**Johnson & Johnson Pharmaceutical Research & Development, L.L.C.**

**ODAC Briefing Document**

# Tipifarnib (ZARNESTRA®) for the Treatment of Elderly Patients With Newly Diagnosed Poor-Risk Acute Myeloid Leukemia

**R115777 (tipifarnib)**

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# TABLE OF CONTENTS


**1. EXECUTIVE SUMMARY ..... 6**

**2. ACUTE MYELOID LEUKEMIA IN THE ELDERLY ..... 9**

**3. TIPIFARNIB: BACKGROUND INFORMATION ..... 12**

3.1. Farnesylation and Farnesyltransferase Inhibition ..... 13

3.2. Mechanism of Action ..... 14

3.2.1. Cellular Pharmacology ..... 14

3.2.2. Molecular Pathways ..... 14

3.3. Clinical Pharmacology ..... 14

3.3.1. Absorption and Bioavailability ..... 15

3.3.2. Distribution ..... 16

3.3.3. Metabolism ..... 17

3.3.4. Elimination and Excretion ..... 17

3.3.5. Impact of Food on the Absorption of Tipifarnib ..... 17

3.3.6. Population Pharmacokinetics ..... 18

3.3.7. Potential for Drug Interactions ..... 18

3.3.7.1. Nonclinical Studies ..... 18

3.3.7.2. Clinical Studies ..... 18

**4. CLINICAL DEVELOPMENT PROGRAM OF TIPIFARNIB ..... 18**

4.1. Assessment of Efficacy in AML ..... 20

4.2. Study CTEP-1 ..... 21

4.2.1. Biologic Activity ..... 22

4.2.2. Recommended Dose ..... 22

4.3. Study CTEP-20 ..... 23

4.3.1. Study Population ..... 23

4.3.2. Treatment Regimen ..... 27

4.3.2.1. Treatment Compliance ..... 27

4.3.3. Study Endpoints ..... 27

4.3.4. Efficacy ..... 27

4.3.4.1. Complete Remissions ..... 27

4.3.4.2. Independent, Blinded Central Review of Bone Marrow Biopsies ..... 33

4.3.4.3. Complete Remission and Risk Factors ..... 33

4.3.4.4. Overall Survival ..... 34

4.3.4.5. Exploratory Analysis of Impact of Complete Remission on Survival ..... 35

4.3.4.6. Retreatment With Tipifarnib ..... 36

4.3.4.7. Salvage Therapy ..... 36

4.3.4.8. Efficacy Update ..... 37

4.4. Study INT-17 ..... 38

4.4.1. Study Population ..... 38

4.4.2. Treatment Regimen ..... 40

# TABLE OF CONTENTS (Continued)


4.4.3. Study Endpoints ..... 40
4.4.4. Biologic Activity ..... 41
4.5. Study CTEP-50 ..... 41
4.6. Study AML-301 ..... 41

**5. SUMMARY AND CONCLUSIONS ON EFFICACY OF TIPIFARNIB IN AML ..... 42**

**6. SAFETY AND TOLERABILITY OF TIPIFARNIB ..... 43**
6.1. Background ..... 43
6.2. Determination of Phase 2 Dose in Patients With AML ..... 43
6.3. Patients Included in the Analysis of Safety ..... 43
6.4. Safety in Patients With AML ..... 44
6.4.1. Safety Population and Extent of Exposure ..... 44
6.4.2. Adverse Events and Clinical Laboratory Evaluations ..... 45
6.4.2.1. Overview ..... 45
6.4.2.2. Hematologic Adverse Events and Laboratory Evaluations 46
6.4.2.3. Nonhematologic Adverse Events and Laboratory Evaluations ..... 47
6.4.2.4. Deaths ..... 51
6.4.2.5. Serious Adverse Events and Hospitalizations ..... 52
6.4.2.6. Adverse Events Leading to Permanent Discontinuation ..... 54
6.4.2.7. Adverse Events Leading to Dose Modification ..... 54
6.4.3. Summary of Myelosuppression ..... 55
6.4.3.1. Overview ..... 55
6.4.3.2. Neutropenia and Infection ..... 56
6.4.3.3. Thrombocytopenia and Bleeding Events ..... 57
6.4.4. Summary of Renal Dysfunction ..... 59
6.4.4.1. Serum Creatinine and Creatinine Clearance ..... 59
6.4.4.2. Hypokalemia ..... 60
6.4.4.3. Clinical Adverse Events ..... 60
6.4.5. Long-Term Safety ..... 61
6.4.6. Effect of Age ..... 61
6.5. Safety in Patients With Solid Tumors ..... 62
6.5.1. Safety Population and Extent of Exposure ..... 62
6.5.2. Adverse Events ..... 63
6.5.2.1. Overview ..... 63
6.5.2.2. Hematologic Adverse Events ..... 63
6.5.2.3. Nonhematologic Adverse Events ..... 64
6.5.2.4. Deaths and Other Serious Adverse Events ..... 64
6.6. Safety Findings of Special Interest in Patients With AML or Solid Tumors ..... 65
6.6.1. Neurotoxicity ..... 65

# TABLE OF CONTENTS (Continued)


6.6.1.1. Central Nervous System ..... 65
6.6.1.2. Peripheral Neurotoxicity ..... 65
6.6.2. Cardiotoxicity ..... 66
6.7. Safety in Other J&JPRD Studies ..... 67
6.8. March 2005 Update ..... 67

**7. OVERALL BENEFIT/RISK ASSESSMENT ..... 68**

**8. REFERENCES ..... 71**

# TABLE OF CONTENTS (Continued)

**APPENDICES** ..... 74

**APPENDIX 1: LIST OF ABBREVIATIONS** ..... 75

**APPENDIX 2: SERIOUS ADVERSE EVENTS IN OTHER J&JPRD HEMATOLOGIC STUDIES** ..... 77

# 1. EXECUTIVE SUMMARY

Untreated acute myeloid leukemia (AML) is typically a rapidly progressive and fatal illness in the elderly, with median survival ranging from 1 to 3 months (Menzin 2002). The incidence of AML increases with age, with the majority of cases diagnosed in patients older than 60 years of age. Elderly patients diagnosed with AML currently have a limited choice of therapeutic options. According to the 2005 National Comprehensive Cancer Network (NCCN) guidelines, the recommended treatment for elderly patients with AML, patients with AML and significant comorbidities, or patients with antecedent hematologic disease (e.g., myelodysplastic syndrome [MDS]) is either best supportive care (which could also include hydroxyurea) or investigational treatment in the setting of a clinical study. Clearly, additional options for the treatment of elderly patients with poor-risk leukemia are needed.

The intensely myelosuppressive chemotherapy treatment regimens typically used in a younger patient population induce severe and potentially life-threatening adverse effects in elderly patients, routinely requiring meticulous monitoring and hospitalization to manage the symptoms and complications associated with treatment toxicity. Treatment-related mortality is generally reported to be approximately 25% for elderly patients who receive intensive combination chemotherapy regimens for AML. Moreover, the effectiveness of these treatment regimens is reduced in elderly patients, and the increased treatment-related toxicities often result in a substantial portion of a patient's remaining life being spent in the hospital.

As a result, elderly patients diagnosed with AML often do not receive the intensive induction/consolidation chemotherapy regimens used in younger patients, as reflected by the treatment patterns in the oncology community and by enrollment in clinical studies. Furthermore, little progress has been made in the treatment of this patient population. Elderly patients with AML are typically under-represented in clinical studies (relative to the incidence of AML in this age group).

Tipifarnib is a novel oral, selective farnesyltransferase inhibitor that has shown biologic (antileukemic) activity, including complete clinical remissions, in patients with AML in Phase 1 and Phase 2 studies. Tipifarnib has been demonstrated to produce complete remissions, with relatively modest treatment-related toxicity, in elderly patients with newly diagnosed poor-risk AML. Complete remissions have been accepted as a surrogate likely to predict clinical benefit for hematologic malignancies; examples include clofarabine and gemtuzumab ozogamicin. While clinical research is continuing to further characterize the use of tipifarnib, the Sponsor seeks accelerated approval for the following indication: "Tipifarnib is indicated for the treatment of elderly patients with newly diagnosed poor-risk acute myeloid leukemia."

**Clinical Program – Efficacy**

A Phase 1 study (CTEP-1) in patients with hematologic malignancies was conducted in collaboration with the National Cancer Institute (NCI) in 1999 under the terms of a Cooperative Research and Development Agreement (CRADA). This study explored the clinical pharmacology of tipifarnib and determined the initial safety profile. This study demonstrated the first complete remissions for AML patients treated with tipifarnib and led to further studies in AML. The data obtained formed the basis for the selection of the dose regimen (600 mg b.i.d. for 21 days, 28-day treatment cycle) explored in the subsequent

studies in leukemia. This dose regimen was selected to maximize farnesyltransferase inhibition and provide AML patients with the best chance of response at a well-tolerated dose. To date, the AML development program has explored three distinct AML-related medical problems: newly diagnosed AML in elderly patients with poor-risk AML (CTEP-20), relapsed and refractory AML (INT-17), and a pilot study of the use of tipifarnib as maintenance therapy, following successful induction of remission with intensive combination chemotherapy (INT-21).

The CTEP-20 study of tipifarnib in the treatment of newly diagnosed poor-risk AML (focusing on elderly patients) provides the primary evidence in support of the proposed indication for tipifarnib. The CTEP-20 protocol initially enrolled primarily elderly patients with hematologic malignancies or MDS, for whom there was an unfavorable benefit/risk profile such that they were not optimal candidates for intensive induction chemotherapy. The endpoints, target population, and key design features of this protocol were the subject of review and discussion with the Cancer Therapy Evaluation Program (CTEP), Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), and the Food and Drug Administration (FDA) in July 2003. Based on the protocol amendment that was implemented as a result of this review, the final target population to be assessed in CTEP-20 was expanded and focused on patients with AML who were ≥ 75 years of age or patients with prior MDS who were 65 to 74 years of age.

CTEP-20 is one of the largest studies conducted to date in elderly patients (≥65 years) with newly diagnosed poor-risk AML. This study found a complete response rate, defined by investigators' assessment, of 15% (n=136; 95% confidence interval [CI] = 9.4-22.0). As a quality-assurance measure, an independent, blinded, central review of bone marrow biopsies was undertaken to verify the initial diagnosis of AML at study entry and to verify investigators' assessments of complete response. Complete responses (CR) were found to be durable, with a median CR duration of 220 days (95% CI = 154-275 days) and median overall survival for patients with CR of 433 days (95% CI = 279-572 days).

**Clinical Program – Safety**

The safety profile of tipifarnib has been established in over 1,000 patients studied in the AML (n=409) and solid tumor (n=605) clinical development programs. This large safety population provides a well-defined safety profile. Compared with typically used chemotherapy agents, tipifarnib is well tolerated. In all treated patients with AML, reversible myelosuppression (i.e., neutropenia [grade 3 or 4] and thrombocytopenia [grade 3 or 4]) is the primary treatment-related toxicity. Tipifarnib is not myeloablative or intensely myelosuppressive. Although there is a high degree of grade 3 or 4 neutropenia, the incidence of febrile neutropenia is relatively low compared with combination chemotherapy; this may be related in part to the low incidence of severe mucositis. The most commonly reported nonhematologic adverse events were hypokalemia (17% grade 3 or 4), diarrhea (5% grade 3 or 4), fatigue (14% grade 3 or 4), rash (6% grade 3 or 4), and confusion (6% grade 3 or 4). Early mortality (within 28 days after first dose of study medication) related to adverse events was relatively low (8%) for the AML population.

At the start of the CTEP-20 study, patients were routinely hospitalized for observation, but this was subsequently deemed unnecessary for many patients. Overall, a substantial proportion of patients enrolled in this study (40%) were never hospitalized for treatment or for treatment-related adverse events. The median hospital stay (15 days) was short,

representing only 14% of the total time spent in the study. This duration of hospitalization is an improvement over the usual experience with standard induction chemotherapy, which is associated with nearly a 100% hospitalization rate and up to 50% of survival time spent in hospital.

**Clinical Program – Ongoing Confirmatory Study**

A Phase 3 study protocol (AML-301) comparing tipifarnib to best supportive care, with overall survival as the primary endpoint, was the subject of a special protocol assessment (SPA) by the FDA during 2004. AML-301 is intended to fulfill the postapproval commitment that would be required under terms of a possible accelerated approval. The FDA's SPA for AML-301 was completed in May 2004, with the first patient entered into the study in October 2004. Based on the current accrual rate and a target enrollment of 300 patients, AML-301 is predicted to be completed in late 2006.

**Conclusions**

This tipifarnib New Drug Application (NDA) program was granted fast-track status, priority review, and acceptance into a continuous marketing application (CMA-Pilot 1) during 2004. Tipifarnib has also been granted Orphan Drug status for the AML indication. The Oncologic Drugs Advisory Committee will be asked to consider the tipifarnib NDA in the context of possible accelerated approval. Accelerated approvals are considered for NDAs that address an unmet medical need, and allow for consideration of approval based on a surrogate endpoint that is deemed likely to predict clinical benefit while data to confirm clinical benefit are being collected. Complete response has been accepted as a surrogate for clinical benefit for agents developed to treat AML.

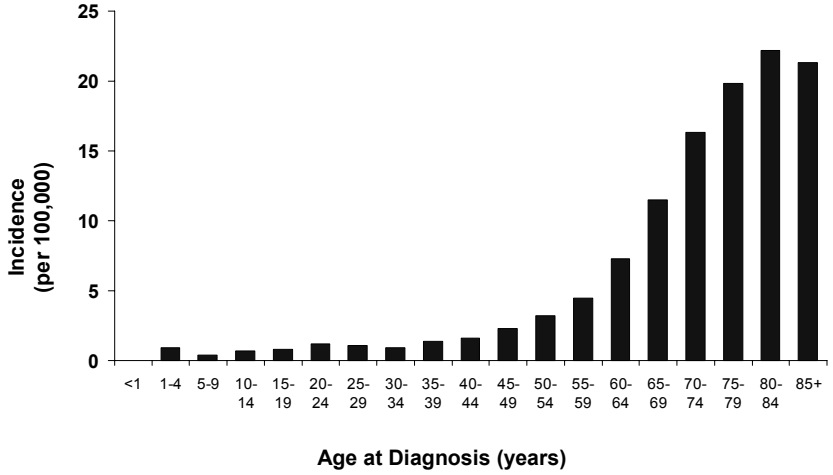
In the case of tipifarnib, complete response was assessed as the primary endpoint in the key CTEP-20 study. Tipifarnib offers a new therapeutic option for elderly patients with newly diagnosed poor-risk AML. The well-defined and acceptable safety profile of tipifarnib in elderly patients, in the context of proven biologic activity in poor-risk AML, argues in favor of a positive benefit/risk assessment for the accelerated approval process.

As summarized above, this briefing document provides a short background on AML, an overview of the clinical development program in AML, a review of the efficacy findings from the CTEP-20 study and of the safety data from both AML and solid tumor studies, and an overall benefit/risk assessment.

# 2. ACUTE MYELOID LEUKEMIA IN THE ELDERLY

The annual incidence of AML in the United States is approximately 12,000, with 9,000 deaths per year due to AML (Ries 2004). The incidence of AML increases with age (**Figure 1**). However, the benefits of currently available treatments for AML are diminished with advancing age (NCCN 2005, Stone 2002), as well as in the presence of other adverse prognostic indicators such as a prior history of MDS (Menzin 2002, Löwenberg 1999, Jackson 2002). Standard therapy for AML (combination induction chemotherapy, followed by consolidation chemotherapy in patients who achieve a complete remission) has changed little over the past three decades and is often not suited for the treatment of elderly patients who have AML (NCCN 2005, Stone 2002). Standard induction chemotherapy regimens commonly include a combination of cytarabine and an anthracycline with or without additional agents. One example of a chemotherapeutic induction regimen is a regimen consisting of a seven-day continuous infusion of cytarabine (100 to 200 mg/m$^2$/day) and a three-day course of idarubicin (12 to 13 mg/m$^2$/day) during the first three days of cytarabine administration. Well-defined risk factors that are associated with poor treatment outcome (decreased antileukemic effect) when using standard therapy (Menzin 2002, Löwenberg 1999) generally become more prevalent with advancing age and include AML arising from prior MDS, unfavorable cytogenetics, and increased MDR-1 gene expression (Jackson 2002).

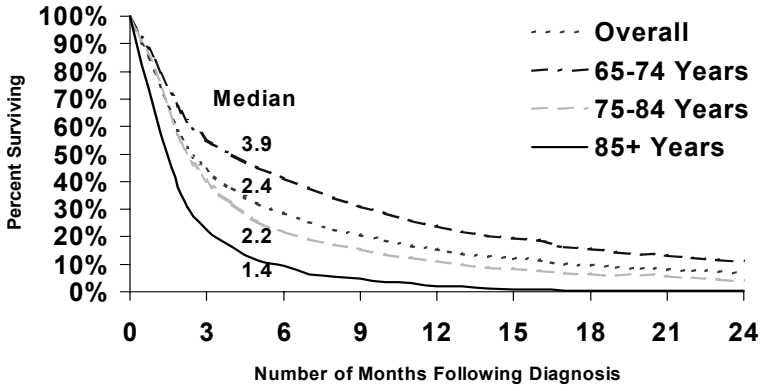
**Figure 1:** Incidence of AML by Age




Cross-reference: Ries 2003.

The ability of patients to tolerate the adverse effects of treatment is also diminished with age, as well as with coexisting physiological conditions such as renal or hepatic impairment. For these reasons, clinical studies of standard combination chemotherapy treatment approaches for AML generally have enrolled younger patients. In the older segment (age ≥65 years) of the AML population, median survival generally is quite short, ranging from 3.9 months among those who are 65 to 74 years of age to 1.4 months among those who are 85 years of age or older (**Figure 2**) (Menzin 2002, Ries 2003).

**Figure 2:** AML Survival by Age




Cross-reference: Ries 2003.

Risk factors usually linked to decreased treatment tolerance include advanced age (≥75 years), presence of cardiac or renal comorbidity, and poor performance status at the time of presentation (Löwenberg 1999, Jackson 2002). It is evident that older patients with AML experience significantly more toxicity when treated with standard combination induction chemotherapy regimens, which are intended to induce profound myelosuppression (Stone 2002). A recent review indicated that: "AML in older adults is a biologically and clinically distinct entity (Stone 2002)." Based on analysis of cytogenetic and molecular data, it is known that leukemic cells in older patients may be intrinsically more resistant to standard chemotherapy. Due to comorbid disease and impaired bone marrow stem cell reserve, older adults tolerate myelosuppressive chemotherapy poorly, with a treatment-related mortality rate of approximately 25 percent (Stone 2002).

Many elderly AML patients do not receive standard induction/consolidation chemotherapy treatment given the relatively poor outcomes observed and due to their difficulty in tolerating the side effects of chemotherapy (**Table 1**) (Menzin 2002, Goldstone 2001, Vey 2004). In addition, older patients self-select nonintensive therapy or best supportive care (Sekeres 2004). Elderly patients are also substantially under-represented in AML studies (**Table 2**) (Goldstone 2001, Talarico 2004, Baudard 1994). In the community setting, older patients with AML typically are managed with supportive care, hydroxyurea, and low-dose cytarabine. However, there are no established treatment approaches with proven benefit for these patients.

**Table 1:** Percentage of Patients With AML Who Received Intravenous Chemotherapy, by Age

| 65-74 years (N=1,507) | 75-84 years (N=1,407) | ≥85 years (N=525) |
|---|---|---|
| 49% | 28% | 7% |

Cross-reference: Menzin 2004 and Lang submitted.

**Table 2:** Enrollment of Older Patients in AML Studies

| Study Conducted By: | N | Year | Median Age (y) | Age ≥60 y (%) |
|---|---|---|---|---|
| German AML Cooperative Group | 419 | 1985 | 49 | 35 |
| British Medical Research Council | 1127 | 1986 | 44 | 27 |
| Cancer and Leukemia Group B | 668 | 1987 | 43 | 16 |
| Cancer and Leukemia Group B | 326 | 1991 | 52 | 31 |
| Southeastern Cancer Study Group | 218 | 1992 | 60 | 51 |
| Cancer and Leukemia Group B | 1088 | 1994 | 52 | 32 |
| German AML Cooperative Group | 1044 | 1995 | 53 | 35 |
| British Medical Research Council | 923 | 1996 | 53 | 36 |
| International AML Study Group | 521 | 1997 | 54 | 38 |

Cross-reference: Hiddemann 1999.

Even for those elderly patients who do receive more intensive chemotherapy, median survival has been shown to decrease with age (**Table 3**). Elderly patients receiving more intensive chemotherapy have higher chemotherapy-related mortality rates and higher relapse rates, inability to tolerate intensive post-remission chemotherapy, and longer hospitalization periods associated with the chemotherapy than younger patients.

**Table 3:** Median Survival of Elderly AML Patients Treated With Chemotherapy by Age

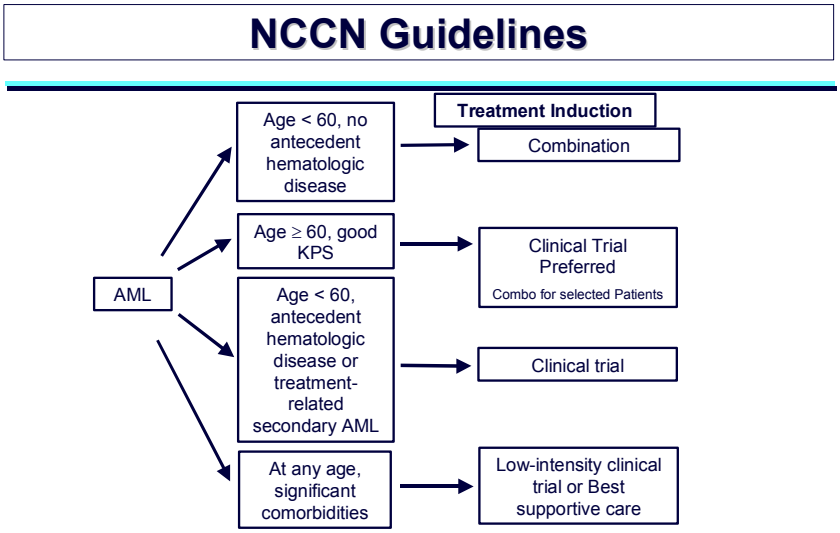
| | Median Survival (months) | |
|---|---|---|
| Patient Age (years) | Treated | Not Treated |
| All patients ≥65 | 6.8 | 1.7 |
| 65-74 | 8.1 | 2.0 |
| 75-84 | 4.9 | 1.8 |
| ≥85 | 2.5 | 1.3 |

Cross-reference: Menzin 2004 and Lang submitted.

Thus, elderly patients with poor-risk AML have limited options. Untreated, AML typically is rapidly progressive, with early death. Aggressive chemotherapy, used in otherwise healthy, young patients, is not well tolerated in elderly patients and can cause early mortality (toxic death) in a substantial proportion of patients. Alternative treatment approaches are needed for elderly patients with AML.

The limitations of standard induction therapy in older patients with AML underlie efforts to develop new therapeutic options for this patient population. The NCCN Clinical Practice Guidelines for AML, defining older patients as patients who are at least 60 years of age, attest to the unmet medical need in this patient population. As illustrated in **Figure 3**, the NCCN recommends investigational therapy in patients with AML who are 60 years of age or older (NCCN 2005).

**Figure 3:** NCCN Treatment Recommendation Guidelines

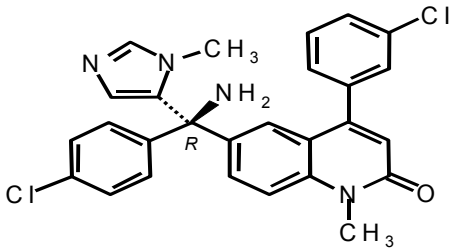



The J&JPRD development program for tipifarnib in AML has focused on the elderly patient population as a well-characterized group of patients with an unmet medical need. The proposed indication for tipifarnib is the treatment of elderly patients with newly diagnosed poor-risk AML. With few exceptions, consistent with NCCN guidelines, patients 75 years or older or 65 to 74 years with antecedent MDS are recommended to receive best supportive care or investigational treatment in a clinical study. Tipifarnib provides a treatment option for older patients with poor-risk AML because of the observed complete responses and the safety profile of the drug.

