NDA 22-489

Onrigin™ (laromustine) Injection
For Induction Therapy For Patients 60 Years or Older
with *De novo* Poor-Risk Acute Myeloid Leukemia

Sponsor's Background Package

for the

Oncologic Drugs Advisory Committee Meeting
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New Haven, CT 06511 USA

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EXECUTIVE SUMMARY

Introduction

Acute myeloid leukemia (AML) is a rapidly progressive and uniformly fatal disease. It is the most common type of acute leukemia seen in adults with approximately 13,000 cases diagnosed annually in the United States (US). The median age at onset is 67 years, with incidence increasing from 4 cases per 100,000 among individuals in the sixth decade of life to over 20 cases per 100,000 in patients in the ninth decade of life. The incidence of this hematologic malignancy can be expected to increase as the US population ages.

AML comprises a group of well-characterized hematologic malignancies involving cells of the myeloid line of differentiation. The pathophysiology of AML consists of a clonal maturational arrest, followed by uncontrolled growth of immature bone marrow cells. This causes impaired normal blood cell production and subsequent anemia, thrombocytopenia, and neutropenia, as well as an accumulation of leukemic blast cells in the bone marrow, spleen, and liver. Symptoms at presentation usually include multiple complications of pancytopenia, such as weakness and fatigue, infection, and hemorrhage.

The initial goal of treatment of AML is the same regardless of age at diagnosis: to achieve a complete remission by reducing the malignant clone(s) and leukemia cells to allow recovery of peripheral blood production and re-population of the bone marrow with normal hematopoietic stem cells. In the induction treatment of AML, complete remission is considered the only clinically important form of response. The ability to achieve such a response has been directly correlated with survival and is a necessary first step in a curative treatment strategy.

This briefing document presents a summary of the efficacy and safety results from clinical studies performed with Onrigin™ administered at a dose 600 mg/m^2 for remission induction in patients 60 years or older with *de novo* poor-risk AML. Efficacy claims for this patient population are based on outcomes from 2 clinical studies conducted by Vion Pharmaceuticals: Study CLI-033 conducted from March 2004 through June 2006 and Study CLI-043 conducted from May 2006 through December 2007. Each study examined Onrigin™ Injection as a single-agent, induction therapy in older patients with AML.

Treatment of AML in Elderly Patients Represents an Unmet Need

Elderly patients with AML are biologically and clinically distinct from younger patients and have many poor-risk factors, including poorer Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores, lower tolerance for intensive therapies, presence of comorbidities, and worse cytogenetic profiles than younger patients. Furthermore, AML in the elderly is more often associated with multi-drug resistance (MDR) expression, which contributes to a lower response to other anti-leukemic agents.

These differences in elderly patients with AML lead to poorer outcomes, including both lower response rates and shorter overall survival. For patients who are able to receive standard chemotherapy, complete remission rates are considerably lower in older patients (45%) than in younger patients (75%). Additionally, these patients experience a treatment mortality rate of 25%. In general, older patients with comorbid medical illnesses which result in limited cardiac, pulmonary, renal and/or hepatic functional reserve may be less able to tolerate intensive

cytotoxic induction with standard regimens. Currently, ~30% of AML patients over the age of 65 receive treatment. The most common cause of death is disease progression. The median survival for untreated older AML patients is just 1.7 months.

Given that approximately two-thirds of older AML patients remain untreated, investigational therapy may be the only intensive chemotherapy option in poor-risk older patients; however, elderly patients are often excluded from clinical trials because of stringent requirements for adequate performance status, organ function, and absence of active infection or another malignancy. Patients ineligible for clinical trials are left with the sole option of supportive care, with no hope of a remission.

Overview of Onrigin™ and the Early Clinical Development Program

Onrigin™ Injection (active ingredient laromustine) is an alkylating agent from the sulfonylhydrazine prodrug class that spontaneously decomposes to produce chloroethylating species that preferentially alkylate the O^6 position of guanine in DNA. This guanine lesion progresses to form a highly lethal DNA cross-link believed to be responsible for the cytotoxicity and therapeutic effectiveness of Onrigin™.

