# ODAC Briefing Document for Zarnestra NDA-021824

# by DODP, CDER, FDA

## Table of Contents

## List of Tables

**I. Basic Information**:

| | |
|---|---|
| **Established Name** | Zarnestra |
| **Trade Name** | Tipifarnib |
| **Therapeutic Class** | Inhibitor of farnesyl transferase |
| **Sponsor** | Johnson & Johnson |
| **Designation** | Priority |

**Formulation**

Zarnestra is formulated in film-coated tablets. Each tablet contains an equivalent to 100 mg of tipifarnib base.

**Proposed Dosing Regimen**

Zarnestra is administered orally with food at the dose of 600 mg twice daily for 21 days, followed by a rest period of a minimum of 7 days. The rest period may be extended to a maximum of 42 days depending on toxicity.

**Proposed Indication**

Zarnestra is indicated for the treatment of elderly patients with newly diagnosed poor-risk acute myeloid leukemia.

## II. Background

*FDA approvals for AML*

For approval, a drug must demonstrate substantial evidence of effectiveness in a defined patient population. Generally, FDA has accepted survival and other clinically meaningful outcomes for regular approval of oncology drugs. FDA has accepted endpoints other than survival or irreversible morbidity, such as durable complete response for regular approval in hematological malignancies. This has been the case since durable remissions are associated with reduced morbidity and mortality in many hematologic malignancies.

In general, regular approvals for leukemia indications have been based on evaluation of complete remissions (CR) and remission duration. For second-line and refractory indications, these endpoints have been evaluated mainly in single arm trials. For first-line indications, evidence of benefit was derived from single arm and randomized trials. Randomized trials were necessary in some settings given the context of evaluating multi-drug regimens in order to provide information regarding isolation of a drug's effect in the context of a combination regimen.

In the case of approvals under subpart H regulations (accelerated approval) , evidence of benefit was derived from single arm trials, with reliance on response rates. With respect to response duration, there was variability in terms of demonstration of durable remissions, and in a few cases, lack of documentation of duration of response/remission.

Focusing on AML specifically, approvals are summarized in Table 1. First-line indications included idarubicin and daunorubicin. Both were regular approvals based on demonstration of durable remissions. In both cases, randomized trials were conducted. In the case of idarubicin, a survival advantage was also demonstrated in two randomized trials.

In the case of gemtuzumab ozogamicin, accelerated approval for patients age 60 or older with CD33+ disease who are not candidates for cytotoxic chemotherapy was based on complete remission in three single arm studies. Although relapse-free survival was evaluated (2.3 months median RFS for age $\geq$60 and 17 months for those age < 60), duration of remission could not be reliably ascertained as 45% of patients who achieved a remission received additional anti-leukemic therapy.

Tretinoin and arsenic trioxide received regular approval for the second-line treatment of patients with acute promyelocytic leukemia. These approvals were based on single arm trials demonstrating significant remission rates.

In addition, 5-azacytidine (Vidaza) recently received regular approved for treatment of all subtypes of MDS, based on a 15% response rate (CR+PR) in a randomized study (n = 191) comparing Vidaza to best supportive care (CALGB 9221). Supportive data was provided by two additional single arm trials. There were a small fraction of AML patients in CALGB 9221 and in the two single arm trials conducted. Response rates for these patient subgroups are summarized in Table 1.

**Table 1: Approvals for AML and MDS**

| Drug | Indication | Trial Design | Benefit |
|---|---|---|---|
| Idarubicin | Adult AML M1-M7 in combination with other drugs (first line) | 4 randomized trials in combination with cytarabine, compared to daunorubicin/cytarabine N = 823 | CR rates of 67-78% versus 55-58% for dauno<br>Survival advantage in 2 studies |
| Daunorubicin | Remission induction in adult ANLL | Single arm and randomized | 40-50% CR rate as single agent and 53%-65% CR rate with Ara-C |
| Gemtuzumab ozogamicin (Mylotarg) | 2nd line AML, 60 yrs or older, CD33+, not candidates for cytotoxics | 3 single arm studies; total N= 142 | CR = 16%<br>CR + CRp = 30% |
| Tretinoin | APL, 2nd line | Single arm study (MSKCC N = 35) and two NCI cohorts (total 94 relapsed and 52 de novo patients) | MSKCC 73-80% CR rate<br>NCI Cohorts 36-68% CR rates |
| Arsenic Trioxide | APL, 2nd line | Single arm study (N = 40) | CR = 70% |
| 5-Azacytidine | MDS (clinical study included some AML patients) | Randomized trial of BSC vs BSC+ vidaza (N=191)<br><br>Two single arm trials in RAEB, RAEB-T, CMMoL or AML (N = 72 and N = 48) | Randomized study results:<br>Overall CR+PR = 16% versus 0% ; transfusion independence<br>AML subgroup N = 10 in vidaza arm with 12.5% CR rate<br><br>Single arm study results:<br>Overall CR+PR = 14%<br>Overall CR+PR = 19%<br>AML subgroups N=17 and N=1, combined CR rate = 18% |

*Standard AML 1st line treatment and elderly poor-risk AML*

Patients with newly diagnosed AML, if not treated, will progress rapidly to a fatal outcome. The treatments for AML are designed to be sufficiently aggressive to achieve complete remission because partial remission offers no substantial survival benefit. The goal of remission induction therapy in AML is to reduce the leukemia burden to a level undetectable by standard morphologic techniques. For almost two decades, the standard remission induction for AML has been a combination of seven days of cytarabine at 100-200 mg/m$^2$ daily with three days of daunorubicin at 60 mg/m$^2$ daily (7/3 regimen). In patients who achieved complete remission, consolidation therapy is given. Salvage therapies are reserved for the time of relapse. With this 7/3 combination therapy, complete remission can be expected in approximately 60% to 75% of adult patients. Recent studies designed to improve AML induction therapy have involved changes in the higher dose of cytarabine, alternatives to the use of daunorubicin (idarubicin or mitoxantrone), the addition of other chemotherapy agents (etoposide) to the combination, and use of hematopoietic growth factors. The results of these studies did not suggest significant clinical benefit and have changed little in standard induction therapy.

Elderly patients with AML present a unique clinical entity. The efficacy of therapy in elderly patients with newly diagnosed AML is limited by a higher incidence of intrinsic resistance to chemotherapy and a reduced ability to tolerate both antileukemic therapy itself and the associated supportive care (e.g., nephrotoxic anti-infective therapy). Existing data indicate that patients older than 60 years of age who have a good performance status and meet the medical criteria of adequate organ function are usually offered standard induction therapy and have an overall probability of complete remission of 50%. Other clinical studies suggest that lowering the dose of daunorubicin from 60 mg/m$^2$ to either 45 or 30 mg/m$^2$ for patients age 60 or older would diminish the incidence of severe toxicity and toxic death. This decrease in toxicity more than overcomes any decrease in the antileukemic effects from the attenuated dose of anthracycline, as estimated by a 30-50% decrease in treatment efficacy.

A high rate of early treatment-related mortality is a major contributor to the lower survival rates observed in elderly patients with poor-risk AML. Reduced tolerability and increased risk factors to induction chemotherapy, both related to increasing age, represent a multifactorial risk/benefit outcome, affected by duration and severity of treatment-induced myelosuppression, gastrointestinal mucositis, baseline organ dysfunction or co-existing medical conditions leading to organ malfunction, poor performance status and pre-malignant conditions. Treatment-related mortality in elderly patients with poor-risk AML may be as high as 25%. In a study of patients at least 80 years of age, the mortality rate at 1 month was 48%. As a result, elderly patients with poor-risk AML often are offered palliative treatments or supportive care alone. For such patients, the benefit-risk ratio of conventional cytotoxic chemotherapy was expected to be low; and they were not usually considered as optimal candidates to receive standard induction chemotherapy. Retrospective analysis on 2657 AML patients whose age is 65 or older by Menzin et al., indicated that only 30% of them received chemotherapy, and there is an inverse relationship between age and likelihood of receiving induction or palliative chemotherapy.

Zarnestra, a farnesyl treansferase inhibitor, has been tested in clinical studies with the aim of developing induction regimens that might result in less toxicity without a sacrifice in antileukemic effects.

## III. Summary of Studies Submitted:

There were 11 studies submitted in the Zarnestra NDA. All 11 studies are relevant to safety and dose finding (Table 2). The studies relevant to the Zarnestra efficacy in AML are summarized in Table 3. The population most relevant to Zarnestra's proposed indication, induction therapy in elderly patients with untreated poor-risk AML, is a subgroup of subjects in study CTEP-20 (79% of enrollment). The studies INT-17 (refractory and relapsed AML) and CTEP-1 (dose escalation in hematological malignancy) are less relevant to the proposed indication.

**Table 2: Safety Studies**

| Clinical Study ID | Evaluable Subjects[a] | Study Design and Dosing Regimen |
|---|---|---|
| CTEP-20 | 157[b]/171 | Single arm, open label in untreated AML. Oral 600 mg twice daily (b. i. d.) for 21 days of each 28- day cycle |
| INT- 17 | 252 | Single arm, open label in refractory and relapsed AML, Oral 600 mg b. i. d. for 21 days of each 28- day cycle, with dose escalations to 900 mg b. i. d. |
| USA- 1 | 27 | Dose escalation, single-Agent advanced solid tumor, 25 to 850 mg b. i. d. oral solution; 500 to 1,300 mg b. i. d. oral beaded capsules for 5 days followed by at least 7 days of rest |
| USA-3 | 34 | Dose finding in advanced cancer, Oral 100 to 850 mg b. i. d. for the 1st 21 days of each 28-day cycle |
| BEL-2 | 28 | Single arm study in advanced cancer , Oral 50 mg b. i. d. for 3 weeks (1st subject), then successive intersubject dose escalation (100 to 500 mg b. i. d.) for 3 weeks |
| BEL-7 | 9 | Single arm, single agent dose finding study in solid tumors, Oral 200 to 500 mg b. i. d. for the 1st 28 days of each 35- to 42- day cycle |
| USA-7 | 9 | Single arm, single agent study in bladder cancer, 300 mg b. i. d. continuous for up to 50 days |
| USA- 8 | 22 | Single arm study in lung cancer, 400 mg b. i. d. for 1st 14 days of 1st 21- day cycle; intrasubject dose escalation in 100- mg b. i. d. increments from Cycle 2 on |
| GBR-1 | 76 | Single agent study in breast cancer, Cohort 1: 300 or 400 mg b. i. d. continuously, Cohort 2: 300 mg b. i. d. for 1st 21 days of each 28- day cycle |
| INT- 10 | 34 | Single agent study in bladder cancer, 300 mg b. i. d. for 1st 21 days of each 28- day cycle |
| INT-9 | 233 tipifarnib,<br><br>133 placebo | Randomized study in colorectal cancers, 300 mg b. i. d. for 1st 21 days of each 28- day cycle |

a Number of subjects evaluated by the sponsor for safety.
b Number of all-treated AML subjects evaluated by the sponsor for safety.
Reference: Zarnestra NDA.

**Table 3: Clinical Studies Submitted for Efficacy in AML**

| Clinical Study | Evaluable Subjects[a] Elderly poor-risk AML / AML | Study Description | Endpoints |
|---|---|---|---|
| CTEP-20 | 136[b]/ 157 (N=171) | Single arm, open label, single agent, in previously untreated elderly poor-risk AML patients | Efficacy and safety |
| INT-17 | 99[c]/ 252 (N= 252) | Single arm, open label, single agent, in refractory or relapsed AML patients | Efficacy, safety, and pharmacokinetics |
| CTEP-1 | 25/? (N = 34) | Single arm, open label, single agent, dose escalation | Phase 2 recommend dose, pharmacokinetics and initial tolerability |

a Number of subjects evaluated by the sponsor for efficacy.
b Number of subjects evaluated by the sponsor for efficacy and ≥ 75 years old or 65 to 74 years old with prior MDS.
c Number of elderly subjects (≥ 65 years old) evaluated for efficacy.
References: Zarnestra NDA.

## IV. CTEP-20 Study Design and Significant Milestones

This open-label, single-arm, multicenter study was supported and conducted by the United States National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) as part of a Cooperative Research and Development Agreement with Johnson & Johnson Pharmaceutical Research and Development, L. L. C. (J&JPRD). This study opened on October 10, 2002, and originally assessed the efficacy and safety of tipifarnib in subjects with previously untreated poor-risk hematologic malignancies. After enrolling 110 patients (amendment 6, September 16, 2003), the target population was re-defined as subjects (1) 75 years or older with newly diagnosed AML or (2) 65 to 74 years of age with secondary AML arising from prior myelodysplastic syndrome (MDS). The study objectives were redefined as follows:

- The primary objective was to determine the complete response (CR) rate of tipifarnib in elderly subjects with previously untreated poor-risk acute myeloid leukemia (AML).
- Secondary objectives were to determine the progression- free survival (PFS), overall survival (OS), duration of response, and safety profile.

The major eligibility criteria were also redefined in amendment 6:

**Inclusion Criteria**

• Pathologic confirmation of AML (≥ 20% marrow or peripheral blasts).
• Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.
• Written informed consent for participation in the study, given before undergoing any study- specific procedures.
• Bilirubin within the normal range.
• Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 × the upper limit of normal (ULN) (grade 1).
• Serum creatinine ≤ 1.5 × ULN (grade 1).
• No active systemic infection.
• Disease- specific criteria – AML (any of the following):
    - Newly diagnosed AML in adults 75 years or older.
    - Secondary AML arising from prior MDS in adults 65 years or older.