## 3. TIPIFARNIB: BACKGROUND INFORMATION

Tipifarnib is a selective inhibitor of the enzyme farnesyltransferase (FTase). The molecular formula of tipifarnib is $C_{27}H_{22}Cl_2N_4O$ and its molecular weight is 489.4 (**Figure 4**).

**Figure 4:** Chemical Structure of Tipifarnib

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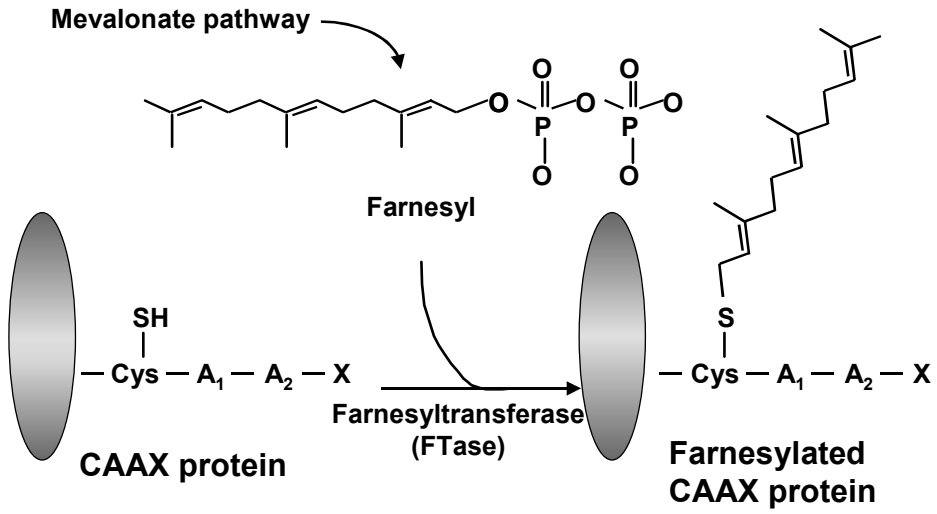
The correlative biology of FTase inhibition by tipifarnib has been studied extensively. The findings support the specificity of tipifarnib for inhibiting FTase, and document the ability of this agent to inhibit protein farnesylation in accessible tissues, including the bone marrow. Tipifarnib is not a substrate for the p-glycoprotein product of the MDR-1 gene (Mannens 2004).

## 3.1. Farnesylation and Farnesyltransferase Inhibition

The farnesyl moiety is a 15-carbon unsaturated isoprene polymer derived from the mevalonate pathway of cholesterol synthesis. Protein farnesylation is catalyzed by the 48 kd cytosolic metallo-enzyme FTase (**Figure 5**), a heterodimeric enzyme. The beta subunit recognizes CAAX motifs on proteins. The farnesyl binding site is located on the alpha subunit of FTase. High levels of FTase activity have been measured in the bone marrow of patients with AML (Karp 2001).

Tipifarnib is a selective nonpeptidomimetic competitive inhibitor of FTase at the CAAX binding site. In vitro, the concentration resulting in 50% of maximum inhibition ($IC_{50}$) values for isolated human FTase depends on the nature of its substrate, ranging from 0.86 nM for lamin B, a nuclear protein, to 7.9 nM for K-Ras. Mean total plasma concentrations of tipifarnib over a 12-hour interval resulting from a single 600-mg dose are markedly higher than those required to inhibit farnesylation. The unbound plasma concentrations of tipifarnib are within the range or greater than these $IC_{50}$ values. Tipifarnib inhibits FTase activity in human peripheral blood lymphocytes isolated from patients after doses as low as 100 mg b.i.d. Inhibition of FTase is reversible within three to seven days upon discontinuation of tipifarnib administration. In patients with AML, tipifarnib rapidly suppresses bone marrow FTase activity by up to 95% at twice-daily doses of 300 to 900 mg, without any clear dose-effect relationships at these dose levels (Karp 2001).

**Figure 5:** Protein Farnesylation



## 3.2. Mechanism of Action

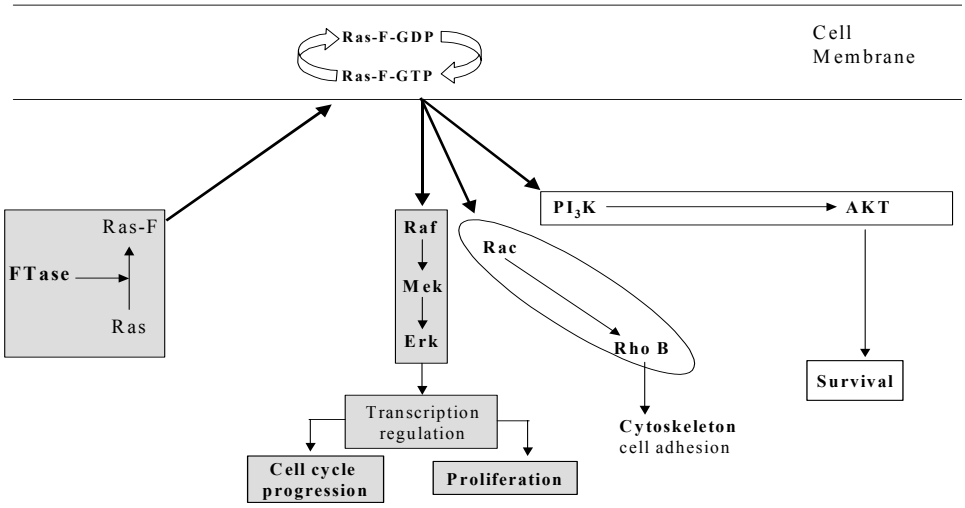
### 3.2.1. Cellular Pharmacology

Inhibition of farnesylation by tipifarnib is associated with inhibition of myeloid leukemic cell growth and progenitor colony formation. In vitro, human leukemic cells are more sensitive to the growth-inhibitory effects of tipifarnib than normal bone marrow cells (Goemans 2002). Consistent with observations in solid tumors, the presence of *ras* mutations was not required for the antiproliferative effect of tipifarnib. In animals, the growth-inhibitory effects of tipifarnib persist beyond the period of drug exposure, consistent with the finding that an intermittent dosing schedule, such as the one recommended in this application, is effective in the clinical setting of AML.

### 3.2.2. Molecular Pathways

Proteins requiring FTase are involved indirectly in leukemic cell signaling. Indeed, proteins such as Ras and RhoB are FTase substrates that regulate cellular homeostasis and proliferation (**Figure 6**). In addition, a farnesylated protein(s) upstream of phosphatidyl inositol-3 kinase ($PI_3K$) and the serine-threonine kinase AKT is involved in the regulation of this important anti-apoptotic/cell survival pathway. These are often mutated or dysregulated in AML (Lancet 2003). Hence, tipifarnib is representative of a new class of anticancer agents (FTase inhibitors) whose mechanism of action is believed to involve the suppression of downstream effectors of the therapeutic target, FTase. Exactly which downstream effectors are responsible for the anticancer activity of tipifarnib in patients with leukemia is not understood well.

**Figure 6:** Molecular Pathways in AML Potentially Affected by Tipifarnib




## 3.3. Clinical Pharmacology

The tipifarnib dose for AML was determined based on the safety profile, with measurable concentrations of tipifarnib achieved in the bone marrow in CTEP-1, a Phase 1 dose-escalation study (Sections 4.2.2 and 6.2). The plasma concentrations of tipifarnib in patients with AML who received a single dose of 600 mg of tipifarnib are provided in

**Table 4**. On average, total and unbound maximum plasma concentrations ($C_{max}$) of tipifarnib following this dosage regimen exceed the concentrations required to inhibit FTase in vitro.

Bioavailability, metabolism, distribution in the bone marrow, impact of food on absorption, and the potential for drug interactions were characterized in 24 biopharmaceutic and clinical pharmacology studies. Notably, tipifarnib exhibits dose-proportional plasma pharmacokinetics from 100 to 600 mg. This may be an important element in the predictable safety profile observed in elderly patients with poor-risk AML. The potential for interaction with drugs commonly administered in the general care of patients with AML has been characterized using population pharmacokinetic analysis techniques. No potentially significant interactions were identified.

**Table 4:** Pharmacokinetic Parameters of Tipifarnib in AML Patients After Single-Dose Oral Administration of 600 mg (Study R115777-INT-17)

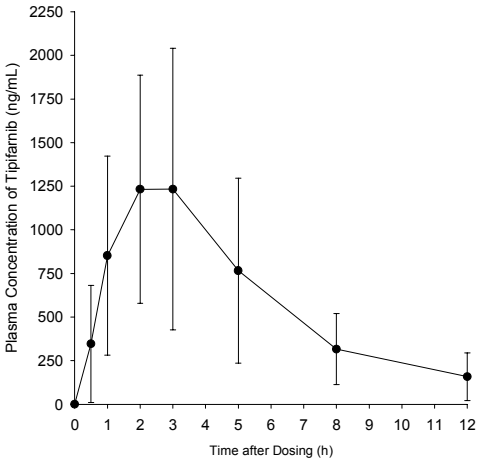
| Parameter | $t_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{12h}$ (ng·h/mL) |
|---|---|---|---|
| N | 16 | 16 | 13 |
| Mean | 2.5 | 1575 | 6739 |
| SD | 1.15 | 800 | 3150 |
| Median | 2.00 | 1480 | 5755 |

$AUC_{12h}$ = area under the plasma concentration-time curve from time zero to 12 hours after administration of study medication, $C_{max}$ = maximum concentration, $t_{max}$= time after dosing when $C_{max}$ was observed, and SD = standard deviation.

### 3.3.1. Absorption and Bioavailability

Tipifarnib is absorbed rapidly, and maximum plasma concentrations are reached within two to three hours following oral administration (**Figure 7**).

**Figure 7:** Mean (±SD) Plasma Concentration-Time Profile of Tipifarnib Single-Dose Oral Administration of 600 mg (Study R115777-INT-17)




The absolute oral bioavailability of tipifarnib, administered to healthy volunteers under fed conditions, was 34%.

Estimates of absolute bioavailability were confirmed by population pharmacokinetic analyses. Using a nonlinear mixed-effects model, the absolute bioavailability was estimated at 29.3% and 29.6% in cancer patients and healthy patients. Variation in the oral bioavailability (46.9% coefficient of variation) explained most of the interpatient variability in systemic exposure to tipifarnib. The population analysis also indicated that oral bioavailability is independent of the dose administered. No sex- or age-related differences were noted in the extent to which tipifarnib is absorbed.

### 3.3.2. Distribution

The volume of distribution of tipifarnib (169 L) is compatible with extensive distribution into peripheral tissues. At the recommended starting dose (600 mg orally b.i.d. x 21 days every 28 days), bone marrow concentrations of tipifarnib were approximately three-fold higher than the corresponding plasma concentrations (**Figure 8** and **Table 5**). These concentrations exceed the $IC_{50}$ values of FTase determined in AML cell cultures. At doses of 600 mg twice daily, persistent inhibition of FTase is demonstrated by the accumulation of unfarnesylated pre-HDJ-2 and prelamin A peptides.

Tipifarnib is extensively bound to albumin. The free fraction in patients with cancer is approximately 1%.

**Figure 8:** Mean (±SD) Bone Marrow Concentrations of Tipifarnib Following Repeated Oral Administration in Patients With Leukemia (Study R115777-CTEP-1)

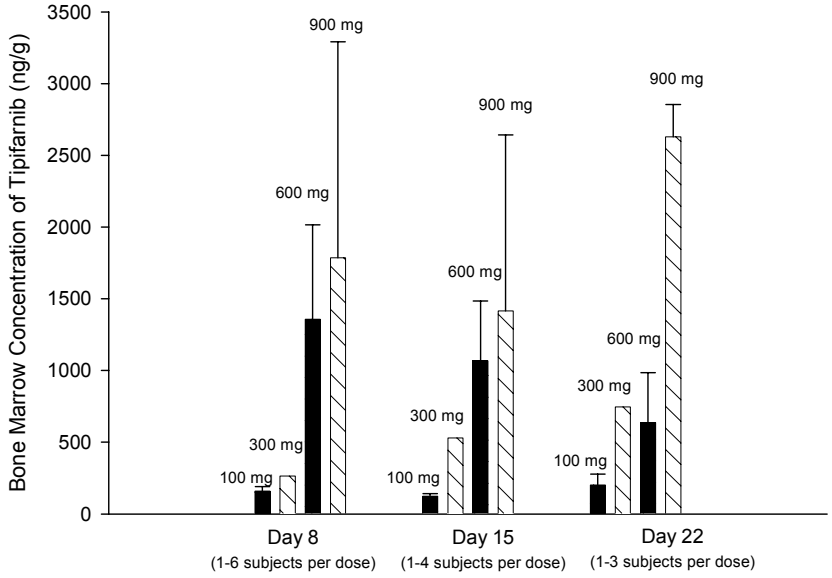


**Table 5:** Mean (±SD) Bone Marrow and Plasma Tipifarnib Concentrations (Study R115777-CTEP-1, Day 8)

| Tipifarnib (mg b.i.d) | Marrow Concentration (ng/g cell pellet) | Plasma $C_{min}$ (ng/mL) | Marrow:Plasma Ratio |
|---|---|---|---|
| 100 (N=3) | 164 ± 35 | 56 ± 46 | 2.9 |
| 600 (N=6) | 1357 ± 658 | 507 ± 271 | 2.7 |
| 900 (N=3) | 1785 ± 1507 | 713 ± 977 | 2.5 |

Note: N=number of patients from whom concentrations of tipifarnib in both plasma and bone marrow were available.

### 3.3.3. Metabolism

In vitro experiments indicate that cytochrome P450 enzymes (CYP) 3A4, 2C19, 2A6, 2D6, and 2C8/9/10 play a role in the oxidative biotransformation of tipifarnib. In addition, tipifarnib undergoes direct glucuronidation.

The concentrations of metabolites identified in plasma are markedly lower compared to those of tipifarnib. One exception is the glucuronide metabolite of tipifarnib, which exhibits plasma concentrations several-fold higher relative to the parent compound. The metabolites identified thus far, including the tipifarnib-glucuronide, are either inactive as inhibitors of farnesyltransferase or have much lower activity relative to the parent compound. Thus, the antiproliferative effects of tipifarnib are believed to be directly related to the parent compound. The population analyses showed that genetic polymorphism of the CYP enzymes has no clinically relevant impact on the pharmacokinetics of tipifarnib.

Consistent with the hepatic metabolism of tipifarnib, the population pharmacokinetic analysis (Section 3.3.6) indicated there is a weak but statistically significant correlation between total serum bilirubin concentration and tipifarnib clearance. For illustrative purposes, a two-fold increase in bilirubin concentration is associated with a 6.9% decrease in tipifarnib clearance. The small magnitude of this effect indicates that adjustment of the tipifarnib dose on the basis of serum bilirubin concentrations is not necessary. A study (NED-3) designed to evaluate the potential impact of hepatic impairment on the clinical pharmacokinetics of tipifarnib is currently ongoing in cancer patients with mild-to-moderate hepatic impairment.

### 3.3.4. Elimination and Excretion

Tipifarnib's pharmacokinetic profile is consistent with a three-compartment disposition model. Urinary excretion of unchanged tipifarnib or its metabolites accounts for 13.7% of the total dose administered. Thus, impaired renal function is expected to have no clinically relevant impact on the pharmacokinetics of tipifarnib.

### 3.3.5. Impact of Food on the Absorption of Tipifarnib

Increases in tipifarnib bioavailability (area under the plasma concentration time-curve [AUC]) by 18% to 34% have been consistently observed after administration with food. The magnitude of this effect is small compared to the variability of pharmacokinetic parameters. Since early Phase 1 studies indicated a lower interpatient variability in plasma $C_{max}$ values under fed conditions (relative to the fasted state), tipifarnib was administered with food throughout the clinical development program. Thus, the oral dosing regimen recommended

for the treatment of elderly patients with poor-risk AML specifies that tipifarnib be taken with food.

### 3.3.6. Population Pharmacokinetics

An open, three-compartment model with first-order elimination from the central compartment best describes the plasma pharmacokinetics of tipifarnib. Age, gender, race, weight, body surface area, and serum concentrations of aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase, alkaline phosphatase, albumin, or creatinine clearance had no significant effect on the pharmacokinetic parameters of tipifarnib.

### 3.3.7. Potential for Drug Interactions

#### *3.3.7.1. Nonclinical Studies*

In human liver microsomes, tipifarnib inhibited the metabolism of CYP450 enzymes 3A4, 2C8/9/10, and 2D6. The inhibitory $IC_{50}$s for the CYP enzymes ranged from 3,200 to 8,600 ng/mL. These $IC_{50}$ values are within the range of maximum plasma concentrations of tipifarnib achieved at the 600-mg dose level (**Table 4**). However, they are markedly higher than the concentration of free, nonprotein bound, drug in patient plasma (≈3-39 ng/mL, based on a free fraction of 0.62%). These results suggest that pharmacokinetic interactions upon coadministration of drugs that are metabolized predominantly by these CYP450 isoenzymes are unlikely.

#### *3.3.7.2. Clinical Studies*

The population pharmacokinetic analysis evaluated the influence of various concomitant medications, including the most common drugs administered in Study INT-17 (relapsed/refractory AML), on the pharmacokinetics of tipifarnib. Amphotericin, antiemetics, $5HT_3$ antagonists (dolasetron, granisetron, ondansetron, and tropisetron), antifungal azoles (econazole, fluconazole, itraconazole, ketoconazole, and miconazole), benzodiazepines, ciprofloxacin, and corticosteroids had no discernible impact on plasma concentrations of tipifarnib. The lack of a discernible impact of antifungal azoles on the clearance of tipifarnib is noteworthy because many agents in this class are potent inhibitors of the CYP3A enzyme.

## 4. CLINICAL DEVELOPMENT PROGRAM OF TIPIFARNIB

Tipifarnib was the first specific inhibitor of FTase to enter clinical studies. The clinical development of tipifarnib began in 1997. It initially investigated solid tumors, including pancreatic and colorectal cancer, two solid tumor types with a high prevalence of *ras* mutations. The clinical development program currently consists of 79 clinical oncology and hematology studies. As of 1 June 2004, 36 J&JPRD-sponsored clinical studies in more than 2,500 patients have been completed or are ongoing with tipifarnib administered as monotherapy or in combination with other chemotherapeutics. An additional 35 studies in more than 1,300 patients are completed or ongoing in collaboration with the U.S. NCI under the auspices of CTEP, and eight investigator-initiated studies in more than 140 patients are completed or ongoing.

The Phase 3 studies in colorectal and pancreatic cancer have shown limited efficacy. A simultaneous program focused on the development of tipifarnib in the treatment of AML and other hematologic malignancies. The rationale for use of tipifarnib in AML includes the following:

1) high expression of FTase in bone marrow,

2) dysregulation of farnesylated protein biology in AML, and

3) induction of complete responses in the initial Phase 1 study.

The development program in AML to date consists of seven clinical studies, with five studies in patients with poor-risk AML: three completed studies (CTEP-1, CTEP-20, and INT-17), one ongoing commitment study (AML-301), and one ongoing pilot study of alternative tipifarnib dosing regimens (CTEP-50) (**Table 6**). The timeline for the clinical development of tipifarnib in these five AML studies is shown in **Figure 9**. The other two studies were designed to obtain initial data on tipifarnib as maintenance therapy in patients who had had complete remission of AML following intensive induction chemotherapy (INT-21 and CTEP-51) (**Table 7**).

**Table 6:** Studies in Patients With Poor-Risk AML

| Clinical Study | Study Status | N[a] | Description | Endpoints |
|---|---|---|---|---|
| **Phase 1** | | | | |
| R115777-CTEP-1 | Complete | 34 | Leukemias | Maximum tolerated dose, pharmacokinetics |
| **Phase 2** | | | | |
| R115777-CTEP-20 | Complete[b] | 171 | Newly diagnosed AML, elderly | Efficacy, safety |
| R115777-INT-17 | Complete | 252 | Relapsed/refractory AML | Efficacy, safety, pharmacokinetics |
| R115777-CTEP-50 | Ongoing | 296 | Newly diagnosed AML, elderly patients (alternative dosing regimens, pilot study) | Efficacy, safety |
| **Phase 3** | | | | |
| R115777-AML-301 | Ongoing | 306 | Newly diagnosed AML, elderly | Efficacy, safety |

[a] Number accrued for completed studies or planned for ongoing studies.
[b] Patients still receiving treatment. No additional analysis is planned.

**Figure 9:** Timeline for Clinical Development of Tipifarnib in Poor-Risk AML

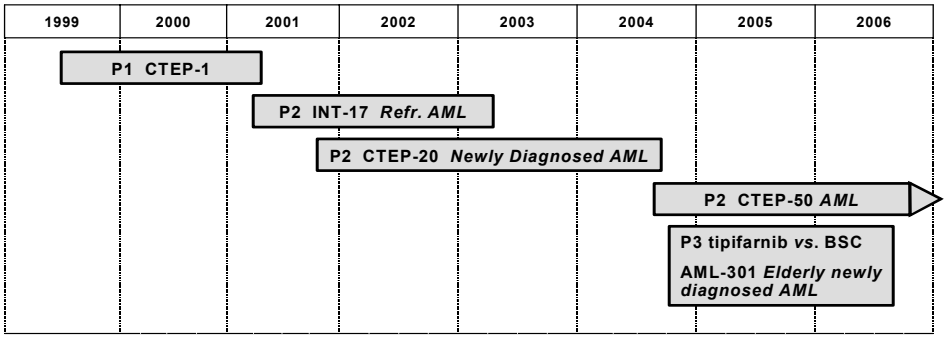


**Table 7:** Studies of Maintenance Therapy in Patients With AML

| Clinical Study | Study Status | N[a] | Description | Endpoints |
|---|---|---|---|---|
| **Phase 2** | | | | |
| R115777-INT-21 | Closed to accrual[b] | 88 | Maintenance therapy (following remission induction using combination chemotherapy) elderly patients | Efficacy, safety, pharmacokinetics |
| **Phase 2** | | | | |
| R115777-CTEP-51 | Ongoing | 139 | Maintenance therapy for AML | Efficacy, safety |

[a] Number accrued for completed studies or planned for ongoing studies.
[b] Analysis pending.

A key principle of the clinical development of tipifarnib postulated that FTase inhibition, and hence prolonged drug administration, would be required for antileukemic activity. Consequently, an oral formulation compatible with prolonged outpatient administration was developed.

The proposed indication for tipifarnib is the treatment of elderly patients with newly diagnosed poor-risk AML. As noted above, the core tipifarnib development program in AML includes three completed clinical studies: CTEP-1, CTEP-20, and INT-17. (Key details and results for these studies are provided in Sections 4.2, 4.3, and 4.4, respectively.) Section 4.5 briefly describes Study CTEP-50, an ongoing pilot study that will evaluate alternative dosing regimens in elderly patients with newly diagnosed AML. Section 4.6 of this document briefly describes an ongoing controlled study of tipifarnib versus best supportive care in elderly patients with newly diagnosed poor-risk AML (Study AML-301, the trial that is deemed the "commitment" study for confirmation of patient benefit, which is a required element for the accelerated approval process).

## 4.1. Assessment of Efficacy in AML

Complete response is a well-established and accepted surrogate endpoint that correlates with clinical benefit in the treatment of AML. Hence, the primary study endpoint in the core AML studies evaluating tipifarnib was CR. Objective response status was assessed by the investigator following each cycle of therapy using the standard criteria summarized in **Table 8** (Cheson 2003).

