Title
A phase 1 trial dose-escalation study of tipifarnib on a week-on, week-off schedule in relapsed, refractory or high-risk myeloid leukemia.

Permalink
https://escholarship.org/uc/item/1jh25821

Journal
Leukemia, 25(10)

ISSN
0887-6924

Authors
Kirschbaum, MH
Synold, T
Stein, AS
et al.

Publication Date
2011-10-01

DOI
10.1038/leu.2011.124

Peer reviewed
A Phase 1 Trial Dose Escalation Study of Tipifarnib on a Week-On, Week-Off Schedule in Relapsed, Refractory or High-Risk Myeloid Leukemia

Mark Kirschbaum, MD¹, Timothy Synold, PhD², Anthony S. Stein, MD¹, Joseph Tuscano, MD³, Jasmine M. Zain, MD¹, Leslie Popplewell, MD¹, Chatchada Karanes, MD¹, Margaret R. O'Donnell, MD¹, Bernadette Pulone, RN¹, Amalia Rincon, BS⁴, John Wright, MD⁵, Paul Frankel, PhD⁴, Stephen J. Forman, MD¹, and Edward M. Newman, PhD²

¹Department of Hematology/HCT, City of Hope, Duarte, CA, USA
²Department of Molecular Pharmacology, City of Hope, Duarte, CA, USA
³Division of Hematology and Oncology, University of California, Davis School of Medicine, Sacramento, California, USA
⁴Department of Biostatistics, City of Hope, Duarte, CA, USA
⁵Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD, USA

Abstract

Inhibition of farnesyltransferase (FT) activity has been associated with in vitro and in vivo anti-leukemia activity. We report the results of a phase 1 dose escalation study of tipifarnib, an oral FT inhibitor, in patients with relapsed, refractory, or newly diagnosed (if over age 70) acute myelogenous leukemia (AML), on a week-on, week-off schedule. Forty-four patients were enrolled, 2 patients were newly diagnosed, the rest were relapsed or refractory to previous treatment, with a median age of 61 (range 33–79). The maximum tolerated dose was determined to be 1200 mg given orally twice-daily (bid) on this schedule. Cycle one dose-limiting toxicities were hepatic and renal. There were 3 complete remissions seen, 2 at the 1200 mg bid dose and one at the 1000 mg bid dose, with minor responses seen at the 1400 mg bid dose level. Pharmacokinetic studies performed at doses of 1400 mg bid showed linear behavior with minimal accumulation between days 1–5. Tipifarnib administered on a week-on week-off schedule shows activity at higher doses, and represents an option for future clinical trials in AML.

Keywords

farnesyltransferase; tipifarnib; Zarnestra®; AML; acute myelogenous leukemia; phase 1 trial
Introduction

Inhibition of farnesyltransferase activity has been associated with activity against leukemias in vitro and in vivo. Farnesylation is essential to proper functioning of ras (1), a key protein in various signaling pathways. After farnesylation, ras localizes at the plasma membrane, where it acts as a molecular switch in response to various tyrosine kinase and other cell surface receptors. Initially, ras was identified as a potential target in myeloid malignancies due to the frequency of N-ras mutations in acute myelogenous leukemia and myelodysplasia. However, clinical trials thus far have shown activity for farnesyltransferase inhibitors (FTI) even in the absence of RAS mutation (2), suggesting that interference with unmutated ras is itself an effective antineoplastic approach, and/or that other farnesylated proteins, such as rhoB or the lamins may also be inhibited (3). As there are over 1000 farnesylated proteins, it remains unclear which are targeted by FTIs, and which are clinically relevant. Inhibition of farnesylation on specific proteins may differ depending on the dosing and schedule of the FTI inhibitor.

Tipifarnib (R115777, Zarnestra®) is a methylquinolone analogue that competes with the CAAX motif for farnesylation. The initial phase1 trial, R115777-USA-1, conducted at the National Cancer Institute, used a 5-day, every 12 hour, dosing regimen with an intra-patient and inter-patient dose-escalation scheme (4). Protocol-defined maximum tolerated dose (MTD) was not achieved at the highest dose level (1300 mg twice daily for five days).

