Blood First Edition Paper, prepublished online June 11, 2009; DOI 10.1182/blood-2009-01-198093

Title: **A Randomized Phase 3 Study of Tipifarnib Compared to Best Supportive Care, Including Hydroxyurea, in the Treatment of Newly Diagnosed Acute Myeloid Leukemia (AML) in Patients 70 Years or Older**

Authors: **Jean-Luc Harousseau[1], Giovanni Martinelli[2], Wieslaw W. Jedrzejczak[3], Joseph M. Brandwein[4], Dominique Bordessoule[5], Tamas Masszi[6], Gert J. Ossenkoppele[7], Julia A. Alexeeva[8], Gernot Beutel[9], Johan Maertens[10], Maria-Belen Vidriales[11], Hervé Dombret[12], Xavier Thomas[13], Alan.K. Burnett[14], Tadeusz Robak[15], Nuriet K. Khuageva[16], Anatoly K. Golenkov[17], Elena Tothova[18], Lars Mollgard[19], Youn C. Park[20], Annick Bessems[20], Peter De Porre[20], Angela J. Howes[20] on behalf of the F.I.G.H.T.-AML-301 Investigators.**

Affiliation: [1]University Hospital Hotel-Dieu, Nantes, France; [2]University of Bologna, Italy; [3]Medical University of Warsaw, Poland; [4]Princess Margaret Hospital, Toronto, Canada; [5]CHU Limoges, France, [6]National Medical Center, Budapest, Hungary; [7]Vrije Universiteit Amsterdam, The Netherlands; [8]St. Petersburg City Clinical Hospital, Russia; [9]Medizinische Hochschule Hannover, Germany; [10]UZ Gasthuisberg, Leuven, Belgium; [11]Hospital Universitario de Salamanca, Salamanca, Spain; [12]a Hospital Saint-Louis, Paris, France; [13]Hospital Edouard Herriot, Lyon, France; [14]Univ. Hospital of Wales, Cardiff, UK; [15]Medical Univ. of Lodz and

Memorial Copernicus Hospital, Lodz, Poland; [16]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [17]Moscow Regional Clinical Research Institute, Moscow, Russia; [18]Hospital University of PJS, Kosice, Slovak Republic; [19]Karolinska University Hospital, Stockholm, Sweden; [20]Ortho-Biotech Oncology R&D, a unit of Johnson & Johnson Pharmaceutical Research & Development, L.L.C., USA.

Support: Supported by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Correspondence: Pr. Jean-Luc HAROUSSEAU,
Service d'Hématologie
Hôtel Dieu
Place Alexis Ricordeau
44093
NANTES CEDEX 01
Tel: +(33) 2 40 08 32 71
Fax: +(33) 2 40 08 32 50
Email: jl-harousseau@nantes.fnclcc.fr

Running Title: Tipifarnib or Best Supportive Care for AML Therapy

Previous Presentations: This work was presented in part at the annual meeting of the American Society of Hematology, Atlanta, GA, December 10, 2007, abstract # 952392.

Key words: **Farnesyltransferase Inhibitor, tipifarnib, Acute Myeloid**

	Leukemia
ClinicalTrials.gov Identifier	**NCT00093990**

A complete list of the investigators of the F.I.G.H.T.-AML-301 study appears in the Supplemental Appendix (available with the article on the Blood website).

ABSTRACT

This Phase 3, multicenter, open-label study evaluated the efficacy and safety of tipifarnib compared to best supportive care (BSC), including hydroxyurea, as first line therapy in elderly patients (≥70 years) with newly diagnosed, de novo or secondary AML. A total of 457 patients were enrolled with 24% ≥80 years of age. Tipifarnib 600 mg p.o. BID was administered for the first 21 consecutive days, in 28-day cycles. The primary endpoint was overall survival (OS). The median survival was 107 days (95% CI: 85, 129 days) for the tipifarnib arm and 109 days (95% CI: 93, 136 days) for the BSC arm. The hazard ratio (tipifarnib vs. BSC) for OS was 1.02 (95% CI: 0.84, 1.24; p-value stratified log-rank test 0.843). The complete response rate for tipifarnib in this study (8%) was lower than that observed previously, but with a similar median duration of 8 months. The most frequent grade 3 or 4 adverse events were cytopenias in both arms, slightly more infections (39% vs. 33%), and febrile neutropenia (16% vs. 10%) were seen in the tipifarnib arm. The results of this randomized study showed that tipifarnib treatment did not result in an increased survival when compared with BSC including hydroxyurea. This trial is registered at http://clinicaltrials.gov as NCT00093990 [ClinicalTrials.gov].

INTRODUCTION

The incidence of acute myeloid leukemia (AML) increases exponentially with age.[1,2] Approximately 55% of all cases occur in patients over 65 years of age.[1,3] There is no established standard of care for treating elderly patients with AML and those who receive treatment have a median survival time of less than 1 year.

When possible, it is recommended to give induction combination chemotherapy in patients with AML. However, for the patients with disease-related risk factors (secondary AML, prior myelodysplastic syndrome [MDS], unfavorable karyotype) associated with poor treatment outcome, or patient-related risk factors (comorbidities, impaired performance status, or increased age) associated with diminished ability to tolerate adverse effects,[3-5] treatment with best supportive care, including hydroxyurea; single agents; or treatment in clinical studies is recommended.[6-9] For those elderly patients who are fit to receive induction chemotherapy, significant toxicity has been reported,[10] including a therapy related mortality rate of approximately 25%.[11] In addition, median survival and remission rates decrease with increasing age. In a retrospective study using data from the Surveillance, Epidemiology, and End Results (SEER) registries and Medicare claims in the United States, median survival was 3.9 months among those aged 65 to 74 years, 2.2 months in those aged 75-84 years, and 1.4 months in those aged 85 years or older.[12] In the Medical Research Council (UK) AML-8 study, an induction therapy consisting of daunorubicin, cytarabine, and 6-thioguanine yielded a remission rate of only 26% for those over 70 years of age compared with 52% for those between 60 and 69 years of age and 70% for those under 50 years of age.[10] For these reasons,

induction chemotherapy is often not a viable treatment option for elderly patients with AML and many patients receive palliative chemotherapy or supportive care alone.[13-15]

Tipifarnib is a selective, nonpeptidomimetic, orally-active inhibitor of the enzyme farnesyltransferase. Tipifarnib has been tested in a wide array of solid tumors and hematologic malignancies, with antitumor activity seen in several tumor types, including MDS[16,17] and AML.[18,19] Tipifarnib was the first farnesyltransferase inhibitor to induce, in the Phase 1 setting, complete remissions in AML.[18] The Phase 2 study, CTEP-20, confirmed the early report with a complete remission rate of 14%, and a median complete remission duration of 7.3 months.[19] Tipifarnib was found to have an acceptable safety profile in elderly patients with AML, with the most common adverse events related to myelosuppression or gastrointestinal disorders. The current study, constitutes the largest prospectively studied cohort of elderly subjects with newly diagnosed AML to date. This Phase 3 study was designed to evaluate safety and to establish the effect on survival of tipifarnib compared with best supportive care in elderly subjects with newly diagnosed AML who are not eligible for induction chemotherapy.