**Table 8:** Clinical Criteria for Determination of Response

| Response | Criteria |
|---|---|
| **Complete response (CR)** | Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines; CR required an ANC of at least 1,000/μL and a platelet count of 100,000/μL, absence of blasts in peripheral blood, absence of identifiable leukemic cells in the bone marrow, and clearance of any previously existing extramedullary disease. |
| **Partial response (PR)** | The presence of trilineage hematopoiesis in the bone marrow with recovery of ANC and platelets to the levels for CR, but with 5% to 19% bone marrow blasts, and at least 50% decrease in bone marrow blast percentage from baseline. |
| **Hematologic improvement (HI)** | The same as PR, except with recovery of ANC to 500 to 1,000/μL and platelet count to 20,000 to 100,000/μL, respectively. |
| **Stable disease** | Any response that did not meet CR, PR, HI, or PD criteria. |
| **Progressive disease (PD)** | Defined as any one of the following:<br>• >50% increase in bone marrow blast percentage from the best assessment.<br>• >50% increase in circulating blasts (with rising trend).<br>• New appearance of circulating blasts (with rising trend on at least two consecutive occasions).<br>• Development of extramedullary leukemia.<br>• In patients who presented with an initial marrow blast percentage sufficiently high to preclude the ability to base disease progression on a >50% increase in marrow blast percentage, disease progression was based upon peripheral blood criteria or development of extramedullary leukemia. |

In addition, in the INT-17 population, morphologic response (specifically, leukemia-free state, <5% blast count [Cheson 2003]) was characterized in an exploratory fashion. Contrary to CR, leukemia-free state is, by definition, not dependent upon recovery of normal hematopoiesis, which may be suppressed by the ongoing administration of tipifarnib together with the residual effects of prior cytotoxic chemotherapy received by these patients.

## 4.2. Study CTEP-1

CTEP-1 was a single-arm, dose-escalation study of single-agent tipifarnib conducted at the University of Maryland and the University of Rochester as part of the CRADA agreement between J&JPRD and CTEP. This study determined the recommended dose of tipifarnib and established several proofs of concepts related to efficacy (complete remission), tolerability (outpatient therapy), and molecular biology (target inhibition, farnesylation inhibition, and signaling inhibition) in patients with leukemia. Tipifarnib was evaluated in 34 patients with hematologic malignancies, including 25 with relapsed/refractory or newly diagnosed poor-risk AML. Tipifarnib was administered orally for 21 days in 28-day cycles, at doses ranging from 100 to 1,200 mg b.i.d. One of the objectives of the study was determination of the maximum tolerated dose (MTD).

### 4.2.1. Biologic Activity

CTEP-1 was the first clinical study to demonstrate that treatment with an agent whose primary therapeutic target was FTase could yield complete remissions in patients with AML, establishing an important landmark in the tipifarnib development program. It provided the clinical rationale to proceed with further clinical development of tipifarnib in AML. In this study, complete and partial remissions were observed at several dose levels (**Table 9**). No dose-response relationship was established for antileukemic activity.

**Table 9:** Remission Induction by Tipifarnib for Patients With AML (Study R115777-CTEP-1)

| Dose[a] (mg b.i.d.) | Age/Gender | Diagnosis, Status | Clinical Outcome | Survival (mo) |
|---|---|---|---|---|
| 100 (n=5) | 51/M | AML M1, Relapsed | CR, 7 mo | 15+ |
| | 72/M | AML M1, New | PR | 14+ |
| 300 (n=2) | 75/M | AML M4, New | PR | 7 |
| 600 (n=7) | 73/M | AML M2, Relapsed | CR, 3 mo | 10 |
| | 73/M | AML M1, New | PR | 12.5+ |
| 900 (n=8) | 73/M | AML M1, Relapsed | PR | 11+ |
| | 26/F | AML M4, Refractory | PR | 9 |
| | 77/M | AML M1, Refractory | PR | 5 |

[a] Tipifarnib was administered x 21 days for a 28-day treatment cycle.

### 4.2.2. Recommended Dose

In this study, tipifarnib exhibited dose-proportional plasma pharmacokinetics, including the pharmacokinetics at the dose recommended for treatment of elderly patients with poor-risk AML. Bone marrow concentrations of tipifarnib increased in a dose-dependent manner (Section 3.3.2). At the 600-mg dose level, tipifarnib concentrations in bone marrow were on average 2.5- to 3.1-fold higher than corresponding plasma concentrations, and pharmacologic activity of tipifarnib was demonstrated against the intended target, FTase (Karp 2001) (Section 3.1).

The recommended Phase 2 dosing regimen (600 mg orally b.i.d. x 21 days every 28 days) was selected on the basis of the pharmacokinetic (Section 3.3.2), pharmacodynamic (FTase inhibition) (Section 3.1), clinical response (Section 4.2.1), and clinical safety profiles (Section 6.2) of tipifarnib observed in Study CTEP-1 (Karp 2001). Based on dose-limiting toxicity at 1,200 mg twice daily and the number of patients who needed dose modifications at 900 mg twice daily, the recommended dose for Phase 2 studies was 600 mg twice daily, given for 21 days in 28-day cycles.

This dose regimen was selected to maximize FTase inhibition and provide AML patients with the best chance of response at a well-tolerated dose. Twice-daily dosing ensures persistent inhibition of FTase. An intermittent schedule (3-week treatment/1-week with no drug) is needed to minimize neurotoxicity while maintaining efficacy.

## 4.3. Study CTEP-20

CTEP-20 was an open-label, single-arm, multicenter, Phase 2 study. The study was initially intended to evaluate the activity of tipifarnib in a broad range of patients with malignant or premalignant hematologic conditions for whom there is no established effective therapy or for whom the benefit/risk of standard chemotherapy was unfavorable. The initial eligibility criteria allowed entry of patients with untreated poor-risk AML, high-risk MDS, and chronic myelomonocytic leukemia (CMML). This initial protocol was submitted to the FDA in October 2001 under the NCI Investigational New Drug Application. The initially planned sample size of the CTEP-20 study was 60 patients.

On 10 July 2003, J&JPRD and members of CTEP met with FDA to discuss the status of this study. Evaluation of preliminary findings in the first 64 patients indicated that most patients enrolled were older patients with AML, and there was significant activity in these patients. With advice from the Division of Oncology Drug Products at the FDA, the protocol was amended on 16 September 2003 and expanded to better characterize the efficacy and safety of tipifarnib, focusing on an elderly population with newly diagnosed poor-risk AML (defined as patients 75 years of age or older, or 65 years of age or older who had a history of MDS prior to diagnosis of AML). Assuming a 10% nonevaluability rate, the amended protocol specified that approximately 140 elderly patients with poor-risk AML were to be enrolled to ensure 125 evaluable patients.

Data for CTEP-20 were originally collected on CTEP-specific case report forms. Following the FDA meeting on 10 July 2003, J&JPRD designed more detailed case report forms for data collection to be completed for all patients enrolled in the study. The data reported in the NDA study report and update were based on the J&JPRD case report forms, which contained data obtained from the source documents (patient records) for patients enrolled in CTEP-20. The data collected were subject to J&JPRD quality review and assessed and analyzed by J&JPRD.

### 4.3.1. Study Population

Of the 171 patients who entered the study, 157 had previously untreated AML. Of these 157 patients, 136 were elderly with newly diagnosed poor-risk AML (**Table 10**) as specified in the final protocol. Although study results were generally consistent for the total AML study population, this subset of elderly patients with poor-risk AML constitutes the population for which the study data are deemed sufficient (in terms of demonstration of activity, in a sufficiently large group of patients with unmet medical need) to support a clinical indication for tipifarnib at this time. In designating the tipifarnib NDA as fast track, the FDA agreed that "poor-risk AML in the elderly represents a therapeutic challenge and an unmet medical need."

In CTEP-20, AML was defined according to the World Health Organization (WHO) classification (≥20% bone marrow or peripheral blast counts).

**Table 10:** Study Population
(Study R115777-CTEP-20)

| | ----------Tipifarnib 600 mg oral b.i.d.---------- n (%) |
|---|---|
| **All enrolled** | **171 (100)** |
| **AML** | **158 (92)** |
| Treated | 157 (92) |
| Not treated[a] | 1 (1) |
| Elderly poor-risk AML | 136 (80) |
| Age ≥75 years | 75 (44) |
| Age 65-74 years with prior MDS | 61 (36) |
| AML age <65 years | 9 (7) |
| AML age 65-74 without prior MDS | 12 (9) |
| **Other** | **13 (8)** |
| MDS | 8 (5) |
| CMML | 5 (3) |

[a] At the time of clinical cutoff; patient not treated was in the elderly poor-risk AML population.

Six investigators from the United States participated in the study (**Table 11**). Enrollment was generally well distributed among sites, which were located in academic and community settings of major urban areas.

**Table 11:** Enrollment by Site,
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| Site | Investigator | Tipifarnib 600 mg oral b.i.d. (N=136) n (%) |
|---|---|---|
| Stanford University Medical Center | Greenberg | 35 (26) |
| University of Maryland, Greenebaum Cancer Center | Gojo | 32 (24) |
| The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins | Karp | 28 (21) |
| New York Presbyterian Hospital – Cornell University | Feldman | 22 (16) |
| University of Rochester Cancer Center | Lancet | 16 (12) |
| Blood & Marrow Transplant Group of Georgia | Morris | 3 (2) |

The median age of the elderly poor-risk AML population enrolled in this study was 75 years (range = 65 - 85 years) (**Table 12**). Most patients were symptomatic from AML or comorbid conditions.

**Table 12:** Demographic Characteristics
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| | ----------Tipifarnib 600 mg oral b.i.d.---------- (N=136) |
|---|---|
| **Sex, n (%)** | |
| N | 136 |
| Male | 86 (63) |
| Female | 50 (37) |
| **Race, n (%)** | |
| N | 136 |
| White | 129 (95) |
| Black | 3 (2) |
| Asian | 2 (1) |
| Other | 2 (1) |
| **Age, years** | |
| N | 136 |
| Mean (standard deviation [SD]) | 74.9 (5.39) |
| Median | 75.0 |
| Range | (65;85) |
| **Baseline ECOG performance status, n (%)** | |
| N | 133 |
| 0 | 32 (24) |
| 1 | 86 (65) |
| 2 | 15 (11) |

ECOG=Eastern Cooperative Oncology Group.

The most common French-American-British Cooperative Group (FAB) classification subtypes of AML were M2 (20%) and M4 (18%) (**Table 13**). The M3 subtype was excluded per protocol eligibility criteria.

The data set for karyotype was very complete, with data available for 94% of patients. Overall, 49% had unfavorable karyotype at the time of diagnosis. Fifty-six (41%) patients had prior MDS and an unfavorable karyotype.

**Table 13:** Baseline Disease Characteristics
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| | Tipifarnib 600 mg oral b.i.d. (N=136) |
|---|---|
| **Diagnosis, n (%)** | |
| De novo AML | 25 (18) |
| AML arising from prior MDS | 110 (81) |
| AML arising from prior MDS and prior chemotherapy | 1 (1) |
| **FAB classification** | |
| M0: AML minimally differentiated | 12 (9) |
| M1: Acute myeloblastic leukemia without maturation | 15 (11) |
| M2: Acute myeloblastic leukemia with maturation | 26 (20) |
| M4: Acute myelomonocytic leukemia | 24 (18) |
| M4E0: Acute myelomonocytic leukemia with eosinophilia | 2 (2) |
| M5: Acute monocytic leukemia with eosinophilia | 7 (5) |
| M6: Erythroleukemia | 5 (4) |
| M7: Acute megakaryocytic leukemia | 5 (4) |
| Unknown | 40 (29) |
| **Karyotype unfavorable, n (%)** | |
| Yes | 66 (49) |
| No | 62 (46) |
| Not done / not available | 8 (6) |
| **Number of patients who are not optimal candidates for combination chemotherapy**[a] | 136 |
| Age | 106 (78) |
| Poor prognostic factors | 60 (44) |
| Other (e.g., patient preference, general medical condition, etc.) | 25 (18) |

[a] Investigators assigned more than one reason for many patients.

CTEP-20 is one of the largest studies to date that has evaluated the treatment of elderly patients with newly diagnosed poor-risk AML. A majority of these patients (111, 82%) had AML arising from prior MDS (55% of those ≥75 years old); 41% had both prior MDS and an unfavorable karyotype. The proportion of patients with two or more risk factors associated with poor prognosis was 90% (**Table 14**).

**Table 14:** AML Risk Factors in Elderly Poor-Risk AML Population
(Study R115777-CTEP-20)

| | ----------Tipifarnib 600 mg oral b.i.d.---------- (N=136) n (%) |
|---|---|
| **Risk factor** | |
| Prior MDS | 111 (82) |
| Baseline organ dysfunction | 83 (61) |
| Age ≥75 years | 75 (55) |
| Unfavorable karyotype | 66 (49) |
| **Number of risk factors per patient** | |
| 1 | 14 (10) |
| 2 | 60 (44) |
| 3 | 47 (35) |
| 4 | 15 (11) |

### 4.3.2. Treatment Regimen

The dosing regimen of tipifarnib was 600 mg twice daily administered orally for 21 days in 28-day cycles. Treatment delays were allowed as needed for recovery from toxicity (myelosuppression). The days on which a patient was not receiving study medication due to recovery from toxicity were not considered part of the 21-day treatment cycle. Every attempt was made to have the patient complete a full 21 days of treatment within 6 weeks of starting a cycle. Total cycle duration could not exceed 63 days. Protocol-defined dose reductions were implemented based on the occurrence of toxicity (with stepwise reduction to 400, 300, or 200 mg orally b.i.d.). No dose escalation was allowed. Dose reductions due to adverse events are reported in Section 6.4.2.7.

Patients who achieved a CR could receive additional tipifarnib treatment until disease progression, or alternatively could receive up to three additional cycles of tipifarnib and stop. Retreatment with tipifarnib was allowed for those CR patients who relapsed after initial treatment termination. The decision to reinitiate tipifarnib in an individual patient was left to the investigator's discretion.

#### *4.3.2.1. Treatment Compliance*

Pharmacy dispensing logs were maintained for each cycle of therapy. This included the starting dose for each cycle of therapy and the number of tablets dispensed. Tablets were dispensed in blister packs for a 21-day treatment schedule. Patients were seen on a weekly basis for hematologic monitoring and by study personnel for assessment according to the protocol. The data collection in CTEP-20 did not include detailed patient diaries or pharmacist/research personnel documentation of actual tipifarnib intake.

### 4.3.3. Study Endpoints

CR is a well-established and accepted surrogate endpoint that correlates with clinical benefit in the treatment of AML. Hence, the primary study endpoint was CR rate. Remission status was assessed by the investigator following each cycle of therapy using the standard criteria summarized in **Table 8**. Bone marrow slides were assessed by an independent central reviewer who was blinded to patient outcome. Central review was undertaken as a quality assurance measure to evaluate the reliability of the institutional site's interpretation of diagnosis (n=118) and repeat bone marrow assessment (n=79).

Secondary efficacy endpoints included duration of CR, survival, and other categories of objective response. Patients were followed until death. Duration of CR was defined as the time (in days) from date of first documentation of CR to the date of first documentation of progressive disease (PD).

### 4.3.4. Efficacy

#### *4.3.4.1. Complete Remissions*

In Study CTEP-20, the CR rate in the elderly poor-risk AML population was 15% (95% confidence interval [CI] = 9.4-22.0) (**Table 15**). Complete responses were documented consistently across study subpopulations (e.g., age, FAB class, ethnic groups). Also, evidence of potentially positive effects on AML progression (i.e., partial response [PR], hematologic improvement, or stable disease) was noted in an additional 54 (40%) of the elderly patients with poor-risk AML.

**Table 15:** Response Summary
(Study R115777-CTEP-20)

| | Tipifarnib 600 mg oral b.i.d. | | |
|---|---|---|---|
| Response | 65-74 y prior MDS (N=61) n (%) | ≥75 y (N=75) n (%) | Total (N=136) n (%) |
| Complete response | 11 (18) | 9 (12) | 20 (15) |
| Partial response | 3 (5) | — | 3 (2) |
| Hematologic improvement | 4 (7) | 3 (4) | 7 (5) |
| Stable disease | 15 (25) | 29 (39) | 44 (32) |
| Progressive disease | 24 (39) | 24 (32) | 48 (35) |
| Not evaluable / not done | 4 (7) | 10 (13) | 14 (10) |

Pertinent characteristics of the 20 complete responders are provided in **Tables 16 and 17**. Three of the 20 patients who achieved a CR were still receiving treatment as of the clinical cutoff date. Seven complete responders terminated treatment as per protocol.

Of the 20 responders, 14 achieved CR in the first cycle, and 5 achieved CR in the second cycle. One patient terminated after one cycle and achieved a CR during the follow-up period. For 3 of the 20 responders, confirmation of CR by a repeat bone marrow aspirate was not available. All three had evidence of continued remission based on peripheral blood counts.

- Patient 100318 (81 years, male, de novo AML, unfavorable karyotype) received two cycles of treatment. Baseline bone marrow was hypercellular with 90% blasts. The Day 8 bone marrow showed significant improvement to 10% blasts. The bone marrow after the first cycle (Study Day 35) contained <5% blasts, and peripheral counts recovered to levels compatible with CR within two weeks. On Study Day 50, Cycle 2 started at the reduced dose of 400 mg bid. At baseline he had 3% peripheral blasts. The peripheral blast count was 0% on Days 8, 16, 20, 34, and 49 and remained at 0% until Day 87, without a repeat bone marrow confirming CR. On Study Day 91, peripheral blast count was 3%. On Study Day 92, before starting Cycle 3, tipifarnib treatment was terminated due to PD, which was noted after the second cycle (Study Day 92), with 33% blasts on repeat bone marrow.
- Patient 100336 (80 years, male, secondary AML, unfavorable karyotype) received two cycles of treatment. Baseline bone marrow showed 22% blasts. The Day 8 bone marrow showed significant improvement to 10% blasts. The bone marrow after the first cycle (Study Day 33) contained <2% blasts, and peripheral counts recovered to levels compatible with CR within two weeks. During the second cycle (Study Day 60), the patient was hospitalized due to *Aspergillus* pneumonia, presumed secondary to tipifarnib-induced myelosuppression. He died due to intercurrent fungal infection (pneumonia) before a repeat bone marrow could be done. Peripheral blasts were 0% at baseline and were confirmed at 0% on Day 45 and Day 65.

- Patient 100508 (79 years, male, secondary AML, unfavorable karyotype) received one cycle of treatment. Baseline bone marrow was hypercellular with 90% blasts. The patient temporarily refused further bone marrow procedures, and further treatment was not given. In follow-up, a repeat bone marrow after three months (Study Day 103) revealed 3% blasts, and peripheral counts recovered to levels compatible with CR. A third bone marrow was performed four months later with evidence of PD. Peripheral blasts were 82% at baseline and dropped to 0% on Day 100. At the time of PD in bone marrow, peripheral blasts had increased to 14% (11 days earlier, on Day 212, they were present, at 4%).

The median time to CR was 43 days. Serial bone marrow aspirates obtained within the first 10 days of tipifarnib therapy show that the kinetics of leukemic cell death (blast cell count) induced by tipifarnib are slower than is typically observed following traditional cytotoxic chemotherapy (**Figure 10**). This gradual decline in leukemic blast counts was achieved without the aplasia commonly observed with conventional induction chemotherapy as summarized in Section 6.4.3.

**Figure 10:** Mean Percent Bone Marrow Blast Count From Baseline to Start of CR
(Study R115777-CTEP-20: Elderly Patients With Poor-Risk AML
Who Achieved a Complete Remission)

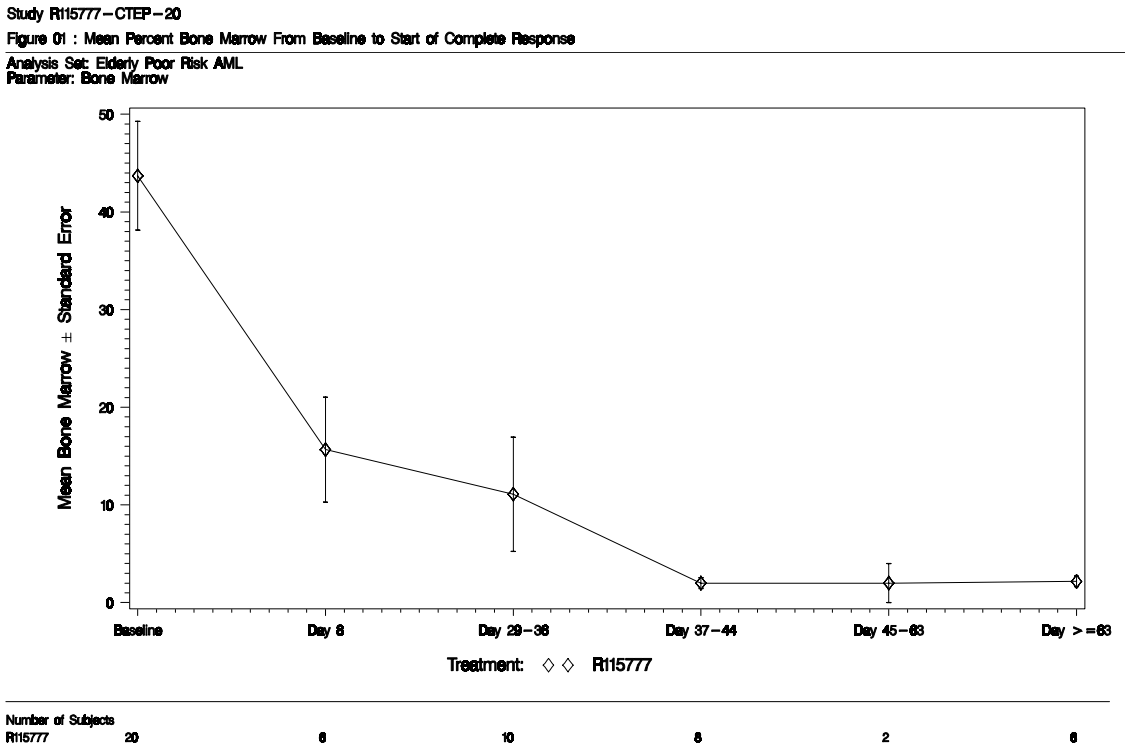


**Table 16:** Patient and Treatment Information for Complete Responders, by Number of Cycles Received
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| Patient Number | Age (years)/Sex/Race | Prior MDS (Yes/No) | FAB Classification of AML | Unfavorable Karyotype | Time From Diagnosis to Treatment (days) | No. Risk Factors | Baseline Bone Marrow Blasts (%) | Number of Dose Reductions |
|---|---|---|---|---|---|---|---|---|
| **1 Cycle (n=3)** | | | | | | | | |
| 100341 | 67/Male/White | Yes | Unknown | No | 80[a] | 1 | 51 | 0 |
| 100508 | 79/Male/Asian | Yes | M1 | Yes | 4 | 4 | 90 | 0 |
| 101049 | 65/Male/Black | Yes | M2 | Yes | 11 | 3 | 72 | 0 |
| **2 Cycles (n=5)** | | | | | | | | |
| 100214 | 73/Female/White | Yes | M4 | Yes | 7 | 2 | 10 | 1 |
| 100318 | 81/Male/White | No | M5 | Yes | 13 | 3 | 90 | 1 |
| 100336 | 80/Male/White | Yes | M0 | Yes | 35 | 4 | 22 | 1 |
| 101021 | 69/Female/White | Yes | M4 | No | 1 | 2 | 40 | 0 |
| 101096 | 69/Male/White | Yes | Unknown | No | 7 | 1 | 50 | 1 |
| **3 Cycles (n=2)** | | | | | | | | |
| 100322 | 73/Male/White | Yes | M6 | Yes | 1 | 3 | 28 | 1 |
| 101107 | 76/Male/White | Yes | Unknown | Not available | 312 | 2 | 20 | 0 |
| **4 Cycles (n=8)** | | | | | | | | |
| 100113 | 82/Male/White | Yes | M2 | Yes | 15 | 4 | 40 | 1 |
| 100321 | 68/Male/White | Yes | Unknown | No | 32 | 1 | 25 | 0 |
| 101008 | 82/Male/White | No | M2 | No | 123[a] | 2 | 50 | 1 |
| 101025 | 70/Male/White | Yes | Unknown | No | 4 | 2 | 31 | 1 |
| 101051 | 70/Male/White | Yes | M7 | Yes | 8 | 2 | 30 | 1 |
| 101057 | 85/Male/White | Yes | M2 | No | 21 | 3 | 35 | 0 |
| 101060 | 73/Male/White | Yes | Unknown | No | 29 | 2 | 17 | 1 |
| 101091 | 71/Male/White | Yes | M2 | No | 30 | 2 | 20 | 0 |
| **5 Cycles (n=2)** | | | | | | | | |
| 100213 | 81/Female/White | Yes | M4 | Yes | 46 | 4 | 77 | 2 |
| 100515 | 79/Male/Hispanic-Latino | Yes | M4 | No | 8 | 2 | 75 | 2 |

[a] Calculated from imputed starting date, i.e., XX June 2002 was imputed as 1 June 2002.