Tipifarnib was studied in myeloid and lymphoid leukemias by Karp, et al. (2), with a dose escalation built upon a 21-day continuous dosing schedule. A 29% overall response rate was noted in 34 patients, including a CR at the lowest dose level (100 mg bid). In a follow-up phase 2 study, dosing at 600 mg twice daily (bid) using the same 21 day schedule, in older patients with previously untreated AML or MDS, CR was observed in 14% of patients, with an additional 10% showing partial response (5). A study at M.D. Anderson, for patients with MDS, also using the 21-day bid dosing schedule, demonstrated a 30% response rate in 20 patients (6). Their MTD was 400 mg bid; above that dose there were several dose limiting toxicities including headache, fatigue, confusion, and vision changes.

It is conceivable that altering the dosing schedule so that tipifarnib is given in a week-on, week-off schedule may allow tolerance of administration at higher dose. In a California Cancer Consortium solid tumor phase 1 study of week-on, week-off dosing, a DLT of grade 3 fatigue occurred at the 900 mg bid dose level; no other significant grade 3 toxicities were noted (7). In hematologic malignancies, a trial of tipifarnib given on a week-on, week-off schedule in patients with high grade myelodysplastic syndrome showed reasonable tolerability and responses at different dose levels. Importantly, correlative studies performed during this trial and others, have demonstrated farnesyl transferase inhibition for seven days after administration of tipifarnib (6–8), suggesting that this alternate-week dosing schedule is mechanistically appropriate, and that dose escalation on this schedule might enhance the activity of tipifarnib in relapsed, refractory AML.

Thus, we propose a study of this dose escalation regimen in acute myeloid malignancies. Pharmacokinetic studies were done to determine the effect of dose on blood levels. Should
this regimen be equally effective as conventional-dose tipifarnib monotherapy, but with better tolerability and advantageous pKs, it could serve as a platform for combination with other agents and chemotherapies.

PATIENTS AND METHODS

Patient Selection

Eligible patients were age 18 or over with acute myeloid leukemia (AML) including: relapsed or refractory disease after one to three prior induction regimens (not counting consolidation therapies while in CR, such as autologous transplant), newly diagnosed disease in patients up to age-70 with poor risk features (unfavorable cytogenetics or findings suggestive of prior myelodysplasia) not fit for standard induction therapy, and newly diagnosed AML patients age 70 – 75 not fit for standard therapy (without history of prior MDS). Patients with acute promyelocytic leukemia of the M3 subtype were excluded. Bone marrow and peripheral blood studies were required for confirmation of diagnosis. Patients who had been treated with prior autologous transplant, were eligible, and patients post allogeneic transplant were allowed in the expansion cohort as long as there was no active graft versus host disease or infectious disease related to transplant. A minimum of 4 weeks must have elapsed since completion of prior chemotherapy in order to be eligible. Standard end organ function criteria were applied, such as serum bilirubin ≤2.0 mg/dl, SGOT and SGPT ≤2.5 times the institutional upper limits of normal and excluding patients with a pretreatment calculated creatinine clearance (absolute value) of less than 60 ml/minute or serum creatinine of < 1.5 × upper limit of normal. There were no minimum hematological parameter requirements prior to enrollment, as patients with AML and MDS are understood to have low ANC and platelet counts when the disease is active. However, patients with WBC greater than 30,000 received hydroxyurea to reduce WBC to below 30,000 at which point they were able to commence therapy. Signed informed consent was obtained for all study participants and registered by the Data Coordinating Center at City of Hope. Protocol and consent forms were approved by the institutional review boards of the participating centers.