METHODS

Patients

Patients, 70 years or older with newly diagnosed, de novo or secondary AML were eligible for enrollment. The main criteria for inclusion were: pathologic confirmation of AML (≥20% bone marrow leukemic blasts), not medically fit or did not wish to be treated with induction chemotherapy, and Eastern Cooperative Oncology Group (ECOG) performance scores of 0, 1 or 2. Patients with previous cytotoxic or biologic treatment for AML were excluded. Additional exclusion criteria included known central nervous system leukemia, acute promyelocytic leukemia, absolute peripheral blast count greater than 30,000/mm^3, uncontrolled systemic infection, and symptomatic neuropathy of grade 2 or worse. Review boards at participating institutions approved the study, which was conducted according to the Declaration of Helsinki, the International Conference on Harmonization, Guidelines for Good Clinical Practice. All patients provided written, informed consent to study participation.

Study Design and Treatment

This was a Phase 3, randomized, multicenter, multinational, open-label study comparing tipifarnib with BSC, for the treatment of 457 elderly patients (aged 70 years and older) with newly diagnosed AML who were not fit for, or not willing to receive, induction chemotherapy. Patients were randomly assigned in a 1:1 ratio to either BSC or tipifarnib treatment using a central interactive voice response system. Patients were stratified at randomization based on ECOG performance status (performance score: 0-1 vs. 2) and age group (<75 years vs. ≥75 years). Randomization was to occur no later than 3 weeks

after diagnosis and no more than 1 day before the start of treatment. Tipifarnib treatment consisted of 28-day cycles with 21 days of consecutive treatment followed by a mandatory 7 day rest period. Adverse events, concomitant medications and clinical laboratory analytes were recorded weekly. Specific dose modifications were allowed as defined in the protocol. The treatment continued until disease progression, intolerable toxicity, death, loss to follow-up, investigator decision, or withdrawal of consent to further treatment. All patients received supportive care, which included blood product transfusions, prophylactic or symptomatic use of anti-infectives and cytokines, according to institutional practices and other therapy appropriate for the symptomatic treatment of AML and it's complications. Hydroxyurea was permitted on the BSC arm only.

The primary endpoint was to compare overall survival of patients treated with tipifarnib and patients treated with BSC, including hydroxyurea. The primary efficacy comparison was performed for all randomized subjects, and a secondary comparison was performed on the subgroup of subjects with "AML with myelodysplasia," which included subjects classified as per the World Health Organization (WHO) classifications "AML with multilineage dysplasia," and "AML and myelodysplasic syndromes, treatment-related". Secondary endpoints included progression-free survival (PFS), complete remission (CR) rate, CR duration, rate of morphologic leukemia-free state (MLFS), and 1-year survival. Complete remission required bone marrow (BM) aspiration showing <5% leukemic blasts and an absence of Auer rods; peripheral blood counts showing absolute neutrophil count ≥1,000/mm^3, platelet count ≥100,000/mm^3, no peripheral leukemic blasts; blood-product transfusion independence, and an absence of extramedullary leukemia.

Morphologic leukemia-free state required BM aspiration showing <5% leukemic blasts, Auer rods not detected, and absence of extramedullary leukemia. Progression was defined as: >50% rise in bone marrow blast count; confirmed unequivocal rise in peripheral blasts in presence of other peripheral blood counts consistent with leukemic infiltration of bone marrow; new appearance of extramedullary disease or circulating blasts, confirmed 1 week later.

Adverse events were collected and reported from the day of informed consent until 30 days after completion of the treatment phase, or until start of another antileukemic therapy. Clinical laboratory tests (serum chemistry and hematology) were performed during the pre-randomization phase, within 48 hours of randomization; weekly thereafter during treatment; and upon study termination.

Statistical Analyses

A total of 450 patients were to be randomized in a 1:1 ratio to provide the required 394 events (deaths) to detect a 33% improvement in median survival when tipifarnib (16 weeks) was compared with best supportive care (12 weeks), with 80% power given a 2-sided significance level of 4.3%.

Hypothesis testing on overall survival involved a 2-step testing procedure (as outlined in the protocol and the statistical analysis plan) with a pre-specified significance level of 0.043 for all randomized patients for testing the composite hypotheses (all randomized

group and subgroup) and pre-specified significance level of 0.10 for testing the subgroup of patients having AML with myelodysplasia.

The Kaplan-Meier method was used to estimate all time-to-event efficacy variables (overall survival, duration of CR, PFS, overall survival at 1 year, time to first hospitalization, duration of hospitalization, and time to first transfusion). PFS was defined as time from randomization to progression or death from any cause. All time-to-event variables were compared between the groups using a stratified log-rank test adjusting for stratification factors (ECOG performance status and age group). Cox regression analysis was used to test for the effects of treatment on survival, while adjusting for potential baseline adverse risk factors (age, ECOG, baseline bone marrow blast counts, AML with myelodysplasia, unfavorable karyotype, baseline LDH, and baseline WBC). The CR and MLFS rates were compared between the groups using the Cochran-Mantel-Haenszel test while adjusting for potential baseline adverse risk factors.

Adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA, Version 9.0) body system and preferred term, according to frequency and toxicity grade per the National Cancer Institute, Common Toxicity Criteria, (NCI CTC, Version 2.0), relationship to study medication, action taken, outcome, and type (hematologic vs. non-hematologic).

