SIMULTANEOUS SESSION II

Acute myeloid leukemia - Trial design and novel agents

1091A

EVALUATION OF THE CLINICAL IMPACT OF DIFFERENT CATEGORIES IN AML WITH MDS-RELATED CHANGES DEFINED ACCORDING TO THE WHO CLASSIFICATION IN A LARGE COHORT OF 2392 NEWLY DIAGNOSED ADULT AML PATIENTS

S Kayser[1], K Doehner[1], J Krauter[2], CH Koehne[3], HA Horst[4], G Held[5], M von Lilienfeld-Toal[6], M Ringhoffer[7], M Rummel[8], U Germing[9], K Goetze[10], D Nachbaur[11], H Salwender[12], B Schlegelberger[13], G Goehring[13], D Spaeth[1], C Morlok[1], V Teleanu[1], A Ganser[2], H Doehner[1], R Schlenk[1]

[1]University Hospital of Ulm, Ulm, Germany
[2]Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover, Germany
[3]Department of Oncology and Hematology, Klinikum Oldenburg, Oldenburg, Germany
[4]Department of Internal Medicine II, University Hospital Schleswig-Holstein Kiel, Kiel, Germany
[5]Department of Internal Medicine, University of Saarland, Homburg, Germany
[6]Department of Internal Medicine III, University Hospital of Bonn, Bonn, Germany
[7]Department of Internal Medicine III, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany
[8]Department of Internal Medicine IV, University Hospital of Giessen, Giessen, Germany
[9]Department of Hematology, Oncology and Immunology, Heinrich-Heine-University, Duesseldorf, Germany
[10]Department of Internal Medicine III, University of Munich, Munich, Germany
[11]Department of Internal Medicine V, University Hospital Innsbruck, Innsbruck, Austria
[12]Asklepios Klinik Altona, Hamburg, Germany
[13]Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover, Germany

Background. The current WHO classification defines acute myeloid leukemia (AML) with a prior history of myelodysplastic/myeloproliferative neoplasm (MDS/MPS), AML with multilineage dysplasia and AML with specific cytogenetic abnormalities as AML with MDS-related changes (MRC-AML). These patients are considered to have an inferior outcome compared with *de novo* AML. Whether this is due to an adverse genetic risk profile or by the fact of MRC-AML per se remains open. In addition, the prognostic impact of the different subcategories has not been evaluated. The minimal time period between diagnosis of preceding MDS/MPN and subsequent AML is defined differently (≥one month by Cheson et al. JCO 2003 versus ≥six months according to WHO 2001). **Aims.** To study the clinical impact of MRC-AML in a large cohort of newly diagnosed AML patients in the context of clinical and genetic characteristics. **Methods.** The study included 3177 adult patients (median age, 54.5 years; range, 16-85 years), entered on five protocols of the German-Austrian AML Study Group between 1993 and 2008, using intensive induction and consolidation therapy. Information on type of AML, karyotype and molecular marker status of *NPM1*, *FLT3* and *CEBPA* was available in 96%, 91%, 90%, 85% and 74% of the patients, respectively. Patients with therapy-related AML (n=200), those with recurrent cytogenetic abnormalities according to the WHO classification (n=452) and those lacking information on type of AML (n=133) were excluded. **Results.** Of 2392 patients, 210 (9%) had a history of preceding MDS/MPN (n=69, one to six months; n=141, >six months) and 197 (8%) had evidence of multilineage dysplasia. MDS-related cytogenetic abnormalities were present in 468 of 2099 (22%) patients with available cytogenetics, in 51 of 201 (25%) with prior MDS/MPN and in 56 of 197 (28%) patients with multilineage dysplasia. MRC-AML patients were significantly older compared with *de novo* AML (median age, 58 versus 53 years, p<0.0001) with highest median age in the subgroup defined by a history of preceding MDS/MPN of at least six months (median age, 62 years). White blood counts were significantly and consistently lower (p<0.0001) in MRC-AML (median 5.0/nl) compared with *de novo* AML (median, 17.4/nl), whereas percentage of blast cells in bone marrow and peripheral blood were equally high in *de novo* AML and AML with MDS-related cytogenetics, but substantially lower in all other subcategories of MRC-AML. Notably, the incidence of *NPM1*-wildtype/*FLT3*-ITDnegative/*CEBPA*negative (triple negative) normal karyotype AML was more than twice as high in MRC-AML compared with *de novo* AML (62% versus 24%; p<0.0001). In uni- as well as multivariable analyses MRC-AML was associated with an inferior outcome for all clinical endpoints compared with *de novo* AML. Within the group of MRC-AML, the subcategory defined by multilineage dysplasia was associated with a superior outcome compared with the other MRC-AML subcategories. Of note, in the genetically defined subset of triple-negative normal karyotype AML MRC-AML lost its prognostic impact. **Conclusions.** In this large cohort of adult AML patients, MRC-AML was an adverse prognostic factor. However, in genetically well defined subgroups this prognostic impact gets lost.