Treatment Plan

Oral tipifarnib was administered twice daily on days 1–7 and days 15–21 of each 28-day cycle. The planned dosing levels are presented in Table 1. Patients received a minimum of one treatment cycle, with no pre-defined maximum number of cycles. Patients were permitted to stay on study as long as there were no unacceptable toxicities. Intra-patient dose escalation was permitted (not beyond the highest dose tested) if CR was not reached in the first cycle and there was no significant toxicity. At the higher dose levels, intravenous hydration was frequently given with the morning tipifarnib dose. For subjects with rapidly rising white blood cell counts after week 1 or 3 of any cycle, hydroxyurea was permitted on the intervening week until 24 hours prior to restarting the next dose of tipifarnib. Allopurinol was started 24 hours before the first dose of tipifarnib and continued until at least day 22 of the first cycle.
Evaluation of response

Bone marrow aspiration and biopsies were performed as part of the on-study evaluation within two weeks prior to starting therapy. Patients were seen a minimum of once weekly while on study, with peripheral blood counts and chemistry monitored at least once weekly. Bone marrow studies were repeated between days 26 to 28 of each cycle. Clinical responses were measured according to International Working Group criteria (9).

Study Design

Patients were enrolled in cohorts of 3, as per standard 3+3 phase 1 study design. Patients completed study diaries which were reviewed as part of the toxicity assessment at each clinic visit. Adverse events (AEs) were graded using the NCI common toxicity criteria (CTCAE) version 3.0. Dose limiting toxicities (DLT) were defined as any grade 2 to 4 non-hematologic toxicity possibly related to study drug, except for nausea, vomiting and diarrhea controllable by routine palliation, any electrolyte disturbance corrected with supplementation, or any grade 4 hematologic toxicity in the absence of circulating blasts not reversible to grade 3 or less, by 21 days after the end of a cycle. In the presence of residual leukemia seen upon aspiration, neutropenia and thrombocytopenia did not count as DLT. Dose escalation proceeded if none of the 3 patients in the cohort had a first cycle DLT. If one of the three patients in a cohort experienced a DLT, three more patients were accrued at that dose level. In the event that a second patient experienced a DLT, that is, 2 or more out of 6 patients, then patients were accrued to the next lower dose level. The maximally tolerated dose (MTD) was defined as that at which no more than one patient out of six experienced a DLT during the first cycle of treatment. Intra-patient dose escalation to highest dose open for accrual was allowed if CR was not reached in the first cycle. If PR or clinical improvement was not reached after 6 cycles, patients were categorized as treatment failure and removed from the study.

Pharmacokinetic studies

Venous blood samples were collected in heparinized tubes at the following times during the first cycle: prior to the dose on Day 1, and then at 0.5, 1, 2, 3, 5, 8 and 12 hours post dosing, and immediately before the dose on Day 5, and then at 0.5, 1, 2, 3, 5, 8 and 12 hours post dosing. Blood was centrifuged for 10 minutes at 1000 × g within 2 hours after collection for separation of plasma, and the resulting plasma samples were stored frozen at < -20°C until batch analysis. Plasma concentrations of tipifarnib were determined using a previously described validated LCMS/MS assay (10).

Individual plasma concentration-time data were analyzed using standard non-compartmental methods and the following pharmacokinetic parameters of tipifarnib were determined for each patient around doses on Days 1 and 5: peak plasma concentration ($C_{\text{max}}$), time to reach the peak plasma concentration ($T_{\text{max}}$), area under the plasma concentration-time curve from 0 to 12 hours post-dosing ($AUC_{12h}$), and the trough plasma concentration ($C_{\text{min}}$). In addition, the accumulation index was determined by dividing the $AUC_{12h}$ on Day 5 by the $AUC_{12h}$ determined on Day 1.
Results

A total of 44 eligible patients with AML were enrolled in the study. Demographic data are listed in Table 1. Median age was 61 (range 33–79). Two patients were newly diagnosed; the remaining 42 had relapsed or failed prior therapy, including 5 patients with prior autologous transplant and 2 patients with prior allogeneic transplant.