**Exclusion Criteria**

• Hyperleukocytosis with ≥ 30,000 leukemic blasts/μL.
• Acute promyelocytic (French- American- British [FAB] M3) subtype.
• Previous treatment with chemotherapy for leukemia (except for hydroxyurea).
• Disseminated intravascular coagulation (diagnosis by laboratory or clinical assessment).
• Leukemic involvement of the central nervous system (CNS).
• Concomitant radiation therapy, chemotherapy, or immunotherapy. Previous therapy for another malignancy was permitted, if at least 1 month had occurred since the subject had received any of these treatments.
• Intrinsic impaired organ function.

After undergoing pretreatment bone marrow aspiration and biopsy as well as other appropriate evaluations, subjects were to receive tipifarnib 600 mg by mouth (p. o.) twice daily (b. i. d.) for 21 days in 28-day cycles. Subsequent cycles were to begin 7 to 42 days following completion of tipifarnib treatment in the previous cycle (on Day 29 to 64).

Bone marrow aspiration and biopsy were performed at the time of peripheral blood count recovery (absolute neutrophil count [ANC] > 500/μL, platelets > 20,000/μL), but no later than Day 63, regardless of peripheral blood count recovery. Subjects underwent weekly laboratory (complete blood counts and chemistries) and clinical monitoring (Table 4).

Subjects who achieved a CR could receive additional tipifarnib treatment until disease progression or receive up to 3 additional cycles of tipifarnib and stop. Retreatment with tipifarnib was allowed. The decision to reinitiate tipifarnib in an individual subject was left to the discretion of the individual investigator. Subjects with progressive disease (PD) at any time during tipifarnib administration were withdrawn from the study.

The first follow-up visit occurred 30 days after treatment termination for subjects who did not have documented progression or had not started subsequent therapy, and every 90 days after documentation of progressive disease (PD) or start of subsequent therapy.

The clinical assessments are summarized in Table 4:

**Table 4: Time and Events Schedule**

| | Baseline (within 72 hours) | Day 8 | Day 15 | Day 22 | Day 28- 63 |
|---|---|---|---|---|---|
| Signed informed consent | X | | | | |
| Medical history[a] | X | | | X | X |
| Physical examination[a] | X | | | | |
| Bone marrow aspirate/biopsy[b] | X[b] | | | | X[c] |
| CBC/differential/platelets[d] | X | X | X | X | X |
| Chemistries[d] | X | X | X | X | X |
| Correlative studiese | X | X | | | X |
| Microarray studiese | X | | | | X |

a Includes a detailed neurologic history and baseline neurologic examination. Documentation of any baseline neuropathy was required.
b Morphologic examination, karyotype, histochemical stains, and immunophenotype pretreatment no more than 1 week before treatment began.
c At the time of ANC and platelet recovery, or by Day 63 at the latest. Within 1 week of subsequent treatment cycle.
d Required once weekly after the first week, though recommended twice weekly or more, at the physician's discretion.
e Correlative and microarray studies, during Cycle 1 only.
Reference: CTEP-20 study report table 1 and Appendix 1.1.

## 5. Study CTEP-20 Efficacy

### 5.1 Study CTEP-20 Population and Risk Factors

FDA reviewed patient eligibility and found that patient (ID101045) should be excluded from all-treated and elderly poor-risk AML patient populations, since this patient's baseline blast count was less than 20,000/mm$^3$ by both the investigator and the sponsor appointed independent reviewer. However, this patient did not respond to Zarnestra treatment. This resulted in 156 patients in the all-treated AML population and 135 patients in the elderly poor-risk AML population. The sponsor's and FDA's patient population summary is as follows:

**Table 5: Summary of Patient Population**

| Patient Population | Number of Patients | |
|---|---|---|
| | Sponsor | FDA |
| All Enrolled | 171 | 171 |
| **All Treated AML** | 157 | **156** |
| **Elderly poor-risk AML** | 136 | **135** |
| Age ≥ 75 years | 75 | **74** |
| Age 65-74 years with prior MDS | 61 | 61 |
| **Per-protocol** | 103 | 103 |

The risk factors in the elderly poor-risk AML patient subset are summarized by the sponsor in Table 5. FDA agrees with the sponsor summary except that this summary has included one patient above, age > 75 years, that did not meet the AML eligibility criteria as discussed. It is noteworthy that more than 80% of subjects in this study subpopulation had AML arising from prior AML. There were 55% subject who were age 75 years or older and 49% of subjects had unfavorable karyotype in the elderly poor-risk AML subpopulation.

**Table 6: AML Risk Factors (Study CTEP-20: Sponsor's Elderly Poor-Risk AML Population)**

| | 65-74 y prior MDS N= 61 (%) | ≥ 75 y N= 75 (%) | Total N= 136 (%) |
|---|---|---|---|
| **Risk factor** | | | |
| Prior MDS | 61 (100) | 50 (67) | 111 (82) |
| Baseline organ dysfunction[a] | 31 (51) | 52 (69) | 83 (61) |
| Age ≥ 75 years | - | 75 (100) | 75 (55) |
| Unfavorable karyotype | 37 (61) | 29 (39) | 66 (49) |
| **Number of risk factors per subject** | | | |
| 1 | 10 (16) | 4 (5) | 14 (10) |
| 2 | 34 (56) | 26 (35) | 60 (44) |
| 3 | 17 (28) | 30 (40) | 47 (35) |
| 4 | - | 15 (20) | 15 (11) |

a Organ dysfunction was defined as the presence of at least 2 dysfunctional conditions. Some subjects had more than 1 type of organ dysfunction.

Reference: Zarnestra NDA CTEP-20 study report.

## 5.2 Complete Response (CR) Analyses

Complete Responses were observed in 4 of the 6 CTEP-20 study sites, as provided by the sponsor (Table 6).

**Table 7: Response by Site (CTEP-20, Elderly Poor Risk AML Population)**

| Site ID | Site Name | Poor Risk Enrollment (N=136, %) | All Resp CR/PR/HR | Poor Risk CR (%) | Sponsor's Site Audit |
|---|---|---|---|---|---|
| 100 | The Sidney Kimmel Cancer Center at Johns Hopkins | 28 (21) | 4/2/1 | 3 (11) | Yes |
| 200 | University of Rochester Cancer Center | 16 (12) | 4/0/0 | 4 (25) | No |
| 300 | University of Maryland Greenebaum Cancer Center | 32 (24) | 10/1/6 | 8 (25) | Yes |
| 500 | Stanford University Medical Center | 35 (26) | 5/1/1 | 5 (14) | Yes |
| 600 | Blood & Marrow Transplant Group of Georgia | 2 (1) | 0/0/0 | 0 | No |
| 700 | Cornell Medical Center New York Presbyterian Hospital | 22 (16) | 0/1/1 | 0 | Yes |

Reference: Zarnestra NDA, Study CTEP-20 Table 4 and Attachment 2.1.2.1.

The sponsor summarized the comparative assessment of CR by the study investigator and the sponsor appointed independent reviewer as shown in Table 7. FDA has added subtotals and footnotes to this table. The information of all CRs claimed by the investigator is shown in Tables 8 and 9, which were summarized by the sponsor and footnoted by FDA. FDA also explored the investigators and independent reviewer claimed CRs by age or by whether patients had prior MDS (Table 10).

**Table 8: Cross-Tabulation of CR–Independent Central Review Versus Site Review (CTEP-20: Elderly Poor-Risk AML Population)**

| Tipifarnib 600 mg oral twice daily (N= 20) | | | |
|---|---|---|---|
| | Local Institute Reading Compatible With: | | |
| Central Review Reading Compatible With: | Confirmed CR | Unconfirmed CR | **Subtotal** |
| Confirmed CR | 15[a] | - | **15** |
| Unconfirmed CR | 1[b] | 2[c] | **3** |
| Slides not available[a] | 1[d] | 1[e] | **2** |
| **Subtotal** | **17** | **3** | **20** |

a. Includes Subject 101021, whose bone marrow slides showing < 5% blasts after Cycle 1 were lost and could not be confirmed by central review, but the slides obtained following Cycle 2 were available and read as compatible with CR.
b. For subject 101057, the site and the central review were not in complete agreement. Although both the local site and independent review agreed that the blast count was < 5% after C1, the subsequent cycle blast count confirmation reading by independent review was >5% whereas that of the site review was <5%.
c. Confirmation slides were not available for Subjects 100336 (early death) and 100318 (early progressive disease).
d. Subject 100508 only a single on study slide was available.
e. Subject 101049 only baseline slides were available.

Reference: Zarnestra NDA, CTEP-20 study report, Independent review report and Appendices 3 and 5.

**Table 9: List of Sponsor Claimed CRs with Treatment Information (CTEP-20, Elderly Poor Risk AML Population) and with FDA Footnotes.**

| Subject Number | Age (years)/Sex/Race | Diagnosis | FAB Class | 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 | Secondary AML + prior MDS | Unknown | No | 80[a] | 1 | 51 | 0 |
| 100508[be] | 79/Male/Asian | Secondary AML + prior MDS | M1 | Yes | 4 | 4 | 90 | 0 |
| 101049[ce] | 65/Male/Black | Secondary AML + prior MDS | M2 | Yes | 11 | 3 | 72 | 0 |
| 2 Cycles (n= 5) | | | | | | | | |
| 100214 | 73/Female/White | Secondary AML + prior MDS | M4 | Yes | 7 | 2 | 10 | 1 |
| 100318[cd] | 81/Male/White | De novo AML | M5 | Yes | 13 | 3 | 90 | 1 |
| 100336[bcd] | 80/Male/White | Secondary AML + prior MDS | M0 | Yes | 35 | 4 | 22 | 1 |
| 101021 | 69/Female/White | Secondary AML + prior MDS | M4 | No | 1 | 2 | 40 | 0 |
| 101096 | 69/Male/White | Secondary AML + prior MDS | Unknown | No | 7 | 1 | 50 | 1 |
| 3 Cycles (n=2) | | | | | | | | |
| 100322 | 73/Male/White | Secondary AML + prior MDS | M6 | Yes | 1 | 3 | 28 | 1 |
| 101107[b] | 76/Male/White | Secondary AML + prior MDS | Unknown | Not available | 312 | 2 | 20 | 0 |
| 4 Cycles (n=8) | | | | | | | | |
| 100113[b] | 82/Male/White | Secondary AML + prior MDS | M2 | Yes | 15 | 4 | 40 | 1 |
| 100321 | 68/Male/White | Secondary AML + prior MDS | Unknown | No | 32 | 1 | 25 | 0 |
| 101008 | 82/Male/White | De novo AML | M2 | No | 123[a] | 2 | 50 | 1 |
| 101025 | 70/Male/White | Secondary AML + prior MDS | Unknown | No | 4 | 2 | 31 | 1 |
| 101051 | 70/Male/White | Secondary AML + prior MDS | M7 | Yes | 8 | 2 | 30 | 1 |
| 101057[bd] | 85/Male/White | Secondary AML + prior MDS | M2 | No | 21 | 3 | 35 | 0 |
| 101060 | 73/Male/White | Secondary AML + prior MDS | Unknown | No | 29 | 2 | 17 | 1 |
| 101091 | 71/Male/White | Secondary AML + prior MDS | M2 | No | 30 | 2 | 20 | 0 |
| 5 Cycles (n=2) | | | | | | | | |
| 100213[b] | 81/Female/White | Secondary AML + prior MDS | M4 | Yes | 46 | 4 | 77 | 2 |
| 100515[b] | 79/Male/Hispanic-Latino | Secondary AML + prior MDS | M4 | No | 8 | 2 | 75 | 2 |

a Calculated from imputed starting date, i. e., XX June 2002 was imputed as 1 June 2002.
b Age > 74 with prior MDS.
c. Unconfirmed CR by the site investigator.
d. Unconfirmed CR by the independent reviewer.
e. Not able to determine by the independent investigator
Reference: Zasrnestra NDA, Study CTEP-20 Report table 24.

**Table 10: The Sponsor Summarized Investigator Claimed CR Patient's CR duration, Time to CR, PFS and Survival. (CTEP-20, Elderly Poor Risk AML Population) with FDA Footnotes**

| Subject Number | Age (years)/Sex/Race | CR Duration | | Time to CR (days) | PFS | | Survival | | Subsequent Combination Chemotherapy[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | (days) | Censor | | (days) | Censor | (days) | Censor | |
| 1 Cycle (n= 3) | | | | | | | | | |
| 100341 | 67/Male/White | 295 | Yes | 39 | 433 | No | 433 | No | No |
| 100508[be] | 79/Male/Asian | 121 | No | 103 | 226 | No | 279 | No | No |
| 101049[ce] | 65/Male/Black | 167 | Yes | 32 | 208 | Yes | 564 | No | No[a] |
| 2 Cycles (n= 5) | | | | | | | | | |
| 100214 | 73/Female/White | 120 | Yes | 78 | 207 | Yes | 395 | No | No |
| 100318[cd] | 81/Male/White | 58 | No | 35 | 93 | No | 151 | No | No |
| 100336[bcd] | 80/Male/White | 35 | Yes | 33 | 67 | No | 67 | No | No |
| 101021 | 69/Female/White | 372 | Yes | 50 | 421 | Yes | 421 | Yes | No |
| 101096 | 69/Male/White | 33 | No | 44 | 76 | No | 129 | Yes | No |
| 3 Cycles (n=2) | | | | | | | | | |
| 100322 | 73/Male/White | 179 | Yes | 34 | 212 | Yes | 237 | Yes | No |
| 101107[b] | 76/Male/White | 76 | Yes | 37 | 113 | Yes | 113 | Yes | No |
| 4 Cycles (n=8) | | | | | | | | | |
| 100113[b] | 82/Male/White | 99 | No | 71 | 170 | No | 211 | No | No |
| 100321 | 68/Male/White | 220 | No | 38 | 257 | No | 701 | Yes | No[a] |
| 101008 | 82/Male/White | 376 | No | 31 | 406 | No | 548 | No | No |
| 101025 | 70/Male/White | 153 | Yes | 42 | 216 | Yes | 223 | Yes | No |
| 101051 | 70/Male/White | 275 | No | 76 | 357 | No | 814 | Yes | No |
| 101057[bd] | 85/Male/White | 154 | No | 38 | 192 | No | 386 | No | No |
| 101060 | 73/Male/White | 92 | Yes | 43 | 134 | Yes | 140 | Yes | No |
| 101091 | 71/Male/White | 104 | Yes | 49 | 153 | Yes | 174 | Yes | No |
| 5 Cycles (n=2) | | | | | | | | | |
| 100213[b] | 81/Female/White | 127 | No | 121 | 247 | No | 257 | No | No |
| 100515[b] | 79/Male/Hispanic-Latino | 118 | No | 80 | 204 | No | 442 | No | No |

a Two subjects received subsequent combination chemotherapy as third- line treatment, after first being retreated with tipifarnib.
b Age > 74 with prior MDS.
c. Unconfirmed CR by the site investigator.
d. Unconfirmed CR by the independent reviewer.
e. Not able to determine by the independent investigator
Reference: Zarnestra NDA, Study CTEP-20 Report Appendix Table 25.