1091B

THE GERMAN AML INTERGROUP STUDY: COMPARISON OF OUTCOME OF THE DIFFERENT TREATMENT STRATEGIES OF FIVE STUDY GROUPS WITH A COMMON STANDARD TREATMENT WHILE ADJUSTING FOR INFLUENTIAL BASELINE VARIABLES

M Pfirrmann[1], R Schlenk[2], M Schaich[3], K Doehner[2], R Krahl[4], J Krauter[5], G Heil[6], U Krug[7], M Sauerland[8], A Heinecke[8], D Spaeth[2], M Kramer[3], S Scholl[9], W Berdel[7], W Hiddemann[10], D Hoelzer[11], R Hehlmann[12], J Hasford[13], V Hoffmann[14], H Doehner[2], G Ehninger[3], A Ganser[5], D Niederwieser[4], T Buechner[7]

[1]Depart of Med Inform, Biometry, a. Epidemiology,, Munich, Germany
[2]Department of Internal Medicine III, University of Ulm, Ulm, Germany
[3]Department of Internal Medicine I, University of Dresden, Dresden, Germany
[4]Department of Hematology / Oncology, University of Leipzig, Leipzig, Germany
[5]Depart. of Hematology, Oncology and Stem Cell Transpl., Hannover Medical School, Hannover, Germany
[6]Department of Internal Medicine V, Klinikum Luedenscheid, Luedenscheid, Germany
[7]Depart. of Medicine A - Hematology, Oncology, Pneumology, University of Muenster, Muenster, Germany
[8]Department of Biostatistics and Clinical Research, University of Muenster, Muenster, Germany
[9]Department of Internal Medicine II, Hematology / Oncology, University of Jena, Jena, Germany
[10]Department of Internal Medicine III, Ludwig Maximilian University Munich, Munich, Germany
[11]Department of Hematology / Oncology, University of Frankfurt, Frankfurt, Germany
[12]Department of Internal Medicine Mannheim, University of Heidelberg, Mannheim, Germany
[13]Depart of Med, Inform, Biometry, a. Epidemi., Munich, Germany
[14]Depart. of Med. Inform., Biometry, a. Epidemiology, Ludwig Maximilian University, Munich, Germany