RESULTS

Patient characteristics

From October 2004 to May 2007, 457 patients were randomized at 115 sites in 23 countries. There were more males (54%) than females (46%) (**Table 1**). The median age was 76 years. Twenty-four percent of the patients were 80 years or older. One-third of the patients had unfavorable cytogenetics and 20% had prior MDS (defined as a history of at least 3 months of MDS diagnosed by BM examination). The median duration of prior MDS was 10.7 months (range 2.8-126) in the BSC arm and 7.2 months (range 0.9-178) in the tipifarnib arm. Twenty-three (5%) patients had received prior therapy for MDS, which was mainly biologic or immunotherapy; 3 patients had received prior hydroxyurea, 3 had prior low-dose cytarabine and 2 had prior treatment with demethylating agents. Twenty-four percent of patients entered the study with baseline BM blast counts of 20-30% (formerly classified as MDS by FAB) (**Table 1**). Reasons provided for ineligibility for induction chemotherapy were subject choice (13%), physician assessment (65%) or both (22%). Factors contributing to the physician assessment of ineligibility were age alone (32%); comorbidities, especially cardiovascular, or poor general health (24%), disease factors such as poor karyotype, prior MDS or treatment-related AML (3%) or a combination of 2 or more of these factors (28%). Baseline characteristics (**Table 1**) were generally well balanced between the 2 treatment arms, although the tipifarnib group had more patients who started the study with grade 3 or 4 thrombocytopenia (53% vs 44%).

Efficacy Results

The number of deaths at the time of clinical cutoff (21 May 2007) was 195 (89%) of 229 patients in the BSC group and 201 (88%) of 228 patients in the tipifarnib group. With a median follow-up of 574 days for tipifarnib and 539 days for BSC, the median overall survival was 107 days (95% CI = 85, 129) for the tipifarnib group and 109 days (95% CI = 93, 136) for the BSC group (**Figure 1**). The hazard ratio (tipifarnib versus BSC) for overall survival was 1.02 with 95% CI=(0.84, 1.24). The stratified log-rank test p value for overall survival was 0.843 and the p-value from the un-stratified log rank test was 0.847. There was no statistically significant difference in the 1-year overall survival rate (14.9% for tipifarnib vs. 17.7% for BSC). The lack of treatment effect on survival was shown across the different prognostic factors (**Figure 2**). A Cox proportional hazards model was used to estimate the effect of prognostic factors on overall survival (**Table 2**). The model suggested that age (≥75 years), an ECOG performance score of 2, unfavorable cytogenetics, or baseline BM blast count greater than 50% may lead to a higher risk of death. AML with or without myelodysplasia, baseline LDH > or ≤ 1500, and baseline WBC > or ≤25 giga/l did not significantly affect overall survival.

In the tipifarnib group, 18 (8%) patients achieved a CR. The median duration of the CR was 240 days and the median overall survival of these patients was 666 days (**Table 3**). Most patients who reached CR did so by the end of the second cycle of treatment; median time to CR was 58 days (range 28-107 days). **Table 4** gives the baseline characteristics of the patients with CR. There were no CRs in the BSC group..

The median PFS was similar for the tipifarnib (64 days) and BSC groups (68 days). A Cox proportional hazards model used to estimate the effect of prognostic factors on PFS showed that while a history of prior MDS had no significant effect, an ECOG performance score of 2, unfavorable cytogenetics, and a baseline BM blast percentage of greater than 50% may have adversely influenced PFS.

Safety Results

The most common Grade 3 or 4 adverse events were related to myelosuppression (44% for BSC and 62% for tipifarnib) or infections (33% for BSC and 39% for tipifarnib) (**Table 5**). Tipifarnib is known to have myelosuppressive effects but AML itself is also associated with profound and persistent cytopenias. This was illustrated by the high proportion of patients starting the study with Grade 3 or 4 cytopenias according to laboratory tests; 80% in BSC group and 84% in tipifarnib group had at least one grade 3 or 4 cytopenia at baseline. During treatment, neutropenia and thrombocytopenia were the most common hematologic abnormalities with grade 4 abnormalities occurring more often in the tipifarnib group (neutropenia 72% vs 60%; thrombocytopenia 43% vs 28%). There was no cumulative effect on ANC, platelets or hemoglobin over the cycles. The incidence of grade 3 or 4 hypokalemia was higher with tipifarnib treatment compared with BSC (16% vs 6%). Grade 3 or 4 diarrhea was reported in 7% of patients treated with tipifarnib but there were no occurrences in the BSC group. The incidence of other grade 3 or 4 adverse events (fatigue, pyrexia, dyspnea, and cardiac failure) was similar in both groups.

More patients (72% vs. 62%) were hospitalized on or after randomization in the tipifarnib group, although the incidence of infections leading to hospitalization was similar (34% vs 30%). The most common tipifarnib-related serious adverse events were febrile neutropenia and thrombocytopenia. Tipifarnib-related adverse events led to treatment termination in 25 (11%) of the patients.

The incidence of deaths on study (during treatment and up to 30 days after treatment termination) was similar in the two groups (BSC 43%; tipifarnib 40%) (**Table 6**). There were more deaths due to progressive disease with BSC compared with tipifarnib (26% vs. 18%, respectively). Four (2%) deaths due to adverse events were considered by the investigator to be related to tipifarnib treatment: cerebral hemorrhage, febrile neutropenia, pneumonia, and sepsis. There were more early deaths (within 30 days from randomization) in the tipifarnib group (21% vs. 17%), which were accounted for by the increased number of early deaths due to adverse events (11% vs. 7%; for tipifarnib 1% were drug-related). The most common adverse events leading to early death were cardiac events, infections or bleeding events. The most common reasons for treatment termination are provided in Table 7.

Concomitant therapy

One hundred and twenty-five (55%) patients on the BSC arm received treatment with hydroxyurea. There were 41 patients in the BSC arm whose WBC exceeded 50, 000 during the treatment period. Among those 41 patients, 35 (85%) received hydroxyurea.

Nearly all patients in the study had at least one blood product transfusion. There were slightly more blood product transfusions with tipifarnib treatment (93% vs. 86%). Most of the increased transfusion need was evident within the first 30 days; from 31 days onward (up to 90 days) there were no differences in the number of transfusions for the two treatment groups. The proportion of patients receiving anti-infectives or cytokines was similar on both treatment arms (84% Tipifarnib vs 79% BSC) and amongst sites across geographical regions (Total patients Asia 82%; Eastern Europe 77%; Western Europe 83%; North America 87%; South America 81%).

Subsequent therapy

Eighty-nine (39%) patients in the BSC group and 93 (41%) patients in the tipifarnib group received subsequent therapy. The most frequent therapy given was hydroxyurea (12% BSC group, 15% tipifarnib group) or some form of single agent chemotherapy, such as low dose cytarabine or etoposide (11% BSC group, 15% tipifarnib group). Subsequent induction chemotherapy was received by 15 (7%) patients in the BSC group and 9 (4%) patients in the tipifarnib group. The main reason for receiving subsequent induction chemotherapy was that a change in the disease status required aggressive therapy (18 patients) or that the patient now accepted intravenous chemotherapy (6 patients). Only 1 patient (BSC group) had a response (CR). Five of the 18 patients who had CR on tipifarnib, were retreated with tipifarnib on relapse, as allowed per protocol. One patient had a subsequent PR lasting 6 months and two had stable disease lasting 4 months each.