Toxicity

At the 400 mg bid dose level, a grade 5 hepatorenal failure occurred, potentially related to the study drug. There were no additional DLTs, and no DLTs at 600 mg bid, 800 mg bid or 1000 mg bid. At the 1200 mg bid dose level, a grade 3 elevation of the creatinine was seen in one patient out of 6 treated. At the 1400 mg bid dose level, in an expanded cohort during dose de-escalation one patient experienced a grade 4 hypotension and a rising grade 2 creatinine that were dose limiting, and a second patient had a rising grade 2 creatinine in cycle 1, where treatment was terminated before it reached a grade 3 and was therefore considered dose limiting. At the 1600 mg dose level, a grade 3 LFT and a rising grade 2 creatinine, were dose limiting, and in a second patient, a rapidly rising creatinine was seen and the drug stopped before grade 3 was reached. As result, the 1200 mg bid dose was established as the maximum tolerated dose (MTD) and an additional 7 patients were treated at the MTD. In the total of 13 patients that were treated at the 1200 mg bid dose, there were no grade 4 or 5 toxicities. Grade 2 and 3 toxicities are listed in Table 2: there was one grade 3 creatinine DLT and grade 2 toxicities included hyperglycemia, fatigue, alopecia, hyperkalemia, mouth sores, shortness of breath, dizziness, nausea, vomiting, ataxia, abdominal pain, headache, and dehydration. For this reason, at the higher doses, tipifarnib was administered along with daily IV hydration in most patients. Assessing potential hematologic toxicities is challenging in AML studies due to the underlying disease, however, among the 3 patients who achieved CR, one patient developed pancytopenia resulting in an episode of febrile neutropenia upon subsequent cycles of drug.

Clinical Activity

The number of patients, DLTs and responses for each individual tipifarnib dose are detailed in Table 3. One patient at the 1000 mg oral bid dose, who had relapsed after autologous stem cell transplant, achieved complete remission (CR) after one cycle, and was taken to allogeneic stem cell transplant, and remains in remission for over five years. There were two CRs achieved at the 1200 mg bid dose: One patient with relapsed disease after standard 7-day cytarabine/3-day daunorubicin induction and one cycle of consolidation, entered CR and remained on study for 17 months until relapse; a second patient at the 1200 mg dose level, who had relapsed after first remission, and was resistant to second induction, achieved a CR that lasted one month. Also at the 1200 mg dose level, a third patient patient dropped from 50% to 7% marrow blasts after 3 cycles. At the 800 mg bid dose a patient’s marrow blasts decreased from 36% to 10% over 3 cycles, and at the 1400 mg bid dose bone marrow blasts were decreased by 50% or more in two patients.
Pharmacokinetics

First-dose tipifarnib pharmacokinetic data are available for 10 subjects (Table 4) and 5th dose data for a total of 9 subjects (Table 5). Three subjects received doses of 1400 mg and 7 received 1200 mg bid. The median $C_{\text{max}}$ after the 1st dose on Day 1 was 3920 µg/L and 906 µg/L in subjects receiving 1400 mg and 1200 mg, respectively. The median $C_{\text{max}}$ after the dose on Day 5 was 2630 µg/L in subjects receiving 1400 mg and 1210 µg/L at the 1200 mg dose level. The median $C_{\text{min}}$ after the 1st dose was 237 µg/L and 166 µg/L in subjects receiving 1400 mg and 1200 mg, while the median $C_{\text{min}}$ after Day 5 was 476 µg/L and 166 µg/L, respectively. The median AUC$_{12h}$ after the 1st dose was 13,835 hr·µg/L and 4744 hr·µg/L in subjects receiving 1400 mg and 1200 mg, while the median AUC$_{12h}$ after the dose on Day 5 was 17,148 hr·µg/L and 7366 hr·µg/L. The median AUC$_{12h}$ for two patients with decreased blasts was 16295 hr·µg/L and 13221 hr·µg/L on days 1 and 5 respectively, while for the remaining patients, the median AUC$_{12h}$ was 7576 hr·µg/L and 4325 hr·µg/L on days 1 and 5 respectively. Similarly, median Cmax for these two patients was 2442.5 µg/L and 2550 µg/L on days 1 and 5, while median Cmax for the remaining patients was 1290 µg/L and 881 µg/L on days 1 and 5 respectively. These differences were not statistically significant. The median accumulation index in subjects receiving doses of 1400 mg and 1200 mg daily were 1.17 and 1.2, respectively.

