L, HE, DN, AN, RS-B, SS, SAK, CS, MS, MS-H, SZ, ADH, UP, CDB, CM-T, MB, HS, ML, PM, and CR contributed patients and critically revised the manuscript. CTh performed research and critically revised the manuscript. All authors reviewed and approved the final manuscript.

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### Data-sharing statement

Questions regarding data sharing should be addressed to the corresponding author.

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