DISCUSSION

This Phase 3, multicenter, open-label study evaluated the effect on survival of tipifarnib compared to BSC, including hydroxyurea, as first line therapy in elderly patients with newly diagnosed AML and considered to be unfit for or unwilling to be treated with induction chemotherapy. There was no survival benefit with tipifarnib treatment for the overall population.

The concept of this study was based on an earlier Phase 2 study, CTEP-20, demonstrating that tipifarnib treatment resulted in CR among elderly patients with AML.[19] In that study of 154 patients, the median age was 74 years (range 34 to 85) with a high proportion of the patients (75%) having prior MDS. Twenty-two (14%) patients had a CR, with a further 15 (9%) patients having a partial remission (PR) or hematologic improvement (HI). The median duration of CR was 7.3 months and the median survival of complete responders was 18 months. In the current study, which had a minimum age of 70 years, the median age of the study population was 76 years, with 24% being over the age of 80 years. The two study arms were well balanced for baseline demographic and disease characteristics, specifically for the presence/absence of unfavorable karyotype, the WHO classification of AML, and the time since initial diagnosis of AML. The best response to treatment in this patient population was a CR in 18 (8%) patients treated with tipifarnib (there were no CRs in the BSC group), with a further 20 (9%) patients having a PR or HI. The CR rate was lower than previously observed in the Phase 2 study, CTEP-20, but the median duration of 8 months was similar and the median overall survival of CR patients of 21.9 months was longer. Complete remissions were observed in patients with all types

of baseline characteristics including 3 patients with complex karyotypes and several patients with baseline bone marrow blast counts over 90%. The reason for the lower CR rate in this study compared to the Phase 2 study is not clear, but could be related to the generally older population and higher proportion of patients with ECOG performance status 2. Also, this study was conducted at 115 sites around the world compared with 4 sites in one country for the phase 2 study, so variation in treatment practice and experience with tipifarnib could also play a role. Although the numbers of patients recruited were not sufficient to analyze outcome by country, an analysis of supportive care treatments by geographical region revealed no obvious differences.

In the current study the CR rate was probably too low to have a positive affect on overall survival. Survival was not negatively affected by the rate of early deaths (17% for BSC and 21% for tipifarnib) or total drug-related deaths (4 patients, 2%). Nor is it likely that survival was influenced by subsequent therapy. The two arms were similarly matched for numbers of patients receiving subsequent, induction (7% on BSC and 4% on tipifarnib) or other chemotherapy, or treatment with other agents. It is likely that a higher CR rate is needed in order to positively affect survival. The challenge is to identify the patients who are likely to respond to tipifarnib. Review of the baseline disease characteristics of responding patients in this and other studies, has not identified any particular predictors of response. However recently, a 2-gene classifier for predicting response to tipifarnib has been identified and validated, which could have application in future studies.[20]

AML represents a heterogeneous disease associated with poor outcomes. Some of the factors complicating the poor outcomes include older age, presence of specific karyotypes, and properties of multidrug resistance.[21-24] The current study represents the largest study of elderly (>70 years) patients ever conducted. Since there was no confounding effect of treatment, the prognostic factors of survival are particularly interesting. Consistent with previous reports, older age (≥75 years), higher ECOG performance score, unfavorable cytogenetics and high BM blast count were strong predictors of poor survival. Interestingly, AML with myelodysplasia (including prior MDS), baseline LDH > 1500 U/L and baseline WBC > 25 giga/l did not significantly affect survival.

A large number of older patients with AML do not receive specific treatment, and those who receive standard regimens have a median survival time of <1 year.[1] Recently, two large retrospective analyses have been conducted in older patients with AML, particularly those aged 75 years or older, by the Southwest Oncology Group and the MD Anderson Cancer Center, demonstrating poor median OS durations, particularly in the 75 and older age group.[25,26] The poor outcomes observed in this group of elderly patients is most likely a reflection of low initial remission rates, higher treatment-related toxicity, high likelihood of relapse, and increased mortality.[1,4,11] A more recent study (AML-14 trial) conducted in elderly patients by the National Cancer Research Institute (UK) demonstrated that low-dose cytarabine (Ara-C) therapy was associated with a higher CR rate (18% vs. 1%) and longer overall survival compared to hydroxyurea ($P < .001$).[27] In that study, the 1-year survival of the entire population was reported as 13% and it is clear

from the survival curve that the majority of patients that were alive were in the LD Ara-C arm, with all patients in the hydroxyurea arm having died shortly after 1 year. In our study, the 1-year survival rate of patients on tipifarnib was 14.9%, with a median survival of 15.3 weeks, which was in-line with the assumed median (16 weeks) for the sample size calculation. However, the median survival of the BSC patients of 15.6 weeks was higher than anticipated and with a 1-year survival rate of 17.7%, suggests that this group included a number of patients with smoldering leukemia. A review of patient characteristics for those surviving more than 300 days did not reveal major differences between the 2 arms (data not shown).

This study was predicated on the CR rate observed in previous single arm studies. The assumption was that CR is a good surrogate for survival in AML. This study confirmed that assumption in responding patients. However, the results of this study indicate that treatment with tipifarnib does not result in a rate of CR sufficient to increase the survival in this patient population (elderly with a median age of 76 years and not suitable for induction chemotherapy) when compared with BSC.

ACKNOWLEDGEMENTS

We would like to thank the patients who took part in this study. This study, R115777-AML-301, was sponsored by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. and was registered with ClinicalTrials.gov (NCT00093990). We would also like to thank Ali Nourbakhsh, MD for assistance with medical review, Angelique Langlois for trial management, Xinyu Wei, Ph.D. for statistical analysis and Namit Ghildyal, PhD for writing contributions.

AUTHORSHIP

Conception and design: Jean-Luc Harousseau, Youn Park, Peter De Porre, Angela Howes.

Administrative support: Annick Bessems, Angela Howes.

Provision of study materials or patients: Jean-Luc Harousseau, Giovanni Martinelli, Wieslaw W. Jedrzejczak, Joseph Brandwein, Dominique Bordessoule, Tamas Masszi, Gert Ossenkoppele, Julia A. Alexeeva, Gernot Beutel, Johan Maertens, Maria-Belen Vidriales, Hervé Dombret, Xavier Thomas, Alan K. Burnett, Tadeusz Robak, Nuriet K. Khuageva, Anatoly K. Golenkov, Elena Tothova, Lars Mollgard.