Discussion

Tipifarnib is a methylquinolone analogue that competes with the CAAX motif for farnesylation, leading to competitive inhibition of the enzyme farnesyltransferase, which is critical to the function of multiple proteins involved in essential pathways for cell survival. While initially developed as an agent targeting ras, it appears that tipifarnib may act on multiple pathways, and it is possible that its effects on other farnesylated proteins might be enhanced if higher doses of the drug could be delivered in a safe manner. For this reason we studied escalating doses of tipifarnib in a week-on week-off schedule, which maintains the molecular activity of the drug while potentially decreasing toxicity.

In this phase 1 study, consisting almost entirely of patients with relapsed disease, at the 1000 mg and 1200 mg BID dosing levels, we saw 3 CRs, two of which were of long duration, one lasting 17 months and one that enabled the patient to undergo allogeneic stem cell transplant; this patient remains disease free for over 5 years. These three patients all had relapsed disease and cytogenetic abnormalities (trisomy 21, −7, del20). No formal responses were seen among patients treated in the lower dose levels at this schedule.

Tipifarnib pharmacokinetics have been extensively studied at lower doses (13–15), however, relatively few data have been reported for doses above 1000 mg. Karp et al. (2) presented data for three subjects receiving 1200 mg and Zujewski et al. (4) reported data for 3 subjects given doses of 1300 mg. The results presented here are in general agreement with the earlier studies, and taken together, the data suggest that the pharmacokinetic behavior of tipifarnib is linear up to doses as high as 1400 mg bid. We have also confirmed that relatively modest tipifarnib accumulation occurs between days 1 and 5, even at these higher doses. While the pharmacokinetic sampling did not include the two patients with complete responses at 1200 mg, there was a 2–3 fold higher median AUC and Cmax on both day 1 and day 5 observed.
in the two patients with decreased blasts assayed when compared to the median of the non-responders. The current data also indicate a significant degree of both inter- and intra-patient variability in tipifarnib pharmacokinetics. The potential sources of such variability, as well as its clinical impact, need to be further elucidated.

Although the expansion group is too small (7 patients) to cause concern, it is interesting that no complete responses were seen in this group. However, these were the last patients accrued to the study, raising the theoretical possibility that resistance to tipifarnib could be correlated with prior exposure to hypomethylating agents, which had recently entered standard clinical use. This hypothesis should be examined in a larger study in light of known resistance mechanisms to 5-aza-2’-deoxycytidine (16) and tipifarnib (17).

Tipifarnib is an agent with clear activity in leukemia; however, it is increasingly clear that this activity is limited to disease with certain characteristics, best typified thus far by the correlation with the RASGRP1/APTX ratio as determined by gene signature analysis. Our study suggests that clinical studies designed to study the role of tipifarnib in these populations should consider higher doses on a week-on, week-off schedule.

Acknowledgements

We would like to thank the City of Hope medical, nursing and administrative staff for their dedication and support for this study. We would also like to thank Sandra Thomas for assistance with editing and review of the manuscript. This work was supported by grant #s U01-CA-62505 and N01-CM-62209 (NCI Cancer Therapy Evaluation Program) and P30-CA-033572 (City of Hope).