**Table 11: Summary of CR Assessment by Investigator and Independent Review Grouped by Age or by Whether Patient Had Prior MDS (CTEP-20, Elderly Poor Risk AML Population)**

| Results | | CR (%) | | CRu | | Unable Accessed | |
|---|---|---|---|---|---|---|---|
| Reviewer | | Site | Independent | Site | Independent | Site | Independent |
| **Total (N = 135)** | | **17 (13)** | **15 (11)** | **3** | **3** | **0** | **2** |
| Age | 65-74 (N=61) | 10 (16) | 10 (16) | 2 | 2 | 0 | 1 |
| | ≥ 75 (N = 74) | 7 (9) | 5 (7) | 1 | 1 | 0 | 1 |
| Prior MDS | Yes (N = 110) | 16 (14) | 14 (13) | 2 | 2 | 0 | 2 |
| | No (N = 25) | 1 (4) | 1 (4) | 1 | 1 | 0 | 0 |

After reviewing the CTEP-20 study report and data sets provided in the sponsor's NDA, FDA agrees with the sponsor appointed independent reviewer's assessment of CRs, i.e., 15 subjects with confirmed complete responses based on the FDA identified elderly poor-risk AML patient subgroup (one patient excluded, see section 5.1). The FDA assessment of complete response rate is summarized in Table 11.

**Table 12: FDA Assessment of CR Rates (CTEP-20: Reviewer Defined Elderly Poor-Risk AML Population)**

| Subgroup | Level | No. of Patients | CR Rate (n/N) [95% CI] | |
|---|---|---|---|---|
| | | | confirmed only | conformed + unconfirmed |
| CTEP-20 FDA Elderly Poor-Risk AML | All | 135 | 11.1% (15/135) 6.6 – 18.0% | 13.3% (18/135) 8.3 – 20.5% |
| Age | 65 – 74 years | 61 | 16.4% (10/61) 8.6 – 28.5% | 18.0% (10/61) 8.6 – 28.5% |
| | ≥ 75 years | 74 | 6.8% (5/74) 3.1 – 18.8% | 10.8% (8/74) 6.2 – 24.8% |
| Prior MDS | Yes | 110 | 12.7% (14/110) 7.4 – 20.8% | 14.5% (16/110) 8.8 – 22.8% |
| | No | 25 | 4% (1/25) 0.2 – 22.3% | 8% (2/25) 1.4 – 27.5% |

**5.3 Response Duration:**

The FDA has explored the duration of confirmed CRs, a secondary endpoint of study CTEP-20. Per CTEP-20 protocol, no anti-leukemia therapy other than Zarnestra was given to patients who achieved a response until after disease progression and removal from the study. As shown in Table 12, there is a trend toward longer duration of CR in the younger age group, 65-74 year old. In comparison to AML patients with prior MDS, there was only one patient with *de novo* AML who had a confirmed CR.

**Table 13: FDA Assessment of Duration of Confirmed Complete Response (Elderly Poor-Risk Population)**

| Subgroup | Level | Analysis | FDA Results |
|---|---|---|---|
| CTEP-20 Elderly Poor-Risk AML | All | Number failed*/ Number assessed# | 7/15 (47%) |
| | | Median duration in days [95% CI] | 275 [127 – 376] |
| Age | 65 – 74 years | Number failed*/ Number assessed# | 3/10 |
| | | Median duration in days [95% CI] | 275 [220 – xxx][a] |
| | ≥ 75 years | Number failed*/ Number assessed# | 4/5 |
| | | Median duration in days [95% CI] | 122 [99 – 376] |
| Prior MDS | Yes | Number failed*/ Number assessed# | 6/14 |
| | | Median duration in days [95% CI] | 220 [127 – xxx][a] |
| | No | Number failed*/ Number assessed# | 1/1 |
| | | Median duration in days [95% CI] | 376 |

* Number failed = number of patients who had disease progression or died.

# Number assessed = number of patients who had a CR.

### 5.4 Overall Survival:

FDA has conducted an exploratory analysis of overall survival in the FDA defined CTEP-20 elderly poor-risk population. This analysis is considered exploratory given the single arm nature of the study design.

**Table 14: FDA's Exploratory Results of Overall Survival (Elderly Poor-Risk AML Population)**

| Subgroup | Level | Analysis | FDA Results |
|---|---|---|---|
| Elderly Poor-Risk AML | All | Number failed/ Number assessed | 88/135 (65%) |
| | | Median duration in days [95% CI] | 164 [125 -242] |
| | | 6-month survival rate [95% CI][a] | 44.7% [35.0 – 54.4%] |
| | | 12-month survival rate [95% CI][a] | 24.8% [15.1 – 34.5%] |
| Age | 65 – 74 years | Number failed/ Number assessed | 32/61 (52%) |
| | | Median duration [95% CI] | 278 [179 – 433] |
| | | 6-month survival rate [95% CI][a] | 62.6% [48.3 – 76.9%] |
| | | 12-month survival rate [95% CI][a] | 38.5% [21.9 – 55.1%] |
| | ≥ 75 years | Number failed/ Number assessed | 56/74 (76%) |
| | | Median duration [95% CI] | 107 [68 – 157] |
| | | 6-month survival rate [95% CI][a] | 31.3% [19.4 – 43.2%] |
| | | 12-month survival rate [95% CI][a] | 14.2% [3.5 – 24.9%] |
| Prior MDS | Yes | Number failed/ Number assessed | 67/110 (61%) |
| | | Median duration [95% CI] | 209 [157 – 254] |
| | | 6-month survival rate [95% CI][a] | 51.3% [40.4 – 62.1%] |
| | | 12-month survival rate [95% CI][a] | 26.7% [15.6 – 38.0%] |
| | No | Number failed/ Number assessed | 21/25 (84%) |
| | | Median duration [95% CI] | 54 [33 – 151] |
| | | 6-month survival rate [95% CI][a] | 18.3% [1.4 – 35.2%] |
| | | 12-month survival rate [95% CI][a] | 18.3% [1.4 – 35.2%] |

[a] Based on Kaplan-Meier product limit estimates.

## 6. Study CTEP-20 Safety

### 6.1 Drug Exposure:

In CTEP-20, the majority of patients had 1-2 cycles of treatment (Table 14). In addition to the exposure by cycles, the sponsor has also summarized drug exposure by cycle and by day. FDA does not consider that there is a difference between the two, since there were no patient self drug administration dairies implemented in study CTEP-20 and the days were based on pharmacy record, most of which are outpatient weekly dispensation records. Of the total 171 subjects enrolled in the study CTEP-20, 158 of them had AML. At the time of clinical cut off, 157 AML subjects were treated with at least one cycle of Zarnestra. Of them, 136 were elderly subjects with poor-risk AML and are most relevant to the safety evaluation for the proposed indication. Please note that one of the elderly subjects with poor-risk AML was excluded from FDA's efficacy analysis as discussed before.

**Table 15: Study Treatment by Cycle (Study CTEP-20: Sponsor defined Elderly Poor-Risk Subset))**

| Category, n (%) | Cycle 1 (N= 136) | Cycle 2 (N= 64) | Cycle 3 (N= 27) |
|---|---|---|---|
| Cycle duration | | | |
| 1-28 days | 39 (29) | 13 (20) | 7 (26) |
| 29-35 days | 21 (15) | 12 (19) | 5 (19) |
| 36-42 days | 29 (21) | 19 (30) | 8 (30) |
| 43-49 days | 26 (19) | 10 (16) | 5 (19) |
| 50-56 days | 7 (5) | 4 (6) | - |
| 57- 63 days | 6 (4) | 3 (5) | 1 (4) |
| ≥ 64 days | 8 (6) | 3 (5) | 1 (4) |
| Mean (SD) | 36.8 (16.88) | 37.6 (15.06) | 36.4 (14.39) |
| Median | 38 | 38 | 36 |
| Range | (3; 92) | (5; 75) | (10; 85) |
| Starting dose, mg/day | | | |
| Mean (SD) | 1191 (72.5) | 1000 (236.4) | 993 (257.1) |
| Median | 1200 | 1200 | 1200 |
| Range | (600; 1200) | (400; 1200) | (400; 1200) |
| Cumulative dose, mg | | | |
| Mean (SD) | 23338 (4599.3) | 19663 (6129.7) | 20000 (5448.5) |
| Median | 25200 | 16800 | 18000 |
| Range | (3600; 25200) | (2000; 25200) | (8400; 25200) |
| Dose intensity, mg/day | | | |
| Mean (SD) | 749.4 (277.40) | 597.3 (251.93) | 631.2 (282.9) |
| Median | 663.2 | 566.4 | 586.1 |
| Range | (273.9; 1200.0) | (168.0; 1200.0) | (197.6; 1200.0) |
| Relative dose intensity | | | |
| Mean (SD) | 0.76 (0.204) | 0.62 (0.216) | 0.65 (0.247) |
| Median | 0.74 | 0.63 | 0.65 |
| Range | (0.30; 1.04) | (0.19; 1.00) | (0.22; 1.00) |

Reference: Zarnestra NDA, Study CTEP-20 report Table 21 and Attachment 1.11.2.1.

### 6.2 Overall Toxicity:

The safety results for the elderly subjects with poor-risk AML and all AML subjects (21/157 patients younger than age 65) enrolled on CTEP-20 study were reviewed, with the focus on the elderly poor-risk AML population. Overall adverse events are summarized in Table 15. There were 98% all treatment emergent adverse events (AEs), of which 87% were thought related to the study drug by the investigator. There were 83% treatment emergent and 61% drug related grade 3 or 4 AEs, with 15% (n=136) treatment emergent which includes 10% (n = 136) drug related severe AEs that lead to termination of the treatment. There were 9 (7%, n = 136) deaths in the elderly poor-risk population due to treatment emergent AEs. One of them was due to AEs that related to the study drug by investigators assessment.

**Table 16: Overview of Adverse Events (CTEP-20: Elderly Poor-Risk AML and All-Treated AML Data Sets)**

| Number (%) of Subjects With: | Elderly Poor- Risk AML | | | All- Treated AML |
|---|---|---|---|---|
| | 65-74 y prior MDS N = 61 (%) | ≥ 75 y N = 75 (%) | *Total N= 136 (%)* | Total (N= 157) (%) |
| **AEs** | **60 (98)** | **74 (99)** | ***134 (99)*** | **155 (99)** |
| Drug-related AEs | 53 (87) | 65 (87) | *118 (87)* | 134 (85) |
| **Grade 3 or 4 AEs** | **51 (84)** | **62 (83)** | ***113 (83)*** | **131 (83)** |
| Drug- related grade 3 or 4 AEs | 37 (61) | 46 (61) | *83 (61)* | 92 (59) |
| **SAEs** | **38 (62)** | **50 (67)** | ***88 (65)*** | **103 (66)** |
| Drug- related SAEs | 23 (38) | 35 (47) | *58 (43)* | 64 (41) |
| **AEs leading to treatment termination** | **11 (18)** | **10 (13)** | ***21 (15)*** | **26 (17)** |
| Drug- related AEs leading to treatment termination[a] | 7 (11) | 7 (9) | *14 (10)* | 18 (11) |
| **Deaths due to an AE[a]** | **2 (3)** | **7 (9)** | ***9 (7)*** | **11 (7)** |
| Drug- related AEs resulting in death[a] | 0 | 1 (1) | *1 (1)* | 1 (1) |
| Early deaths due to an AE[b] | 2 (3) | 3 (4) | *5 (4)* | 6 (4) |

a AEs resulting in death within 30 days after treatment termination or until start of subsequent therapy, whichever was ealier.

b AEs resulting in death within 30 days after the first dose of study medication regardless of the cause of death.

Reference: Zarnestra NDA, CTEP study report Table 42 and attachments 3.1.1, 3.1.2, 3.2.1.1., 3.6.2.1, and 3.6.2.2.

## 6.3 Common Adverse Events

For all treatment emergent AEs, those reported most frequently (79%) were in the body-as-a-whole and gastrointestinal body systems. The most frequently reported AEs (all grades) were diarrhea (47%), fatigue (44%), nausea (38%), and rash (35%).