**Table 17:** Efficacy Data for Complete Responders, by Number of Cycles Received
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| Patient Number | Time to Complete Response (days) | Duration of CR (days) | Progression-Free Survival (days) | Overall Survival (days) | Retreated With Tipifarnib | Subsequent Combination Chemotherapy[a] |
|---|---|---|---|---|---|---|
| **1 Cycle (n=3)** | | | | | | |
| 100341 | 39 | 295+ | 433 | 433 | No | No |
| 100508 | 103 | 121 | 226 | 279 | Yes | No |
| 101049 | 32 | 167+ | 208+ | 564 | Yes | Yes[a] |
| **2 Cycles (n=5)** | | | | | | |
| 100214 | 78 | 120+ | 207+ | 395 | No | No |
| 100318 | 35 | 58 | 93 | 151 | No | No |
| 100336 | 33 | 35+ | 67 | 67 | No | No |
| 101021 | 50 | 372+ | 421+ | 421+ | No | No |
| 101096 | 44 | 33 | 76 | 129+ | No | No |
| **3 Cycles (n=2)** | | | | | | |
| 100322 | 34 | 179+ | 212+ | 237+ | No | No |
| 101107 | 37 | 76+ | 113+ | 113+ | No | No |
| **4 Cycles (n=8)** | | | | | | |
| 100113 | 71 | 99 | 170 | 211 | Yes | No |
| 100321 | 38 | 220 | 257 | 701+ | Yes | Yes[a] |
| 101008 | 31 | 376 | 406 | 548 | Yes | No |
| 101025 | 42 | 153+ | 216+ | 216+ | No | No |
| 101051 | 76 | 275 | 357 | 825+ | Yes | No |
| 101057 | 38 | 154 | 192 | 386 | Yes | No |
| 101060 | 43 | 92+ | 134+ | 134+ | No | No |
| 101091 | 49 | 104+ | 153+ | 153+ | No | No |
| **5 Cycles (n=2)** | | | | | | |
| 100213 | 121 | 127 | 247 | 257 | No | No |
| 100515 | 80 | 118 | 204 | 442 | No | No |

[a] Two patients received subsequent combination chemotherapy as third-line treatment, after first being retreated with tipifarnib.

+ Censored observation. If patients with CR did not have PD, the duration of CR was censored at the date of last disease assessment or start date of subsequent therapy, whichever was earlier. Patients without documented PD and having received subsequent therapy were censored at the start date of subsequent therapy; patients without any documented PD and not having started any new therapy were censored at the last available laboratory or bone marrow date, whichever was later. Patients who were alive or lost to follow-up were censored at the last contact date.

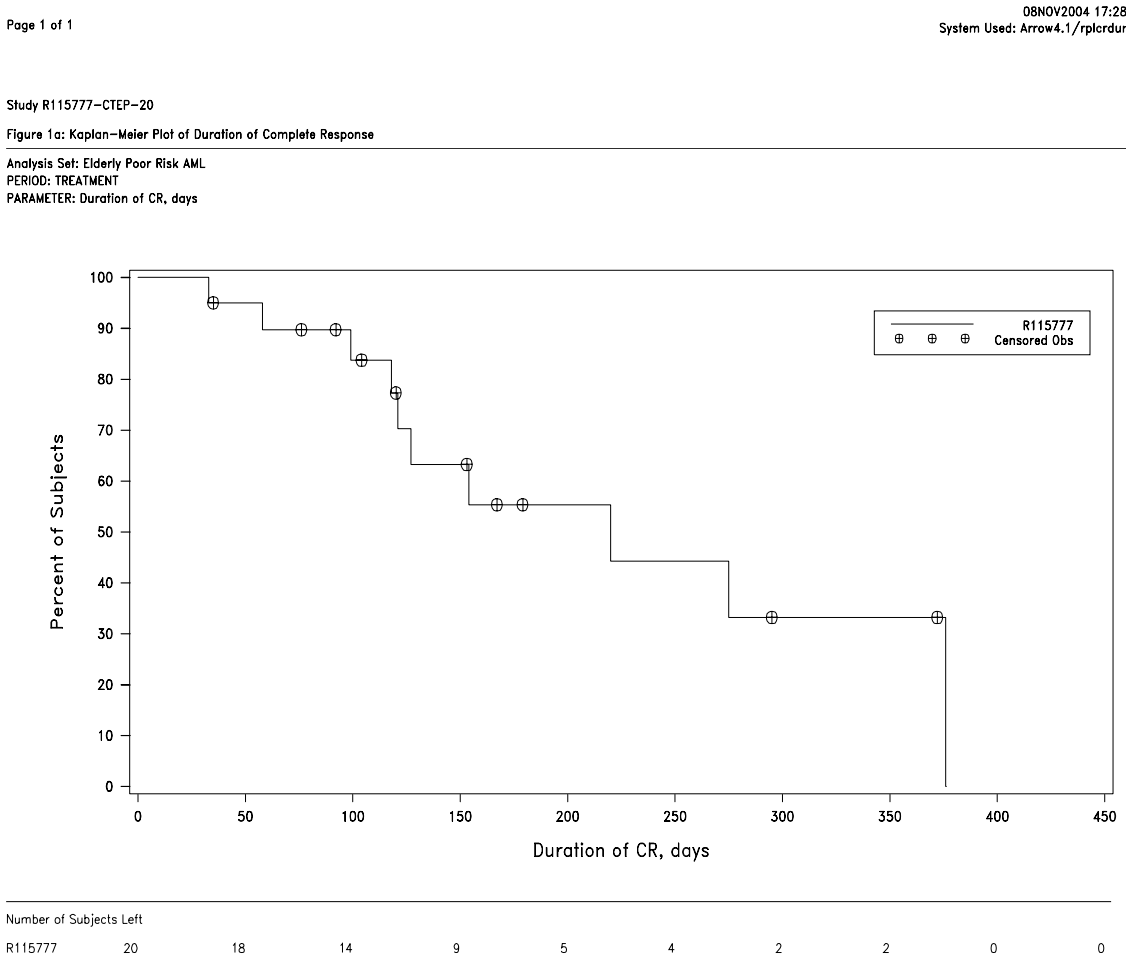
The median duration of CR, 220 days (95% CI = 121-376), must be considered in the context of the poor prognosis generally associated with AML in the elderly (**Table 18**). A Kaplan-Meier plot showing duration of CR is provided in **Figure 11**.

**Table 18:** Duration of Complete Response
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| | ----------Tipifarnib 600 mg oral b.i.d.---------- (N=136) |
|---|---|
| Number assessed | 20 |
| Number censored,[a] % | 10 (50) |
| Number relapsed, % | 10 (50) |
| **Duration of CR, days**[b] | |
| 25% Quantile (95% CI) | 121 (99;220) |
| Median (95% CI) | 220 (121;376) |
| 75% Quantile (95% CI) | 376 (220;376) |

[a] If patients with CR did not have PD, the duration of CR was censored at the date of last disease assessment or start date of subsequent therapy, whichever was earlier.
[b] Based on Kaplan-Meier product limit estimates.

**Figure 11:** Duration of Complete Response
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)



#### *4.3.4.2. Independent, Blinded Central Review of Bone Marrow Biopsies*

The primary endpoint of the CTEP-20 study was CR rate as determined by the investigators according to the objectively defined criteria in **Table 8**. The independent central reviewer was blinded to the CTEP-20 investigators' assessments of the bone marrow biopsies, and to the investigators' assessments of patient responses to treatment. Morphologic assessments of bone marrow samples represent a primary determinant of CR. It is recognized that variability of experience of hematopathologists at different institutions can lead to variable interpretations of bone marrow results (Cheson 2003). Thus, an independent, blinded central review was performed in this study as a quality-control measure. The review was performed according to a standard operating procedure for handling, cataloging, and determination of diagnosis and subsequent response.

Touch preparations or clot sections were not used. Most peripheral blood smears were not available at the local institutions and, hence, were not submitted for independent central review. The investigators provided all available bone marrow aspirate and biopsy slides for patients (including responders and nonresponders) to a central laboratory (Quest Diagnostics Clinical Trials), which then forwarded the clinical samples to the independent hematopathologist (Maher Albitar, M.D., Nichols Institute).

In general, all available bone marrow slides for an individual patient were read in chronological order in a single session. The central reviewer assessed baseline bone marrow slides for 118 patients and post-baseline bone marrow slides for 79 patients.

Of the 20 patients judged by the investigators to have a CR, bone marrow slides were available from 18 patients for the independent review. Agreement regarding the determination of CR for these 18 patients, with the same evaluation provided by the site and by the central reviewer, was 100%. Of these 20 patients classified as having attained CR, 17 had a follow-up bone marrow performed at least four weeks later to confirm the CR. The follow-up bone marrow slides for independent review were available for 16 of these 17 patients. In 15 of these cases, the confirmation of CR was validated by the independent review.

For the one patient for whom the site and central review were not in concordance, both the local site and central review had a reading after Cycle 1 of <5% blasts on bone marrow aspirate. The local site readings at later time points remained consistent with CR, whereas the central reading gave results slightly >5% leading to a classification of "unconfirmed CR" by central review for this patient. Per protocol, the local reading by the investigator took precedence.

#### *4.3.4.3. Complete Remission and Risk Factors*

In contrast to most reports of chemotherapy in patients with poor-risk AML (Rathnasabapathy 2003), tipifarnib induced CRs independent of the presence or type of risk factors (**Table 19**). Seventeen of the 20 patients who achieved CR had more than one adverse prognostic risk factor (**Table 20**).

**Table 19:** Response by Risk Factor, Elderly Poor-Risk AML Analysis Set
(Study R115777-CTEP-20)

| | ----------Tipifarnib 600 mg oral b.i.d.---------- | | |
|---|---|---|---|
| | | Response, n (%) | |
| | n (%) | CR | PR |
| Age | 136 | 20 (15) | 3 (2) |
| 65-74 y with prior MDS | 61 | 11 (18) | 3 (5) |
| ≥75 y | 75 | 9 (12) | — |
| Unfavorable karyotype | 136 | 20 (15) | 3 (2) |
| Yes | 66 | 9 (14) | 3 (5) |
| No | 62 | 10 (16) | — |
| Not available | 8 | 1 (13) | — |
| Organ dysfunction | 136 | 20 (15) | 3 (2) |
| Yes | 83 | 13 (16) | 2 (2) |
| No | 53 | 7 (13) | 1 (2) |
| Prior MDS | 136 | 20 (15) | 3 (2) |
| Yes | 111 | 18 (16) | 3 (3) |
| No | 25 | 2 (8) | — |

**Table 20**: Response by Number of Risk Factors
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| | ----------Tipifarnib 600 mg oral b.i.d.---------- | | | | |
|---|---|---|---|---|---|
| | ----------Number of Risk Factors---------- | | | | |
| | 1 | 2 | 3 | 4 | Total |
| | (N=14) | (N=60) | (N=47) | (N=15) | (N=136) |
| Response | n (%) | n (%) | n (%) | n (%) | n (%) |
| Complete response | 3 (21) | 9 (15) | 4 (9) | 4 (27) | 20 (15) |
| Partial response | — | 1 (7) | 2 (4) | — | 3 (2) |
| Hematologic improvement | — | 4 (7) | 3 (6) | — | 7 (5) |
| Stable disease | 2 (14) | 18 (31) | 21 (45) | 3 (20) | 44 (33) |
| Progressive disease | 7 (50) | 21 (35) | 13 (28) | 7 (47) | 48 (35) |
| Not evaluable / not done | 2 (14) | 7 (12) | 4 (9) | 1 (7) | 14 (10) |

#### *4.3.4.4. Overall Survival*

The median overall survival for the elderly patients with poor-risk AML was 164 days (95% CI = 125-242) (**Table 21**). The estimated survival rates at 6 months and 12 months were 45% and 25%, respectively.

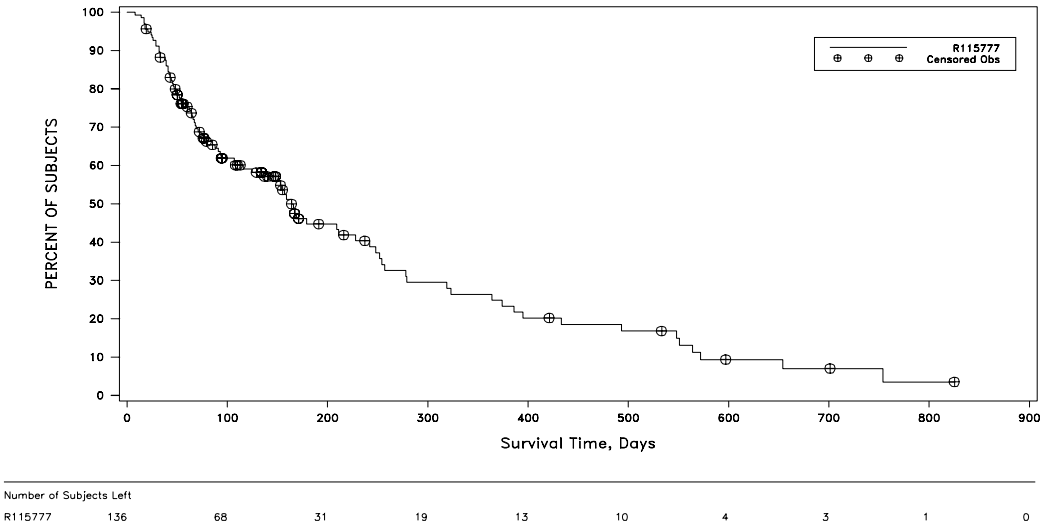
**Table 21:** Overall Survival
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| | ----------Tipifarnib 600 mg oral b.i.d.---------- (N=136) |
|---|---|
| Number assessed | 136 |
| Number censored,[a] % | 48 (35) |
| Number died, % | 88 (65) |
| **Survival time, days**[b] | |
| 25% Quantile (95% CI) | 62 (45;78) |
| Median (95% CI) | 164 (125;242) |
| 75% Quantile (95% CI) | 364 (254;548) |
| **Estimated survival rate**[b] | |
| 6-Month survival rate, % (95% CI) | 44.7 (35.0;54.4) |
| 12-Month survival rate, % (95% CI) | 24.8 (15.1;34.5) |

[a] Patients who were alive or lost to follow-up were censored at the last contact date.
[b] Based on Kaplan-Meier product limit estimates.

A Kaplan-Meier figure showing overall survival over time is presented in **Figure 12**.

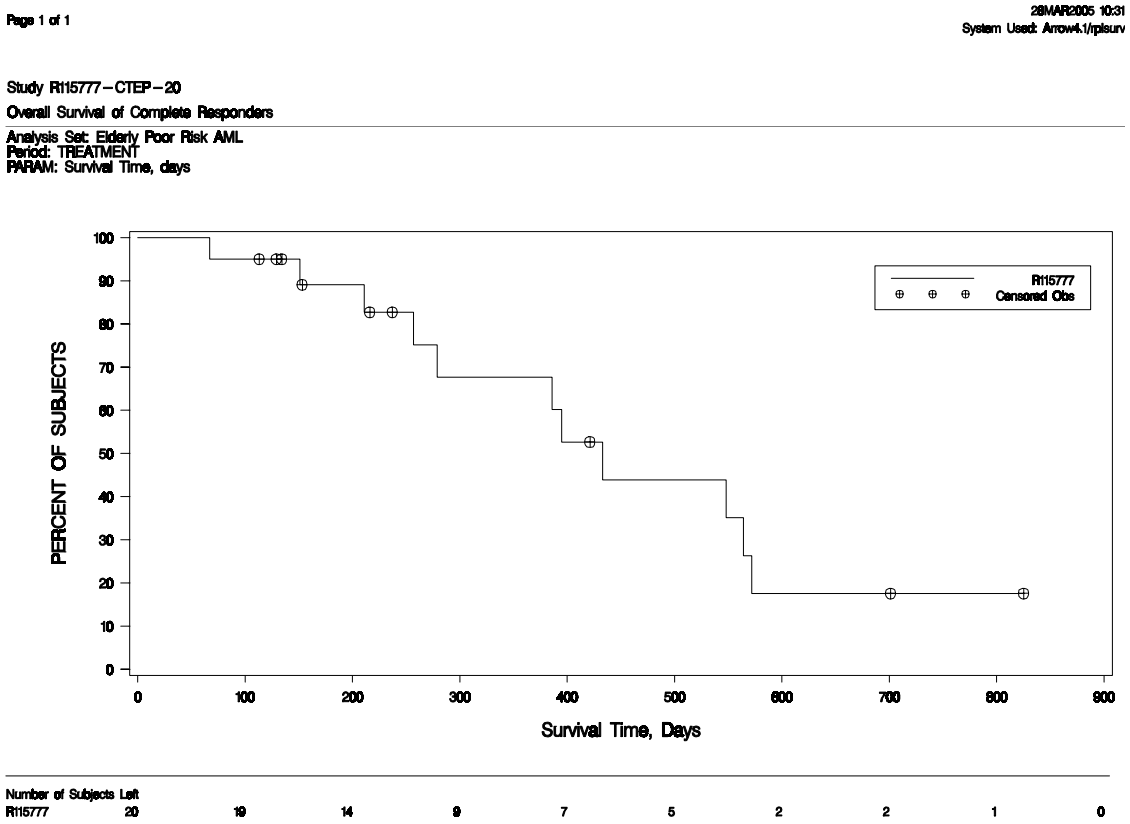
**Figure 12:** Overall Survival
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)




### *4.3.4.5. Exploratory Analysis of Impact of Complete Remission on Survival*

The median overall survival for patients who achieved a CR was 433 days (95% CI = 279 - 572). A Kaplan-Meier plot of overall survival time for the complete responders is provided in **Figure 13**. The estimated survival rates for the complete responders at 6 months and 12 months were 90% and 70%, respectively.

**Figure 13:** Overall Survival of Complete Responders
(Study R115777-CTEP-20)




### *4.3.4.6. Retreatment With Tipifarnib*

The Phase 1 CTEP-1 study had documented that re-treating patients with tipifarnib can induce second remissions. The CTEP-20 study verified this observation. CTEP-20 patients who achieved a complete remission could continue to receive tipifarnib until evidence of progressive disease. Alternately, they could receive 3 additional cycles of tipifarnib after achieving CR (consistent with common oncology practice), stop treatment, and then resume tipifarnib at the time of relapse. Of the seven CR patients who were retreated with tipifarnib, one had a second CR lasting 225 days, three had stable disease, one had PD, and two had not yet been assessed for response.

### *4.3.4.7. Salvage Therapy*

The CTEP-20 study population consisted of patients for whom treatment with experimental agents, in a clinical study, is the recommended therapeutic option. Patients were not considered to be optimal candidates to receive standard combination induction chemotherapy by their treating physician given the limited benefit and high mortality/morbidity due to the chemotherapy. In accordance with this, only a relatively small proportion of patients who were enrolled in CTEP-20 went on to receive combination chemotherapy after their study participation. Among the 136 elderly patients with poor-risk AML, following completion of study participation (including tipifarnib retreatment in some cases as noted above), 67% of patients received supportive care alone; 26% received treatment with hydroxyurea or low-intensity chemotherapy; and only 7% (n=10) of patients received subsequent

combination chemotherapy, consisting mostly of cytarabine with an anthracycline (**Table 22**). Six of the 10 patients responded to subsequent combination chemotherapy.

**Table 22:** Patients Who Received Subsequent Combination Chemotherapy
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| Patient No. | Age (y) | Site | Response to Tipifarnib | Post-Tipifarnib Treatment | Response to Subsequent Treatment | Duration of Response |
|---|---|---|---|---|---|---|
| 100201 | 83 | Rochester | SD | cytarabine + mitoxantrone | CR | <2 wk |
| 100203 | 74 | Rochester | PD | cytarabine + mitoxantrone | CR | 6 wk |
| 100204 | 69 | Rochester | SD | cytarabine + mitoxantrone | CR | 8+ mo |
| 100209 | 73 | Rochester | PD | cytarabine + mitoxantrone | CR | <6 mo |
| 100210 | 68 | Rochester | PD | cytarabine + daunorubicin | CR | Unknown |
| 100212 | 70 | Rochester | SD | cytarabine + mitoxantrone | CR | 18+ mo |
| 100320 | 78 | Maryland | HI | cytarabine + idarubicin | PD | — |
| 100333 | 65 | Maryland | SD | cytarabine + mitoxantrone | PD | — |
| 101046 | 66 | Johns Hopkins | PD | cyclophosphamide + mercaptopurine | PD | — |
| 101066 | 69 | Maryland | PD | cytarabine + idarubicin | Not recorded | — |

HI = hematologic improvement; PD = progressive disease, SD = stable disease.

Two additional patients (101049 and 100321) received subsequent combination chemotherapy, as third-line treatment, after first being retreated with tipifarnib (**Table 17**). One of these patients achieved a CR after subsequent combination treatment and the other was not evaluated.

Age appeared to be the most common determining factor in the physicians' decisions to administer cytotoxic combination chemotherapy after failure of tipifarnib. A total of 81% of patients never received any subsequent chemotherapy. In general, combination chemotherapy was administered to the younger segment of this elderly population (age 65 to 74 years). Treatment of patients ≥75 years was mostly limited to supportive care with or without hydroxyurea.

#### *4.3.4.8. Efficacy Update*

The original clinical cutoff for efficacy data reported for Study CTEP-20 in the NDA was 30 August 2004. The efficacy data in this section reflect the updated efficacy data provided to the FDA on 8 March 2005 (clinical cutoff date, 15 November 2004).

In the clinical study report submitted with the NDA, 157 treated patients constituted the all-treated AML population, and 136 patients constituted the elderly poor-risk AML population. Eighteen elderly patients with poor-risk AML were still receiving treatment at the time of the NDA cutoff. The patient who had been enrolled but not treated as of the NDA cutoff is included in the updated analysis sets. Of the updated 137 treated elderly patients with poor-risk AML, 7 were still receiving treatment as of 15 November 2004.

Results of the efficacy analyses in the updated analysis set are similar to those submitted in the NDA. No additional CR or PR was reported in any analysis set. The median CR duration did not change: 220 days (95% CI = 154-275) for updated data and 220 days (95% CI= 121-376) for NDA data. The updated data for the duration of CR are provided in **Table 23**.

**Table 23:** Duration of Complete Response Update
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| | Duration of Complete Response (days) | |
|---|---|---|
| Patient No. | NDA | Update |
| 101021 | 372+ | 473 |
| 101025 | 153+ | 197 |
| 101049 | 167+ | 272 |
| 101060 | 92+ | 134+ |
| 101091 | 104+ | 167 |
| 101096 | 33 | 149+ |
| 101107 | 76+ | 139+ |

+ If patients with CR did not have PD, the duration of CR was censored at the date of last disease assessment or start date of subsequent therapy, whichever was earlier.

Twelve additional patients died. The median overall survival for the updated analysis set was similar to that presented in the NDA: 159 days (95% CI = 116 - 194) for the update compared with 164 days (95% CI = 125 - 242) for the NDA. The estimated survival rates at 6 months (45%) and 12 months (25% [NDA] to 24% [update]) did not change substantially.

## 4.4. Study INT-17

INT-17 was an open-label, multicenter, Phase 2 study conducted by J&JPRD that evaluated tipifarnib monotherapy in patients with relapsed or refractory AML. This study population was very different from the CTEP-20 population, in that all INT-17 patients had disease progression following prior cytotoxic combination induction therapy, and there was no age restriction for study entry.

### 4.4.1. Study Population

A total of 154 evaluable patients with relapsed (n=99) or refractory (n=55) AML were to be enrolled. A Simon 2-stage design was applied to each cohort (relapsed or refractory), and the overall sample size was based on the anticipated objective response in each group. Due to the aggressive nature of the underlying disease, it was assumed that a substantial number of patients (~10%) would drop out before being evaluable. During the conduct of the study, it was noted that more than 10% of patients enrolled in the study dropped out before reaching the protocol definition of being evaluable. The sample size was increased accordingly. There also was an approximate 10% over-accrual into this multicenter study with a final accrual of 252 patients..