Collection and assembly of data: Youn Park, Annick Bessems, Angela Howes.

Data analysis and interpretation: Jean-Luc Harousseau, Youn Park, Peter De Porre, Angela Howes.

Manuscript writing: Jean-Luc Harousseau, Youn Park, Peter De Porre, Angela Howes.

Final approval of manuscript: Jean-Luc Harousseau, Giovanni Martinelli, Wieslaw W. Jedrzejczak, Joseph Brandwein, Dominique Bordessoule, Tamas Masszi, Gert Ossenkoppele, Julia A. Alexeeva, Gernot Beutel, Johan Maertens, Maria-Belen Vidriales, Hervé Dombret, Xavier Thomas, Alan K. Burnett, Tadeusz Robak, Nuriet K. Khuageva, Anatoly K. Golenkov, Elena Tothova, Lars Mollgard.

Conflict-of-interest disclosure: J.H. has received honoraria from OrthoBiotech Janssen Cilag, G.M. has been a consultant to Novartis and Bristol Myers Squibb and has received research funding from Novartis, Y.C.P. and A. B. are employed by Johnson & Johnson Pharmaceutical Research & Development, P.D.P. and A.J.H. are employed by Ortho-Biotech Oncology Research & Development. Y.C.P., A.B., P.D.P., and A.J.H. own stock in Johnson & Johnson. The remaining authors declare no competing financial interests.

ABBREVIATIONS

AE, adverse event; AML, Acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; BSC, best supportive care; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FAB, French American British classification; FTI, farnesyltransferase inhibitor; HI, hematologic improvement; HU, hydroxyurea; LD-AraC, low dose-cytarabine; LDH, lactate dehydrogenase; MedDRA, Medical Dictionary for Regulatory Activities; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; NCI, National Cancer Institute; CTC, Common Toxicology Criteria; ORR, objective response rate; PFS, progression-free survival, PR, partial response; T,

tipifarnib; UK, United Kingdom; WBC, white blood cell counts; WHO, World Health Organization.

REFERENCES

1. Estey E. Acute myeloid leukemia and myelodysplastic syndromes in older patients. J Clin Oncol. 2007;25:1908-1915.

2. Rodriguez-Abreu D, Bordoni A, Zucca E. Epidemiology of hematological malignancies. Ann Oncol. 2007;18 Suppl 1:i3-i8.

3. Jackson GH, Taylor PR. Acute myeloid leukaemia: optimising treatment in elderly patients. Drugs Aging. 2002;19:571-581.

4. Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. N Engl J Med. 1999;341:1051-1062.

5. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. 2002;100:2292-2302.

6. Estey EH. How I treat older patients with AML. Blood. 2000;96:1670-1673.

7. Hiddemann W, Kern W, Schoch C, et al. Management of acute myeloid leukemia in elderly patients. J Clin Oncol. 1999;17:3569-3576.

8. Schaich M. Elderly acute myeloid leukemia: patients are not all the same. Haematologica. 2004;89:261-263.

9. Fey MF, Greil R, Jost LM. ESMO Minimum Clinical Recommendations for the diagnosis, treatment and follow-up of acute myeloblastic leukemia (AML) in adult patients. Ann Oncol. 2005;16 Suppl 1:i48-49.

10. Bolam S, Hamblin T. Colony-stimulating factors in the treatment of older patients with acute myelogenous leukaemia. Drugs Aging. 1999;15:451-460.

11. Stone RM. The difficult problem of acute myeloid leukemia in the older adult. CA Cancer J Clin. 2002;52:363-371.

12. Lang K, Earle CC, Foster T, Dixon D, Van Gool R, Menzin J. Trends in the treatment of acute myeloid leukaemia in the elderly. Drugs Aging. 2005;22:943-955.

13. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. Arch Intern Med. 2002;162:1597-1603.

14. Goldstone AH, Burnett AK, Wheatley K, Smith AG, Hutchinson RM, Clark RE. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood. 2001;98:1302-1311.

15. Vey N, Coso D, Bardou VJ, et al. The benefit of induction chemotherapy in patients age > or = 75 years. Cancer. 2004;101:325-331.

16. Kurzrock R, Kantarjian HM, Blascovich MA, et al. Phase I study of alternate-week administration of tipifarnib in patients with myelodysplastic syndrome. Clin Cancer Res. 2008;14:509-514.

17. Fenaux P, Raza A, Mufti GJ, et al. A multicenter phase 2 study of the farnesyltransferase inhibitor tipifarnib in intermediate- to high-risk myelodysplastic syndrome. Blood. 2007;109:4158-4163.

18. Karp JE, Lancet JE, Kaufmann SH, et al. Clinical and biologic activity of the farnesyltransferase inhibitor R115777 in adults with refractory and relapsed acute leukemias: a phase 1 clinical-laboratory correlative trial. Blood. 2001;97:3361-3369.

19. Lancet JE, Gojo I, Gotlib J, et al. A phase 2 study of the farnesyltransferase inhibitor tipifarnib in poor-risk and elderly patients with previously untreated acute myelogenous leukemia. Blood. 2007;109:1387-1394.

20. Raponi M, Lancet JE, Fan H, et al. A 2-gene classifier for predicting response to the farnesyltransferase inhibitor tipifarnib in acute myeloid leukemia. Blood. 2008;111:2589-2596.

21. Leith CP, Kopecky KJ, Godwin J, et al. Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. Blood. 1997;89:3323-3329.

22. Leith CP, Kopecky KJ, Chen IM, et al. Frequency and clinical significance of the expression of the multidrug resistance proteins MDR1/P-glycoprotein, MRP1, and LRP in acute myeloid leukemia: a Southwest Oncology Group Study. Blood. 1999;94:1086-1099.

23. Lancet JE, Willman CL, Bennett JM. Acute myelogenous leukemia and aging. Clinical interactions. Hematol Oncol Clin North Am. 2000;14:251-267.

24. Litzow MR. The therapy of relapsed acute leukaemia in adults. Blood Rev. 2004;18:39-63.

25. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood. 2006;107:3481-3485.

26. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer. 2006;106:1090-1098.

27. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and

high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer. 2007;109:1114-1124.