Background. Patients with acute myeloid leukemia (AML) used to participate in different clinical trials launched by five German study groups. Each study group pursued its own treatment strategy with respect to dosage of chemotherapy during induction and consolidation therapy as well as to the use of allogeneic hematopoietic stem cell transplantation (HSCT) and maintenance therapy. **Aims.** To possibly identify a treatment strategy superior to the others, adjusted clinical outcome was compared between the study groups. **Methods.** The five groups agreed on upfront randomization of 10% of their patients into a common standard treatment arm. Standard induction treatment consisted of two courses of cytarabine 100 mg/m²/d for one week plus daunorubicin 60 mg/m²/d on three days. Consolidation therapy consisted of either three cycles of standard high-dose cytarabine or, based on cytogenetic risk, an allogeneic HSCT. The remaining 90% of the patients of each study group were allocated / randomized to treatments according to each study groups' own trial design. Inclusion criteria were primary AML or AML secondary to cytotoxic treatment or to myelodysplastic syndrome, diagnosed at 16-60 years. Patients with acute promyelocytic leukemia were excluded. Endpoints for the intention-to-treat comparisons of each study-internal treatment strategy with the common standard treatment were percentage of complete remission (CR) and CR with incomplete recovery (CRi) after induction therapy, overall survival (OS), relapse-free survival (RFS), and event-free survival (EFS). To adjust for variations in baseline characteristics, differences in survival probabilities were assessed through multiple Cox regression. Direct adjusted survival curves based on the Cox model were estimated. Regarding CR / CRi, adjustment for prognostic variables was performed through multiple logistic regression. **Results.** Of 3171 patients eligible for analysis, 305 were randomized to the standard treatment and 828, 373, 235, 808, and 622 to the five study group-specific treatment arms, respectively. CR/CRi rate after induction therapy was 70% (95% confidence interval (CI): 65-76%) in the common standard arm and ranged from 74% to 82% in the study group-internal treatment strategies. Also when adjusted for prognostically significant baseline variables, with 82%, one study group presented a significantly better result than the standard treatment arm. With the standard treat-

ment, the adjusted five-year OS probability was 44% [95% CI: 37-50%]. The five-year OS probabilities of the studies' internal treatment strategies ranged from 42-48%. Adjusted five-year RFS probabilities were 46% [95% CI: 38-53%] in the standard arm and 36-48% in the studies' internal treatment groups. The adjusted five-year EFS probability of the standard arm was 33% [95% CI: 27-39%] and 29-39% in the studies' internal groups. Adjusting for influential baseline variables, no significant difference with regard to OS, RFS, or EFS was observed between the standard treatment arm and any of the five internal treatment strategies. **Conclusions.** Due to the lacking differences with regard to all survival endpoints, we conclude that the overall treatment strategies of the five study groups were neither worse nor better than the concept of the standard treatment arm. However, in further detailed analysis, AML subgroups may profit from specific regimen used within the study groups.

1091C

EPIGENETIC THERAPY IS ASSOCIATED WITH SIMILAR SURVIVAL COMPARED WITH INTENSIVE CHEMOTHERAPY IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

A Quintas-Cardama, J Cortes, T Liu-Dumlao, F Ravandi, M Brandt, S Faderl, S Pierce, G Borthakur, G Garcia-Manero, H Kantarjian
M.D. Anderson Cancer Center, Houston, United States of America

Background. The prognosis of pts with acute myeloid leukemia (AML) aged 60 and above (AML>60) is very poor. The complete remission (CR) rates among older patients with AML treated with a standard combination of cytarabine and an anthracycline (e.g. 7+3) are 35%-60% but the early (4-8 weeks) mortality is high (20-50%), which result in median survival of 4-7 months. Epigenetic therapy (decitabine, azacitabine, histone deacetylase inhibitors) is standard in MDS. We compared the outcomes of elderly patients with AML treated with standard chemotherapy vs epigenetic therapy.**Methods**. We examined 909 pts with newly diagnosed AML>60 treated either with epigenetic therapy (n=130, 78 decitabine-based, 52 azacitidine-based) or with intensive chemotherapy (n=779) between 2000 and 2010. Of the 779 pts receiving chemotherapy, 34% received AI (ara-C 1.5g/m^{2}x3d and idarubicin 12mg/m^{2}x3d) and 22% high dose araC-based chemotherapy. No differences were observed regarding cytogenetic grouping (p=0.44), including the proportion of patients with poor karyotypes (25% vs 32%; p=0.13), or regarding performance status 0-2 (740 [95%] vs 124 [95%], p=0.8).