References

1. Rowinsky EK, Windle JJ, Von Hoff DD. Ras protein farnesyltransferase: A strategic target for anticancer therapeutic development. J Clin Oncol. 1999 Nov; 17(11):3631–3652. [PubMed: 10550163]

2. Karp JE, Lancet JE, Kaufmann SH, End DW, Wright JJ, Bol K, 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 Jun 1; 97(11):3361–3369. [PubMed: 11369625]

3. Cox AD, Der CJ. Farnesyltransferase inhibitors and cancer treatment: targeting simply Ras? Biochim Biophys Acta. 1997 Aug 8; 1333(1):F51–F71. [PubMed: 9294018]

4. Zujewski J, Horak ID, Bol CJ, Woestenborghs R, Bowden C, End DW, et al. Phase I and pharmacokinetic study of farnesyl protein transferase inhibitor R115777 in advanced cancer. J Clin Oncol. 2000 Feb; 18(4):927–941. [PubMed: 10673536]

5. Lancet JE, Gojo I, Gotlib J, Feldman EJ, Greer J, Liesveld JL, 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 Feb 15; 109(4):1387–1394. [PubMed: 17082323]

6. Kurzrock R, Cortes J, Kantarjian H. Clinical development of farnesyltransferase inhibitors in leukemias and myelodysplastic syndrome. Semin Hematol. 2002 Oct; 39(4 Suppl 3):20–24. [PubMed: 12447848]

7. Lara P, Frankel P, Gumerlock PH, Mack PC, Law LY, Lenz HJ, et al. Intermittent dosing of the farnesyl transferase inhibitor R115777 in advanced malignant solid tumors: A Phase I California Cancer Consortium Trial. Proc Am Soc Clin Oncol. 2003; 22 (abstr 878).

8. Kelland LR. Farnesyl transferase inhibitors in the treatment of breast cancer. Expert Opin Investig Drugs. 2003 Mar; 12(3):413–421.

9. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response
Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003 Dec 15; 21(24):4642–4649. [PubMed: 14673054]

10. Zhang S, Zannikos P, Awada A, Piccart-Gebhart M, Dirix LY, Fumoleau P, et al. Pharmacokinetics of tipifarnib after oral and intravenous administration in subjects with advanced cancer. J Clin Pharmacol. 2006 Oct; 46(10):1116–1127. [PubMed: 16988200]

11. Harousseau JL, Lancet JE, Reiffers J, Lowenberg B, Thomas X, Huguet F, et al. A phase 2 study of the oral farnesyltransferase inhibitor tipifarnib in patients with refractory or relapsed acute myeloid leukemia. Blood. 2007 Jun 15; 109(12):5151–5156. [PubMed: 17351110]

12. Erba HP, Kopecky KJ, Kirschbaum MH, Tallman MS, Larson RA, Willman CL, et al. Phase II Studies of Different Schedules and Doses of the Farnesyl Transferase Inhibitor Tipifarnib (R115777, Zarnestra, NSC-702818) for Patients of Age 70 or Older with Previously Untreated Acute Myeloid Leukemia (AML): A North American Intergroup Study (S0432). ASH Annual Meeting Abstracts 2007 November 16. 2007; 110(11):440.

13. Siegel-Lakhai WS, Crul M, De Porre P, Zhang S, Chang I, Boot H, et al. Clinical and pharmacologic study of the farnesyltransferase inhibitor tipifarnib in cancer patients with normal or mildly or moderately impaired hepatic function. J Clin Oncol. 2006 Oct 1; 24(28):4558–4564. [PubMed: 17008695]

14. Zimmerman TM, Harlin H, Odenike OM, Berk S, Sprague E, Karrison T, et al. Dose-ranging pharmacodynamic study of tipifarnib (R115777) in patients with relapsed and refractory hematologic malignancies. J Clin Oncol. 2004 Dec 1; 22(23):4816–4822. [PubMed: 15570084]

15. Crul M, de Klerk GJ, Swart M, van’t Veer LJ, de Jong D, Boerrigter L, et al. Phase I clinical and pharmacologic study of chronic oral administration of the farnesyl protein transferase inhibitor R115777 in advanced cancer. J Clin Oncol. 2002 Jun 1; 20(11):2726–2735. [PubMed: 12039935]

16. Qin T, Jelinek J, Si J, Shu J, Issa JP. Mechanisms of resistance to 5-aza-2’-deoxycytidine in human cancer cell lines. Blood. 2009 Jan 15; 113(3):659–667. [PubMed: 18931345]