Onrigin™ was selected as a candidate for clinical development based on its *in vitro* potency (particularly against tumor cell lines that are resistant to currently approved alkylating agents), and broad-spectrum *in vivo* antitumor efficacy. Importantly, laromustine is not a substrate for the multidrug resistance proteins MDR-1 and MRP-1; cell lines overexpressing these proteins are less sensitive to anthracyclines such as doxorubicin but remain sensitive to laromustine. This is an important attribute for the use of laromustine in elderly AML patients as MDR-1 expression is detected in 71% of patients 65 years and older and is associated with treatment failure (1).

The early clinical development program for Onrigin™ established the safety and tolerability profile of the chemotherapeutic at different doses and dose schedules in cancer patients with both hematologic malignancies and solid tumors when given as a single agent or in combination with other chemotherapeutic agents.

The maximum tolerated dose for Onrigin™ was established as 600 mg/m^2 in an early phase 1 study. Although evaluation of response was not a primary objective of this study, activity in hematologic malignancies was observed in 2 patients, both achieving a complete remission (CR). These results suggested further evaluation of Onrigin™ for induction of remission in patients with AML.

Clinical Development Program in Patients with De novo, Poor-risk AML

Vion's clinical development program in patients with AML is comprised of 2 clinical studies. The first study, CLI-033, was conducted in patients with AML or high-risk myelodysplastic syndrome (MDS). During this study, an efficacy signal was observed in patients with *de novo* AML, who had the highest levels of response (CR and CR without platelet recovery [CRp]). As a result of this finding, the pivotal study, CLI-043, was prospectively designed to examine the effects of Onrigin™ in elderly patients with *de novo* poor-risk AML.

Study CLI-043 enrolled a total of 85 patients and provides the primary evidence of the efficacy of Onrigin™ Injection in patients with *de novo* poor-risk AML. Patients in CLI-043 were 60 years or older and had an AML diagnosis confirmed independently. Patients were also required to have at least one of the following poor-risk features: disease with unfavorable cytogenetics, ECOG PS of 2, age 70 years or older, cardiac dysfunction, pulmonary dysfunction assumed to be

unrelated to AML, hepatic dysfunction related to chronic hepatitis or liver cirrhosis, or other organ dysfunction or comorbidity.

Response to treatment was assessed 4-6 weeks post infusion using the standard International Working Group (IWG) criteria. Responses were determined by both the site investigators and by an independent reviewer.

The primary data to support the efficacy and safety of Onrigin™ in the proposed indication are based on the 85 patients treated in Study CLI-043. Additional supportive data are provided from a subgroup of 55 patients treated in Study CLI-033 who were retrospectively determined to meet the eligibility criteria established in Study CLI-043 for elderly patients with *de novo* poor-risk AML.

Baseline Characteristics of the Population Studied

The 140 patients with *de novo* poor-risk AML enrolled in the primary and supportive studies (CLI-043 and CLI-033) were elderly with a median age of 74 years and a range of 60 to 88 years; 75% of patients were ≥70 years of age. The majority of patients had other poor-risk features at presentation, including cardiac dysfunction (61%), pulmonary dysfunction (58%), unfavorable cytogenetics (45%), and ECOG PS of 2 (36%). Each of the baseline risk factors identified in these patients has been reported in the literature as a predictor for poor outcome based on either tolerability of therapy or decreased response to therapy. Over 85% of the studied population had 2 or more of these risk factors. It is in the context of this poor-risk population of patients that the efficacy and safety of Onrigin™ should be considered.

Primary Efficacy Findings

The primary efficacy endpoint in both Studies CLI-043 and CLI-033 was overall response rate (ORR) defined as the proportion of patients who achieved CR or CRp based on response determinations from independent review. Investigator assessments were considered secondary and supportive. The primary population for analysis was the Intent-to-Treat (ITT) analysis set, defined as all patients who received at least 1 induction cycle. Secondary endpoints included leukemia-free survival (LFS) and overall survival (OS).