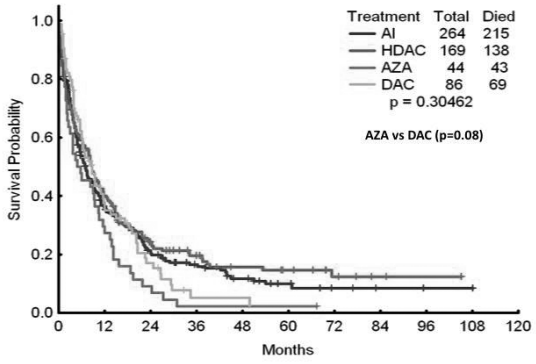

Figure 1. Overall survival of patients with AML>60 according to therapeutic modality

Results. The CR rates for patients treated with chemotherapy and epigenetic therapy were 47% and 28%, respectively (p=0.0001) while the overall response rate (ORR=CR+CR with incomplete platelet recovery) was 53% and 29% (p=0.0001). Early mortality rates (8 weeks) for both groups were 16% and 11%, respectively (p=0.13). The 2-year relapse free survival (RFS) and OS for the chemotherapy and epigenetic therapy groups were similar at 37% vs 37% mos (p=0.9) and 7.6 vs 6.9 mos (p=0.13), respectively. When the analysis was limited to the 325 pts with poor risk cytogenetics (e.g. -5 and/or -7, complex), the CR rates for pts receiving chemotherapy (n=271) or epigenetic therapy (n=54) were 31% and 33% (p=0.06) while median OS was 4.2 vs 6.2 weeks (p=0.3), respectively. The corresponding CR rates for patients with diploid karyotype were 58% vs 31% (p=0.0001). However, median OS was 12.7 vs 9.5 mos, p=0.088. Similarly, CR rates for patients carrying the *FLT3*-ITD mutation were 56% vs 42% (p=0.469) with median OS of 7.6 vs 9.2 months (p=0.73). The CR rate (25% vs 29%, p=0.6) and OS (4.8 vs 8.5 mos, p=0.08) for pts treated with azacitidine/azacitidine-based or decitabine/decitabine-based therapy showed a trend towards improved outcomes with decitabine. A multivariate analysis of these prognostic factors for survival identified the following to be independently adverse: older age (p=0.002), adverse cytogenetics (p=0.004), poor performance (p<0.0001), elevated creatinine (p<0.0001), leukocytosis (p=0.002), and prior chemotherapy for other cancers (p=0.2). Repeating the multivariate analysis for pts ≥70 years identified the same first 4 prognostic factors. The median OS of pts who failed (but not died after) initial AML therapy (114 chemotherapy, 33 azacitidine, 60 decitabine) after first salvage therapy was 1.2 mos with intensive chemotherapy, 1.1 mos with azacitidine and 3.1 mos with decitabine (p=0.036). **Conclusions**. This retrospective analysis in a large cohort of pts with AML>60 treated at our institution over the last decade showed similar long-term outcomes with epigenetic therapy versus intensive chemotherapy

1091D

THE SEQUENTIAL COMBINATION OF GEMTUZUMAB OZOGAMICIN AND INTENSIVE CHEMOTHERAPY DOES NOT BENEFIT OLDER PATIENTS WITH UNTREATED AML: RESULTS OF THE EORTC-GIMEMA AML-17 RANDOMIZED TRIAL

S Amadori[1], S Suciu[2], H Salih[3], D Selleslag[4], P Muus[5], P De Fabritiis[6], A Venditti[1], A Ho[7], M Lubbert[7], X Thomas[8], R Latagliata[9], C Halkes[10], F Falzetti[11], D Magro[12], JE Guimarães[13], Z Berneman[11], G Specchia[11], P Fazi[14], M Vignetti[14], M Karrasch[2], R Willemze[10], T De Witte[5], JP Marie[15]
[1]Tor Vergata University Hospital, Roma, Italy
[2]EORTC, Brussels, Belgium
[3]E.K. University, Tuebingen, Germany
[4]A.Z. St. Jan, Brugge, Belgium
[5]Radboud University, Nijmegen, Netherlands
[6]San Eugenio Hospital, Rome, Italy
[7]University Klin., Heidelberg, Germany
[8]E. Herriot Hospital, Lyon, France
[9]University Sapienza, Rome, Italy
[10]University Medical Center, Leiden, Netherlands
[11]University Hospital, Perugia, Italy
[12]Pugliese Hospital, Catanzaro, Italy
[13]Sao Joao Hospital, Porto, Portugal
[14]GIMEMA Data Center, Rome, Italy
[15]Hopital St. Antoine, Paris, France