AEs reported in at least 10% of all subjects are summarized below in Tables 16 and 17:

**Table 17: Adverse Events Reported in at Least 10% of Subjects (All Grades) – Part 1 (CTEP-20: Elderly Poor-Risk AML Subset)**

| WHO Preferred Term | 65-74 y prior MDS (N = 61) n (%) | ≥ 75 y (N = 75) n (%) | *Total N= 136 n (%)* |
|---|---|---|---|
| **Total no. subjects with at least 1 AE** | **60 (98)** | **74 (99)** | ***134 (99)*** |
| **Body as a whole –general disorders** | **47 (77)** | **60 (80)** | ***107 (79)*** |
| Fatigue | 30 (49) | 30 (40) | *60 (44)* |
| Fever | 21 (34) | 21 (28) | *42 (31)* |
| Edema peripheral | 9 (15) | 13 (17) | *22 (16)* |
| Rigors | 8 (13) | 9 (12) | *17 (13)* |
| Chest pain | 7 (11) | 6 (8) | *13 (10)* |
| **Gastrointestinal system disorders** | **45 (74)** | **62 (83)** | ***107 (79)*** |
| Diarrhea | 29 (48) | 35 (47) | *64 (47)* |
| Nausea | 25 (41) | 26 (35) | *51 (38)* |
| Anorexia | 15 (25) | 22 (29) | *37 (27)* |
| Constipation | 13 (21) | 20 (27) | *33 (24)* |
| Vomiting | 12 (20) | 20 (27) | *32 (24)* |
| Stomatitis | 11 (18) | 15 (20) | *26 (19)* |
| Abdominal pain | 11 (18) | 11 (15) | *22 (16)* |
| **Respiratory system disorders** | **38 (63)** | **46 (61)** | ***84 (62)*** |
| Dyspnea | 15 (25) | 17 (23) | *32 (24)* |
| Coughing | 15 (25) | 12 (16) | *27 (20)* |
| Pneumonia | 8 (13) | 13 (17) | *21 (15)* |
| Pharyngitis | 10 (16) | 8 (11) | *18 (13)* |
| **Central and peripheral nervous system disorders** | **32 (52)** | **45 (60)** | ***77 (57)*** |
| Dizziness | 16 (26) | 20 (27) | *36 (26)* |
| Headache | 17 (28) | 7 (9) | *24 (18)* |
| Ataxia | 5 (8) | 11 (15) | *16 (12)* |
| Tremor | 6 (10) | 9 (12) | *15 (11)* |
| **Skin and appendages disorders** | **38 (62)** | **34 (45)** | ***72 (53)*** |
| Rash | 25 (41) | 23 (31) | *48 (35)* |
| Skin reaction localized | 11 (18) | 16 (21) | *27 (20)* |

(Continue)

**Table 18: Adverse Events Reported in at Least 10% of Subjects (All Grades) – Part 2 (CTEP-20: Elderly Poor-Risk AML Subset)**

| WHO Preferred Term | 65-74 y prior MDS (N = 61) n (%) | ≥ 75 y (N = 75) n (%) | *Total N= 136 n (%)* |
|---|---|---|---|
| **Platelet, bleeding, & clotting disorders** | **28 (46)** | **37 (49)** | ***65 (48)*** |
| Purpura | 10 (16) | 19 (25) | *29 (21)* |
| Thrombocytopenia | 12 (20) | 14 (19) | *26 (19)* |
| Epistaxis | 11 (18) | 11 (15) | *22 (16)* |
| **Metabolic and nutritional disorders** | **29 (48)** | **34 (45)[a]** | ***63 (46)[a]*** |
| Creatinine blood increased | 12 (20) | 18 (24)[a] | *30 (22)[a]* |
| Dehydration | 4 (7) | 13 (17) | *17 (13)* |
| Hypokalemia | 10 (16) | 6 (8) | *16 (12)* |
| **Psychiatric system disorders** | **27 (44)** | **34 (45)** | ***61 (45)*** |
| Confusion | 12 (20) | 17 (23) | *29 (21)* |
| Insomnia | 10 (16) | 10 (13) | *20 (15)* |
| **White cell disorders** | **26 (43)** | **31 (41)** | ***57 (42)*** |
| Neutropenia febrile | 18 (30) | 22 (29) | *40 (29)* |
| Neutropenia | 9 (15) | 8 (11) | *17 (13)* |
| **Resistance mechanism disorders** | **22 (36)** | **27 (36)** | ***49 (36)*** |
| Infection bacterial | 13 (21) | 14 (19) | *27 (20)* |
| Moniliasis | 8 (13) | 6 (8) | *14 ( 10)* |
| **Musculoskeletal system disorders** | **14 (23)** | **15 (20)** | ***29 (21)*** |
| Arthralgia | 8 (13) | 5 (7) | *13 (10)* |
| **RBC disorders** | **7 (11)** | **20 (27)** | ***27 (20)*** |
| Anemia | 7 (11) | 17 (23) | *24 (18)* |
| **Special senses other, disorders** | **8 (13)** | **5 (7)** | ***13 (10)*** |
| Taste perversion | 8 (13) | 5 (7) | *13 (10)* |

a For 2 subjects (101005 and 101039), hypercreatinemia was coded to urinary system disorders rather than metabolic and nutritional disorders. For consistency, these 2 subjects are included in the latter body system in this report.

Reference: Zarnestra NDA, CTEP-20 study report Table 43 and attachment 3.2.1.1.

## 6.4 Grade 3 or 4 Adverse Events

FDA agrees with the sponsor that 83% of subjects experienced Grade 3 or 4 AEs.

The most frequent treatment emergent grade 3 or 4 hematological and nonhematologic AEs were secondary to myelosuppression, including neutropenia with or without neutropenic fever (41%), infections (27%), thrombocytopenia (17%), fatigue (13%), pneumonia (10%), rash (9%) anemia (8%), dyspnea (8%), and confusion (7%). Besides grade 3 and 4 AEs that were reported with an incidence of 5% or greater, the reviewer has also included some less than 5% AEs that occurred in the elderly poor-risk AML subset in the reviewer's summary (see Tables 18 and 19 and footnotes). These AEs (marked with * in Tables 18 to 21), although less than 5%, may represent certain clinically relevant events in the view of the reviewer. For example, the sponsor has categorized Candida infection (4%) and other fungal infection (4%) separately and therefore excluded both from the sponsor's 5% or higher AEs summary (Table 19). However, the true total fugal infection frequency (Candida + other) should be 8%.

**Table 19: Treatment Emergent Grade 3 and 4 AEs Reported (≥ 5% or < 5% but may have clinical significance) - Part 1 (CTEP-20: Elderly Poor-Risk AML Subset)**

| Body System<br>WHO Preferred Term | 65-74 y prior MDS (N = 61) n (%) | | | ≥ 75 y (N = 75) n (%) | | | *Total N= 136 n (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | All | Grade | | All | Grade | | *All* | *Grade* | |
| | | 3 | 4 | | 3 | 4 | | *3* | *4* |
| **Total no. subjects with grade 3 or 4 AE** | **51 (84)** | | | **62 (83)** | | | ***113 (83)*** | | |
| **White cell disorders** | **26 (43)** | **12 (20)** | **14 (23)** | **29 (39)** | **23 (31)** | **6 (8)** | ***55 (40)*** | ***35 (26)*** | ***20 (15)*** |
| Neutropenia febrile | 18 (30) | 13 (21) | 5 (8) | 22 (29) | 20 (27) | 2 (3) | *40 (29)* | *33 (24)* | *7 (5)* |
| Neutropenia | 9 (15) | 1 (2) | 8 (13) | 7 (9) | 2 (3) | 5 (7) | *16 (12)* | *3 (2)* | *13 (10)* |
| Pancytopenia | 4 (7) | 2 (3) | 2 (3) | 3 (4) | 3 (4) | 0 | *7 (5)* | *5 (4)* | *2 (1)* |
| **Body as a whole** | **15 (25)** | **15 (25)** | **0** | **22 (29)** | **17 (23)** | **5 (7)** | ***37 (27)*** | ***32 (24)*** | ***5 (4)*** |
| Allergic Reaction* | 1 (2) | 1 (2) | 0 | 1 (1) | 1 (1) | 0 | *2 (1)* | *2 (1)* | *0* |
| Fatigue | 5 (8) | 5 (8) | 0 | 12 (16) | 11 (15) | 1 (1) | *17 (13)* | *16 (12)* | *1 (1)* |
| Fever | 4 (7) | 4 (7) | 0 | 4 (5) | 4 (5) | 0 | *8 (6)* | *8 (6)* | *0* |
| Multiple Organ Failure* | 0 | 0 | 0 | 2 (3) | 0 | 2 (3) | *2 (1)* | *0* | *2 (1)* |
| Pain* | 0 | 0 | 0 | 2 (3) | 1 (1) | 1 (1) | *2 (1)* | *1 (1)* | *1 (1)* |
| Pain, Back* | 1 (2) | 1 (2) | 0 | 2 (3) | 1 (1) | 1 (1) | *3 (2)* | *2 (1)* | *1 (1)* |
| Pain, Chest* | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | *1 (1)* | *1 (1)* | *0* |
| Pain, Leg* | 0 | 0 | 0 | 2 (3) | 2 (3) | 0 | *2 (1)* | *2 (1)* | *0* |
| Rigors* | 2 (3) | 2 (3) | 0 | 0 | 0 | 0 | *2 (1)* | *2 (1)* | *0* |
| Syncope* | 1 (2) | 1 (2) | 0 | 2 (3) | 2 (3) | 0 | *3 (2)* | *3 (2)* | *0* |

** Grade 3/4 AEs, which frequency was less than 5% and did not include in the sponsor's CTEP-20 study report Table 40, are included by the reviewer based on potential clinical significance.*

*Note: The denominator used for percentages of toxicity grade calculation were the number of subjects in each age group (65-74, or 75 and older). The denominator used for percentages in ' Total' column was the number of subjects in elderly poor-risk AML subsets.*

*Note: Table includes adverse events reported any time during treatment until treatment termination plus 30 days or subsequent therapy, whichever is earlier. Incidence is based on the number of subjects, not the number of events.*

*Toxicity grade: NCI common toxicity criteria, version 2.0 (CTC, v2.0).*

*Reference: Zarnestra NDA, CTEP-20 study report, Attachment 3.3.1.*

Continued next page

**Table 20: Treatment Emergent Grade 3 and 4 AEs Reported (≥ 5% or < 5% but may have clinical significance) - Part 2 (CTEP-20: Elderly Poor-Risk AML Subset)**

| **Body System** WHO Preferred Term | 65-74 y prior MDS N = 61 (%) | | | ≥ 75 y N = 75 (%) | | | *Total N= 136 n (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | All | Grade | | All | Grade | | *All* | *Grade* | |
| | | 3 | 4 | | 3 | 4 | | *3* | *4* |
| **Resistance mechanism disorders** | **19 (31)** | **17 (28)** | **2 (3)** | **18 (24)** | **12 (16)** | **6 (8)** | ***37 (27)*** | ***29 (21)*** | ***8 (6)*** |
| Infection bacterial | 12 (20) | 12 (20) | 0 | 13 (17) | 9 (12) | 4 (5) | *25 (18)* | *21 (15)* | *4 (3)* |
| Sepsis | 5 (8) | 3 (5) | 2 (3) | 4 (5) | 0 | 4 (5) | *9 (7)* | *3 (2)* | *6 (4)* |
| Infection Fungal* | 4 (7) | 4 (7) | 0 | 2 (3) | 2 (3) | 0 | *6 (4)* | *6 (4)* | *0* |
| Moniliasis* | 5 (8) | 5 (8) | 0 | 0 | 0 | 0 | *5 (4)* | *5 (4)* | *0* |
| Infection, other* | 1 (2) | 1 (2) | 0 | 2 (3) | 2 (3) | 0 | *3 (2)* | *3 (2)* | *0* |
| Infection Viral* | 2 (3) | 2 (3) | 0 | 1 (1) | 1 (1) | 0 | *3 (2)* | *3 (2)* | *0* |
| **Gastrointestinal system disorders** | **13 (21)** | **12 (20)** | **1 (2)** | **15 (20)** | **14 (19)** | **1 (1)** | ***28 (21)*** | ***26 (19)*** | ***2 (1)*** |
| Diarrhea | 5 (8) | 4 (7) | 1 (2) | 3 (4) | 3 (4) | 0 | *8 (6)* | *7 (5)* | *1 (1)* |
| Nausea* | 3 (5) | 3 (5) | 0 | 3 (4) | 3 (4) | 0 | *6 (4)* | *6 (4)* | *0* |
| Vomiting* | 3 (5) | 3 (5) | 0 | 3 (4) | 3 (4) | 0 | *6 (4)* | *6 (4)* | *0* |
| Constipation* | 2 (3) | 2 (3) | 0 | 2 (3) | 2 (3) | 0 | *4 (3)* | *4 (3)* | *0* |
| Stomatitis* | 2 (3) | 2 (3) | 0 | 2 (3) | 2 (3) | 0 | *4 (3)* | *4 (3)* | *0* |
| Abdominal Pain* | 2 (3) | 2 (3) | 0 | 1 (1) | 1 (1) | 0 | *3 (2)* | *3 (2)* | *0* |
| GI Haemorrhage* | 1 (2) | 1 (2) | 0 | 1 (1) | 0 | 1 (1) | *2 (1)* | *1 (1)* | *1 (1)* |
| Melaena* | 0 | 0 | 0 | 1 (1) | 1 (1) | 0 | *1 (1)* | *1 (1)* | *0* |
| **Respiratory system disorders** | **12 (20)** | **10 (16)** | **2 (3)** | **16 (21)** | **10 (13)** | **6 (8)** | ***28 (21)*** | ***20 (15)*** | ***8 (6)*** |
| Pneumonia | 5 (8) | 5 (8) | 0 | 9 (12) | 5 (7) | 4 (5) | *14 (10)* | *10 (7)* | *4 (3)* |
| Dyspnea | 5 (8) | 5 (8) | 0 | 6 (8) | 5 (7) | 1 (1) | *11 (8)* | *10 (7)* | *1 (1)* |
| Pneumonia Lobar* | 2 (3) | 2 (3) | 0 | 1 (1) | 1 (1) | 0 | *3 (2)* | *3 (2)* | *0* |
| Hypoxia* | 1 (2) | 0 | 1 (2) | 1 (1) | 1 (1) | 0 | *2 (1)* | *1 (1)* | *1 (1)* |
| Adult Respiratory Stress Syndrome* | 1 (2) | 0 | 1 (2) | 0 | 0 | 0 | *1 (1)* | *0* | *1 (1)* |
| Haemoptysis* | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | *1 (1)* | *1 (1)* | *0* |

See Table 19 footnotes.