In Study INT-17, refractory AML was defined as (1) failure to achieve a CR following up to three regimens of induction therapy or (2) relapse within six months of achieving CR.

Relapsed AML was defined as recurrence of AML more than six months following achievement of a CR. Patients were to have had bone marrow blast counts of ≥20% or >5% with increasing counts on at least two consecutive examinations. Approximately half of the

patients with relapsed AML had experienced failure of additional salvage therapy, including bone marrow transplantation.

Most (250 of 252) INT-17 patients were heavily pretreated. Standard cytarabine-based combination induction chemotherapy had been administered to 95% of patients. Two or more regimens had been administered to 27% of patients, while 19% had undergone bone marrow or stem-cell transplantation.

The demographic and disease characteristics for the INT-17 population are provided in **Table 24**. Most patients were symptomatic. For 27%, the ECOG performance status score was 2. The median age of the INT-17 population was lower than that of CTEP-20 (62 years, range = 18 - 85 years).

Based on the outcome of the initial induction, 152 of the 252 patients (60%) had refractory AML. Approximately half of the patients with relapsed AML also had failure of salvage therapy, which explains the relatively long time interval separating the initiation of tipifarnib from the date of diagnosis.

Of the 252 patients, 20% had AML arising from prior MDS. The rate of prior MDS is consistent with that from other trials reported in the literature and substantially lower than the rate reported in CTEP-20 (82%).

**Table 24:** Demographic and Disease Characteristics
(Study R115777-INT-17: Elderly AML Analysis Set)

| | ----------Tipifarnib 600 mg oral b.i.d.---------- (N=252) |
|---|---|
| **Sex, n (%)** | |
| Male | 147 (58) |
| Female | 105 (42) |
| **Race, n (%)** | |
| White | 236 (94) |
| Black | — |
| Hispanic | 3 (1) |
| Asian | 2 (1) |
| Other | 11 (4) |
| **Age, years** | |
| Mean (SD) | 57.0 (0.99) |
| Median | 62 |
| Range | 18-85 |
| **Baseline ECOG performance status, n (%)** | |
| 0 | 76 (30) |
| 1 | 107 (43) |
| 2 | 66 (26) |
| **Baseline cytogenetics results, n (%)** | |
| Total no. patients with results | 211 |
| Normal | 88 (35) |
| Abnormal | |
| Chromosome 5 or 7 or 11 | 39 (16) |
| t(8,21) | 7 (3) |
| Inv 16 | 3 (1) |
| Other | 96 (38) |
| **Time from diagnosis to first dose, months** | |
| Mean (SD) | 18.9 (1) |
| Median | 13.25 |
| Range | 0.0-154.8 |
| **Time from diagnosis to first relapse, months** | |
| Mean (SD) | 17.6 (1) |
| Median | 12.85 |
| Range | 1.5-134.2 |

### 4.4.2. Treatment Regimen

The dosing regimen specified oral administration of tipifarnib at 600 mg twice daily for 21 consecutive days in 28-day cycles, and emphasized continuity of drug exposure. The rules governing dose reductions were similar to those utilized in the CTEP-20 study (see Section 4.3.2).

### 4.4.3. Study Endpoints

The primary efficacy endpoint for INT-17 was confirmed CR rate, as defined in **Table 8.** which was defined as a CR with a confirmatory bone marrow aspirate and biopsy obtained at least 28 days after documentation of first response. Overall best response was evaluated and verified by a J&JPRD clinical reviewer using bone marrow counts reported by an

independent central reviewer. The major secondary efficacy endpoints for INT-17 were objective response rate (CR + complete response with incomplete platelet recovery [CRp] + PR), duration of response, time to disease progression, progression-free survival, overall survival, and clinical benefit. Leukemia-free state was also characterized in an exploratory analysis.

### 4.4.4. Biologic Activity

Although CRs are rare in patients with relapsed or refractory AML, biologic activity was observed in the INT-17 population. Overall response (CR and CRp) was documented and confirmed at 4 weeks in 3 of 252 patients (2 with relapsed AML and 1 with refractory AML, 1%). Objective response (CR, CRp, and PR) was documented and confirmed at 4 weeks in 11 of 252 patients (7 relapsed and 4 refractory, 4%).

An exploratory analysis of leukemia-free state was also performed. This is particularly relevant to the INT-17 study, which was conducted in a heavily pretreated population, which may have had impaired stem-cell regenerative capacity.

Post-baseline bone marrow evaluations were available for 134/252 patients (55%). Reductions in bone marrow blasts by 50% from baseline, or absolute bone marrow blast counts less than 5%, were documented in 46/252 patients (18%). For 19 (8%) of the 46 patients, at least one bone marrow evaluation resulted in a blast count <5%.

## 4.5. Study CTEP-50

CTEP-50 is an open-label, randomized, multicenter, Phase 2 study designed to evaluate two doses and two schedules of tipifarnib in patients 70 years and older with previously untreated AML. Oral doses of tipifarnib (300 or 600 mg) will be administered twice daily for 21 days of each 28-day cycle. CTEP-50 was initiated on 15 September 2004.

## 4.6. Study AML-301

AML-301 is an open-label, randomized, controlled, multicenter, Phase 3 study designed to evaluate treatment with tipifarnib compared with best supportive care, including hydroxyurea, in newly diagnosed AML patients ≥70 years old who are not candidates to receive combination induction chemotherapy. This study was the subject of a special protocol assessment (SPA) in which the endpoints and study design were reviewed by FDA. AML-301 was initiated in October 2004. As of 24 March 2005, 58 patients from 60 study centers in 14 countries have been entered into AML-301. Final results are expected by the end of 2006. AML-301 is intended to fulfill the commitment that would be required under terms of a possible accelerated approval.

# 5. SUMMARY AND CONCLUSIONS ON EFFICACY OF TIPIFARNIB IN AML

Tipifarnib has demonstrated antileukemic activity in three separate studies of patients with AML, with CRs noted across a variety of patient groups having various degrees of risk factors and chemotherapy resistance. Furthermore, in CTEP-20, durable complete remissions were observed.

**CTEP-1**

- First study to demonstrate that treatment with an agent whose primary therapeutic target was FTase inhibition could yield complete remissions in AML.
- Tipifarnib exhibited dose-proportional plasma pharmacokinetics, including pharmacokinetics at the dose recommended for the treatment of elderly patients with poor-risk AML.
- Bone marrow concentrations of tipifarnib increased in a dose-dependent manner.
- Based on dose-limiting toxicity at 1,200 mg twice daily and the number of patients who needed dose modifications at 900 mg twice daily, the recommended dose for Phase 2 studies was 600 mg twice daily given for 21 days in 28-day cycles.

**INT-17**

- In this extensively pretreated patient population, overall response (CR and CRp) was documented and confirmed at four weeks in 3/252 patients (two relapsed and one refractory, 1%).
- Reduction in bone marrow blasts by 50% from baseline, or absolute bone marrow blast counts less than 5%, were documented in 18% of patients.

**CTEP-20**

- The CR rate for this elderly poor-risk AML population was 20 (15%) of 136 patients (95% CI =9.4-21.9).
- CRs were observed despite the presence of risk factors associated with poor prognosis.
- Evidence of disease control (PR, hematologic improvement, or stable disease) was documented in an additional 40% of patients.
- The median duration of CR was 220 days (95% CI = 154 – 275).
- The median overall survival was 159 days (95% CI = 116 – 194). The estimated 6-month and 12-month survival rates were 45% and 24%, respectively.

**Conclusion**

Tipifarnib is a novel targeted outpatient treatment with demonstrated antileukemic activity. This oral therapy provides an additional potential treatment option for elderly patients with newly diagnosed poor-risk AML (patients 65-74 years of age with prior MDS or patients ≥75 years of age). This patient group currently has very limited treatment options. The benefit/risk profile of oral tipifarnib treatment in newly diagnosed poor-risk elderly AML patients who are not optimal candidates to receive conventional combination chemotherapy is supported by a CR rate of 15%, with a favorable safety profile.

# 6. SAFETY AND TOLERABILITY OF TIPIFARNIB

## 6.1. Background

The toxicologic profile of tipifarnib in animal studies identified the hematopoietic system and the male reproductive tract as the primary systems that were affected at higher (toxic) doses. Changes seen in these systems were generally reversible, following a recovery period.

## 6.2. Determination of Phase 2 Dose in Patients With AML

A Phase 1 study in patients with AML, the CTEP-1 study, provided the clinical rationale to proceed with further development of tipifarnib in this illness. In this study, tipifarnib was evaluated in 34 subjects with relapsed/refractory or newly diagnosed poor-risk leukemia for whom standard chemotherapy was not appropriate. This study included 25 patients with AML. The dosing regimen was 100 to 1,200 mg twice daily given orally for the first 21 days in 28-day cycles. This study was performed at the Universities of Maryland and Rochester. CTEP-1 was an open-label, dose-escalation, single-arm, Phase 1 study that evaluated the safety of tipifarnib. The recommended Phase 2 dose (600 mg twice daily given orally for 21 days in 28-day cycles) was based on a combination of pharmacokinetic (Section 3.3.2) and pharmacodynamic observations (Section 3.1), evidence of biological activity in producing disease remission (Section 4.2.1), and the tolerability findings in CTEP-1 (**Table 25**).

Based on dose-limiting toxicity (central nervous system [CNS] events) at 1,200 mg twice daily and the number of patients who needed dose modifications at 900 mg twice daily, the recommended dose for Phase 2 studies was 600 mg twice daily, given for 21 days in 28-day cycles.

**Table 25:** Safety Data by Dose
(Study R115777-CTEP-1)

| | Dose (mg b.i.d. cyclically) | | | | |
|---|---|---|---|---|---|
| Toxicity, n | 100 (N=6) | 300 (N=5) | 600 (N=8) | 900 (N=11) | 1,200 (N=4) |
| Fatigue | 2 (grade 1) | | 1 (grade 1) | 2 (grade 1-2) | 2 (grade 2) |
| Neurologic | | | | | |
| Visual | | | | | 1 (grade 1) |
| Confusion | | | 2 (grade 1) | | 2 (grade 3) |
| Ataxia | | | | | 1 (grade 3) |
| Neuropathy | | | | 2 (grade 1) | |
| Headache | | | 2 (grade 1) | | |
| Renal/endocrine | | | | | |
| Polydipsia | | | 2 (grade 1) | 4 (grade 2) | |
| Creatinine | | | 2 (grade 1) | 4 (grade 1-2) | |
| Gastrointestinal | | | | | |
| Nausea | 1 (grade 1) | | 2 (grade 1) | 3 (grade 2) | 3 (grade 2) |
| Vomiting | | | | 2 (grade 1) | 1 (grade 2) |
| Neutropenia | | | | | |
| $<500/mm^3$ | | | 2 | 5 | |
| Fever/infection | | | 1 (grade 2) | 3 (grade 2) | |

Cross-reference: Karp 2001.

## 6.3. Patients Included in the Analysis of Safety

The safety profile of tipifarnib monotherapy is based on data from 1,014 patients from 11 completed single-agent trials. The safety database included 409 AML patients and 605 patients with solid tumors. Safety in AML populations is based primarily on studies CTEP-20 (n=157), conducted in patients with newly diagnosed poor-risk AML, and

INT-17 (n=252), conducted in patients with relapsed or refractory AML. The majority of patients (n= 247, 60%) enrolled in these studies were 65 years of age or older. In these studies, tipifarnib was administered at a dose of 600 mg twice daily. Dose escalation to 900 mg twice daily was allowed in INT-17.

Safety data are also provided from 9 monotherapy studies in solid tumors (USA-1, USA-3, BEL-2, BEL-7, USA-7, USA-8, GBR-1, INT-10, and INT-9) that were conducted in patients treated with tipifarnib (n=472) or placebo (n=133). A total of 169 (36%) tipifarnib-treated patients were 65 years or older. In these studies, tipifarnib was administered in continuous or cyclical regimens at doses ranging from 25 to 1,300 mg twice daily. Most (n=386, 82%) tipifarnib-treated patients with solid tumors received 300 mg twice daily.

The cutoff date for the safety analysis in the NDA was 1 June 2004. Results of the updated safety data as of the cutoff date of 15 November 2004 are provided in Section 6.8. The updated data revealed no changes in the safety profile of tipifarnib.

## 6.4. Safety in Patients With AML

### 6.4.1. Safety Population and Extent of Exposure

The safety of tipifarnib in AML populations is based on 409 (157 newly diagnosed poor-risk and 252 relapsed/refractory) patients from Studies CTEP-20 and INT-17. Sixty percent (n=247) of patients were 65 years of age or older, and 23% were 75 years of age or older. There was a high prevalence of abnormalities at baseline, including abnormal baseline liver function in 35% and abnormal baseline renal function in 55%, that could potentially worsen the toxicity of any treatment intervention. The prevalence of renal impairment at baseline increased as a function of age.

As anticipated in an AML population, 63% had grade 3 or 4 baseline absolute neutrophil counts and 62% had grade 3 or 4 baseline platelet counts, making the interpretation of potential hematologic toxicities complex.

The dosing regimens of CTEP-20 and INT-17 were similar (starting dose: 600 mg twice daily; minimum cycle duration: 28 days). Median treatment duration (46 days vs. 36 days) and median cumulative dose (25.2 g vs. 28.5 g) were also similar in both studies (**Table 26**). The highest dose administered was 900 mg twice daily, in patients with relapsed/refractory AML, who received this escalated dose level in the INT-17 study. Data from Studies CTEP-20 and INT-17 were also analyzed separately to examine the impact on tipifarnib safety findings of prior chemotherapy and relapsed disease (demographic features of the INT-17 patient population).

**Table 26:** Duration of Treatment, Cumulative Dose and Dose Intensity, AML Studies

| | Tipifarnib Starting Dose of 600 mg b.i.d. n (%) | |
|---|---|---|
| | CTEP-20 (N=157) | INT-17 (N=252) |
| **Number of treatment cycles** | | |
| 1 cycle | 82 (52) | 115 (46) |
| 2 cycles | 44 (28) | 71 (28) |
| 3 cycles | 13 (8) | 34 (13) |
| 4 cycles | 13 (8) | 12 (5) |
| 5 cycles | 3 (2) | 8 (3) |
| 6 cycles | 1 (1) | 3 (1) |
| >6 cycles | 1 (1) | 9 (4) |
| Mean (SD) | 1.8 (1.16) | 2.2 (1.83) |
| Median | 1.0 | 2.0 |
| Range | 1 – 7 | 1 – 14 |
| **Total duration, days** | | |
| Mean (SD) | 67.7 (55.07) | 55.1 (57.22) |
| Median | 46.0 | 36.0 |
| Range | 3 – 274 | 2 – 399 |
| **Cumulative dose, mg**[a] | | |
| Mean (SD) | 39855 (26592) | 44747 (50257) |
| Median | 25200 | 28500 |
| Range | 3600 – 176400 | 1200 – 495000 |

[a] Numbers rounded to nearest whole integer.

## 6.4.2. Adverse Events and Clinical Laboratory Evaluations

### *6.4.2.1. Overview*

The most frequent adverse events in the AML studies of tipifarnib were myelosuppression, gastrointestinal events, fever, fatigue, hypokalemia, and skin rash. In contrast to the patterns usually observed with conventional combination induction chemotherapy in similar patient populations, the incidence of drug-related nonhematologic grade 4 adverse events was relatively low (9%) (**Table 32**).

The most common adverse events were infection and fatigue, which are influenced by the underlying disease. Mucositis and rash each occurred in approximately one-third of tipifarnib-treated patients; these were mostly grade 1 or 2. The low rate of grade 4 mucositis (1%) is noteworthy, given that this toxicity is a major determinant of neutropenic sepsis and death in this patient population.

The safety profile was similar between the elderly poor-risk patients (n=136) and the all treated (n=157) AML populations in CTEP-20 (**Table 27**). Therefore, for completeness, the safety data in CTEP-20 are presented for the all treated AML population.

The overall incidence of adverse events was similar between Studies CTEP-20 and INT-17 (**Table 27**). The higher incidence of grade 3 or 4 adverse events and drug-related withdrawals in the INT-17 study may indicate a possible effect on treatment tolerance in patients with prior chemotherapy treatment or a more advanced treatment phase.

**Table 27:** Safety Profile, AML Studies

| Total n (%) with: | Tipifarnib 600 mg b.i.d. CTEP-20 (N=136) | CTEP-20 (N=157) | INT-17 (N=252) | Total (N=409) |
|---|---|---|---|---|
| **Adverse events (AEs)** | **134 (99)** | **155 (99)** | **251 (>99)** | **406 (99)** |
| Drug-related AEs | 118 (87) | 134 (85) | 205 (81) | 339 (83) |
| **Grade 3 or 4 AEs** | **113 (83)** | **131 (83)** | **241 (96)** | **372 (91)** |
| Drug-related grade 3 or 4 AEs | 83 (61) | 92 (59) | 163 (65) | 255 (62) |
| **Serious AEs** | **88 (65)** | **103 (66)** | **207 (82)** | **310 (76)** |
| Drug-related serious AEs | 58 (43) | 64 (41) | 97 (38) | 161 (39) |
| **AE leading to treatment termination** | **21 (15)** | **33 (21)** | **106 (42)** | **139 (34)** |
| Drug-related AE leading to treatment termination | 14 (10) | 17 (11) | 52 (21) | 69 (17) |
| **Deaths with AE as cause of death** | | | | |
| Within 14 days of first dose | 0 | 0 | 13 (5) | 13 (3) |
| Within 28 days of first dose | 5 (4) | 6 (4) | 28 (11) | 34 (8) |
| During study or within 30 days of last dose | 9 (7) | 11 (7) | 61 (24) | 72 (18) |
| Drug-related deaths with AE as main cause of death | 1 (1) | 1 (1) | 16 (6) | 17 (4) |

### *6.4.2.2. Hematologic Adverse Events and Laboratory Evaluations*

**Hematologic Adverse Events**

Myelosuppression was commonly reported during the studies (**Table 28**). The incidence of neutropenia was similar in CTEP-20 and INT-17. In contrast, the incidence rates for thrombocytopenia (56% vs. 18%) and anemia (54% vs. 15%) reported as adverse events were higher in INT-17 than in CTEP-20, indicating a possible effect of prior chemotherapy on treatment tolerance in the patients with relapsed/refractory AML.

**Table 28:** Hematologic Adverse Events in ≥10% of Patients in Either Study, AML Studies

| | Tipifarnib 600 mg b.i.d. CTEP-20 (N=157) n (%) | INT-17 (N=252) n (%) | Total (N=409) n (%) |
|---|---|---|---|
| **Total with adverse event** | **155 (99)** | **251 (>99)** | **406 (99)** |
| **Total with hematologic AE** | **81 (52)** | **214 (85)** | **295 (72)** |
| **White cell and RES disorders** | **64 (41)** | **152 (60)** | **216 (53)** |
| Neutropenia febrile | 47 (30) | 63 (25) | 110 (27) |
| Neutropenia | 21 (13) | 50 (20) | 71 (17) |
| Leukocytosis | 1 (1) | 41 (16) | 42 (10) |
| Leukopenia | 2 (1) | 35 (14) | 37 (9) |
| Pancytopenia | 8 (5) | 24 (10) | 32 (8) |
| **Platelet, bleeding & clotting disorders** | **30 (19)** | **144 (57)** | **174 (43)** |
| Thrombocytopenia | 29 (18) | 142 (56) | 171 (42) |
| **Red blood cell disorders** | **25 (16)** | **137 (54)** | **162 (40)** |
| Anemia | 24 (15) | 136 (54) | 160 (39) |

RES = reticuloendothelial system.
Note: A common dictionary (WHO Adverse Reaction Terms) and severity grading scheme, NCI Common Toxicity Criteria Version 2.0 (NCI CTC V.2), were used for all studies.

**Hematologic Laboratory Evaluations**

Thrombocytopenia, neutropenia, and anemia were common adverse events in the AML studies (**Table 28**). Laboratory evaluations are consistent with these adverse event findings (**Table 29**). The shift table below shows incidence of toxicity at baseline for each grade and the number of patients who changed to a different toxicity grade during treatment. For

example, of the 87 patients with grade 3 neutrophils at baseline, five improved to a grade 0 or 2, 6 remained at grade 3, and 76 worsened to a grade 4. As shown in the table, baseline and on-treatment values needed to perform this analysis were available for almost all of the 409 patients.

The majority of patients (n=372/401, 93%) had grade 3 or 4 thrombocytopenia documented during treatment with tipifarnib. Of these 372 patients, 298 (80%) had entered the study with decreased platelet counts (grade ≥2).

Grade 3 or 4 neutropenia were reported for 332 (86%) patients during treatment with tipifarnib. Of these 332 patients, 266 (80%) had entered the study with depressed neutrophil counts (grade ≥2).

**Table 29:** Hematologic Laboratory Analysis: Shift in Value From Baseline to Worst Grade During Treatment, AML Studies

| Laboratory Variables | Tipifarnib 600 mg b.i.d. (N=409) Worst grade during treatment n (%) | | | | | |
|---|---|---|---|---|---|---|
| Baseline Tox Grade | Total | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| **Hemoglobin** | **401 (98)** | **0** | **23** | **158** | **166** | **54** |
| 0 | 23 (6) | 0 | 2 | 12 | 7 | 2 |
| 1 | 138 (34) | 0 | 17 | 59 | 46 | 16 |
| 2 | 197 (48) | 0 | 4 | 72 | 96 | 25 |
| 3 | 38 (9) | 0 | 0 | 14 | 17 | 7 |
| 4 | 5 (1) | 0 | 0 | 1 | 0 | 4 |
| **Neutrophils[a]** | **387 (95)** | **38** | **3** | **14** | **32** | **300** |
| 0 | 88 (22) | 29 | 1 | 8 | 13 | 37 |
| 1 | 22 (5) | 2 | 1 | 3 | 4 | 12 |
| 2 | 36 (9) | 2 | 1 | 0 | 2 | 31 |
| 3 | 87 (21) | 2 | 0 | 3 | 6 | 76 |
| 4 | 154 (38) | 3 | 0 | 0 | 7 | 144 |
| **Platelet count** | **401 (98)** | **4** | **9** | **16** | **191** | **181** |
| 0 | 40 (10) | 4 | 4 | 2 | 23 | 7 |
| 1 | 55 (13) | 0 | 5 | 6 | 31 | 13 |
| 2 | 57 (14) | 0 | 0 | 4 | 35 | 18 |
| 3 | 212 (52) | 0 | 0 | 4 | 94 | 114 |
| 4 | 37 (9) | 0 | 0 | 0 | 8 | 29 |
| **WBC** | **401 (98)** | **111** | **20** | **31** | **59** | **180** |
| 0 | 198 (48) | 103 | 17 | 17 | 29 | 32 |
| 1 | 30 (7) | 4 | 1 | 6 | 7 | 12 |
| 2 | 72 (18) | 2 | 2 | 6 | 16 | 46 |
| 3 | 74 (18) | 2 | 0 | 2 | 6 | 64 |
| 4 | 27 (7) | 0 | 0 | 0 | 1 | 26 |

[a] Neutrophils=Absolute neutrophil count.

### *6.4.2.3. Nonhematologic Adverse Events and Laboratory Evaluations*

**Nonhematologic Adverse Events**

Most patients reported nonhematologic adverse events (**Table 30**). Diarrhea, nausea, fatigue, vomiting, anorexia, dyspnea, and purpura occurred at similar frequencies in each study. Gastrointestinal events were mostly mild to moderate (grade 1 or 2) and could be managed with appropriate medication, temporary interruption of therapy, or dose modification. Skin

rash was more frequent in the CTEP-20 study. Fever, asthenia, and hypokalemia were reported more frequently in the INT-17 study. The increased incidence of hypokalemia in the INT-17 study may be explained in part by the administration of nephrotoxic anti-infectives in many of these patients.