17. Raponi M, Lancet JE, Fan H, Dossey L, Lee G, Gojo I, et al. A 2-gene classifier for predicting response to the farnesyltransferase inhibitor tipifarnib in acute myeloid leukemia. Blood. 2008 Mar 1; 111(5):2589–2596. [PubMed: 18160667]

Leukemia. Author manuscript; available in PMC 2012 April 01.
Table 1

**Patient Characteristics**

| Patient Characteristics                        | Number (percent) |
|-----------------------------------------------|------------------|
| **Total patients**                            | 44 (100)         |
| **Age in years (median)**                     | 61               |
| Age range                                     | 33–79            |
| Age < 65 years                                | 24 (55)          |
| **Sex**                                       |                  |
| Male                                          | 24 (55)          |
| Female                                        | 20 (45)          |
| **Race/ethnicity**                            |                  |
| Caucasian                                     | 34 (77)          |
| Hispanic                                      | 6 (14)           |
| Asian                                         | 4 (9)            |
| **Median time from diagnosis, months**        | 9.6              |
| **Karnofsky performance status (KPS)**        |                  |
| 100                                           | 11 (25)          |
| 90                                            | 17 (39)          |
| 80                                            | 11 (25)          |
| 70                                            | 4 (9)            |
| 60                                            | 1 (2)            |
| **Relapsed / refractory disease**             | 41 (93)          |
| **Prior hematopoietic cell transplant**       |                  |
| Autologous                                    | 7 (16)           |
| Allogeneic                                    | 5 (11)           |
| Allogeneic                                    | 2 (5)            |
Table 2
Toxicity grades 2 and above attributable to treatment at 1200 mg bid dose (excluding hematology toxicities and infection)

| Toxicity              | Course 1 |               | Subsequent |               |
|-----------------------|----------|---------------|------------|---------------|
|                       | Grade 2  | Grade 3       | Grade 2    | Grade 3       |
| ALT, SGPT             | 2        |               | 1          |               |
| Anorexia              | 2        |               | 1          |               |
| AST, SGOT             |          | 1             |            |               |
| Ataxia                |          | 1             |            |               |
| Bilirubin             | 2        |               | 1          |               |
| Constipation          |          | 1             |            |               |
| Creatinine            | 2        | 1             | 3          |               |
| Creatinine            |          |               |            | 3             |
| Dehydration           | 1        |               |            |               |
| Fatigue               | 3        |               | 2          |               |
| Febrile neutropenia   |          |               |            | 1             |
| Hyperglycemia         |          |               |            | 2             |
| Hypoalbuminemia       | 2        |               | 2          |               |
| Nausea                | 1        | 1             | 2          |               |
| Rash / desquamation   | 1        |               |            |               |
| Restless leg syndrome |          |               |            | 1             |
| Syncope (fainting)    |          |               |            | 1             |
| Vomiting              | 2        |               | 2          |               |
| Weight loss           |          |               |            | 1             |
Table 3

Outcomes for each tipifarnib dose

| Dose (mg bid) | # patients treated | # patients inevaluable | # of cycles median (range) | # DLTs | DLT descriptions | Responses |
|---------------|-------------------|------------------------|----------------------------|--------|-----------------|-----------|
| 400           | 7                 | 1                      | 1 (1–3)                    | 1      | hepatic         |           |
| 600           | 3                 | 0                      | 3 (1–3)                    | 0      |                 |           |
| 800           | 5                 | 2                      | 1 (1–3)                    | 0      |                 | 1 CMML patient cleared leukemic blasts |
| 1000          | 3                 | 0                      | 2 (2–3)                    | 0      |                 | 1 CR went to transplant |
| 1200          | 13                | 1                      | 2 (1–15)                   | 1      | renal           | 2 CRs, 1 marrow response (from 50%-7% blasts) |
| 1400          | 6                 | 0                      | 3 (1–5)                    | 2      | renal           | 2 patients with decreased peripheral blasts |
| 1600          | 7                 | 2                      | 1 (1–2)                    | 2*     | hepatic, renal* |           |

DLT=dose limiting toxicity, CR=complete remission

* Rapidly progressing grade 2 creatinine was considered dose limiting and dose reduction was initiated.