Continued next page

**Table 21: Treatment Emergent Grade 3 and 4 AEs Reported (≥ 5% or < 5% but may have clinical significance) - Part 3 (CTEP-20: Elderly Poor-Risk AML Subset)**

| Body System<br>WHO Preferred Term | 65-74 y prior MDS<br>(N = 61) n (%) | | | ≥ 75 y<br>(N = 75) n (%) | | | *Total*<br>*N= 136 n (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | All | Grade | | All | Grade | | *All* | *Grade* | |
| | | 3 | 4 | | 3 | 4 | | *3* | *4* |
| **Platelet, bleeding, & clotting disorders** | **12 (20)** | **7 (11)** | **5 (8)** | **15 (20)** | **12 (16)** | **3 (4)** | ***27 (20)*** | ***19 (14)*** | ***8 (6)*** |
| Thrombocytopenia | 10 (16) | 5 (8) | 5 (8) | 13 (17) | 10 (13) | 3 (4) | *23 (17)* | *15 (11)* | *8 (6)* |
| Epistaxis* | 1 (2) | 1 (2) | 0 | 3 (4) | 3 (4) | 0 | *4 (3)* | *4 (3)* | *0* |
| Purpura* | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | *1 (1)* | *1 (1)* | *0* |
| **Skin and appendages disorders** | **9 (15)** | **9 (15)** | **0** | **13 (17)** | **13 (17)** | **0** | ***22 (16)*** | ***22 (16)*** | ***0*** |
| Rash | 4 (7) | 4 (7) | 0 | 8 (11) | 8 (11) | 0 | *12 (9)* | *12 (9)* | *0* |
| Skin reaction localized | 4 (7) | 4 (7) | 0 | 6 (8) | 6 (8) | 0 | *10 (7)* | *10 (7)* | *0* |
| Angioedema* | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | *1 (1)* | *1 (1)* | *0* |
| **Metabolic and nutritional disorders** | **10 (16)** | **6 (10)** | **4 (7)** | **10 (13)** | **10 (13)** | **0** | ***20 (15)*** | ***16 (12)*** | ***4 (3)*** |
| Hypokalemia | 5 (8) | 5 (8) | 0 | 3 (4) | 3 (4) | 0 | *8 (6)* | *8 (6)* | *0* |
| Dehydration* | 3 (5) | 2 (3) | 1 (2) | 3 (4) | 3 (4) | 0 | *6 (4)* | *5 (4)* | *1 (1)* |
| Creatinine Blood Increased* | 2 (3) | 2 (3) | 0 | 2 (3) | 2 (3) | 0 | *4 (3)* | *4 (3)* | *0* |
| **Psychiatric system disorders** | **5 (8)** | **5 (8)** | **0** | **12 (16)** | **11 (15)** | **1 (1)** | ***17 (13)*** | ***16 (12)*** | ***1 (1)*** |
| Confusion | 2 (3) | 2 (3) | 0 | 7 (9) | 6 (8) | 1 (1) | *9 (7)* | *8 (6)* | *1 (1)* |
| Hallucination* | 1 (2) | 1 (2) | 0 | 2 (3) | 2 (3) | 0 | *3 (2)* | *3 (2)* | *0* |
| Delirium* | 0 | 0 | 0 | 2 (3) | 2 (3) | 0 | *2 (1)* | *2 (1)* | *0* |
| **Nervous System Disorders*** | **5 (8)** | **5 (8)** | **0** | **10 (13)** | **9 (12)** | **1 (1)** | ***15 (11)*** | ***14 (10)*** | ***1 (1)*** |
| Ataxia* | 0 | 0 | 0 | 3 (4) | 3 (4) | 0 | *3 (2)* | *3 (2)* | *0* |
| Coma* | 1 (2) | 1 (2) | 0 | 1 (1) | 0 | 1 (1) | *2 (1)* | *1 (1)* | *1 (1)* |
| Dizziness* | 0 | 0 | 0 | 2 (3) | 2 (3) | 0 | *2 (1)* | *2 (1)* | *0* |
| Encephalopathy* | 1 (2) | 1 (2) | 0 | 1 (1) | 1 (1) | 0 | *2 (1)* | *2 (1)* | *0* |
| Neuropathy Peripheral* | 2 (3) | 2 (3) | 0 | 0 | 0 | 0 | *2 (1)* | *2 (1)* | *0* |

See Table 19 footnotes.

Continued next page

**Table 22: Treatment Emergent Grade 3 and 4 AEs Reported (≥ 5% or < 5% but may have clinical significance) - Part 4 (CTEP-20: Elderly Poor-Risk AML Subset)**

| Body System<br>WHO Preferred Term | 65-74 y prior MDS<br>(N = 61)<br>n (%) | | | ≥ 75 y<br>(N = 75)<br>n (%) | | | *Total*<br>*N= 136*<br>*n (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | All | Grade | | All | Grade | | *All* | *Grade* | |
| | | 3 | 4 | | 3 | 4 | | *3* | *4* |
| **Cardiovascular disorders, general** | **7 (11)** | **6 (10)** | **1 (2)** | **7 (9)** | **3 (4)** | **4 (5)** | ***14 (10)*** | ***9 (7)*** | ***5 (4)*** |
| Hypotension | 4 (7) | 4 (7) | 0 | 4 (5) | 1 (1) | 3 (4) | *8 (6)* | *7 (5)* | *1 (1)* |
| Cardiac failure | 3 (5) | 2 (3) | 1 (2) | 4 (5) | 3 (4) | 1 (1) | *7 (5)* | *3 (2)* | *4 (3)* |
| Circulatory Failure* | 0 | 0 | 0 | 1 (1) | 0 | 1 (1) | *1 (1)* | *0* | *1 (1)* |
| Hypotension Postural* | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | *1 (1)* | *1 (1)* | *0* |
| **Heart Rate And Rhythm Disorders*** | **6 (10)** | **5 (8)** | **1 (2)** | **3 (4)** | **2 (3)** | **1 (1)** | ***9 (7)*** | ***7 (5)*** | ***2 (1)*** |
| Fibrillation Atrial* | 4 (7) | 3 (5) | 1 (2) | 2 (3) | 2 (3) | 0 | *6 (4)* | *5 (4)* | *1 (1)* |
| Arrhythmia Atrial* | 2 (3) | 2 (3) | 0 | 1 (1) | 0 | 1 (1) | *3 (2)* | *2 (1)* | *1 (1)* |
| AV Block* | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | *1 (1)* | *1 (1)* | *0* |
| Palpitation* | 0 | 0 | 0 | 1 (1) | 1 (1) | 0 | *1 (1)* | *1 (1)* | *0* |
| Tachycardia* | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | *1 (1)* | *1 (1)* | *0* |
| **RBC disorders** | **1 (2)** | **1 (2)** | **0** | **11 (15)** | **11 (15)** | **0** | ***12 (9)*** | ***12 (9)*** | ***0*** |
| Anemia | 1 (2) | 1 (2) | 0 | 10 (13) | 10 (13) | 0 | *11 (8)* | *11 (8)* | *0* |
| **Urinary System Disorders*** | **0** | **0** | **0** | **7 (9)** | **6 (8)** | **1 (1)** | ***7 (5)*** | ***6 (4)*** | ***1 (1)*** |
| Urinary Tract Infection* | 0 | 0 | 0 | 3 (4) | 3 (4) | 0 | *3 (2)* | *3 (2)* | *0* |
| Haematuria* | 0 | 0 | 0 | 2 (3) | 2 (3) | 0 | *2 (1)* | *2 (1)* | *0* |
| Micturition Frequency* | 0 | 0 | 0 | 1 (1) | 1 (1) | 0 | *1 (1)* | *1 (1)* | *0* |
| Renal Failure Acute* | 0 | 0 | 0 | 1 (1) | 0 | 1 (1) | *1 (1)* | *0* | *1 (1)* |
| **Liver and Biliary System Disorders*** | **3 (5)** | **3 (5)** | **0** | **3 (4)** | **3 (4)** | **0** | ***6 (4)*** | ***6 (4)*** | ***0*** |
| Bilirubinaemia* | 2 (3) | 2 (3) | 0 | 3 (4) | 3 (4) | 0 | *5 (4)* | *5 (4)* | *0* |
| Cholelithiasis* | 0 | 0 | 0 | 1 (1) | 1 (1) | 0 | *1 (1)* | *1 (1)* | *0* |
| Hepatic Function Abnormal* | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | *1 (1)* | *1 (1)* | *0* |

See Table 19 footnotes.

Most frequent drug related AEs were neutropenic fever (17%), creatininemia (5%), bacterial infection (5%) and diarrhea (4%). Drug-related grade 3 or 4 AEs that occurred in more than one subject are summarized as below:

**Table 23: Drug-Related Serious Adverse Events (> 1 Subject, CTEP-20: Elderly Poor-Risk AML Subset)**

| WHO Preferred Term | 65-74 y prior MDS (N = 61) n (%) | | ≥ 75 y (N = 75) n (%) | | *Total N= 136 n (%)* | |
|---|---|---|---|---|---|---|
| | All | Drug Related | All | Drug Related | *All* | *Drug Related* |
| Total no. subjects with SAE[a] | 38 (62) | 23 (38) | 50 (67) | 35 (47) | *88 (65)* | *58 (43)* |
| Neutropenia febrile | 17 (28) | 14 (23) | 16 (21) | 9 (12) | *33 (24)* | *23 (17)* |
| Creatinine blood increased | 5 (8) | 2 (3) | 6 (8)[b] | 5 (7) | *11 (8)[b]* | *7 (5)* |
| Infection bacterial | 8 (13) | 3 (5) | 8 (11) | 4 (5) | *16 (12)* | *7 (5)* |
| Diarrhea | 2 (3) | 2 (3) | 4 (5) | 3 (4) | *6 (4)* | *5 (4)* |
| Anemia | 2 (3) | 2 (3) | 3 (4) | 2 (3) | *5 (4)* | *4 (3)* |
| Dehydration | 3 (5) | 1 (2) | 5 (7) | 3 (4) | *8 (6)* | *4 (3)* |
| Fever | 8 (13) | 2 (3) | 6 (8) | 2 (3) | *14 (10)* | *4 (3)* |
| Neutropenia | 1 (2) | 1 (2) | 4 (5) | 3 (4) | *5 (4)* | *4 (3)* |
| Pancreas enzymes increased | 2 (3) | 2 (3) | 2 (3) | 2 (3) | *4 (3)* | *4 (3)* |
| Infection fungal | 4 (7) | 2 (3) | 1 (1) | 1 (1) | *5 (4)* | *3 (2)* |
| Nausea | 1 (2) | 1 (2) | 3 (4) | 2 (3) | *4 (3)* | *3 (2)* |
| Pancytopenia | 3 (5) | 3 (5) | 0 | 0 | *3 (2)* | *3 (2)* |
| Pneumonia | 3 (5) | 1 (2) | 6 (8) | 2 (3) | *9 (7)* | *3 (2)* |
| Rash | 3 (5) | 2 (3) | 3 (4) | 1 (1) | *6 (4)* | *3 (2)* |
| Vomiting | 2 (3) | 2 (3) | 2 (3) | 1 (1) | *4 (3)* | *3 (2)* |
| Ataxia | 0 | 0 | 2 (3) | 2 (3) | *2 (1)* | *2 (1)* |
| Bilirubinemia | 1 (2) | 1 (2) | 2 (3) | 1 (1) | *3 (2)* | *2 (1)* |
| Confusion | 2 (3) | 1 (2) | 2 (3) | 1 (1) | *4 (3)* | *2 (1)* |
| Fatigue | 2 (3) | 1 (2) | 6 (8) | 1 (1) | *8 (6)* | *2 (1)* |
| Hypotension postural | 1 (2) | 1 (2) | 1 (1) | 1 (1) | *2 (1)* | *2 (1)* |
| Pneumonia lobar | 1 (2) | 1 (2) | 2 (3) | 1 (1) | *3 (2)* | *2 (1)* |
| Skin reaction localized | 2 (3) | 1 (2) | 6 (8) | 1 (1) | *8 (6)* | *2 (1)* |
| Thrombocytopenia | 2 (3) | 1 (2) | 2 (3) | 1 (1) | *4 (3)* | *2 (1)* |

a Some subjects had more than 1 SAE or drug-related SAE.
b For 1 subject (101005), an SAE of hypercreatinemia was coded to urinary system disorders rather than metabolic and nutritional disorders.
Reference: Zarnestra NDA, CTEP-20 study report Table 48, attachments 3.7.1.1 and 3.7.2.1.