**Table 30:** All Grades of Nonhematologic Adverse Events in ≥25% of Patients in Either Study or Any Body System, AML Studies

| | Tipifarnib 600 mg b.i.d. | | |
|---|---|---|---|
| | CTEP-20 (N=157) n (%) | INT-17 (N=252) n (%) | Total (N=409) n (%) |
| **Total with adverse event** | **155 (99)** | **251 (>99)** | **406 (99)** |
| **Total with nonhematologic AE** | **155 (99)** | **249 (99)** | **404 (99)** |
| **Body as a whole - general disorders** | **121 (77)** | **216 (86)** | **337 (82)** |
| Fever | 48 (31) | 125 (50) | 173 (42) |
| Fatigue | 68 (43) | 93 (37) | 161 (39) |
| Asthenia | 0 | 63 (25) | 63 (15) |
| **Gastrointestinal system disorders** | **124 (79)** | **213 (85)** | **337 (82)** |
| Diarrhea | 72 (46) | 101 (40) | 173 (42) |
| Nausea | 58 (37) | 113 (45) | 171 (42) |
| Vomiting | 37 (24) | 86 (34) | 123 (30) |
| Anorexia | 43 (27) | 76 (30) | 119 (29) |
| **Respiratory system disorders** | **98 (62)** | **156 (62)** | **254 (62)** |
| Dyspnea | 35 (22) | 64 (25) | 99 (24) |
| Pneumonia | 24 (15) | 66 (26) | 90 (22) |
| **Metabolic and nutritional disorders** | **72 (46)** | **159 (63)** | **231 (56)** |
| Hypokalemia | 17 (11) | 111 (44) | 128 (31) |
| **Central & peripheral nervous system disorder** | **84 (54)** | **111 (44)** | **195 (48)** |
| **Resistance mechanism disorders** | **62 (39)** | **127 (50)** | **189 (46)** |
| **Skin and appendages disorders** | **83 (53)** | **95 (38)** | **178 (44)** |
| Rash | 57 (36) | 48 (19) | 105 (26) |
| **Psychiatric disorders** | **71 (45)** | **87 (35)** | **158 (39)** |
| **Platelet, bleeding & clotting disorders** | **48 (31)** | **103 (41)** | **151 (37)** |
| Purpura | 30 (19) | 64 (25) | 94 (23) |
| **Musculoskeletal system disorders** | **33 (21)** | **66 (26)** | **99 (24)** |
| **Urinary System Disorders** | **46 (29)** | **49 (19)** | **95 (23)** |

**Table 31** presents grade 3 or 4 nonhematologic adverse events in ≥5% of the patients, and **Table 32** presents drug-related grade 3 or 4 adverse events in ≥2% of the patients.

Eighty-two percent (82%) of patients experienced at least one grade 3 or 4 nonhematologic adverse event (**Table 31**). The percentage experiencing at least one grade 4 event was 35%, of which only 9% were considered drug related (**Table 32**). Sepsis was the most common grade 4 nonhematologic adverse event. Approximately one-half of the nonhematologic grade 3 or 4 adverse events were considered drug related. The most common drug-related grade 3 or 4 adverse events were fatigue and rash. The rates of severe (grade 3 or 4) gastrointestinal events, such as diarrhea, nausea, and vomiting, were notably low.

**Table 31:** Grade 3 and 4 Nonhematologic Adverse Events in ≥5% Patients by Body System, AML Studies

| | Tipifarnib 600 mg b.i.d. (N=409) | | |
|---|---|---|---|
| | Grade 3+4 n (%) | Grade 3 n (%) | Grade 4 n (%) |
| **Total no. with nonhematologic grade 3 or 4 AE** | **337 (82)** | **195 (48)** | **142 (35)** |
| **Body as a whole – general disorders** | **159 (39)** | **125 (31)** | **34 (8)** |
| Fatigue | 59 (14) | 49 (12) | 10 (2) |
| Fever | 47 (11) | 40 (10) | 7 (2) |
| Asthenia | 34 (8) | 28 (7) | 6 (1) |
| **Resistance mechanism disorders** | **127 (31)** | **75 (18)** | **52 (13)** |
| Sepsis | 51 (12) | 13 (3) | 38 (9) |
| Infection bacterial | 47 (11) | 38 (9) | 9 (2) |
| Infection | 21 (5) | 18 (4) | 3 (1) |
| Infection fungal | 21 (5) | 15 (4) | 6 (1) |
| **Respiratory system disorders** | **110 (27)** | **68 (17)** | **42 (10)** |
| Pneumonia | 59 (14) | 42 (10) | 17 (4) |
| Dyspnea | 40 (10) | 27 (7) | 13 (3) |
| **Metabolic and nutritional disorders** | **105 (26)** | **76 (19)** | **29 (7)** |
| Hypokalemia | 70 (17) | 57 (14) | 13 (3) |
| Dehydration | 19 (5) | 18 (4) | 1 (<1) |
| **Gastrointestinal system disorders** | **98 (24)** | **82 (20)** | **16 (4)** |
| Diarrhea | 21 (5) | 19 (5) | 2 (<1) |
| **Skin and appendages disorders** | **46 (11)** | **45 (11)** | **1 (<1)** |
| Rash | 25 (6) | 24 (6) | 1 (<1) |
| **Psychiatric disorders** | **44 (11)** | **38 (9)** | **6 (1)** |
| Confusion | 24 (6) | 21 (5) | 3 (1) |

**Table 32:** Drug-Related (as Determined by the Investigator) Grade 3 and 4 Nonhematologic Adverse Events in ≥2% Patients by Body System, AML Studies

| | Tipifarnib 600 mg b.i.d. (N=409) | | |
|---|---|---|---|
| | Grade 3+4 n (%) | Grade 3 n (%) | Grade 4 n (%) |
| **Total no. with nonhematologic drug-related grade 3 or 4 AE** | **187 (46)** | **150 (37)** | **37 (9)** |
| **Body as a whole – general disorders** | **58 (14)** | **50 (12)** | **8 (2)** |
| Fatigue | 21 (5) | 18 (4) | 3 (1) |
| **Gastrointestinal system disorders** | **50 (12)** | **44 (11)** | **6 (1)** |
| Diarrhea | 14 (3) | 13 (3) | 1 (<1) |
| **Resistance mechanism disorders** | **32 (8)** | **21 (5)** | **11 (3)** |
| Sepsis | 11 (3) | 2 (<1) | 9 (2) |
| Infection bacterial | 14 (3) | 14 (3) | 0 |
| **Metabolic and nutritional disorders** | **31 (8)** | **26 (6)** | **5 (1)** |
| Hypokalemia | 16 (4) | 15 (4) | 1 (<1) |
| Creatinine blood increased | 8 (2) | 8 (2) | 0 |
| **Skin and appendages disorders** | **28 (7)** | **27 (7)** | **1 (<1)** |
| Rash | 19 (5) | 18 (4) | 1 (<1) |
| **Central & peripheral nervous system disorder** | **25 (6)** | **24 (6)** | **1 (<1)** |
| Ataxia | 7 (2) | 7 (2) | 0 |
| **Psychiatric disorders** | **18 (4)** | **14 (3)** | **4 (1)** |
| Confusion | 10 (2) | 8 (2) | 2 (<1) |
| **Respiratory system disorders** | **17 (4)** | **15 (4)** | **2 (<1)** |
| Pneumonia | 12 (3) | 11 (3) | 1 (<1) |
| **Liver and biliary system disorders** | **14 (3)** | **11 (3)** | **3 (1)** |
| Bilirubinemia | 10 (2) | 9 (2) | 1 (<1) |

**Clinical Biochemistry Evaluations**

In contrast to the hematologic laboratory abnormalities, few patients entered the AML studies with grade 3 or 4 biochemical abnormalities, consistent with eligibility criteria. Grade 3 baseline laboratory values were noted for hypokalemia, hyponatremia, and total bilirubin (**Table 33**).

Except for hypokalemia, few patients developed a grade 4 biochemical laboratory abnormality. During the study, grade 3 and grade 4 hypokalemia were recorded for 81 and 31 patients, respectively. Approximately 25% (n=89) of the 355 patients with normal baseline potassium concentrations developed grade 3 or 4 hypokalemia during treatment. Severe hepatic impairment (i.e., grade 3 or 4 total bilirubin) was observed in 8% of patients (29/345), with a higher proportion in the heavily pretreated population of INT-17 and frequently associated with fungal infections, febrile neutropenia, multiple organ failure, and sepsis. Of these 29 patients, 23 (79%) had normal total bilirubin at baseline. Other grade 3 biochemical laboratory abnormalities that were frequently reported were hyponatremia and elevated creatinine concentration.

**Table 33:** Nonhematologic Laboratory Analytes: Shift in Value From Baseline to Worst Grade During Treatment, AML Studies

| Laboratory Analyte<br>Baseline Tox Grade | Tipifarnib 600 mg b.i.d.<br>(N=409)<br>Worst grade during treatment<br>n (%) | | | | | |
|---|---|---|---|---|---|---|
| | Total | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| **ALT (SGPT)** | **344 (84)** | **205** | **102** | **27** | **8** | **2** |
| 0 | 249 (61) | 172 | 62 | 11 | 2 | 2 |
| 1 | 86 (21) | 33 | 37 | 13 | 3 | 0 |
| 2 | 9 (2) | 0 | 3 | 3 | 3 | 0 |
| **AST (SGOT)** | **346 (85)** | **216** | **101** | **24** | **3** | **2** |
| 0 | 283 (69) | 200 | 68 | 13 | 0 | 2 |
| 1 | 60 (15) | 16 | 32 | 9 | 3 | 0 |
| 2 | 3 (1) | 0 | 1 | 2 | 0 | 0 |
| **Bicarbonate** | **154 (38)** | **73** | **71** | **9** | **1** | **0** |
| 0 | 135 (33) | 69 | 60 | 5 | 1 | 0 |
| 1 | 18 (4) | 3 | 11 | 4 | 0 | 0 |
| 2 | 1 (<1) | 1 | 0 | 0 | 0 | 0 |
| **Creatinine** | **395 (97)** | **193** | **98** | **89** | **15** | **0** |
| 0 | 344 (84) | 187 | 82 | 65 | 10 | 0 |
| 1 | 47 (11) | 6 | 16 | 21 | 4 | 0 |
| 2 | 4 (1) | 0 | 0 | 3 | 1 | 0 |
| **Hyperkalemia** | **397 (97)** | **365** | **22** | **4** | **4** | **2** |
| 0 | 388 (95) | 362 | 18 | 2 | 4 | 2 |
| 1 | 8 (2) | 3 | 3 | 2 | 0 | 0 |
| 2 | 1 (<1) | 0 | 1 | 0 | 0 | 0 |
| **Hypernatremia** | **395 (97)** | **354** | **32** | **4** | **2** | **3** |
| 0 | 389 (95) | 351 | 29 | 4 | 2 | 3 |
| 1 | 4 (1) | 3 | 1 | 0 | 0 | 0 |
| 2 | 2 (<1) | 0 | 2 | 0 | 0 | 0 |
| **Hypokalemia** | **397 (97)** | **138** | **147** | **0** | **81** | **31** |
| 0 | 355 (87) | 132 | 134 | 0 | 66 | 23 |
| 1 | 35 (9) | 6 | 12 | 0 | 13 | 4 |
| 3 | 7 (2) | 0 | 1 | 0 | 2 | 4 |
| **Hyponatremia** | **395 (97)** | **207** | **147** | **0** | **40** | **1** |
| 0 | 349 (85) | 202 | 121 | 0 | 26 | 0 |
| 1 | 42 (10) | 5 | 26 | 0 | 10 | 1 |
| 3 | 4 (1) | 0 | 0 | 0 | 4 | 0 |
| **Total bilirubin** | **345 (84)** | **222** | **53** | **41** | **27** | **2** |
| 0 | 316 (77) | 215 | 45 | 33 | 21 | 2 |
| 1 | 19 (5) | 6 | 7 | 4 | 2 | 0 |
| 2 | 9 (2) | 1 | 0 | 4 | 4 | 0 |
| 3 | 1 (<1) | 0 | 1 | 0 | 0 | 0 |

#### *6.4.2.4. Deaths*

Disease progression was the most common cause of death in CTEP-20 (**Table 34**). The proportion of adverse events leading to death was higher in the INT-17 study (relapsed/refractory population), which may be explained by the more precarious status of these heavily pretreated patients. Infections were the leading cause of death due to adverse events in both studies. However, the incidence of early mortality (within 28 days of first dose) related to adverse events was relatively low (8%) (**Table 27**). No aplastic death was documented in either study.

**Table 34:** Deaths in ≥2% of Patients in Either Study, AML Studies

| | Tipifarnib 600 mg b.i.d. | | |
|---|---|---|---|
| Cause of death | CTEP-20 (N=157) n (%) | INT-17 (N=252) n (%) | Total (N=409) n (%) |
| **Total n (%) who died**[a] | **45 (29)** | **122 (48)** | **167 (41)** |
| **Disease progression** | **31 (20)** | **61 (24)** | **92 (22)** |
| **Consequence of adverse event(s)** | **11 (7)** | **61 (24)** | **72 (18)** |
| Drug-related AE | 1 (1) | 16 (6) | 17 (4) |
| **Adverse event (WHO preferred term)**[b] | | | |
| Sepsis | 3 (2) | 20 (8) | 23 (6) |
| Pneumonia | 2 (1) | 16 (6) | 18 (4) |
| Cerebral hemorrhage | — | 6 (2) | 6 (1) |
| Infection fungal | 4 (3) | 1 (<1) | 5 (1) |
| Multiple organ failure | 1 (1) | 4 (2) | 5 (1) |
| Cardiac failure | 3 (2) | 1 (<1) | 4 (1) |

[a] Includes deaths during treatment or within 30 days after last dose (for CTEP-20, treatment termination date was used instead of last dose date).
[b] Some patients had more than one adverse event that resulted in death.

In the elderly patient population with leukemia, the causality of deaths on study is difficult to determine due to the nature of the disease, underlying comorbidities, and disease treatment. The treating physician (investigator) is in the best position to determine the relationship of the observed deaths to study drug treatment. Therefore, CTEP and J&JPRD relied upon the investigator assessment of causality.

In Study CTEP-20, one patient (100336) had an adverse event considered drug related (by the investigator) that resulted in death. This 80-year-old male had AML arising from prior MDS and an unfavorable karyotype. His medical history included bronchiolitis obliterans with pneumonia, interstitial pneumonitis, coronary artery bypass surgery, and nephrolithiasis. Clinically relevant concomitant disorders included coronary artery disease. Complete response was documented on Study Day 33. On Study Day 60, the patient was hospitalized for a grade 3 *Aspergillus* infection of the sinus and was treated with antifungals and antibiotics. On Study Day 65, the hospitalization was prolonged due to grade 4 neutropenia. The following day (Study Day 66), *Aspergillus* pneumonia was diagnosed. On Study Day 67, the patient died due to the neutropenic fungal sepsis (absolute neutrophil count = 11 ($10^9$) giga/L on Day 66). The investigator considered both events to be drug related.

#### *6.4.2.5. Serious Adverse Events and Hospitalizations*

The incidence of drug-related serious adverse events was similar in INT-17 and CTEP-20 (38% vs 41%). The most frequent serious nonhematologic adverse events were fever, pneumonia, sepsis, bacterial infection, fatigue, and elevated serum creatinine concentrations.

In both studies, most patients required hospitalization (**Table 35**). The median duration of hospitalization, however, represented 28% or less of the total study time (median: 18 days). Furthermore, complications related to tipifarnib accounted for approximately one-third of the total hospitalization burden. Hence, the attributes of tipifarnib allowed outpatient treatment in the majority of patients. In CTEP-20, patients were at first routinely hospitalized for observation when they started protocol treatment. With increasing investigator experience, the need for in-patient administration and monitoring was determined to be unnecessary.

**Table 35:** Hospitalizations, AML Studies

| | Tipifarnib 600 mg b.i.d. | | |
|---|---|---|---|
| | CTEP-20 (N=157) | INT-17 (N=252) | Total (N=409) |
| **Hospitalizations, n (%)** | | | |
| No. of patients hospitalized | 95 | 207 | 302 |
| No. of hospitalizations, n (%) | | | |
| 1 | 50 (32) | 105 (42) | 155 (38) |
| 2 | 33 (21) | 68 (27) | 101 (25) |
| ≥3 | 12 (8) | 34 (13) | 46 (11) |
| **Duration of hospitalization, days** | | | |
| Median | 14.0 | 20.0 | 18.0 |
| Range | 2-73 | 1-101 | 1-101 |
| **Percentage of hospitalization**[a] | | | |
| Mean (SD) | 19.20 (17.37) | 32.81 (23.745) | 28.53 (22.808) |
| Median | 13.2 | 28.2 | 22.0 |
| Range | 1.6-98.3 | 0.8-100 | 0.8-100 |
| **Reason for hospitalization, n (%)**[b] | | | |
| AE related to disease | 42 (27) | 113 (45) | 155 (38) |
| AE related to tipifarnib | 57 (36) | 58 (23) | 115 (28) |
| Transfusion | 2 (1) | 58 (23) | 60 (15) |
| AE related to nonstudy medication | 2 (1) | 35 (14) | 37 (9) |
| Pain relief/symptom control | 0 | 37 (15) | 37 (9) |
| Chemotherapy | 3 (2) | 18 (7) | 21 (5) |
| Radiotherapy | 0 | 1 (<1) | 1 (<1) |
| Other reason | 20 (13) | 53 (21) | 73 (18) |
| Unknown | 0 | 1 (<1) | 1 (<1) |

[a] Time spent in the hospital calculated as a percentage of total study duration.
[b] Some patients had more than one reason for hospitalization.

### 6.4.2.6. Adverse Events Leading to Permanent Discontinuation

Adverse events led to the permanent discontinuation of tipifarnib in 24% of AML patients (**Table 36**). Thrombocytopenia, skin rash, sepsis, elevated serum creatinine, pneumonia, and neuropathy were the most common causes.

**Table 36:** Permanent Discontinuation Due to Adverse Events in ≥1% of Patients, AML Studies

| | Tipifarnib 600 mg b.i.d. | | |
|---|---|---|---|
| | CTEP-20 (N=157) n (%) | INT-17 (N=252) n (%) | Total (N=409) n (%) |
| **Total n (%) with AE as main discontinuation reason** | **26 (17)** | **74 (29)** | **100 (24)** |
| **Nonhematologic** | | | |
| **Respiratory system disorders** | **1 (1)** | **15 (6)** | **16 (4)** |
| Pneumonia | — | 7 (3) | 7 (2) |
| Respiratory insufficiency | — | 4 (2) | 4 (1) |
| **Metabolic and nutritional disorders** | **7 (4)** | **8 (3)** | **15 (4)** |
| Serum creatinine increased | 6 (4) | 8 (3) | 10 (2) |
| Dehydration | 1 (1) | 4 (2) | 4 (1) |
| **Resistance mechanism disorders** | **1 (1)** | **14 (6)** | **15 (4)** |
| Sepsis | — | 11 (4) | 11 (3) |
| **Body as a whole – general disorders** | **2 (1)** | **10 (4)** | **12 (3)** |
| Fatigue | 1 (1) | 3 (1) | 4 (1) |
| Fever | 1 (1) | 2 (1) | 3 (1) |
| **Central & peripheral nervous system disorders** | **3 (2)** | **9 (4)** | **12 (3)** |
| Neuropathy | — | 6 (2) | 6 (2) |
| **Skin and appendages disorders** | **6 (4)** | **6 (2)** | **12 (3)** |
| Rash | 5 (3) | 6 (2) | 11 (3) |
| **Gastrointestinal system disorders** | **4 (3)** | **7 (3)** | **11 (3)** |
| Diarrhea | 1 (1) | 2 (1) | 3 (1) |
| Nausea | — | 2 (1) | 3 (1) |
| Vomiting | — | 3 (1) | 3 (1) |
| **Psychiatric disorders** | **3 (2)** | **7 (3)** | **10 (2)** |
| Confusion | 2 (1) | 3 (1) | 5 (1) |
| Somnolence | — | 4 (2) | 4 (1) |
| **Liver and biliary system disorders** | **2 (1)** | **5 (2)** | **7 (2)** |
| Bilirubinemia | 1 (1) | 3 (1) | 4 (1) |
| **Vascular (extracardiac) disorders** | — | **6 (2)** | **6 (1)** |
| Cerebral hemorrhage | — | 3 (1) | 3 (1) |
| **Hematologic** | | | |
| **Platelet, bleeding & clotting disorders** | **1 (1)** | **12 (5)** | **13 (3)** |
| Thrombocytopenia | 1 (1) | 12 (5) | 13 (3) |
| **White cell and RES disorders** | **1 (1)** | **15 (6)** | **16 (4)** |
| Neutropenia | — | 6 (2) | 6 (1) |
| Pancytopenia | — | 4 (2) | 4 (1) |
| Leukopenia | — | 3 (1) | 3 (1) |
| Neutropenia febrile | 1 (1) | 2 (1) | 3 (1) |

### 6.4.2.7. Adverse Events Leading to Dose Modification

In CTEP-20, 47 (35%) elderly patients with poor-risk AML had an adverse event that led to dose reduction during the study (**Table 37**). The adverse event was considered drug related for 35 subjects (26%). The most common drug-related adverse events leading to dose reduction were febrile neutropenia (4%), ataxia (4%), and increased serum creatinine (3%). Fifty-six (41%) patients with elderly poor-risk AML had an adverse event that led to temporary interruption of tipifarnib. The adverse event was considered drug related for 45 patients (33%). The most common drug-related adverse events leading to temporary

interruption of tipifarnib were neutropenia (6%), increased blood creatinine (5%), nausea (4%), febrile neutropenia (4%), and rash (4%).

**Table 37:** Drug-Related Adverse Events Leading to Dose Reduction
(Study R115777-CTEP-20: Elderly Poor-Risk AML Analysis Set)

| | Tipifarnib 600 mg b.i.d. (N=136) | |
|---|---|---|
| WHO Preferred Term | All n (%) | Drug Related n (%) |
| **Total no. patients with AE[a]** | **47 (35)** | **35 (26)** |
| Neutropenia febrile | 9 (7) | 6 (4) |
| Ataxia | 5 (4) | 5 (4) |
| Creatinine blood increased | 6 (4) | 4 (3) |
| Confusion | 6 (4) | 3 (2) |
| Diarrhea | 4 (3) | 3 (2) |
| Neutropenia | 4 (3) | 3 (2) |
| Pancreas enzymes increased | 3 (2) | 3 (2) |
| Rash | 5 (4) | 3 (2) |
| Renal function abnormal | 3 (2) | 3 (2) |
| Amnesia | 2 (1) | 2 (1) |
| Bilirubinemia | 3 (2) | 2 (1) |
| Fatigue | 2 (1) | 2 (1) |
| Hypotension postural | 2 (1) | 2 (1) |
| Infection bacterial | 3 (2) | 2 (1) |
| Tremor | 2 (1) | 2 (1) |
| Vomiting | 2 (1) | 2 (1) |
| Abdominal pain | 1 (1) | 1 (1) |
| Anxiety | 1 (1) | 1 (1) |
| Blood urea nitrogen increased | 1 (1) | 1 (1) |
| Dizziness | 1 (1) | 1 (1) |
| Hypokalemia | 1 (1) | 1 (1) |
| Hypotension | 1 (1) | 1 (1) |
| Nausea | 1 (1) | 1 (1) |
| Pancytopenia | 2 (1) | 1 (1) |
| Polyuria | 1 (1) | 1 (1) |
| Syncope | 1 (1) | 1 (1) |
| Thrombocytopenia | 1 (1) | 1 (1) |

[a] Some patients had more than 1 AE or drug-related AE leading to dose reduction.

In INT-17, 81 (32%) patients had a dose modification, including dose escalation. An adverse event led to dose reduction, interruption of treatment, or both for 62 patients. Of these 62 patients, 21 had a dose modification for hematologic adverse events, 22 for nonhematologic adverse events, and 19 for both. Nonhematologic adverse events that led most frequently to dose modification included infection (e.g., sepsis, pneumonia) along with gastrointestinal and CNS events. Adverse events leading only to dose reductions were not specifically identified in INT-17.

### 6.4.3. Summary of Myelosuppression

#### *6.4.3.1. Overview*

Myelosuppression was the most frequent toxicity documented in all studies with tipifarnib. The causal interpretation of myelosuppression is difficult in AML, as the disease itself is frequently associated with profound cytopenias. Prophylactic antibiotics were administered according to each institution's practice.