In all cases, elevation of creatinine reversed during the week off drug.
### Table 4

#### Day 1 tipifarnib pharmacokinetics

| Subject | Dose (mg) | $C_{\text{max}}$ (µg/L) | $T_{\text{max}}$ (hr) | $C_{\text{min}}$ (µg/L) | AUC$_{12h}$ (hr·µg/L) |
|---------|-----------|--------------------------|-----------------------|--------------------------|------------------------|
| 1       | 1400      | 4240                     | 3.1                   | ND                       | ND                     |
| 2       | 1400      | 3920                     | 2.0                   | 329                      | 18715                  |
| 3       | 1400      | 1690                     | 3.2                   | 145                      | 8954                   |

| Median = | 3920 | 3.1 | 237 | 13835 |
| Low =    | 1690 | 2.0 | 145 | 8954  |
| High =   | 4240 | 3.2 | 329 | 18715 |

| 4       | 1200      | 804                      | 2.0                   | 132                      | 3905                   |
| 5       | 1200      | 1180                     | 2.0                   | 339                      | 7727                   |
| 6       | 1200      | 479                      | 2.1                   | 166                      | 3242                   |
| 7       | 1200      | 2300                     | 2.1                   | ND                       | ND                     |
| 8       | 1200      | 906                      | 3.0                   | 82                       | 4744                   |
| 9       | 1200      | 3160                     | 3.0                   | 402                      | 15653                  |
| 10      | 1200      | 404                      | 3.0                   | ND                       | ND                     |

| Median = | 906  | 2.1 | 166 | 4744  |
| Low =    | 404  | 2.0 | 82  | 3242  |
| High =   | 3160 | 3.0 | 402 | 15653 |

ND = Not done
### Table 5

**Day 5 tipifarnib pharmacokinetics**

| Subject | Dose (mg) | $C_{\text{max}}$ (µg/L) | $T_{\text{max}}$ (hr) | $C_{\text{min}}$ (µg/L) | $\text{AUC}_{12\text{h}}$ (hr·µg/L) | Accumulation Index |
|---------|-----------|--------------------------|------------------------|--------------------------|----------------------------------|-------------------|
| 1       | 1400      | ND                       | ND                     | ND                       | ND                               | ND                |
| 2       | 1400      | 3890                     | 3.0                    | 781                      | 25589                            | 1.37              |
| 3       | 1400      | 1370                     | 5.0                    | 170                      | 8707                             | 0.97              |
|         |           | Median = 2630            | 4.0                    | 476                      | 17148                            | 1.17              |
|         |           | Low = 1370               | 3.0                    | 170                      | 8707                             | 0.97              |
|         |           | High = 3890              | 5.0                    | 781                      | 25589                            | 1.37              |
| 4       | 1200      | 762                      | 3.0                    | 97                       | 4815                             | 1.23              |
| 5       | 1200      | 995                      | 1.0                    | 204                      | 7001                             | 0.91              |
| 6       | 1200      | 1880                     | 1.0                    | 234                      | 7787                             | 2.40              |
| 7       | 1200      | 2500                     | 5.0                    | 283                      | 14233                            | ND                |
| 8       | 1200      | 1210                     | 5.0                    | 166                      | 7366                             | 1.55              |
| 9       | 1200      | 2490                     | 3.1                    | 113                      | 9221                             | ND                |
| 10      | 1200      | 1020                     | 2.8                    | 101                      | 4625                             | ND                |
|         |           | Median = 1210            | 3.0                    | 166                      | 7366                             | 1.23              |
|         |           | Low = 762                | 1.0                    | 97                       | 4625                             | 0.59              |
|         |           | High = 2500              | 5.0                    | 283                      | 14233                            | 1.55              |

ND = Not done