Table 1: Baseline Characteristics for All Randomized Patients

	BSC (N=229)	Tipifarnib (N=228)	Total (N=457)
Sex, n (%)			
N	229	228	457
Male	128 (56)	120 (53)	248 (54)
Female	101 (44)	108 (47)	209 (46)
Race, n (%)			
N	228	227	455
White	217 (95)	215 (95)	432 (95)
Black	0	1 (<1)	1 (<1)
Asian	5 (2)	7 (3)	12 (3)
Other	6 (3)	4 (2)	10 (2)
Age, years			
N	229	228	457
Category, n (%)			
69	1 (<1)	2 (1)	3 (1)
70-74	92 (40)	90 (39)	182 (40)
75-79	77 (34)	87 (38)	164 (36)
80-84	53 (23)	38 (17)	91 (20)
≥ 85	6 (3)	11 (5)	17 (4)
Mean (SD)	76.2 (4.43)	76.2 (4.37)	76.2 (4.39)
Median	76.0	76.0	76.0
Range	(69;89)	(69;90)	(69;90)
Weight, kg			
N	229	224	453
Mean (SD)	70.89 (12.858)	70.59 (13.572)	70.74 (13.202)
Median	70.00	70.00	70.00
Range	(44.0;113.1)	(39.0;106.0)	(39.0;113.1)
ECOG performance status, n (%)			
N	229	228	457
0	47 (21)	46 (20)	93 (20)
1	118 (52)	119 (52)	237 (52)
2	64 (28)	63 (28)	127 (28)
AML diagnosis to randomization, days			
N	229	228	457
Category, n (%)			
≤ 14 Days	161 (70)	163 (71)	324 (71)
15-21 Days	53 (23)	50 (22)	103 (23)
> 21 Days	15 (7)	15 (7)	30 (7)
Mean (SD)	11.13 (6.408)	11.30 (11.786)	11.21 (9.470)
Median	10.00	9.00	9.00
Range	(1.0;32.0)	(1.0;157.0)	(1.0;157.0)
Unfavorable cytogenetics, n(%)			
N	229	228	457
Yes	76 (33)	68 (30)	144 (32)
No	116 (51)	123 (54)	239 (52)
Not Done / Not Available	37 (16)	37 (16)	74 (16)

WHO Classification:			
Recurrent cytogenetic translocations	12 (5)	6 (3)	18 (4)
AML with t(8;21)(q22;q22) AML1/CBFalpha/ETO	2 (1)	3 (1)	5 (1)
AML with abnormal bone marrow eosinophils Inv(16) (p13;q22) or t(16;16)(p13;q22) CBFbeta/MYH11	1 (<1)	1 (<1)	2 (<1)
AML with 11q23 MLL abnormalities	9 (4)	2 (1)	11 (2)
Multilineage dysplasia	80 (35)	85 (37)	165 (36)
With prior MDS[a]	45 (20)	45 (20)	90 (20)
Without prior MDS	35 (15)	40 (18)	75 (16)
Myelodysplastic syndrome,therapy-related	3 (1)	4 (2)	7 (2)
Alkylating agent	2 (1)	1 (<1)	3 (1)
Other types	1 (<1)	3 (1)	4 (1)
Baseline blasts in marrow, %			
N	229	228	457
Category, n (%)			
[0%, 20%)	3 (1)	0	3 (1)
[20%, 30%)	47 (21)	63 (28)	110 (24)
(30%, 100%]	179 (78)	165 (72)	344 (75)
Mean (SD)	49.96 (22.247)	48.51 (23.383)	49.24 (22.807)
Median	44.80	41.00	43.50
Range	(14.0;100.0)	(20.0;100.0)	(14.0;100.0)
Baseline ANC Grade, n (%)			
N	228	223	451
< Grade 3	103 (45)	98 (44)	201 (45)
Grade 3	36 (16)	47 (21)	83 (18)
Grade 4	89 (39)	78 (35)	167 (37)
Baseline Platelet Count Grade, n (%)			
N	229	228	457
< Grade 3	129 (56)	108 (47)	237 (52)
Grade 3	96 (42)	109 (48)	205 (45)
Grade 4	4 (2)	11 (5)	15 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 2: Multivariate Analysis on Overall Survival

Prognostic Factors	Parameter Estimate	Standard Error	Hazard Ratio	95% CI of Hazard Ratio	p-value
Number of Observations Used (N= 362)					
Treatment group: tipifarnib vs. BSC	0.049	0.114	1.050	(0.84, 1.314)	0.6672
Age: ≥75 vs. <75	0.252	0.116	1.287	(1.025, 1.616)	0.0301
ECOG: 2 vs. 0 and 1	0.832	0.131	2.298	(1.778, 2.97)	0.0000
Unfavorable cytogenetics: yes vs. no	0.564	0.120	1.758	(1.39, 2.223)	0.0000
AML with myelo vs. AML w/o myelo	-0.089	0.124	0.915	(0.718, 1.166)	0.4731
LDH: >1500 vs. ≤1500	0.081	0.271	1.085	(0.638, 1.845)	0.7639
WBC count: >25 giga/l vs. ≤25 giga/l	0.214	0.172	1.239	(0.884, 1.736)	0.2130
Bone marrow blasts: >50% vs. ≤50%	0.542	0.124	1.719	(1.347, 2.194)	0.0000

Regression analysis of survival data based on Cox proportional hazards model.

Table 3: Objective Response Rate for All Randomized Patients

	BSC (N=229)	Tipifarnib (N=228)
Response, n (%)		
N	229	228
Complete Response	0	18 (8)
Partial Response	1 (<1)	6 (3)
Hematologic Improvement	2 (1)	14 (6)
Stable Disease	130 (57)	105 (46)
Progressive Disease	46 (20)	36 (16)
Not Done/not Evaluable	50 (22)	49 (21)

Table 4: Baseline Characteristics for Patients with Complete Response

Characteristic	Proportion of tipifarnib patients with CR (%)
Age, years	
<75	7/92 (8%)
≥75	11/136 (8%)
AML with myelodysplasia	
Yes	8/90 (9%)
No	10/138 (7%)
Unfavorable cytogenetics	
Yes	3/68 (4%)
No	12/123 (10%)
Note done	3/37 (8%)
ECOG performance status	
0	5/46 (11%)
1	9/119 (8%)
2	4/63 (6%)
Baseline blasts in marrow	Range 21%-98%