Background. Gemtuzumab ozogamicin (GO), a calicheamicin-linked anti-CD33 monoclonal antibody, has clinical activity in relapsed AML and has recently been shown to significantly improve survival in older patients when administered in combination with frontline standard chemotherapy (Burnett et al, Blood 2011: a582; Castaigne et al, Blood 2011: a6). **Aims.** Study AML-17 is an open-label randomized phase III trial to evaluate the benefit and toxicity of adding upfront GO to standard induction and consolidation therapy in older patients with untreated AML. **Methods.** Eligible patients (age 61-75 years; WHO PS 0-2; maximum allowed WBC pre-therapy 30x10^9/L [a short course of HU permitted]) with newly diagnosed non-M3 AML were randomized (stratified by age, initial WBC,% CD33 expression, and Institution) to receive, or not, two upfront infusions of GO (6 mg/m^2 on day 1 and 15) prior to a course of MICE (mitoxantrone, cytarabine, etoposide), to be started within 10 days from response assessment to GO (day +43) or sooner whenever disease progression was documented. Patients achieving CR or CRp received consolidation therapy with 2 courses of ICE (idarubicin, cytarabine, etoposide) with or without a single infusion of GO (3 mg/m^2 on day -1 of each course), according to their initial assignment. The primary endpoint was OS; secondary endpoints included CR+CRp rate after induction, RFS, and toxicity. A total of 378 deaths were required in order to detect an increase in OS at 2.5 years from 20% (No GO) to 30% (GO): HR=0.75 (alpha=5%, power=80%). For efficacy endpoints, all analyses were performed according to the intent-to-treat principle. **Results.** Between 09/2002 and 08/2007, 472 patients (median age 67 years) were randomized in the study by 60 centers. After induction CR/CRp was achieved in 223 pts (47%), and at a median follow-up of 5.2 years 414 deaths were reported. As shown in the Table, induction response was comparable in the two arms, but GO treatment was associated with a higher 60-day mortality (mostly due to adverse events) and a shorter OS. Importantly, age emerged as a significant predictor of outcome: while treatment results were comparable in the younger age cohort (61-69 years), pts older than 70 years of age who received GO, as compared with those in the same age group treated with standard chemotherapy only, fared significantly worse in terms of both induction response (P=0.01) and OS (P=0.002), and had a higher 60-day mortality rate. The most common grade

3 or higher adverse events were febrile neutropenia and infection in each treatment arm. Severe liver toxicity occurred in 10% of pts during GO induction resulting in two fatalities. **Conclusions.** In this study, the sequential addition of GO to frontline intensive chemotherapy in older pts with AML was not beneficial overall, and even detrimental in those aged 70 years or more due to a higher risk of early mortality.

Table.

	All patients		Age 61-69 yr		Age 70-75 yr	
	No GO	GO	No GO	GO	No GO	GO
N. Patients	236	236	152	153	84	83
CR+CRp	116 (49%)	107 (45%)	72 (47%)	80 (52%)	44 (52%)	27 (32%)
OR (CI) p-value	0.86 (95%; 0.60-1.23) 0.46		1.22 (99%; 0.67-2.20) 0.42		0.44 (99%; 0.19-1.00) 0.01	
60d mortality (all causes)	17.8%	22.5%	15.8%	17.1%	21.4%	32.5%
2.5y OS (median, mos)	21.7% (10.0)	16.0% (7.1)	21.8% (10.1)	20.4% (8.8)	21.4% (9.1)	7.8% (4.0)
HR (CI) p-value	1.20 (95%; 0.99-1.45) 0.07		1.05 (99%; 0.76-1.45) 0.69		1.64 (99%; 1.08-2.51) 0.002	
2.5y RFS (median, mos)	18% (9.1)	17.4% (9.5)	22.1% (10.1)	17.5% (10.7)	11.4% (7.8)	18.5% (6.2)
HR (CI)	1.08 (95%; 0.81-1.44)		1.14 (99%; 0.71-1.81)		1.11 (99%; 0.57-2.20)	