A summary of the primary efficacy endpoint of ORR based on independent review is provided in Table 1. Results are presented for the pivotal and supportive study separately, and for all 140 patients with *de novo* poor-risk AML.

Table 1: Overall Response Rate Based on Independent Review (Elderly *De novo* Poor-Risk AML Population)

Response	CLI-043 N=85		CLI-033 N=55		Total N=140	
	n (%)	[95% CI]	n (%)	[95% CI]	n (%)	[95% CI]
ORR (CR+CRp)	27 (31.8)	[22.1, 42.8]	21 (38.2)	[25.4, 52.3]	48 (34.3)	[26.5, 42.8]
CR	20 (23.5)	[15.0, 34.0]	18 (32.7)	[20.7, 46.7]	38 (27.1)	[20.0, 35.3]
CRp	7 (8.2)	[3.4, 16.2]	3 (5.5)	[1.1, 15.1]	10 (7.1)	[3.5, 12.7]

Eighty eight percent (88%, 42 of 48 patients) responded following treatment with the first induction cycle and 6 responded following a second induction cycle.

Importantly, ORR was consistent across patient subgroups often associated with lower response rates or inability to tolerate intensive chemotherapy, including patients 70 years of age or older (33%), patients with ECOG PS of 2 (37%), patients with unfavorable cytogenetic profiles (25%) and patients with baseline cardiac (35%) or pulmonary dysfunction (36%). ORR was also maintained in the presence of multiple poor-risk factors. Patients with 2 risk factors had an ORR of 38.5% and patients with 3 risk factors had an ORR of 35.6%.

Responses to Onrigin™ were durable. Kaplan-Meier median duration of response in the primary study was 6.0 months with an estimate of remaining leukemia-free at 6 months of 53%. In the supportive study, median duration of response was 4.9 months with an estimate of remaining leukemia-free at 6 months of 40%.

Median OS across all patients regardless of response to treatment was 3.2 months in Study CLI-043 and 3.4 months in Study CLI-033 with 47 patients (34%) alive at 6 months after first Onrigin™ treatment. In the primary study CLI-043, patients who achieved CR or CRp had a median OS of 12.4 months; 67% of responders were alive 6 months after first induction treatment, and 52% were alive at 1 year.

The ORR coupled with durable complete remissions in all subgroups analyzed, and an estimated overall survival of at least 6 months in 67% and 57% of patients who achieved CR or CRp in the primary and supportive studies, respectively, demonstrate that Onrigin™ is effective as induction therapy in patients 60 years or older with *de novo* poor-risk AML.

Safety Findings

Onrigin™ belongs to a class of cytotoxic drugs, the alkylating agents, which have known toxicities. As a class, and with variable severity, the drugs affect cells in all phases of the cell cycle, with particular cytotoxicity to rapidly proliferating tissues. Organ systems frequently affected by treatment with alkylating agents include the bone marrow, gastrointestinal tract, gonads, lungs, bladder, and liver.