Table 5: Drug-related Grade 3 or 4 Adverse Events in at Least 5% of the Patients

Body System Dictionary-derived Term	BSC (N=229) Total n (%)	Tox Grade, n (%) 3	 4	Tipifarnib (N=225) Total n (%)	Tox Grade, n (%) 3	 4
Total no. subjects with adverse event	**172 (75)**			**202 (90)**		
Blood and Lymphatic System Disorders	100 (44)	36 (16)	64 (28)	140 (62)	41 (18)	99 (44)
Thrombocytopenia	61 (27)	30 (13)	31 (14)	88 (39)	35 (16)	53 (24)
Anemia	58 (25)	39 (17)	19 (8)	75 (33)	47 (21)	28 (12)
Neutropenia	35 (15)	10 (4)	25 (11)	56 (25)	10 (4)	46 (20)
Febrile Neutropenia	24 (10)	19 (8)	5 (2)	37 (16)	28 (12)	9 (4)
Leukopenia	19 (8)	8 (3)	11 (5)	25 (11)	6 (3)	19 (8)
Infections and Infestations	76 (33)	55 (24)	21 (9)	87 (39)	61 (27)	26 (12)
Pneumonia	43 (19)	33 (14)	10 (4)	38 (17)	29 (13)	9 (4)
Sepsis	19 (8)	8 (3)	11 (5)	32 (14)	18 (8)	14 (6)
Metabolism and Nutrition Disorders	22 (10)	15 (7)	7 (3)	54 (24)	40 (18)	14 (6)
Hypokalemia	13 (6)	10 (4)	3 (1)	37 (16)	28 (12)	9 (4)
General Disorders and Administration Site Conditions	46 (20)	40 (17)	6 (3)	48 (21)	42 (19)	6 (3)
Fatigue	29 (13)	25 (11)	4 (2)	31 (14)	28 (12)	3 (1)
Pyrexia	15 (7)	14 (6)	1 (<1)	11 (5)	11 (5)	0
Gastrointestinal Disorders	20 (9)	18 (8)	2 (1)	42 (19)	39 (17)	3 (1)
Diarrhea	0	0	0	16 (7)	16 (7)	0
Respiratory, Thoracic and Mediastinal Disorders	27 (12)	15 (7)	12 (5)	28 (12)	20 (9)	8 (4)
Dyspnea	12 (5)	8 (3)	4 (2)	9 (4)	7 (3)	2 (1)
Cardiac Disorders	33 (14)	13 (6)	20 (9)	25 (11)	7 (3)	18 (8)
Cardiac Failure	17 (7)	4 (2)	13 (6)	12 (5)	2 (1)	10 (4)

Note 1: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator. Percentages of tox grade sub-groups calculated with the number of subjects in each group as denominator.
Note 2: Incidence is based on the number of patients, not the number of events.

Table 6: Deaths During Study

Cause of Death	BSC (N=229) N (%)	Tipifarnib (N=225) n (%)
Total number subjects who died	98 (43)	91 (40)
Progressive disease	59 (26)	41 (18)
Adverse events	35 (15)	43 (19)
Drug-related adverse events	0	4 (2)
Other[a]	4 (2)	7 (3)

[a]Other refers to deaths where the cause was unknown, probable cardiac failure, suspected infection, or probable gastrointestinal hemorrhage.
Note 1: Died any time during treatment, within 30 days after treatment termination or before subsequent treatment, whichever was earlier.
Note 2: Drug-related means possible, probable, or very likely related to trial medication as assessed by the investigator.

Table 7: Primary Reason for Treatment Termination

	BSC (N=229) n (%)	Tipifarnib (N=228) n (%)	Total (N=457) N (%)
Total number of subjects	229 (100)	228 (100)	457 (100)
Reason for treatment termination	221 (97)	227 (>99)	448 (98)
Progressive AML/relapse	97 (42)	98 (43)	195 (43)
Peripheral blood counts	37 (16)	52 (23)	89 (19)
Bone marrow exam	50 (22)	37 (16)	87 (19)
Clinical exam	10 (4)	9 (4)	19 (4)
Death	70 (31)	48 (21)	118 (26)
Adverse events	30 (13)	25 (11)	55 (12)
Progressive disease	37 (16)	18 (8)	55 (12)
Other	3 (1)	5 (2)	8 (2)
Subject choice	33 (14)	35 (15)	68 (15)
Investigator decision	16 (7)	11 (5)	27 (6)
Adverse event	4 (2)	26 (11)	30 (7)
Complete remission	0	9 (4)	9 (2)
Loss to follow-up	1 (<1)	0	1 (<1)
Ongoing	8 (3)	1 (<1)	9 (2)

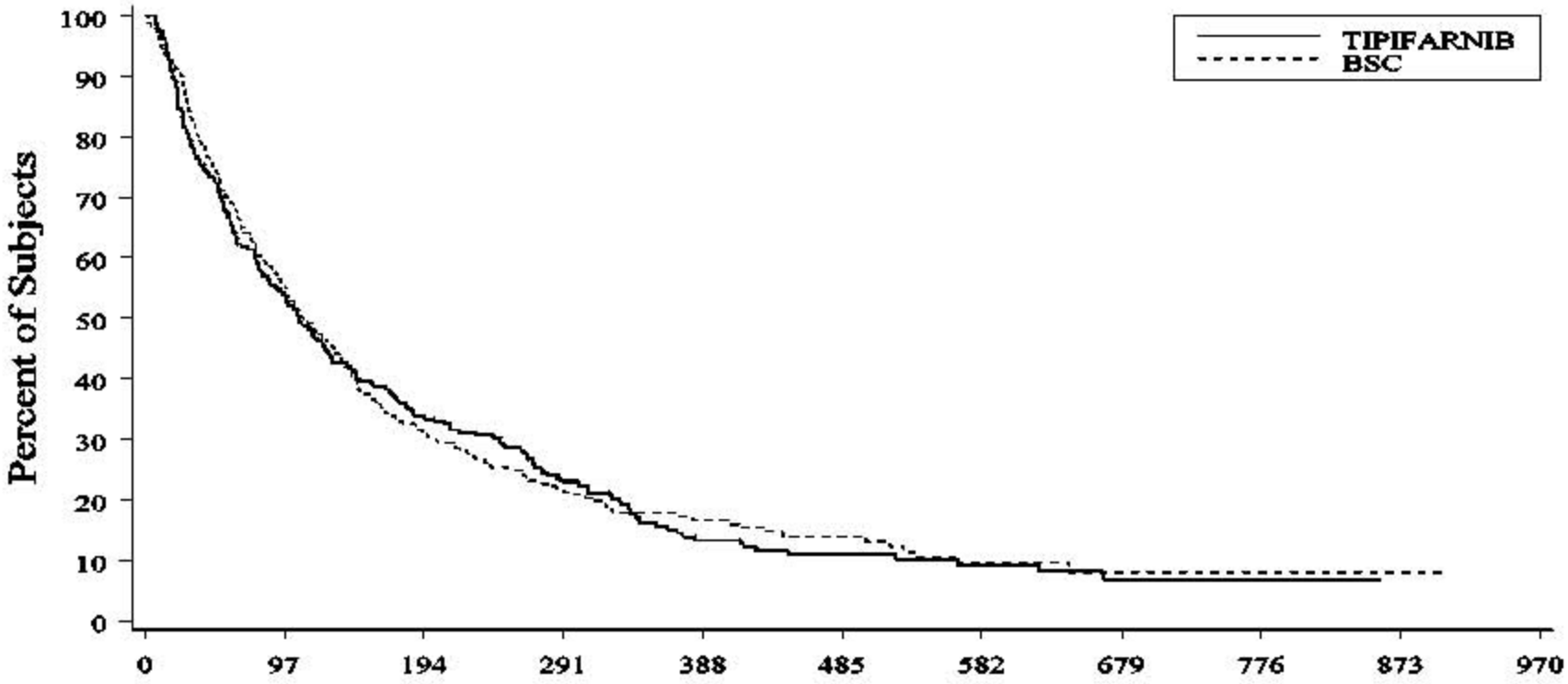
AML = acute myeloid leukemia; BSC = best supportive care, including hydroxyurea.