1091E

F14512 A NOVEL POLYAMINE-VECTORIZED ANTI-CANCER DRUG TARGETING TOPOISOMERASE II IN ADULTS PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML): RESULTS FROM A PHASE 1 STUDY

S De Botton[1], C Berthon[2], CE Bulabois[3], T Prebet[4], N Vey[4], P Chevallier[5], X Thomas[6], F Lefresne[7], S Favrel[7], B Quesnel[2]
[1]Institut Gustave Roussy, Villejuif Cedex, France
[2]Hospital Claude Huriez, Lille, France
[3]CHU Grenoble, Grenoble, France
[4]Institut Paoli-Calmettes, Marseille, France
[5]CHU Nantes, Hôtel Dieu, Nantes, France
[6]Hospital Edouard Herriot, Lyon, France
[7]Institut de Recherche Pierre Fabre, Boulogne Cedex, France

Background. F14512 is a novel class of targeted cytotoxic agent that exploits the polyamine transport system (PTS) to deliver a drug selectively into cancer cells. This polyamine (spermine)-conjugated epipodophyllotoxin is 10-fold more potent than etoposide *in vitro*. This is most likely a consequence of an increased affinity for DNA and a stabilisation of the DNA/Topoisomerase II complex mediated by the polyamine moiety. **Aims.** This first-in man multicenter phase I study was designed to determine the maximal tolerated dose (MTD) of F14512 single agent in patients (pts) with relapsed or refractory AML by determining the incidence of dose-limiting toxicities (DLT) during the first cycle. Secondary objectives include safety, pharmacokinetics (PK) and anti-leukemic activity. **Methods.** Eligible pts were adults aged 18-75 years with *de novo* or secondary AML and previously treated with a maximum of 3 prior induction regimens. Pts received i.v. administration of F14512 from day 1 to day 5 of each cycle. Cycles were repeated every 2 to 6 weeks depending on dose levels, leukaemia response, recovery to sufficient haematopoiesis and resolution of toxicities. Dose escalation was based initially on an accelerated titration design with 50% increment and one pt by dose level until 1 DLT was observed. The activity of the PTS was assessed for each patient on blasts cells and lymphocytes at baseline and blood samples for PK analysis were taken on days 1 and 5 of cycle 1. **Results.** From January 2010 to November 2011, 39 pts (24 males) were treated in 6 participating sites through 12 dose levels ranging from 1 to 44 mg/m^2/day. Median age was 68 years (range: 22-75 years). 27 pts had *de novo* AML, 12 had secondary AML. 14 pts had unfavourable and 18 had intermediate cytogenetics. Drug related adverse events (AE) were reported in 36 pts (92 %). The most frequent grade 3-4 drug-related AEs (≥ 5%) included reversible hypomagnesemia (23%), neutropenia (18%), sepsis (13%), febrile neutropenia (10%), asthenia (5%), hypokaliemia (5%) and thrombocytopenia (5%). Three DLT were reported: second degree atrioventricular block in 1 pt at 15.2 mg/m^2/day, non-blastic aplasia during more than 6 weeks in 1 pt and early life-threatening sepsis in 1 pt at 44 mg/m^2/day. Therefore, MTD was reached at 44 mg/m^2/day, dose at which 2 pts out of 4 experienced a DLT. Anti-leukemic activity was shown at different dose levels: 4 complete responses (CR, 10%) at 1, 15.2, 34 and 39 mg/m^2/day, 3 complete responses with incomplete recovery (CRi, 8%) at 6.8, 34 and 44 mg/m^2/day. Of note, 3 pts experienced haematological improvements respectively at 10.1, 15.2 and 26 mg/m^2/day. The PTS activity results are presented separately. The preliminary PK results illustrated an increase of drug exposure proportional to the dose, and reproducible PK behaviour between days. **Conclusions.** This phase I determined the MTD of F14512 single agent to be 44 mg/m^2/day. Accrual is still ongoing at the recommended dose at 39 mg/m^2/day. Clinical outcome in this heavily pre treated population seems promising and updated results will be presented at the meeting.