Dose-related myelosuppression was documented in solid tumor studies. The incidence, nadir, and duration of myelosuppression appeared dose related, with no evidence of cumulative toxicity upon prolonged administration of tipifarnib (Sections 6.4.3.2 and 6.4.3.3).

The selective distribution of tipifarnib in the bone marrow may explain the dose-related incidence of myelosuppression, and is consistent with the antileukemic activity observed in the AML studies. However, even at the highest doses, the myelosuppressive properties of tipifarnib did not reach myeloablative proportions. In this respect, no death with bone marrow aplasia has been reported to date in either the solid tumor or AML studies.

### *6.4.3.2. Neutropenia and Infection*

Grade 3 or 4 neutropenia, present at baseline in 63% of AML patients in the CTEP-20 and INT-17 studies, was documented during tipifarnib therapy in 85% (grade 4 in 77%) of all patients for whom data were available (**Table 38**). In patients with a normal neutrophil count (grade 0) at baseline, 57% of patients developed grade 3 or 4 neutropenia during tipifarnib treatment.

**Table 38:** Neutropenia, AML Studies

| | Tipifarnib 600 mg b.i.d. | | |
|---|---|---|---|
| | CTEP-20 (N=157) n (%) | INT-17 (N=252) n (%) | Total (N=409) n (%) |
| **Neutropenia Based on Laboratory Test Results** | | | |
| *Baseline Laboratory Test Results* | | | |
| No. with lab test data | 152 | 248 | 400 |
| No. with grade 3 result | 32 | 55 | 87 |
| No. with grade 4 result | 61 | 102 | 163 |
| *During Treatment Result: Worst Grade* | | | |
| No. with lab test result | 155 | 240 | 395 |
| No. with grade 3 result | 10 | 23 | 33 |
| No. with grade 4 result | 119 | 184 | 303 |
| *Worst Grade During Treatment vs. Baseline Value* | | | |
| No. with grade 3 or 4 on-treatment value/ no. with baseline grade 0 | 18 / 35 | 32 / 53 | 50 / 88 |
| No. with worsening of ≥2 grades / no. with baseline grade 0 | 23 / 35 | 35 / 53 | 58 / 88 |
| No. with worsening of ≥2 grades / no. with baseline grade 1 | 8 / 11 | 8 / 11 | 16 / 22 |
| No. with worsening of ≥2 grades / no. with baseline grade 2 | 10 / 13 | 21 / 23 | 31 / 36 |
| **Adverse Event Reports of Neutropenia** | | | |
| No. (%) with at least 1 AE | 21 (13) | 50 (20) | 71 (17) |
| No. (%) with grade 3 or 4 AE | 19 (12) | 49 (19) | 68 (17) |
| No. (%) permanently discontinued | — | 6 (2) | 6 (1) |
| No. (%) with SAE | 7 (4) | 16 (6) | 23 (6) |
| No. (%) hospitalized due to SAE | 6 (4) | 14 (6) | 20 (5) |
| No. (%) died due to AE[a] | — | 1 (<1) | 1 (<1) |

[a] Deaths occurring during treatment or within 30 days of the last dose of study medication.

The median time to onset of grade 3 or 4 neutropenia was 15 days, and the median duration was 30 days. The median time to onset was similar in CTEP-20 and INT-17. Of the 26 patients in CTEP-20 with normal or near-normal baseline values for neutrophils (severity grade 0 or 1 at baseline) who developed grade 3 or 4 neutropenia during treatment, 17 patients had documented recovery of grade 2 or better, with a median duration of neutropenia of 29 days. Of the 40 patients in INT-17 who had normal or near-normal baseline

values for neutrophils and developed grade 3 or 4 neutropenia during treatment, 19 had documented recovery of grade 2 or better, with a median duration of neutropenia of 36 days. The longer duration of grade 3 or 4 neutropenia in INT-17 (36 days) than in CTEP-20 (29 days) may reflect compromised bone marrow function from prior chemotherapy treatments.

There was no evidence of cumulative toxicity. The median nadir neutrophil values for Cycles 1, 2, and 3 among AML patients receiving tipifarnib were comparable, ranging from 0.10 to 0.21 giga ($10^9$)/L, as was the relative day of onset of nadir values during each of these cycles.

The incidence of neutropenia reported as an adverse event was 17% (**Table 38**). Neutropenia was rarely treatment limiting. As assessed by the investigator, there was one tipifarnib-related death (100336), due to fungal sepsis, in the elderly poor-risk AML population (CTEP-20). See Section 6.4.2.4 for more details on this patient.

Infections occurred in 57% of AML subjects and were considered drug related in 14% of subjects. The most common infections (≥10% of subjects overall) included pneumonia, sepsis, bacterial infection, and moniliasis. The incidence of pneumonia and sepsis (all grades and relationship to study drug) was somewhat higher for subjects with relapsed or refractory AML (INT-17). Approximately 80% of drug-related infections (n=45/56) were rated as grade 3 or 4.

Myelosuppression was common in patients who achieved a complete remission. Of the 20 patients who achieved a complete response in CTEP-20, 19 (95%) required concomitant antibiotics.

#### *6.4.3.3. Thrombocytopenia and Bleeding Events*

Grade 3 or 4 thrombocytopenia developed in 93% (grade 4 in 45%) of AML patients in the CTEP-20 and INT-17 studies (**Table 39**). Grade 3 or 4 thrombocytopenia was present at baseline in 62% of these patients. In patients with a normal platelet count (grade 0) at baseline, the proportion of patients who developed grade 3 or 4 thrombocytopenia during tipifarnib treatment was 75%.

**Table 39:** Thrombocytopenia, AML Studies

| | Tipifarnib 600 mg b.i.d. | | |
|---|---|---|---|
| | CTEP-20 (N=157) n (%) | INT-17 (N=252) n (%) | Total (N=409) n (%) |
| **Thrombocytopenia Based on Laboratory Test Results** | | | |
| *Baseline Laboratory Test Results* | | | |
| No. with lab test data | 157 | 252 | 409 |
| No. with grade 3 result | 78 | 140 | 218 |
| No. with grade 4 result | 8 | 29 | 37 |
| *During Treatment Result: Worst Grade* | | | |
| No. with lab test result | 155 | 246 | 401 |
| No. with grade 3 result | 87 | 104 | 191 |
| No. with grade 4 result | 51 | 130 | 181 |
| *Worst Grade During Treatment vs. Baseline Value* | | | |
| No. with grade 3 or 4 on-treatment value/ no. with baseline grade 0 | 12 / 17 | 18 / 23 | 30 / 40 |
| No. with worsening of ≥2 grades / no. with baseline grade 0 | 13 / 17 | 19 / 23 | 32 / 40 |
| No. with worsening of ≥2 grades / no. with baseline grade 1 | 20 / 28 | 24 / 27 | 44 / 55 |
| No. with worsening of ≥2 grades / no. with baseline grade 2 | 5 / 25 | 13 / 32 | 18 / 57 |
| **Adverse Event Reports of Thrombocytopenia** | | | |
| No. (%) with at least 1 AE | 29 (18) | 142 (56) | 171 (42) |
| No. (%) with grade 3 or 4 AE | 26 (17) | 134 (53) | 160 (39) |
| No. (%) permanently discontinued | 1 (1) | 12 (5) | 13 (3) |
| No. (%) with SAE | 4 (3) | 21 (8) | 25 (6) |
| No. (%) hospitalized due to SAE | 2 (1) | 19 (8) | 21 (5) |
| No. (%) died due to AE[a] | — | 1 (<1) | 1 (<1) |

[a] Deaths occurring during treatment or within 30 days of the last dose of study medication.

The median time to onset of grade 3 or 4 thrombocytopenia was 15 days, and median duration was 22 days. The median time to onset was the same in CTEP-20 and INT-17. Of the 32 patients in CTEP-20 with a normal or near-normal platelet count at baseline (thrombocytopenia severity grade 0 or 1) who developed grade 3 or 4 thrombocytopenia during treatment, 23 patients had documented recovery of grade 2 or better, with a median duration of thrombocytopenia of 15 days. Of the 42 patients in INT-17 with a normal or near-normal platelet count at baseline who developed grade 3 or 4 thrombocytopenia during treatment, 18 had documented recovery of grade 2 or better, with a median duration of 25 days. The longer median duration of severe thrombocytopenia in these patients in INT-17 (25 days) than in CTEP-20 (15 days) may reflect compromised bone marrow function from prior chemotherapy in INT-17.

There was no evidence of cumulative toxicity, with median nadir platelet values for Cycles 1, 2, and 3 among tipifarnib-treated AML patients being 17.00, 14.80, and 16.00 giga ($10^9$)/L, respectively.

The incidence of thrombocytopenia reported as a clinical adverse event was 42% (**Table 39**).

Fifteen patients (3 newly diagnosed patients in CTEP-20 and 12 relapsed/refractory patients in INT-17) died of bleeding-related events in the AML studies. Of note, one patient with refractory AML died as a result of thrombocytopenia leading to gastrointestinal hemorrhage, considered not drug related by the investigator, and six died from cerebral hemorrhage,

including two (both in Study INT-17) whose deaths were considered drug related by the investigator.

### 6.4.4. Summary of Renal Dysfunction

The frequent concurrent administration of nephrotoxic antibiotics such as aminoglycosides, vancomycin, and amphotericin B, coupled with the high prevalence of abnormal renal function at baseline in elderly patients, may contribute to the incidence of biochemical abnormalities (elevated serum creatinine, hypokalemia) observed in the AML populations treated with tipifarnib.

#### *6.4.4.1. Serum Creatinine and Creatinine Clearance*

Based on laboratory testing, 13% of AML patients presented with abnormal serum creatinine concentrations at baseline. Treatment with tipifarnib was associated with increased creatinine concentrations in 46% of AML patients. Grade 3 or 4 serum creatinine elevations were documented in 4% of the AML patients (**Table 33**).

Creatinine clearance is a more precise indicator of renal function than serum creatinine in elderly populations. In the AML populations reported, creatinine clearance, calculated by the Cockcroft-Gault formula (Cockcroft 1976), decreased as a function of age. Low clearance values (<60 mL/min) were documented at study entry in 10%, 29%, and 54% of patients <65 years, 65 to 74 years, or 75 years, respectively.

Overall, 62% of the AML patients developed a decrease in creatinine clearance to <60 mL/min at least once during treatment, representing a 31.5% decline (mean worst value: 55.5 mL/min; mean worst change from baseline: -28.5 mL/min) (**Table 40**). There was no appreciable difference between the patients in CTEP-20 and those in INT-17. The median time to onset of a 50% decrease in creatinine clearance was 23 days.

**Table 40:** Creatinine Clearance, AML Studies

| | Tipifarnib 600 mg b.i.d. | | |
|---|---|---|---|
| | CTEP-20 (N=157) | INT-17 (N=252) | Total (N=409) |
| **Worst value** | | | |
| N | 151 | 236 | 387 |
| Category, n (%) | | | |
| <60 mL/min | 110 (73) | 130 (55) | 240 (62) |
| 60 – 80 mL/min | 24 (16) | 59 (25) | 83 (21) |
| ≥80 mL/min | 17 (11) | 47 (20) | 64 (17) |
| Mean (SD) | 49.1 (22.54) | 59.7 (33.05) | 55.5 (29.82) |
| Median | 47.2 | 56.7 | 50.1 |
| Range | 13 – 128 | 13 – 317 | 13 – 317 |
| **Worst value from baseline** | | | |
| N | 151 | 234 | 385 |
| Mean (SD) | -24.7 (23.60) | -31.0 (53.08) | -28.5 (44.0) |
| Median | -20.8 | -20.4 | -20.4 |
| Range | -131 – 19 | -730 – 45 | -730 – 45 |
| **Worst % reduction from baseline** | | | |
| N | | | |
| Category, n (%) | 151 | 234 | 385 |
| >75% | 3 (2) | 14 (6) | 17 (4) |
| >50% – 75% | 36 (24) | 41 (18) | 77 (20) |
| >25% – 50% | 46 (30) | 68 (29) | 114 (30) |
| 0% – 25% | 42 (28) | 91 (39) | 133 (35) |
| No decrease | 24 (16) | 20 (9) | 44 (11) |
| Mean (SD) | -31.7 (25.20) | -31.4 (23.84) | -31.5 (24.35) |
| Median | -29.4 | -27.1 | -27.3 |
| Range | -86 – 33 | -94 – 41 | -94 – 41 |

#### *6.4.4.2. Hypokalemia*

Previous exposure of the relapsed/refractory AML population to nephrotoxic agents such as amphotericin, as well as concurrent use of this and other potassium-wasting agents (e.g., diuretics used in the management of cardiovascular disorders) in the elderly AML population, may contribute to the overall incidence of hypokalemia. Of the AML patients with normal potassium concentrations at baseline, 25% experienced grade 3 or 4 hypokalemia during treatment. This occurred more frequently in INT-17 (32%) than in CTEP-20 (16%).

In CTEP-20 and INT-17, no association was found in AML patients between the occurrence of grade 3 or 4 hypokalemia and decreases in creatinine clearance or increase in serum creatinine concentration. Diarrhea and vomiting did not appear to be significant contributing factors. Hypokalemia was not associated with an increased incidence of cardiovascular events.

#### *6.4.4.3. Clinical Adverse Events*

The incidence of nephrotoxicity was 23% in AML patients in the CTEP-20 and INT-17 studies (**Table 41**). Most events were grade 1 or 2 and were primarily reported as increased blood creatinine. There were no significant symptomatic serious adverse events in the genitourinary system. Renal toxicity did not usually lead to treatment discontinuation or death. Four patients (100202, A30127, A30306, and A30317) in the AML studies died due to

renal toxicity. Of these, one patient (100202) in CTEP-20 died as a result of renal insufficiency secondary to generalized fungal sepsis, considered not to be drug related.

**Table 41:** Renal Toxicity Adverse Event Profile, AML Studies

| | Tipifarnib 600 mg b.i.d. (N=409) |
|---|---|
| No. (%) with renal toxicity[a] | 96 (23) |
| No. (%) with grade 3 or 4 renal toxicity | 21 (5) |
| No. (%) with drug-related renal toxicity | 50 (12) |
| No. (%) with serious renal toxicity | 33 (8) |
| No. (%) hospitalized for serious renal toxicity | 29 (7) |
| No. (%) discontinued due to renal toxicity | 11 (3) |
| No. (%) died due to renal toxicity | 4 (1) |

[a] Adverse event grouping.

### 6.4.5. Long-Term Safety

In general, the toxicities induced by tipifarnib occurred early in the course of treatment and were manageable by appropriate dose modifications. Despite the rapid clinical course of AML, exposure to tipifarnib beyond three cycles of treatment occurred but was not associated with evidence of cumulative toxicity, including myelosuppression.

### 6.4.6. Effect of Age

Within the AML populations, the median age of the elderly poor-risk AML patients (CTEP-20) was higher than that of the elderly refractory/relapsed patients (INT-17) (**Table 42**).

**Table 42:** Age Distribution in AML Studies

| Age Group | CTEP-20 N=157 n (%) | INT-17 N=252 n (%) |
|---|---|---|
| <65 years | 9 (6) | 153 (61) |
| 65-74 years | 73 (47) | 80 (32) |
| ≥75 years | 75 (48) | 19 (8) |

Age did not affect treatment duration, but relative dose intensity for patients ≥65 years was lower compared with patients <65 years.

Accounting for differences in prior treatment, advancing age did not appear to negatively impact the overall safety profile of tipifarnib in the AML studies (**Table 43**).

**Table 43:** Safety Profile by Age, AML Studies

| Total n (%) with: | Tipifarnib 600 mg b.i.d. <65 years (N=162) | 65-74 years (N=153) | ≥75 years (N=94) | Total (N=409) |
|---|---|---|---|---|
| **Adverse events (AEs)** | **162 (100)** | **151 (99)** | **93 (99)** | **406 (99)** |
| Drug-related AEs | 27 (78) | 131 (86) | 81 (86) | 339 (83) |
| **Grade 3 or 4 AEs** | **155 (96)** | **137 (90)** | **80 (85)** | **372 (91)** |
| Drug-related grade 3 or 4 AEs | 94 (58) | 101 (66) | 60 (64) | 255 (62) |
| **Serious AEs** | **129 (80)** | **116 (76)** | **65 (69)** | **310 (76)** |
| Drug-related serious AEs | 56 (35) | 59 (39) | 46 (49) | 161 (39) |
| **AE leading to withdrawal** | **60 (37)** | **55 (36)** | **24 (26)** | **139 (34)** |
| Drug-related AE leading to withdrawal | 24 (15) | 32 (21) | 13 (14) | 69 (17) |
| **Deaths with AE as cause of death** | **59 (36)** | **37 (24)** | **15 (16)** | **111 (27)** |
| Drug-related deaths with AE as cause of death | 12 (7) | 7 (5) | 2 (2) | 21 (5) |

Central neurotoxicity (dizziness and confusion) was more frequent in patients ≥75 years of age with AML than in younger patients. Conversely, the incidence of hematologic adverse events was higher in younger patients, possibly reflecting the fact that they made up the majority of the INT-17 AML population, which would be expected to have compromised marrow function secondary to persistent effects of prior chemotherapy treatment.

## 6.5. Safety in Patients With Solid Tumors

### 6.5.1. Safety Population and Extent of Exposure

A total of 605 patients with solid tumors were evaluated for safety, in nine single-agent studies, including 472 patients treated with tipifarnib and 133 who received placebo. Placebo was given as the comparator arm of a double-blind study in advanced colorectal cancer. Most patients (n=386, 82%) were treated at a dose of 300 mg b.i.d. About one-third (n=169, 36%) of tipifarnib-treated patients were 65 years or older. The prevalence of abnormal liver (31%) or renal function (23%) at baseline was high in tipifarnib-treated patients. Patients with colorectal cancer constituted the majority of the solid tumor population (n=402, 66%) (**Table 44**).

**Table 44:** Cancer Diagnosis From 9 Solid Tumor Studies

| | <300 mg b.i.d. (N=25) | 300 mg b.i.d. (N=386) | >300 mg b.i.d. (N=61) | Total Tipifarnib (N=472) |
|---|---|---|---|---|
| Colorectal | 14 (56) | 244 (63) | 10 (16) | 268 (57) |
| Breast | 6 (24) | 70 (18) | 9 (15) | 85 (18) |
| Bladder | 0 | 43 (11) | 0 | 43 (9) |
| Lung | 0 | 4 (1) | 24 (39) | 28 (6) |
| Breast / colorectal | 0 | 1 (<1) | 0 | 1 (<1) |
| Prostate | 0 | 4 (1) | 0 | 4 (1) |
| Other | 5 (20) | 20 (5) | 18 (30) | 43 (9) |

Cyclic dosing regimens of tipifarnib were administered to 394 (83%) patients. Safety information on continuous, uninterrupted administration was derived mainly from the GBR-1 study conducted in patients with breast cancer. Treatment duration of tipifarnib in the solid tumor studies was sufficient (median 44 days) to allow valid comparisons across dose and age ranges. The highest dose administered was 1,300 mg twice daily.

## 6.5.2. Adverse Events

### *6.5.2.1. Overview*

The adverse events observed in the solid tumor studies were similar in nature to those observed in the AML population. The incidence of the most common tipifarnib-related adverse event, myelosuppression, exhibited a dose–dependent relationship. The most frequent nonhematologic adverse events were gastrointestinal events or fatigue. A direct dose–effect relationship was less apparent for most nonhematologic adverse events. The most common adverse events leading to dose adjustment or temporary interruption of tipifarnib administration were myelosuppression and vomiting. Schedule dependence (continuous vs. cyclical administration) was demonstrated for neuropathy. The generally lower doses of tipifarnib administered in these studies were associated with a lower incidence of grade 3 or 4 adverse events compared with the AML studies. The rate of discontinuation for adverse events was similar, however, reflecting the different criteria implemented in the different populations. The most common adverse events leading to permanent discontinuation of tipifarnib affected the hematologic, gastrointestinal, and nervous systems. Most patients (6/8, 75%) who discontinued due to peripheral neuropathy had received continuous tipifarnib treatment. The incidence of nonhematologic grade 4 adverse events (14%) and drug-related deaths (1%) in this heavily pretreated population was low.

Though myelosuppression was the most frequent toxicity documented in all studies with tipifarnib, neutrophil and platelet counts did not drop precipitously nor was there a high incidence of mucositis. In addition, even at the highest doses, the myelosuppressive properties of tipifarnib did not reach myeloablative proportions. In this respect, no death with bone marrow aplasia was documented in either the solid tumor or AML studies.

The adverse event profile of tipifarnib in a composite solid tumor population is summarized in **Table 45**. Comparisons with the incidences reported in the placebo group highlight the relatively modest toxicity burden added by tipifarnib, mostly due to myelosuppression, which did not result in a higher death rate.

**Table 45:** Safety Profile, Solid Tumor Studies

| Total n (%) of patients with: | Placebo (N=133) | Total Tipifarnib (N=472) |
|---|---|---|
| **Adverse events (AEs)** | **117 (88)** | **460 (97)** |
| Drug-related AEs | 55 (41) | 381 (81) |
| **Grade 3 or 4 AEs** | **68 (51)** | **314 (67)** |
| Drug-related grade 3 or 4 AEs | 8 (6) | 200 (42) |
| **Serious AEs** | **36 (27)** | **207 (44)** |
| Drug-related serious AEs | 1 (1) | 90 (19) |
| **AE leading to withdrawal**[a] | **28 (21)** | **151 (32)** |
| Drug-related AE leading to withdrawal[a] | 2 (2) | 94 (20) |
| **Deaths with AE as cause of death** | **10 (8)** | **25 (5)** |
| Drug-related deaths with AE as cause of death | 0 | 4 (1) |

[a] Includes only those events that were recorded as the main reason for treatment termination.

### *6.5.2.2. Hematologic Adverse Events*

Myelosuppression, affecting the myeloid more than the megakaryocytic lineage, was the major tipifarnib-related toxicity identified in the solid tumor studies. A clear dose-effect relationship was observed. Myelosuppression was manageable by dose reduction.

### 6.5.2.3. Nonhematologic Adverse Events

The most common nonhematologic adverse events affected mainly the gastrointestinal and body-as-a-whole systems. Some dose-effect relationships were identified, with the most marked being for central and peripheral nervous system disorders, renal function, infection, and rash.

Most nonhematologic adverse events were grade 1 or 2. The incidence of grade 3 or 4 adverse events was similar in the total tipifarnib group (56%) and the placebo group (50%). The incidence of grade 4, life-threatening, nonhematologic adverse events was low in tipifarnib-treated patients (14%), and again similar to placebo (16%).

### 6.5.2.4. Deaths and Other Serious Adverse Events

Disease progression accounted for the majority of deaths during treatment (**Table 46**). Most deaths due to an adverse event were related to infection. Four deaths were considered treatment-related by the investigator in the solid tumor studies (**Table 45**). The adverse events listed as cause of death in these four subjects were febrile neutropenia; sepsis; leukopenia and sepsis; and leukopenia, neutropenia, and febrile neutropenia.

**Table 46:** Deaths, Solid Tumor Studies

| Cause of death | Placebo (N=133) n (%) | <300 mg b.i.d. (N=25) n (%) | 300 mg b.i.d. (N=386) n (%) | >300 mg b.i.d. (N=61) n (%) | Total Tipifarnib (N=472) n (%) |
|---|---|---|---|---|---|
| **Total no. who died**[a] | 29 (22)[b] | 0 | 58 (15) | 6 (10) | 64 (14) |
| **Disease progression** | **29 (22)** | **0** | **52 (13)** | **3 (5)** | **55 (12)** |
| **Adverse event (WHO preferred term)** | **1 (1)** | **0** | **6 (2)** | **3 (5)** | **9 (2)** |
| Sepsis | 0 | 0 | 2 (1) | 2 (3) | 4 (1) |
| Leukopenia | 0 | 0 | 1 (<1) | 1 (2) | 2 (<1) |
| Neutropenia febrile | 0 | 0 | 1 (<1) | 1 (2) | 2 (<1) |
| Cerebrovascular disorder | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| Embolism pulmonary | 0 | 0 | 0 | 1 (2) | 1 (<1) |
| Hypoxia | 0 | 0 | 0 | 1 (2) | 1 (<1) |
| Neutropenia | 0 | 0 | 0 | 1 (2) | 1 (<1) |
| Pneumonia | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| Renal function abnormal | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| Pulmonary edema | 1 (1) | 0 | 0 | 0 | 0 |

[a] Includes deaths during treatment or within 30 days after last dose of study medication.
[b] One placebo patient had two primary reasons of death listed on the case report form.
Note: Patients may have had more than one adverse event listed as cause of death.