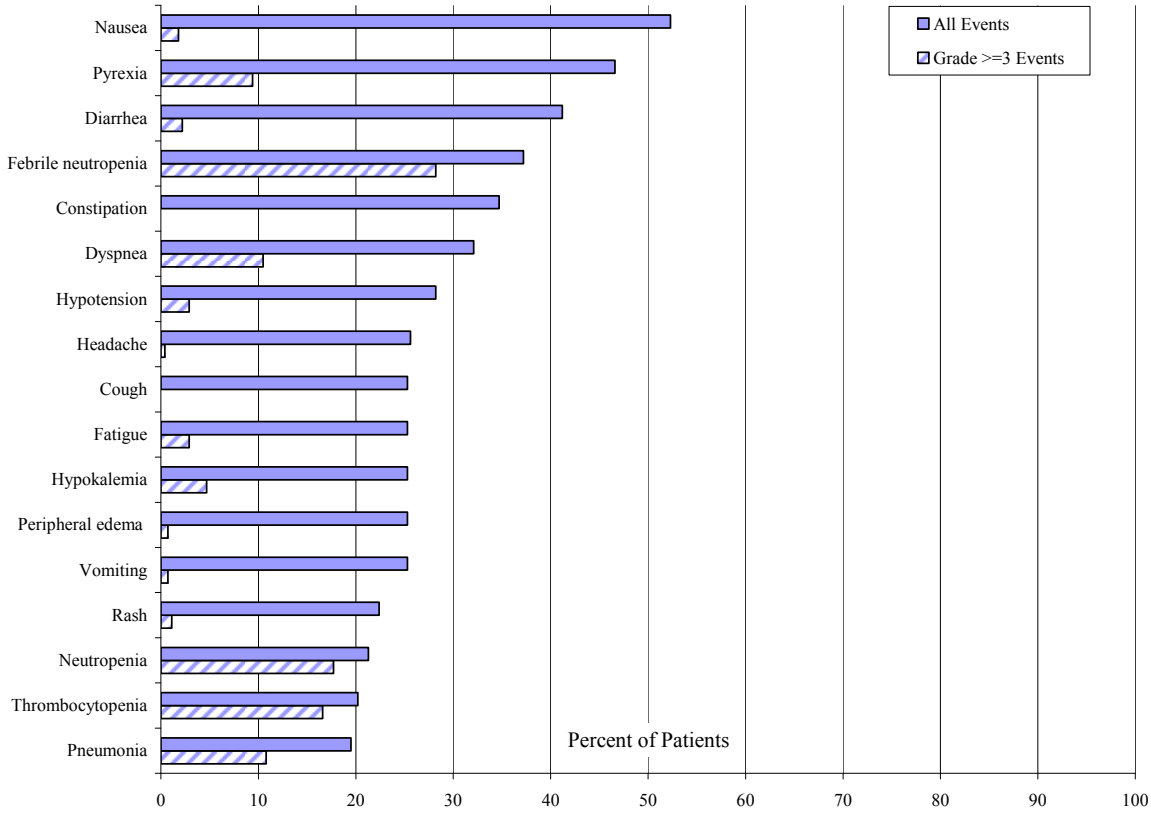
The full safety dataset for Onrigin™ presented in the NDA includes data on a total of 818 adults and pediatric patients with hematologic malignancies and solid tumors who received single or multiple Onrigin™ doses ranging from 3 to 800 mg/m^2 in both Vion-sponsored and investigator-sponsored clinical studies either as a single agent or in combination with other cytotoxic agents. The safety profile in the larger patient population is consistent with the subset of patients with hematologic malignancies treated with single agent Onrigin™ at the dose of 600 mg/m^2 (n=277).

The integrated safety dataset is derived from 3 Vion-sponsored clinical studies, which includes 277 patients treated with Onrigin™ 600 mg/m^2 as a single agent.

All 277 patients experienced at least 1 adverse event (AE) with 84% of patients experiencing at least 1 AE that was reported to be Grade 3 or higher in severity, and 74% of patients experiencing at least one serious adverse event (SAE). This rate of Grade 3 or greater events and SAEs reflects a patient population who received cytotoxic induction treatment with the intent of achieving bone marrow aplasia, and which led to myelosuppression and the consequences of this necessary treatment effect.

Figure 1 provides a graphic display of adverse events reported in 20% or more of all patients and includes the proportion of patients in which these events were assessed by the investigators as Grade 3 or greater in severity.

Figure 1: Overall and Grade 3, 4 or 5 Incidence of Adverse Events, Regardless of Relationship to Study Treatment, Reported in 20% or More of All Patients (Safety Population)



The most commonly reported AEs following induction treatment with Onrigin™ are those related to myelosuppression or the consequences of myelosuppression. The AEs that occurred most frequently at Grade 3 or higher incidence were febrile neutropenia, neutropenia, thrombocytopenia, pneumonia, and dyspnea.