The attribution of AEs to Zarnestra was determined by the investigators' assessments. Total drug-related all grade AEs were reported in 87% of subjects; among them 61% of grade 3 or 4 AEs were drug-related

**Table 24: Drug-Related Adverse Events Reported in at Least 5% of Subjects – Part 1 (CTEP-20: Elderly Poor-Risk AML Subset)**

| Body System<br>WHO Preferred Term | 65-74 y prior MDS<br>N = 61 (%) | | | ≥ 75 y<br>N = 75 (%) | | | *Total*<br>*N= 136 (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | All | Drug Related | | All | Drug Related | | *All* | *Drug Related* | |
| | Any | Any | Grade 3 or 4 | Any | Any | Grade 3 or 4 | *Any* | *Any* | *Grade 3 or 4* |
| **Total no. subjects with AE[a]** | **60 (98)** | **53 (87)** | **37 (61)** | **74 (99)** | **65 (87)** | **46 (61)** | ***134 (99)*** | ***118 (87)*** | ***83 (61)*** |
| **Gastrointestinal system disorders** | **45 (74)** | **27 (44)** | **10 (16)** | **62 (83)** | **48 (64)** | **10 (13)** | ***107 (79)*** | ***75 (55)*** | ***20 (15)*** |
| Diarrhea | 29 (48) | 17 (28) | 4 (7) | 35 (47) | 24 (32) | 2 (3) | *64 (47)* | *41 (30)* | *6 (4)* |
| Nausea | 25 (41) | 18 (30) | 3 (5) | 26 (35) | 23 (31) | 3 (4) | *51 (38)* | *41 (30)* | *6 (4)* |
| Anorexia | 15 (25) | 9 (15) | 0 | 22 (29) | 16 (21) | 0 | *37 (27)* | *25 (18)* | *0* |
| Vomiting | 12 (20) | 10 (16) | 3 (5) | 20 (27) | 15 (20) | 2 (3) | *32 (24)* | *25 (18)* | *5 (4)* |
| Constipation | 13 (21) | 4 (7) | 1 (2) | 20 (27) | 8 (11) | 0 | *33 (24)* | *12 (9)* | *1 (1)* |
| Abdominal pain | 11 (18) | 4 (7) | 2 (3) | 11 (15) | 7 (9) | 1 (1) | *22 (16)* | *11 (8)* | *3 (2)* |
| Stomatitis | 11 (18) | 4 (7) | 2 (3) | 15 (20) | 3 (4) | 1 (1) | *26 (19)* | *7 (5)* | *3 (2)* |
| **Body as a whole – general disorders** | **47 (77)** | **22 (36)** | **4 (7)** | **60 (80)** | **27 (36)** | **8 (11)** | ***107 (79)*** | ***49 (36)*** | ***12 (9)*** |
| Fatigue | 30 (49) | 17 (28) | 1 (2) | 30 (40) | 18 (24) | 5 (7) | *60 (44)* | *35 (26)* | *6 (4)* |
| Fever | 21 (34) | 6 (10) | 2 (3) | 21 (28) | 6 (8) | 1 (1) | *42 (31)* | *12 (9)* | *3 (2)* |
| **Nervous system disorders** | **32 (52)** | **19 (31)** | **3 (5)** | **45 (60)** | **30 (40)** | **7 (9)** | ***77 (57)*** | ***49 (36)*** | ***10 (7)*** |
| Dizziness | 16 (26) | 9 (15) | 0 | 20 (27) | 8 (11) | 1 (1) | *36 (26)* | *17 (13)* | *1 (1)* |
| Ataxia | 5 (8) | 3 (5) | 0 | 11 (15) | 11 (15) | 3 (4) | *16 (12)* | *14 (10)* | *3 (2)* |
| Tremor | 6 (10) | 6 (10) | 0 | 9 (12) | 6 (8) | 0 | *15 (11)* | *12 (9)* | *0* |
| Headache | 17 (28) | 6 (10) | 0 | 7 (9) | 3 (4) | 0 | *24 (18)* | *9 (7)* | *0* |
| **Skin and appendages disorders** | **38 (62)** | **20 (33)** | **6 (10)** | **34 (45)** | **20 (27)** | **8 (11)** | ***72 (53)*** | ***40 (29)*** | ***14 (10)*** |
| Rash | 25 (41) | 13 (21) | 3 (5) | 23 (31) | 17 (23) | 6 (8) | *48 (35)* | *30 (22)* | *9 (7)* |

a Table sorted by descending incidence of any drug related AEs by system. The toxicity grade followed NCI CTC2.0

(Continued)

Reference: Zarnestra NDA, CTEP-20 study report attachments 3.2.1.1, 3.4.1.1, and 3.4.2.1.

**Table 25: Drug-Related Adverse Events Reported in at Least 5% of Subjects – Part 2 (CTEP-20: Elderly Poor-Risk AML Subset)**

| Body System<br>WHO Preferred Term | 65-74 y prior MDS<br>N = 61 (%) | | | ≥ 75 y<br>N = 75 (%) | | | *Total*<br>*N= 136 (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | All | Drug Related | | All | Drug Related | | *All* | *Drug Related* | |
| | Any | Any | Grade 3 or 4 | Any | Any | Grade 3 or 4 | *Any* | *Any* | *Grade 3 or 4* |
| **White cell disorders** | **26 (43)** | **20 (33)** | **20 (33)** | **31 (41)** | **19 (25)** | **19 (25)** | ***57 (42)*** | ***39 (29)*** | ***39 (29)*** |
| Neutropenia febrile | 18 (30) | 14 (23) | 14 (23) | 22 (29) | 13 (17) | 13 (17) | *40 (30)* | *27 (20)* | *27 (20)* |
| Neutropenia | 9 (15) | 7 (11) | 7 (11) | 8 (11) | 6 (8) | 5 (7) | *17 (13)* | *13 (10)* | *12 (9)* |
| **Metabolic and nutritional disorders** | **29 (48)** | **15 (25)** | **3 (5)** | **34 (45)[b]** | **18 (24)** | **5 (7)** | ***63 (46)[b]*** | ***33 (24)*** | ***8 (6)*** |
| Creatinine blood increased | 12 (20) | 5 (8) | 1 (2) | 18 (24)[b] | 12 (16) | 2 (3) | *30 (22)[b]* | *17 (13)* | *3 (2)* |
| Dehydration | 4 (7) | 1 (2) | 1 (2) | 13 (17) | 6 (8) | 2 (3) | *17 (13)* | *7 (5)* | *3 (2)* |
| **Psychiatric disorders** | **27 (44)** | **11 (18)** | **2 (3)** | **34 (45)** | **19 (25)** | **7 (9)** | ***61 (45)*** | ***30 (22)*** | ***9 (7)*** |
| Confusion | 12 (20) | 5 (8) | 1 (2) | 17 (23) | 10 (13) | 5 (7) | *29 (21)* | *15 (11)* | *6 (4)* |
| Amnesia | 6 (10) | 5 (8) | 0 | 6 (8) | 5 (7) | 1 (1) | *12 (9)* | *10 (7)* | *1 (1)* |
| **Platelet, bleeding, & clotting disorders** | **28 (46)** | **14 (23)** | **9 (15)** | **37 (49)** | **11 (15)** | **7 (9)** | ***65 (48)*** | ***25 (18)*** | ***16 (12)*** |
| Thrombocytopenia | 12 (20) | 10 (16) | 8 (13) | 14 (19) | 8 (11) | 7 (9) | *26 (19)* | *18 (13)* | *15 (11)* |
| **Urinary system disorders** | **25 (41)** | **12 (20)** | **0** | **19 (25)** | **7 (9)** | **1 (1)** | ***44 (32)*** | ***19 (14)*** | ***1 (1)*** |
| Renal function abnormal | 5 (8) | 3 (5) | 0 | 5 (7) | 4 (5) | 0 | *10 (7)* | *7 (5)* | *0* |
| **Resistance mechanism disorders** | **22 (36)** | **7 (11)** | **6 (10)** | **27 (36)** | **9 (12)** | **7 (9)** | ***49 (36)*** | ***16 (12)*** | ***13 (10)*** |
| Infection bacterial | 13 (21) | 4 (7) | 4 (7) | 14 (19) | 6 (8) | 5 (7) | *27 (20)* | *10 (7)* | *9 (7)* |
| **RBC disorders** | **7 (11)** | **6 (10)** | **1 (2)** | **20 (27)** | **6 (8)** | **4 (5)** | ***27 (20)*** | ***12 (9)*** | ***5(4)*** |
| Anemia | 7 (11) | 6 (10) | 1 (2) | 17 (23) | 6 (8) | 4 (5) | *24 (18)* | *12 (9)* | *5(4)* |
| **Special senses and other disorders** | **8 (13)** | **6 (10)** | **0** | **5 (7)** | **4 (5)** | **0** | ***13 (10)*** | ***10 (7)*** | ***0*** |
| Taste perversion | 8 (13) | 6 (10) | 0 | 5 (7) | 4 (5) | 0 | *13 (10)* | *10 (7)* | *0* |

a Table sorted by descending incidence of any drug related AEs by systems.

b For 2 subjects (101005 and 101039), hypercreatinemia was coded to urinary system disorders rather than metabolic and nutritional disorders. For consistency, these 2 subjects are included in the latter body system in this report.

Reference: Zarnestra NDA, CTEP-20 study report attachments 3.2.1.1, 3.4.1.1, and 3.4.2.1.

## 6.5 Significant Adverse Events that Caused Treatment Termination or Other Clinically Significant Outcome

6.5.1 AEs that Caused Treatment Termination:

Examining the CTEP-20 study report and data sets, the reviewer agrees with the sponsor that the incidence of AEs leading to treatment termination was 15% (Table 25). Among them, 10% of treatment terminations were due to drug-related AEs. The most common drug-related AEs leading to treatment termination were increased creatinine (3 subjects), rash (3 subjects), and increased pancreatic enzymes (2 subjects).

**Table 26: Drug-Related Adverse Events Leading to Treatment Termination (CTEP-20: Elderly Poor-Risk AML Subset)**

| | 65-74 y prior MDS (N = 61) n (%) | | ≥ 75 y (N = 75) n (%) | | **Total N= 136 n (%)** | |
|---|---|---|---|---|---|---|
| WHO Preferred Term | All | Drug Related | All | Drug Related | **All** | **Drug Related** |
| Total no. subjects with AE[a] | 11 (18) | 7 (11) | 10 (13) | 7 (9) | **21 (15)** | **14 (10)** |
| Creatinine blood increased | 2 (3) | 1 (2) | 2 (3) | 2 (3) | **4 (3)** | **3 (2)** |
| Rash | 3 (5) | 2 (3) | 1 (1) | 1 (1) | **4 (3)** | **3 (2)** |
| Pancreas enzymes increased | 0 | 0 | 2 ( 3) | 2 (3) | **2 (1)** | **2 (1)** |
| Dehydration | 0 | 0 | 1 (1) | 1 (1) | **1 (1)** | **1 (1)** |
| Diarrhea | 0 | 0 | 1 (1) | 1 (1) | **1 (1)** | **1 (1)** |
| Dizziness | 0 | 0 | 1 (1) | 1 (1) | **1 (1)** | **1 (1)** |
| Fatigue | 1 (2) | 1 (2) | 0 | 0 | **1 (1)** | **1 (1)** |
| Insomnia | 1 (2) | 1 (2) | 0 | 0 | **1 (1)** | **1 (1)** |
| Nausea | 1 (2) | 1 (2) | 0 | 0 | **1 (1)** | **1 (1)** |
| Neuropathy peripheral | 1 (2) | 1 (2) | 0 | 0 | **1 (1)** | **1 (1)** |
| Sweating increased | 1 (2) | 1 (2) | 0 | 0 | **1 (1)** | **1 (1)** |

a Some subjects had more than 1 AE or drug-related AE that resulted in treatment termination.

Reference: Zarnestra NDA, CTEP-20 study report Table 49, attachments 3.8.1.1 and 3.8.2.1

6.5.2 AEs that Caused Dose Reduction:

Examining CTEP-20 data, the reviewer agrees with the sponsor findings of AEs leading to dose reduction. There were 47 subjects (35%) with at least 1 AE leading to dose reduction at any time during the study. The AE was considered drug-related for 35 (26%) subjects. The most common drug-related AEs leading to dose reduction were febrile neutropenia (4%), ataxia (4%), and increased creatinine (3%). If grouping the AEs by general medical conditions, it appears that most AEs resulting in dose reduction can be attributed to infections, CNS, and renal conditions.