FIGURE LEGENDS

FIGURE 1. Shows a Kaplan-Meier plot of the Overall Survival for the BSC and tipifarnib groups.

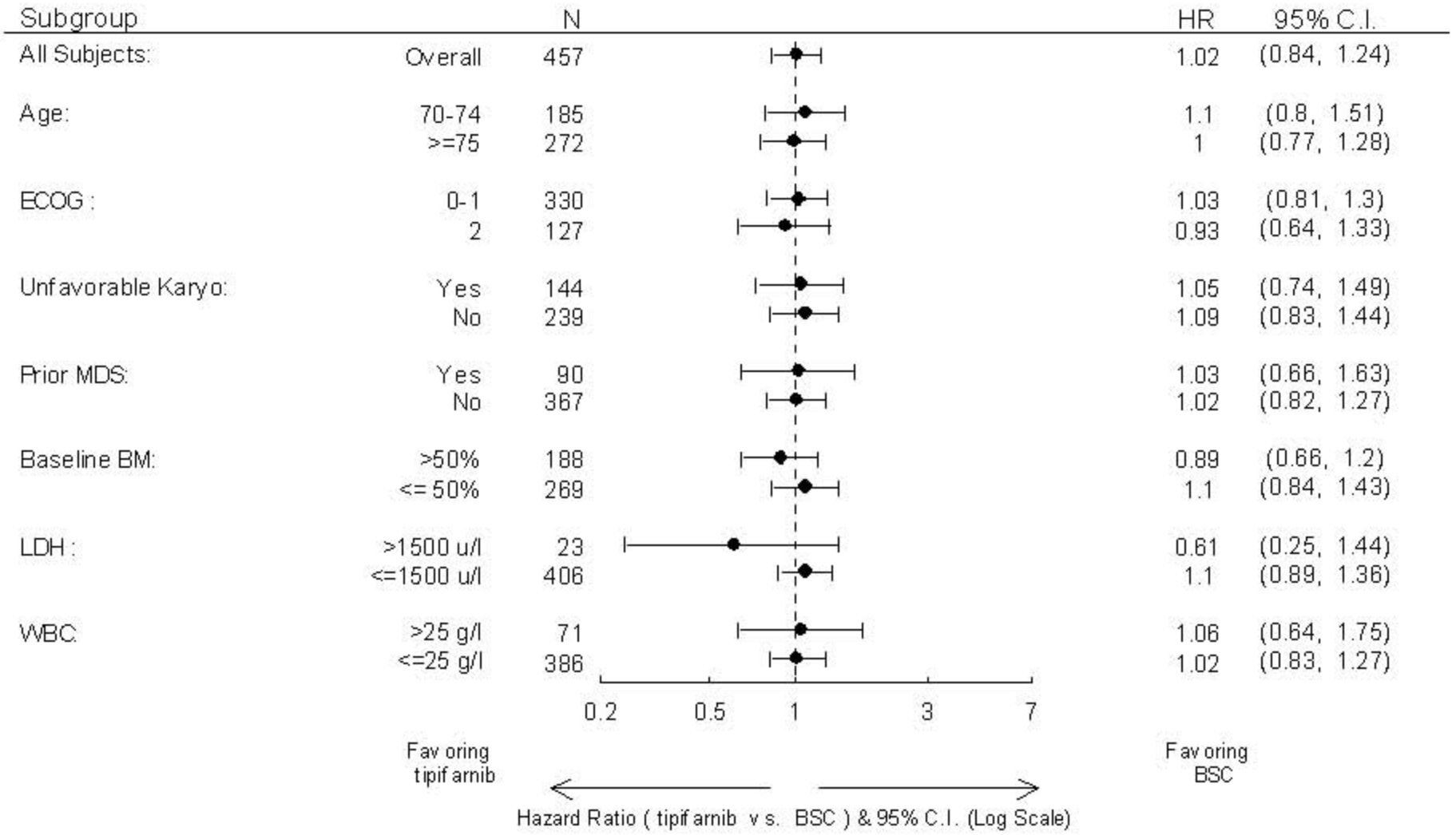
FIGURE 2. Shows a hazard ratio estimates for Overall Survival (BSC and tipifarnib Groups) for all randomized patients and various subgroups.

Figure 1. Kaplan-Meier Plot of the Overall Survival in the BSC and Tipifarnib Groups



No. Subjects at Risk										
TIPIFARNIB	228	121	75	49	23	14	10	5	2	0	0
BSC	229	122	69	46	26	17	8	4	1	1	0

Figure 2: Overall Survival by Prognostic Factors-Hazards Ratio and 95% CI in the BSC and Tipifarnib Groups



Prepublished online May 21, 2009;
doi:10.1182/blood-2009-01-198093 originally published online
May 21, 2009

A randomized phase 3 study of tipifarnib compared to best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia (AML) in patients 70 years or older

Jean-Luc Harousseau, Giovanni Martinelli, Wieslaw W. Jedrzejczak, Joseph M. Brandwein, Dominique Bordessoule, Tamas Masszi, Gert J. Ossenkoppele, Julia A. Alexeeva, Gernot Beutel, Johan Maertens, Maria-Belen Vidriales, Herve Dombret, Xavier Thomas, Alan K. Burnett, Tadeusz Robak, Nuriet K. Khuageva, Anatoly K. Golenkov, Elena Tothova, Lars Mollgard, Youn C. Park, Annick Bessems, Peter De Porre and Angela J. Howes

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.