The incidence of hematologic serious adverse events was 13% and the incidence of nonhematologic serious events was 40% in tipifarnib-treated patients. The most frequent (≥5% of patients in total tipifarnib group) serious adverse events were neutropenia, thrombocytopenia, and vomiting. Most occurred at tipifarnib doses of 300 mg twice daily or higher.

# 6.6. Safety Findings of Special Interest in Patients With AML or Solid Tumors

## 6.6.1. Neurotoxicity

Tipifarnib-induced neurotoxicity pertains to both the central and peripheral nervous systems. The onset of CNS toxicity is subacute (days) and appears to be dose related, while severe manifestations of peripheral nervous system toxicity (if seen) are observed following prolonged, uninterrupted administration of tipifarnib. Although tipifarnib appears to penetrate poorly into the brain of rats and dogs, farnesylated proteins play a role in the cellular biology of neurons, through activation of the $PI_3K$/AKT pathway (Virdee 1999), and may underlie the clinical observations summarized in this section.

### *6.6.1.1. Central Nervous System*

Tipifarnib appears to cross the blood-brain barrier in humans as evidenced by the occurrence of subacute CNS symptoms. Confusion-related CNS symptoms were its most common manifestation and was reversible upon discontinuation of treatment. In CTEP-20, 17 (81%) of 21 patients with confusion of grade 2 or higher had symptoms that resolved to grade 1 or better and in INT-17, 18 (46%) of 39 had symptoms that resolved to grade 1 or better. Median time to reversibility of confusion was 8 days in CTEP-20 and 23 days in INT-17. Central nervous system toxicity was a dose-limiting toxicity at 1,200 mg twice daily in the CTEP-1 study. Patients with dose-limiting toxicity immediately discontinued study drug, and all CNS symptoms resolved within 72 hours.

The incidence of CNS symptoms was higher in CTEP-20 (54%) than in INT-17 (38%). The difference included higher rates of confusion (22% vs. 12%), ataxia (11% vs. 3%), and abnormal gait (8% vs. 1%), which may have been influenced by the higher median age of the CTEP-20 population. CNS symptoms were infrequently rated as severe grade 3 or 4 or serious in either AML population.

### *6.6.1.2. Peripheral Neurotoxicity*

Peripheral neurotoxicity was identified as a complication of uninterrupted tipifarnib administration in a Phase 2 breast cancer study (GBR-1) in which tipifarnib was administered at a dose of 300 mg twice daily on a continuous basis without treatment interruption. In that study, 37% of patients developed peripheral sensorimotor neuropathy (grade 3 in 15%). The median time to onset was 86 days, and the median cumulative tipifarnib dose at the time of onset was 47 g. A schedule modification to include a seven-day rest period every four weeks significantly reduced the incidence of peripheral neuropathy (**Table 47**). These results suggest that severe peripheral neurotoxicity is mainly a schedule-dependent phenomenon that can be reduced with cyclic dosing.

**Table 47:** Median Time and Cumulative Tipifarnib Dose to First Reported Occurrence of Drug-Related Peripheral Neurotoxicity in a Phase 2 Breast Cancer Study (Study R115777-GBR-1)

| | First Cohort | | Second Cohort | Total |
|---|---|---|---|---|
| | 400 mg b.i.d. Continuous n=6 | 300 mg b.i.d. Continuous n=35 | 300 mg b.i.d. Cyclic n=35 | N=76 |
| No. events (%) | 1 (17) | 14 (40) | 1 (3) | 16 (21) |
| Median time to neurotoxicity (min;max), days | 173 | 86.5 (45;161) | 141 | 100.5 (45;173) |
| Median cumulative dose up to neurotoxicity (min;max), g | 73.5 | 45.9 (19.8;67.8) | 63.3 | 47.4 (19.8;73.5) |
| No. patients with cumulative dose ≥19.8 g[a] | 5 | 30 | 26 | 61 |
| No. events (%) in this subgroup | 1 (20) | 14 (47) | 1 (3.8) | 16 (26) |
| No patients with cumulative dose ≥47.4 g[b] | 3 | 19 | 12 | 34 |
| No. events (%) in this subgroup | 1 (33) | 9 (47) | 1 (8) | 11 (32) |

[a] Minimum cumulative dose that led to neurotoxicity.
[b] Median cumulative dose that led to neurotoxicity.

In patients with AML receiving tipifarnib, the incidence of peripheral neurotoxicity was 16% and similar between CTEP-20 and INT-17. When considering events that lasted for more than three days, the incidence decreased to 5%. The median time to onset of peripheral neurotoxicity was 53.0 days, and the median cumulative dose at the time of onset was 43.2 g in Study INT-17.

### 6.6.2. Cardiotoxicity

Tipifarnib contains an imidazole functionality; imidazoles are a class of compounds that have been associated with cardiotoxicity, specifically, prolongation of the QT interval. The development of another, chemically unrelated, FTase inhibitor (L-778,123) was discontinued due to cardiac conduction abnormalities (Britten 2001, Brunner 2003, and Caponigro 2003). Therefore, investigations of potential cardiac effects, including extensive electrocardiogram (ECG) monitoring, were implemented from the inception of the tipifarnib development program.

In vitro, tipifarnib has modest cardiovascular effects at therapeutically relevant concentrations. In human embryonic kidney cell lines, tipifarnib (0.3 μM) induced a small, reversible decrease in potassium channel current. Inhibition was distinct at 10 μM. Tipifarnib, however, did not affect electrophysiological parameters in guinea pig papillary muscle or rabbit Purkinje fibers.

Clinically, no consistent changes in ECGs (including effects on QT interval corrected for heart rate [$QT_c$]) were noted as a result of either oral or intravenous tipifarnib administration in the Phase 1 solid tumor studies.

Findings from clinical studies must be interpreted in the context of population age and incidence of comorbidity. In the AML studies, 24% of the patients were enrolled with active cardiovascular disease.

There was a low incidence of grade 3 or 4 heart rate/rhythm disorders in AML patients (6%). Ventricular arrhythmia was reported for one patient (<1%) in the AML studies, was rated as grade 1, and resolved without treatment.

Ischemic cardiac events were uncommon. The incidence of grade 3 or 4 congestive heart failure was 2%, myocardial infarction was <1%, myocardial ischemia was <1%, and angina pectoris was 0% in the AML population. No event was considered to be related to tipifarnib.

According to the Third National Health and Nutrition Examination Survey (NHANES III 2002), the age-adjusted prevalence of coronary heart disease was 7.8% for men and 4.9% for women. Based upon these data, the incidence of cardiotoxicity in the tipifarnib studies appears to be similar to that observed in the general population.

## 6.7. Safety in Other J&JPRD Studies

A total of 171 patients were treated in the two other J&JPRD studies in hematologic indications, including maintenance therapy in elderly patients with AML (INT-21) and patients with high-risk MDS (INT-28). These patients received tipifarnib at planned dosages of 300 mg b.i.d. Ninety-seven cases of serious adverse events were reported (Appendix 2). The most frequently reported serious adverse events were pyrexia (n=19), sepsis (n=11), pneumonia (n=10), febrile neutropenia (n=10), and thrombocytopenia (n=10).

Study AML-301 was not yet ongoing at the time of the 1 June 2004 clinical data cutoff, and therefore, is not included in this safety database.

## 6.8. March 2005 Update

Results of the updated (clinical cutoff of 15 November 2004) safety analyses from Study CTEP-20 are similar to those submitted in the original NDA. The overall adverse event profile is similar to that previously reported. Four new, unique adverse events not previously reported were identified; 2 of these events were considered drug related (grade 1 skin discoloration and grade 3 vasculitis allergic). Three additional patients died within 30 days after treatment termination or before subsequent treatment; none of these deaths were considered drug related. Two additional patients had drug-related serious adverse events (delirium, nonprotein nitrogen increased, confusion, and hallucination, and vasculitis allergic), and one additional patient had treatment terminated due to a drug-related adverse event (fatigue). Overall, consideration of the updated data revealed no changes in the safety profile of tipifarnib in CTEP-20 or other J&JPRD studies in hematologic indications (INT-21, INT-28, and AML-301).

# 7. OVERALL BENEFIT/RISK ASSESSMENT

**Background**

AML is typically a rapidly progressive malignancy, and is universally fatal when left untreated (Cervera 1997). Elderly patients with poor-risk AML face a particularly grim prognosis. This results from 1) an increased incidence of refractoriness to standard combination chemotherapy, linked to the presence of unfavorable cytogenetics, pre-existence of MDS, and/or increased MDR-1 gene expression (Jackson 2002) and 2) a high incidence of life-threatening toxicity from standard combination chemotherapy, linked to the advanced age of the population and the frequent occurrence of comorbidities. Thus, the literature indicates that in elderly populations treated with standard combination chemotherapy, the benefits of antileukemic treatment are diminished (Stone 2002, Goldstone 2001, Löwenberg 2001), and the benefits provided are counterbalanced by increased toxicity (leading to frequent and prolonged hospitalization [Stone 2002, DeLima 1996] with drug-induced mortality rates of up to 25% [Stone 2002]). Clearly, elderly patients with AML are not well served by standard combination chemotherapy, have unmet medical need, and will benefit from the availability of additional treatment options. Consistent with this fact, elderly AML patients commonly do not receive standard combination chemotherapy, but rather are offered palliative chemotherapy, supportive care alone, or investigational therapy (Menzin 2002, Goldstone 2001, Vey 2004).

Study CTEP-20, enrolled 171 patients with poor-risk hematologic disorders (AML, CMML, and MDS). Of the 157 AML patients treated, 136 met the definition of elderly poor-risk AML. The median age of the elderly poor-risk population was 75 years, which is representative of the overall AML population. Most patients were symptomatic from AML and/or underlying comorbid conditions at the time of diagnosis. Clinical factors deemed to make the benefit/risk for standard combination chemotherapy unfavorable were noted in 78% of patients (age ≥75 years or organ dysfunction). Additionally, biologic evidence of poor-risk AML other than advanced age (i.e., unfavorable cytogenetics and prior MDS) was present in 41% of patients. Ninety percent of patients had two or more factors associated with poor prognosis. This represents a patient population with poorer prognosis than in most clinical trials.

The dosing regimen of tipifarnib was 600 mg given orally twice daily for 21 days, in 28-day cycles, the recommended dosing regimen identified in the Phase 1 setting (Study CTEP-1 [Karp 2001]). Thus, per protocol, the cyclical rest period was scheduled for seven days; depending on treatment tolerance, this rest period could be extended to a maximum of 42 days. Although the treatment was relatively well tolerated in CTEP-20, the median treatment duration was 46 days (per protocol but greater than the expected 28 days). This observation together with a relative dose intensity of 0.75 and a 25% dose reduction rate in patients who received more than one cycle of treatment, indicate that the proposed dosing regimen may be considered the maximum dose. Serious toxicities, when they occurred, were generally manageable by dose interruption, dose reduction, and supportive care measures.

**Efficacy**

Tipifarnib was the first FTase inhibitor shown to induce complete remissions in AML (Study CTEP-1). In CTEP-20, the CR rate was 15% (95% CI: 9.4-22.0). The baseline diagnosis and responses were subject to independent quality assurance review. CRs were

observed independent of the presence of multiple risk factors. The CRs were durable, with a median duration of 220 days (95% CI: 154-275), exceeding the expected survival of 1 to 3 months typically reported for this population (Menzin 2002).

**Safety**

The safety profile of tipifarnib may be explained in part by its design as a high-affinity inhibitor of a specific enzyme target, farnesyltransferase. The high concentrations of tipifarnib in bone marrow cells may contribute to the relative end-organ specificity of tipifarnib. Determining the causality of hematologic toxicity is difficult in an individual patient with AML, a disease that is usually associated with profound and persistent cytopenias. As expected in an AML population, the majority of patients had evidence of myelosuppression at baseline, and developed increased myelosuppression with study treatment.

The incidence of life-threatening nonhematologic toxicity is low, especially for an elderly population of patients with AML. At the recommended dose level, gastrointestinal, neurologic, renal, and dermatologic toxicities are the most prevalent nonhematologic adverse events. The low rate of grade 4 mucositis (1%) is noteworthy, as mucositis along with neutropenia is a major contributing factor for infectious complications, including septic death, in patients undergoing intensive chemotherapy treatment for AML.

In some patients, tipifarnib caused dose-related central neurotoxicity (typically manifested by confusion), which was reversible and usually not severe in magnitude. Analyses of the incidence of treatment-induced renal dysfunction were compounded by the frequent concurrent administration of nephrotoxic anti-infectives in this patient population. In general, the incidence of severe laboratory abnormalities (e.g., prolonged grade 4 myelosuppression or grade 3 or 4 hyperbilirubinemia) was lower than that typically associated with high-dose standard combination chemotherapy for AML (Anderson 2002).

Consistent with the rapid course of AML, the major reason for treatment termination in the CTEP-20 study was progressive disease. Compared with standard combination chemotherapy, the rate of treatment termination due to drug-related adverse events (10%) is relatively modest.

Most deaths during treatment were related to disease progression, and often attributed to some form of infection. According to the investigators' assessments, there was one tipifarnib-related death in CTEP-20. This patient died from neutropenic fungal sepsis. Early mortality (within 28 days after first dose of study medication) related to adverse events was relatively low (8%) for the AML population, which is better than the treatment toxicity profile generally observed with standard combination chemotherapy regimens in elderly patients.

The attributes of tipifarnib allowed outpatient treatment for 40% of patients in the CTEP-20 study. Approximately 38% of patients required hospitalization for complications related to tipifarnib. Transfusions were an infrequent cause of hospitalization. The median duration of hospitalization in CTEP-20 for elderly patients with poor-risk AML was short (15 days) and represented 14% of the total time spent in the study. This is an improvement over the usual experience with standard combination therapy (a nearly 100% hospitalization rate with

induction chemotherapy, with up to 50% of survival time spent in a hospital [Stone 2002, DeLima 1996, Hernandez-Boluda 1998, Ferrara 1998; Manoharan 2002]).

**Conclusions**

Tipifarnib is a novel targeted outpatient treatment with demonstrated antileukemic activity. In the patient population for which tipifarnib would be indicated, benefit/risk considerations weigh against the use of more standard combination chemotherapy. Thus, oral therapy with tipifarnib provides a valuable additional treatment option for elderly patients with poor-risk AML (patients 65-74 years of age with prior MDS or patients ≥75 years of age), a patient group that currently has limited treatment options. The benefit-to-risk ratio of oral tipifarnib treatment in newly diagnosed poor-risk elderly AML patients who are not optimal candidates to receive standard combination chemotherapy is supported by a CR rate of 15%. This CR rate is associated with a potential for prolonged survival (this is in the process of being evaluated in the ongoing confirmatory study, AML-301), with a low rate of treatment-related death. Other evidence of antileukemic activity (including PR, hematologic improvement, or leukemia-free survival) is observed in additional patients, although the relationship of these lesser degrees of response to survival and to other patient benefits is less well known. Tipifarnib therapy administered at a starting dose of 600 mg twice daily for 21 days in 28-day cycles in the outpatient setting also results in low rates of relatively short hospitalizations. Elderly patients with AML, for whom benefit/risk considerations with standard combination chemotherapy are marginal or unfavorable, can thus utilize tipifarnib, with anticipation of meaningful antileukemic activity and an acceptable safety/toxicity profile.

In conclusion, tipifarnib has demonstrated substantial activity with an acceptable safety profile in a unique patient population not previously represented in most clinical studies. Tipifarnib represents a new therapeutic option for this group of patients.

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# APPENDICES

## **Appendix 1:** List of Abbreviations

| | |
|---|---|
| AE | adverse event |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| AUC | area under the plasma concentration-time curve |
| $AUC_{12h}$ | area under the plasma concentration-time curve from time zero to 12 hours after administration of study medication |
| b.i.d. | twice daily |
| CI | confidence interval |
| $C_{max}$ | maximum concentration |
| CMML | chronic myelomonocytic leukemia |
| CNS | central nervous system |
| CR | complete response |
| CRADA | Collaborative Research and Development Agreement |
| CRp | complete response with incomplete platelet recovery |
| CTEP | Cancer Therapy Evaluation Program |
| CYP | cytochrome P450 |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| FAB | French-American-British Cooperative Group |
| FDA | U.S. Food and Drug Administration |
| FTase | farnesyltransferase |
| HI | hematologic improvement |
| $IC_{50}$ | concentration resulting in 50% of maximum inhibition |
| J&JPRD | Johnson & Johnson Pharmaceutical Research & Development, L.L.C. |
| KPS | Karnofsky performance score |
| MDS | myelodysplastic syndrome |
| MTD | maximum tolerated dose |
| NCCN | National Cancer Centers Network |
| NCI | National Cancer Institute |
| NCI CTC v.2 | National Cancer Institute Common Toxicity Criteria version 2.0 |
| NDA | New Drug Application |
| NHANES | National Health and Nutrition Examination Survey |
| NOS | not otherwise specified |
| Obs | observation |
| ODAC | Oncologic Drugs Advisory Committee |
| PD | progressive disease |
| $PI_3K$ | phosphatidyl inositol-3 kinase |

## **Appendix 1:** List of Abbreviations

| | |
|---|---|
| PR | partial response |
| $QT_c$ | QT interval corrected for heart rate |
| RES | reticuloendothelial system |
| SAE | serious adverse event |
| SD | standard deviation or stable disease |
| SPA | Special Protocol Assessment |
| $t_{max}$ | time after dosing when the maximum concentration was observed |
| U.S. | United States |
| WBC | white blood cell |
| WHO | World Health Organization |

**Appendix 2:** Serious Adverse Events in Other J&JPRD Hematologic Studies

| **System Organ Class**<br>Adverse Event | Number of cases |
|---|---|
| **Total number of serious cases reported** | **97** |
| **General disorders and administration site conditions** | **34** |
| Pyrexia | 19 |
| Condition aggravated | 7 |
| Disease progression NOS | 3 |
| Asthenia | 2 |
| Fall | 2 |
| Lethargy | 2 |
| Catheter site pain | 1 |
| Chest pain | 1 |
| Death NOS | 1 |
| Hyperpyrexia | 1 |
| Multi-organ failure | 1 |
| **Infections and infestations** | **31** |
| Sepsis NOS | 11 |
| Pneumonia NOS | 10 |
| Bacterial infection NOS | 2 |
| Infection NOS | 2 |
| Urinary tract infection NOS | 2 |
| Bronchopneumonia NOS | 1 |
| Cellulitis | 1 |
| Lobar pneumonia NOS | 1 |
| Lower respiratory tract infection NOS | 1 |
| Otitis media NOS | 1 |
| Pseudomonas infection NOS | 1 |
| Upper respiratory tract Infection NOS | 1 |
| **Blood and lymphatic system disorders** | **29** |
| Febrile neutropenia | 10 |
| Thrombocytopenia | 10 |
| Anaemia NOS | 5 |
| Neutropenia | 4 |
| Pancytopenia | 4 |
| Leukopenia NOS | 3 |
| Anaemia NOS aggravated | 1 |
| Lymphopenia | 1 |
| Normochromic normocytic anaemia | 1 |
| **Gastrointestinal disorders** | **15** |
| Diarrhoea NOS | 3 |
| Nausea | 3 |
| Vomiting NOS | 3 |
| Gastric ulcer | 2 |
| Abdominal pain NOS | 1 |
| Antibiotic associated colitis | 1 |
| Constipation | 1 |
| Gastrointestinal haemorrhage NOS | 1 |
| Inguinal hernia, obstructive | 1 |
| Proctalgia | 1 |
| Rectal haemorrhage | 1 |
| Umbilical hernia NOS | 1 |

(Continued)

**Appendix 2:** Serious Adverse Events in Other J&JPRD Hematologic Studies (Continued)

| System Organ Class<br>Adverse Event | |
|---|---|
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **14** |
| Acute myeloid leukaemia aggravated | 6 |
| Acute myeloid leukaemia NOS | 4 |
| Malignant neoplasm aggravated | 2 |
| Erythroleukaemia | 1 |
| Malignant neoplasm progression | 1 |
| Tumour lysis syndrome | 1 |
| **Nervous system disorders** | **12** |
| Cerebral haemorrhage | 3 |
| Cerebrovascular accident | 3 |
| Dizziness | 1 |
| Encephalopathy | 1 |
| Headache | 1 |
| Hemiparesis | 1 |
| Peripheral neuropathy NOS | 1 |
| Subarachnoid haemorrhage NOS | 1 |
| Syncope | 1 |
| **Cardiac disorders** | **11** |
| Bradycardia NOS | 2 |
| Cardiac arrest | 2 |
| Coronary artery disease NOS | 2 |
| Angina pectoris | 1 |
| Arrhythmia NOS | 1 |
| Atrial fibrillation aggravated | 1 |
| Cardio-respiratory arrest | 1 |
| Coronary artery insufficiency | 1 |
| Myocardial infarction | 1 |
| Myocardial ischaemia | 1 |
| Pericarditis | 1 |
| Pulmonary oedema NOS | 1 |
| **Respiratory, thoracic and mediastinal disorders** | **10** |
| Pneumonitis NOS | 2 |
| Cryptogenic organizing pneumonia | 1 |
| Haemoptysis | 1 |
| Hypoxia | 1 |
| Lung infiltration NOS | 1 |
| Pleural effusion | 1 |
| Pleurisy | 1 |
| Pulmonary embolism | 1 |
| Respiratory arrest | 1 |
| Respiratory failure | 1 |
| **Vascular disorders** | **6** |
| Arterial aneurysm NOS | 1 |
| Haemorrhage NOS | 1 |
| Hypertension NOS | 1 |
| Hypotension NOS | 1 |
| Shock | 1 |
| Thrombosis | 1 |

(Continued)

**Appendix 2:** Serious Adverse Events in Other J&JPRD Hematologic Studies (Continued)

| System Organ Class<br>Adverse Event | |
|---|---|
| **Injury, poisoning and procedural complications** | **5** |
| Hip fracture | 1 |
| Injury NOS | 1 |
| Post procedural pain | 1 |
| Spinal fracture NOS | 1 |
| Therapeutic agent poisoning | 1 |
| **Skin and subcutaneous tissue disorders** | **4** |
| Dermatitis NOS | 1 |
| Pruritus | 1 |
| Rash NOS | 1 |
| Telangiectasia | 1 |
| Urticaria NOS | 1 |
| **Investigations** | **3** |
| Alanine aminotransferase increased | 1 |
| Aspartate aminotransferase increased | 1 |
| Blood creatinine increased | 1 |
| Cardiac enzymes increased | 1 |
| Gamma-glutamyltransferase ncreased | 1 |
| **Musculoskeletal and connective tissue disorders** | **3** |
| Bursitis | 1 |
| Osteoporosis NOS | 1 |
| Rheumatoid arthritis aggravated | 1 |
| **Surgical and medical procedures** | **3** |
| Coronary angioplasty | 1 |
| Hospitalisation | 1 |
| Operation NOS | 1 |
| **Hepatobiliary disorders** | **2** |
| Cholecystitis NOS | 1 |
| Hepatic cirrhosis NOS | 1 |
| **Immune system disorders** | **2** |
| Hypersensitivity NOS | 2 |
| **Metabolism and nutrition disorders** | **2** |
| Dehydration | 1 |
| Hypokalaemia | 1 |
| **Psychiatric disorders** | **2** |
| Delirium | 1 |
| Disorientation | 1 |
| **Ear and labyrinth disorders** | **1** |
| Hearing impaired | 1 |
| **Renal and urinary disorders** | **1** |
| Nephrolithiasis | 1 |

Serious adverse events were collected from studies R115777-INT-21 and R115777-INT-28 using a clinical cutoff date of 01 June 2004.
Table is ordered by decreasing frequency of total number of cases of serious adverse events reported within each System Organ Class, followed by decreasing frequency of serious adverse events within that category.
NOS=Not otherwise specified.