**Table 27: Drug-Related Adverse Events Leading to Dose Reduction (CTEP-20: Elderly Poor-Risk AML Subset)**

| | 65-74 y prior MDS (N = 61) n (%) | | ≥ 75 y (N = 75) n (%) | | ***Total (N= 136) n (%)*** | |
|---|---|---|---|---|---|---|
| WHO Preferred Term | All | Drug Related | All | Drug Related | ***All*** | ***Drug Related*** |
| Total no. subjects with AE[a] | 23 (38) | 19 (31) | 24 (32) | 16 (21) | ***47 (35)*** | ***35 (26)*** |
| Neutropenia febrile | 5 (8) | 3 (5) | 4 (5) | 3 (4) | ***9 (7)*** | ***6 (4)*** |
| Ataxia | 2 (3) | 2 (3) | 3 (4) | 3 (4) | ***5 (4)*** | ***5 (4)*** |
| Creatinine blood increased | 3 (5) | 2 (3) | 3 (4) | 2 (3) | ***6 (4)*** | ***4 (3)*** |
| Confusion | 3 (5) | 2 (3) | 3 (4) | 1 (1) | ***6 (4)*** | ***3 (2)*** |
| Diarrhea | 1 (2) | 1 (2) | 3 (4) | 2 (3) | ***4 (3)*** | ***3 (2)*** |
| Neutropenia | 2 (3) | 2 (3) | 2 (3) | 1 (1) | ***4 (3)*** | ***3 (2)*** |
| Pancreas enzymes increased | 2 (3) | 2 (3) | 1 (1) | 1 (1) | ***3 (2)*** | ***3 (2)*** |
| Rash | 1 (2) | 0 | 4 (5) | 3 (4) | ***5 (4)*** | ***3 (2)*** |
| Renal function abnormal | 1 (2) | 1 (2) | 2 (3) | 2 (3) | ***3 (2)*** | ***3 (2)*** |
| Amnesia | 1 (2) | 1 (2) | 1 (1) | 1 (1) | ***2 (1)*** | ***2 (1)*** |
| Bilirubinemia | 2 (3) | 1 (2) | 1 (1) | 1 (1) | ***3 (2)*** | ***2 (1)*** |
| Fatigue | 1 (2) | 1 (2) | 1 (1) | 1 (1) | ***2 (1)*** | ***2 (1)*** |
| Hypotension postural | 0 | 0 | 2 (3) | 2 (3) | ***2 (1)*** | ***2 (1)*** |
| Infection bacterial | 3 (5) | 2 (3) | 0 | 0 | ***3 (2)*** | ***2 (1)*** |
| Tremor | 1 (2) | 1 (2) | 1 (1) | 1 (1) | ***2 (1)*** | ***2 (1)*** |
| Vomiting | 2 (3) | 2 (3) | 0 | 0 | ***2 (1)*** | ***2 (1)*** |
| Abdominal pain | 1 (2) | 1 (2) | 0 | 0 | ***1 (1)*** | ***1 (1)*** |
| Anxiety | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| BUN increased | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Dizziness | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Hypokalemia | 1 (2) | 1 (2) | 0 | 0 | ***1 (1)*** | ***1 (1)*** |
| Hypotension | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Nausea | 1 (2) | 1 (2) | 0 | 0 | ***1 (1)*** | ***1 (1)*** |
| Pancytopenia | 1(2) | 1 (2) | 1(1) | 0 | ***2(1)*** | ***1(1)*** |
| Polyuria | 0 | 0 | 1 (1) | 1(1) | ***1(1)*** | ***1(1)*** |
| Syncope | 0 | 0 | 1 (1) | 1(1) | ***1(1)*** | ***1(1)*** |
| Thrombocytopenia | 1 (2) | 1 (2) | 0 | 0 | ***1 (1)*** | ***1 (1)*** |

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

Reference: Zarnestra NDA, CTEP-20 study report Table 50, attachments 3.9.1.1 and 3.9.2.1.

6.5.3 AEs that Caused Treatment Interruption:

Examining the CTEP-20 data, the reviewer agrees with the sponsor findings that 56 subjects (41%) had at least 1 AE leading to temporary interruption of Zarnestra. The AE was considered drug related for 45 (33%) subjects. The most common drug-related AEs leading to temporary interruption of tipifarnib were neutropenia (6%), increased creatinine (5%), nausea (4%), febrile neutropenia (4%), and rash (4%). When grouping the AEs by general medical conditions, most AEs resulting in temporary interruption of tipifarnib can be attributed to infections, renal, gastrointestinal, and CNS conditions.

**Table 28: Drug-Related Adverse Events Leading to Temporary Interruption of Zanestra (CTEP-20: Elderly Poor-Risk AML Subset)**

| | 65-74 y prior MDS (N = 61) n (%) | | ≥ 75 y (N = 75) n (%) | | ***Total N= 136 n (%)*** | |
|---|---|---|---|---|---|---|
| WHO Preferred Term | All | Drug Related | All | Drug Related | ***All*** | ***Drug Related*** |
| Total no. subjects with AE[a] | 25 (41) | 20 (33) | 31 (41) | 25 (33) | ***56 (41)*** | ***45 (33)*** |
| Neutropenia | 6 (10) | 4 (7) | 4 (5) | 4 (5) | ***10 (7)*** | ***8 (6)*** |
| Creatinine blood increased | 2 (3) | 2 (3) | 8 (11) | 5 (7) | ***10 (7)*** | ***7 (5)*** |
| Nausea | 4 (7) | 4 (7) | 2 (3) | 2 (3) | ***6 (4)*** | ***6 (4)*** |
| Neutropenia febrile | 4 (7) | 4 (7) | 4 (5) | 2 (3) | ***8 (6)*** | ***6 (4)*** |
| Rash | 2 (3) | 2 (3) | 3 (4) | 3 (4) | ***5 (4)*** | ***5 (4)*** |
| Confusion | 0 | 0 | 3 (4) | 3 (4) | ***3 (2)*** | ***3 (2)*** |
| Pancytopenia | 4 (7) | 3 (5) | 0 | 0 | ***4 (3)*** | ***3 (2)*** |
| Vomiting | 2 (3) | 2 (3) | 1 (1) | 1 (1) | ***3 (2)*** | ***3 (2)*** |
| Ataxia | 0 | 0 | 2 (3) | 2 (3) | ***2 (1)*** | ***2 (1)*** |
| Bilirubinemia | 1 (2) | 0 | 2 (3) | 2 (3) | ***3 (2)*** | ***2 (1)*** |
| Diarrhea | 3 (5) | 2 (3) | 0 | 0 | ***3 (2)*** | ***2 (1)*** |
| Gait abnormal | 1 (2) | 1 (2) | 1 (1) | 1 (1) | ***2 (1)*** | ***2 (1)*** |
| Infection bacterial | 1 (2) | 1 (2) | 2 (3) | 1 (1) | ***3 (2)*** | ***2 (1)*** |
| Infection fungal | 1 (2) | 1 (2) | 1 (1) | 1 (1) | ***2 (1)*** | ***2 (1)*** |
| Neuropathy peripheral | 2 (3) | 2 (3) | 0 | 0 | ***2 (1)*** | ***2 (1)*** |
| Pneumonia | 1 (2) | 0 | 3 (4) | 2 (3) | ***4 (3)*** | ***2 (1)*** |
| Amnesia | 1 (2) | 1 (2) | 0 | 0 | ***1 (1)*** | ***1 (1)*** |
| Anemia | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Anorexia | 1 (2) | 0 | 1 (1) | 1 (1) | ***2 (1)*** | ***1 (1)*** |
| Dehydration | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Gastroenteritis | 1 (2) | 1 (2) | 0 | 0 | ***1 (1)*** | ***1 (1)*** |
| Leukopenia | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Pneumonia lobar | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Pruritus | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Renal function abnormal | 2 (3) | 1 (2) | 0 | 0 | ***2 (1)*** | ***1 (1)*** |
| Sepsis | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Skin reaction localized | 0 | 0 | 2 (3) | 1 (1) | ***2 (1)*** | ***1 (1)*** |
| Stomatitis | 0 | 0 | 1 (1) | 1 (1) | ***1 (1)*** | ***1 (1)*** |
| Thrombocytopenia | 3 (5) | 1 (2) | 1 (1) | 0 | ***4 (3)*** | ***1 (1)*** |

a Some subjects had more than 1 AE or drug-related AE leading to temporary interruption of tipifarnib.
Reference: Zarnestra NDA, CTEP-20 study report Table 50, attachments 3.9.3.1 and 3.9.4.1.

6.5.4. Drug-Related AEs with Unfavorable Outcome:

Based on the sponsor provided data, most of the treatment emergent AEs reported from CTEP-20 study were reversible. However, there were some treatment emergent drug-related AEs that had clinically unfavorable outcome (persistent toxicity or death), which the reviewer summarized as follows:

**Table 29: Drug-Related AEs that Had Unfavorable Outcome (persistent toxicity or death)**

| | Total (N= 136) | | |
|---|---|---|---|
| Body System Who Preferred Term | Total n (%) | Persistent | Death |
| Total No. Subjects With Adverse Event | 118 (87) | | |
| **Gastro-Intestinal System Disorders** | **75 (55)** | **20** | **0** |
| Diarrhoea | 41 (30) | 5 | 0 |
| Nausea | 41 (30) | 7 | 0 |
| Anorexia | 25 (18) | 8 | 0 |
| Vomiting | 25 (18) | 4 | 0 |
| Constipation | 12 (9) | 2 | 0 |
| Abdominal Pain | 11 (8) | 2 | 0 |
| Stomatitis | 7 (5) | 2 | 0 |
| **Body As A Whole - General Disorders** | **49 (36)** | **16** | **0** |
| Fatigue | 35 (26) | 14 | 0 |
| Oedema | 2 (1) | 1 | 0 |
| Multiple Organ Failure | 1 (1) | 1 | 0 |
| Pallor | 1 (1) | 1 | 0 |
| **Centr & Periph Nervous System Disorders** | **49 (36)** | **9** | **0** |
| Dizziness | 17 (13) | 3 | 0 |
| Tremor | 12 (9) | 4 | 0 |
| Headache | 9 (7) | 1 | 0 |
| Muscle Contraction Involuntary | 1 (1) | 1 | 0 |
| Nystagmus | 1 (1) | 1 | 0 |
| **Skin And Appendages Disorders** | **40 (29)** | **9** | **0** |
| Rash | 30 (22) | 6 | 0 |
| Skin Disorder | 1 (1) | 1 | 0 |
| Sweating Increased | 1 (1) | 1 | 0 |
| **White Cell And RES Disorders** | **39 (29)** | **8** | **0** |
| Neutropenia Febrile | 27 (20) | 3 | 0 |
| Neutropenia | 13 (10) | 5 | 0 |
| Pancytopenia | 4 (3) | 1 | 0 |
| **Metabolic And Nutritional Disorders** | **33 (24)** | **9** | **0** |
| Creatinine Blood Increased | 17 (13) | 7 | 0 |
| Dehydration | 7 (5) | 1 | 0 |
| Weight Decrease | 5 (4) | 2 | 0 |
| **Psychiatric Disorders** | **30 (22)** | **10** | **0** |
| Confusion | 15 (11) | 4 | 0 |
| Amnesia | 10 (7) | 3 | 0 |
| Insomnia | 5 (4) | 3 | 0 |
| **Platelet, Bleeding & Cloting disorders** | **25 (18)** | **5** | **0** |
| Thrombocytopenia | 18 (13) | 4 | 0 |
| Purpura | 4 (3) | 1 | 0 |

(Continue)

| | Total (N= 136) | | |
|---|---|---|---|
| Body System Who Preferred Term | Total n (%) | Persistent | Death |
| **Respiratory System Disorders** | **23 (17)** | **4** | **0** |
| Pneumonia | 6 (4) | 2 | 0 |
| Sinusitis | 4 (3) | 1 | 0 |
| Pulmonary Granuloma | 2 (1) | 1 | 0 |
| Haemoptysis | 1 (1) | 1 | 0 |
| Hypoxia | 1 (1) | 1 | 0 |
| **Urinary System Disorders** | **19 (14)** | **2** | **0** |
| Renal Function Abnormal | 7 (5) | 1 | 0 |
| Nocturia | 3 (2) | 1 | 0 |
| **Resistance Mechanism Disorders** | **16 (12)** | **4** | **1** |
| Infection Fungal | 4 (3) | 2 | 1 |
| Infection Viral | 2 (1) | 1 | 0 |
| Herpes Zoster | 1 (1) | 1 | 0 |
| **Red Blood Cell Disorders** | **12 (9)** | **4** | **0** |
| Anemia | 12 (9) | 4 | 0 |
| **Special Senses Other, Disorders** | **10 (7)** | **4** | **0** |
| Taste Perversion | 10 (7) | 4 | 0 |
| **Vision Disorders** | **9 (7)** | **5** | **0** |
| Conjunctivitis | 3 (2) | 1 | 0 |
| Conjunctival Discolouration | 2 (1) | 2 | 0 |
| Vision Abnormal | 2 (1) | 2 | 0 |
| **Liver And Biliary System Disorders** | **8 (6)** | **3** | **0** |
| Bilirubinaemia | 6 (4) | 2 | 0 |
| Sgot Increased | 2 (1) | 1 | 0 |
| Sgpt Increased | 2 (1) | 1 | 0 |
| **Musculo- Skeletal System Disorders** | **3 (2)** | **1** | **0** |
| Muscle Weakness | 3 (2) | 1 | 0 |

Reference: Zarnestra NDA, CTEP-20 study report attachment 3.4.3.1

## 6.6 Deaths

Thirty-one patients (23%) of the 136 elderly poor-risk AML subjects in CTEP-20 study died either within 30 days of treatment termination or within 30 days of receiving the first dose of medication. Based on the sponsor provided data, the reviewer verified the sponsor's summary and agrees that the cause of 61% of deaths (19/31) was disease progression and 29% (9/31) was due to AEs. There was one patient (3%, 1/31) who died due to drug related AEs (neutropenic fever, fungal infection, and renal dysfunction, ID 100336). There were 3/31 (10%) of deaths attributed to AEs or progression of disease on subsequent treatment after patients progressed from tipifarnib, which the sponsor categorized as other cause of death. The finding is summarized as follows:

**Table 30: Main Cause of Death Within 30 Day of Study Termination and Within 30 Days of Receiving the Fist Dose (CTEP-20: Elderly Poor-Risk AML Population)**

| Cause of Death | 65-74 y prior MDS N = 61 (%) | ≥ 75 y N = 75 (%) | *Total N= 136 (%)* |
|---|---|---|---|
| **Deaths during the study[a]** | **8 (13)** | **23 (31)** | ***31 (23)*** |
| Progressive disease | 6 (10) | 13 (17) | *19 (14)* |
| Adverse event | 2 (3) | 7 (9) | *9 (7)* |
| Drug related | 0 | 1 (1) | *1 (1)* |
| Other[c] | 0 | 3 (4) | *3 (2)* |
| **Early deaths[b]** | **3 (5)** | **13 (17)** | ***16 (12)*** |
| *Death within 14 days of first dose* | *1 (2)* | *3 (4)* | *4 (3)* |
| Progressive disease | 1 (2) | 2 (3) | *3 (2)* |
| Other[c] | 0 | 1 (1) | *1 (1)* |
| *Death within 15-30 days of first dose* | *2 (3)* | *10 (13)* | *12 (9)* |
| Adverse event | 2 (3) | 3 (4) | *5 (4)* |
| Drug related | 0 | 0 | *0* |
| Progressive disease | 0 | 6 (8) | *6 (4)* |
| Other[c] | 0 | 1 (1) | *1 (1)* |

a Deaths within 30 days after treatment termination or before subsequent treatment, whichever occurred first.
b Deaths within 30 days after the first dose of tipifarnib.
c. Death due to AE or PD on subsequent treatment
Reference: Zarnestra NDA, CTEP-20 study report Table 46, attachments 3.1.1, 3.6.1.1, 3.5.1, 3.5.2, 5.5.3, 3.6.2.1, and 3.6.4.1.

All deaths (9/136, 7%) due to AEs were thought not to be study drug related by the investigator, except one patient who died of drug related neutropenic fever (very likely related), fungal infection (possible related) and renal dysfunction (probably related). Again, the treatment emergent all grade AEs in study CTEP-20 were 89% and the deaths due to AE(s) were 3%. All lethal AEs reported by the sponsor are summarized as below:

**Table 31: Death during the Study Caused by Adverse Events (CTEP- 20: Elderly Poor-Risk AML Subset)**

| WHO Preferred Term | 65-74 y prior MDS N = 61 (%) | ≥ 75 y N = 75 (%) | **Total N= 136 (%)** |
|---|---|---|---|
| Total no. subjects who died[a] | 2 (3) | 7 (9) | **9 (7)** |
| Cardiac failure | 1 (2) | 2 (3) | **3 (2)** |
| Sepsis | 1 (2) | 2 (3) | **3 (2)** |
| Infection fungal | 1 (2) | 1 (1) | **2 (1)** |
| Pneumonia | 0 | 2 (3) | **2 (1)** |
| Arrhythmia atrial | 0 | 1 (1) | **1 (1)** |
| Circulatory failure | 0 | 1 (1) | **1 (1)** |
| Fibrillation atrial | 1 (2) | 0 | **1 (1)** |
| Gastrointestinal hemorrhage | 0 | 1 (1) | **1 (1)** |
| Hypoxia | 1 (2) | 0 | **1 (1)** |
| Multiple organ failure | 0 | 1 (1) | **1 (1)** |
| Neutropenia febrile | 1 (2) | 0 | **1 (1)** |
| Pulmonary hemorrhage | 1 (2) | 0 | **1 (1)** |
| Renal failure acute | 0 | 1 (1) | **1 (1)** |

a Includes deaths within 30 days after treatment termination or before subsequent treatment, whichever was earlier. Some subjects may have had more than 1 AE or drug- related AE that resulted in death.
Reference: Zarnesstra NDA, CTEP-20 study report appendixes 3.5.1 and 3.6.5.1.

## 7. FDA's Efficacy and Safety Summary

By FDA analysis, the CTEP-20 single arm study included 135 eligible patients, age 65 or older, with untreated poor-risk AML for efficacy evaluation. FDA's assessment of efficacy and safety of CTEP-20 study are as follows:

A. Efficacy:

1. The primary endpoint is CR rate. FDA determined that the confirmed CR rate is 11% with 95% CI of 6.6-18% in elderly patients with untreated poor-risk AML.

2. The secondary endpoint of duration of CR was analyzed based on the FDA determined CRs. The median duration of CR was 275 days with 95% CI of 127-376 days in elderly patients with untreated poor-risk AML.

B. Safety:

1. The safety results for elderly subjects with poor-risk AMLfrom CTEP-20 study (n= 136) are reviewed. The majority of patients had 1-2 cycles of treatment. There were 98% all treatment emergent adverse events (AEs), of which 87% were thought related to the study drug by the investigator. For all treatment emergent AEs, those reported most frequently (79%) were in the body-as-a-whole and gastrointestinal body systems. The most frequently reported AEs (all grades) were diarrhea (47%), fatigue (44%), nausea (38%), and rash (35%).

2. There were 83% treatment emergent and 61% drug related grade 3 or 4 AEs. The most frequent treatment emergent grade 3 or 4 hematological and nonhematologic AEs were secondary to myelosuppression, including neutropenia with or without neutropenic fever (41%), infections (27%), thrombocytopenia 17%, fatigue (13%), pneumonia (10%), rash (9%) anemia (8%), dyspnea (8%), and confusion (7%). Most frequent drug related AEs were neutropenic fever (17%), creatininemia (5%), bacteria infection (5%) and diarrhea (4%).

3. The incidence of AEs leading to treatment termination was 15%. Among them, 10% of treatment terminations were due to drug-related AEs. The most common drug-related AEs leading to treatment termination were increased creatinine, rash, and increased pancreatic enzymes.

4. There were 35% (47/136) of subjects with at least 1 AE leading to dose reduction at any time during the study, which includes 26% (35/136) of subjects with drug related AE. The most common drug-related AEs leading to dose reduction were febrile neutropenia (4%), ataxia (4%), and increased creatinine (3%), indicating that most AEs resulting in dose reduction can be attributed to infections, CNS, and renal conditions.

5. Forty-one percent (56/136) of subjects had at least one AE leading to temporary interruption of Zarnestra, of which 33% (45/136) were drug related AEs. The most

common drug-related AEs leading to temporary interruption of tipifarnib were neutropenia (6%), increased creatinine (5%), nausea (4%), febrile neutropenia (4%), and rash (4%).

6. Thirty-one patients (23%) died either within 30 days of treatment termination or within 30 days of receiving the first dose of medication. The cause of 61% of deaths (19/31) was disease progression and of 29% (9/31) was due to AEs which includes one subject (3%, 1/31) who died due to AEs that related to Zarnestra (neutropenia, fungal infection, and renal dysfunction).

## VIII. References

1. Cervera A, Djulbegovic B. Acute myelogenous leukemia. Decision Making in Oncology: Evidence-Based Management. Djulbegovic B, Sullivan DM, eds. 1997; Churchill Livingstone: 29- 36. EDMS- PSDB- 3408747.

2. American Cancer Society.: Cancer Facts and Figures 2005. Atlanta, Ga: American Cancer Society, 2005. Also available online. Last accessed January 27, 2005.

3. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. Arch Intern Med 2002; 162: 1597- 1603. EDMS- PSDB- 3732474.

4. Lowenberg B, Downing JR, and Burnett A. Acute myeloid leukemia. NEJM, 341 (4) 105101062, 1999.

5. Brunning RD, Matutes E, Harris NL, et al.: Acute myeloid leukaemia: introduction. In: Jaffe ES, Harris NL, Stein H, et al., eds.: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press, 2001. World Health Organization Classification of Tumours, 3, pp 77-80.

6. Cheson BD, Cassileth PA, Head DR, et al.: Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. J Clin Oncol 8 (5): 813-9, 1990.

7. Vardiman JW, Harris NL, Brunning RD. The world health organization (WHO) classification of the myeloid neoplasms. Blood, 2002; 100:2292-2302.

8. Scheinberg DA, Maslak P, Weiss M: Acute leukemias. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds.: Cancer: Principles and Practice of Oncology. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2001, pp 2404-32.

9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology- v. 1.2004. Acute Myeloid Leukemia Version 1.2004. http:// www. nccn. org/ professionals/ physician_ gls/ PDF/ aml. pdf. Accessed September 16, 2004.

10. Stone R. Treatment of acute myeloid leukemia: state-of-the-art and future directions. Semin Hematol 2002; 39( Suppl 2): 4- 10. EDMS- PSDB- 3408749.

11. Bishop JF, Matthews JP, Young GA, et al.: A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood 87 (5): 1710-7, 1996.

12. Geller RB, Burke PJ, Karp JE, et al.: A two-step timed sequential treatment for acute myelocytic leukemia. Blood 74 (5): 1499-506, 1989.

13. Weick JK, Kopecky KJ, Appelbaum FR, et al.: A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with

previously untreated acute myeloid leukemia: a Southwest Oncology Group study. Blood 88 (8): 2841-51, 1996.

14. Büchner T, Hiddemann W, Wörmann B, et al.: Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. Blood 93 (12): 4116-24, 1999.

15. Wiernik PH, Banks PL, Case DC Jr, et al.: Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. Blood 79 (2): 313-9, 1992.

16 Vogler WR, Velez-Garcia E, Weiner RS, et al.: A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: a Southeastern Cancer Study Group Study. J Clin Oncol 10 (7): 1103-11, 1992.

17. Berman E, Heller G, Santorsa J, et al.: Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia. Blood 77 (8): 1666-74, 1991.

18. Mandelli F, Petti MC, Ardia A, et al.: A randomised clinical trial comparing idarubicin and cytarabine to daunorubicin and cytarabine in the treatment of acute non-lymphoid leukaemia. A multicentric study from the Italian Co-operative Group GIMEMA. Eur J Cancer 27 (6): 750-5, 1991.

19. Arlin Z, Case DC Jr, Moore J, et al.: Randomized multicenter trial of cytosine arabinoside with mitoxantrone or daunorubicin in previously untreated adult patients with acute nonlymphocytic leukemia (ANLL). Lederle Cooperative Group. Leukemia 4 (3): 177-83, 1990.

20. Bishop JF, Lowenthal RM, Joshua D, et al.: Etoposide in acute nonlymphocytic leukemia. Australian Leukemia Study Group. Blood 75 (1): 27-32, 1990.

21. Geller RB: Use of cytokines in the treatment of acute myelocytic leukemia: a critical review. J Clin Oncol 14 (4): 1371-82, 1996.

22. Rowe JM, Andersen JW, Mazza JJ, et al.: A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood 86 (2): 457-62, 1995.

23. Stone RM, Berg DT, George SL, et al.: Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. N Engl J Med 332 (25): 1671-7, 1995.

24. Dombret H, Chastang C, Fenaux P, et al.: A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. AML Cooperative Study Group. N Engl J Med 332 (25): 1678-83, 1995.

25. Buchner T, Hiddemann W, Wormann B, et al.: GM-CSF multiple course priming and long-term administration in newly diagnosed AML: hematologic and therapeutic effects. Blood 84 (10 Suppl 1): A-95, 27a, 1994.

26. Löwenberg B, Boogaerts MA, Daenen SM, et al.: Value of different modalities of granulocyte-macrophage colony-stimulating factor applied during or after induction therapy of acute myeloid leukemia. J Clin Oncol 15 (12): 3496-506, 1997.

27. Witz F, Sadoun A, Perrin MC, et al.: A placebo-controlled study of recombinant human granulocyte-macrophage colony-stimulating factor administered during and after induction treatment for de novo acute myelogenous leukemia in elderly patients. Groupe Ouest Est Leucémies Aiguës Myéloblastiques (GOELAM). Blood 91 (8): 2722-30, 1998. [PUBMED Abstract]

28. Myint H, Lucie NP: The prognostic significance of the CD34 antigen in acute myeloid leukaemia. Leuk Lymphoma 7 (5-6): 425-9, 1992. [PUBMED Abstract]

29. Goldstone AH, Burnett AK, Wheatley K, et al. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood 2001; 98: 1302- 1311. EDMS-PSDB- 3368426.

30. Baudard M, Marie JP, Cadiou M, Viguié F, Zittoun R. Acute myelogenous leukaemia in the elderly: Retrospective study of 235 consecutive patients. Br J Haematol 1994; 86: 82- 91. EDMS- PSDB- 3787132.

31. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. Arch Intern Med 2002; 162: 1597- 1603. EDMS-PSDB- 3732474.

33. Rule S, Poirer V, Singer C. Management of acute myeloid leukemia. A regional audit in the south and west of the United Kingdom. Clin Med 2001; 1: 313- 316. EDMS-PSDB- 3938915.

34. Rathnasabapathy R, Lancet JE. Management of acute myelogenous leukemia in the elderly. Cancer Control 2003: 10: 469- 477. EDMS- PSDB- 3330251.

35. Estey EH. How I treat older patients with AML. Blood 96 (5) 1670-1673, 2000.

36. Jackson GH, Taylor PRA. Acute myeloid leukaemia: optimising treatment in elderly patients. Drugs Aging 2002; 19: 571- 581. EDMS- PSDB- 3408745.

37. Stone RM. The difficult problem of acute myeloid leukemia in the older adult. CA Cancer J Clin 2002; 52: 363- 371. EDMS- PSDB- 3385498.

38. DeLima M, Ghaddar H, Pierce S, Estey E. Treatment of newly-diagnosed acute myelogenous leukaemia in patients aged 80 years and above. Br J Haematol 1996; 93: 89- 95. EDMS- PSDB- 3368417.

39. Vey N, Coso D, Bardou VJ, et al. The benefit of induction chemotherapy in patients age $\geq$ 75 years: a retrospective study of 1109 patients from a single institution. Cancer 2004; 101: 325- 331. EDMS- PSDB- 3787235.

40. Karp JE, Lancet JE, Kaufman SH, et al. Clinical and biologic activity of the farnesyltransferase inhibitor R115777 in adults with refractory and relapsed acute leukemias: a Phase 1 clinical- laboratory correlative trial. Blood 2001; 97( 11): 3361-3369. EDMS- PSDB- 3510015.

41. CFR21, 314 subpart H: Accelerated approval of new drugs for life threatening illness. 2004

42. Bross PF, Beitzm J, Chen G et al. Aproval Summary: Gemtuzumab Ozogamicin in relapsed acute myeloid leukemia. Clinical Cancer Research 7: 1490-1496, 2001.