Following induction, the nadir of absolute neutrophil count (ANC) and platelet counts generally occurred approximately 2 weeks after induction. Patients recovered approximately 2 weeks later. Many patients experienced AEs that may be related to myelosuppression, including pneumonia and other infections (62%) and hemorrhagic events (47%).

Respiratory AEs were among the more frequent types of events reported. Overall, 26% of patients had Grade 3 or greater respiratory AEs, primarily dyspnea (10.5%). Not unexpectedly, the incidence of respiratory AEs was higher among patients with pulmonary dysfunction at baseline (80.2%) compared to patients without baseline pulmonary dysfunction (66.2%).

There is a delayed pattern of non-infectious pulmonary events observed in 9.0% of Onrigin™ treated patients occurring 3 to 8 weeks after therapy, with bilateral pulmonary infiltrates, with or without pleural effusions, and with no obvious alternative explanations.

Gastrointestinal events were also commonly reported and antiemetic prophylaxis is recommended. Nausea (52%) and vomiting (25%) are frequent and are likely related to administration of Onrigin™. Diarrhea (41%), constipation (35%), and abdominal pain (12%) are also frequent. Gastrointestinal disturbances were primarily Grade 1 and 2 in severity.

Infusion-related events can occur during or immediately following therapy with Onrigin™. AEs that occurred up to 24 hours following the infusion of Onrigin™ most commonly included nausea, hypotension, pyrexia, and headache. Hypotension was reported in 28% of patients.

Treatment with Onrigin™ does not appear to be associated with a significant risk of cardiac, renal or hepatic consequences, or with alopecia or mucositis. As expected in patients with AML undergoing induction therapy, tumor lysis syndrome can occur following treatment with Onrigin™.

The SAE profile of Onrigin™ mirrors the AE profile, reflecting myelosuppression and the consequences of myelosuppression, as well as respiratory AEs.

A total of 42 patients (15.2%) died within 30 days of the first induction with Onrigin™. This mortality profile is consistent with the reported induction morality for older individuals with AML.

Benefit/Risk Conclusions

In the treatment of AML, complete remission is the only clinically significant form of response and has been directly correlated with an increase in survival.

Onrigin™ Injection induces durable complete remissions in elderly patients with *de novo* poor-risk AML and offers an important therapeutic option for this patient population. The ORR of 34% was based on independent review of data across a total of 140 patients 60 years of age or older with *de novo* poor-risk AML who were enrolled in two phase 2 studies. Thirty seven percent (37%) of patients achieving a complete remission had a duration of response lasting 6 months or longer. Twenty percent (20%) of patients achieving a complete remission had a duration of response lasting a year or longer.

The safety profile associated with Onrigin™ is consistent and predictable. AEs, including SAEs, are predominantly related to myelosuppression. Commonly occurring gastrointestinal and infusion-related AEs are low grade, transient and easily managed.

The data presented in support of the NDA for Onrigin™ demonstrate benefit in a definable patient population for which appropriate labeling recommendations will allow safe and effective use in the indicated population.

The benefit risk profile is positive for Onrigin™ when used as single agent induction treatment at a dose of 600 mg/m^2 for patients 60 years or older with *de novo* poor-risk AML.

In the context of currently available treatments for elderly poor-risk AML patients, the data presented in the 2 Onrigin™ clinical trials demonstrate its role as a therapeutic option.

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Abbreviations

Abbreviation	Definition
AE	adverse event
AGT	alkylguanine-DNA alkyltransferase
ALC	absolute lymphocyte count
ALT/SGPT	alanine transaminase
AML	acute myeloid leukemia
AMLSG	German-Austrian AML Study Group
AMML	acute myelomonocytic leukemia
ANC	absolute neutrophil count
ara-C	cytosine arabinoside or cytarabine
AST/SGOT	aspartate transaminase
AUC	area under the curve
BCNU	1,3-bis(2-chloroethyl)-1-nitrosourea
BMI	body mass index
BSA	body surface area
CALGB	Cancer and Leukemia Group B
CBC	complete blood count
CCNU	1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CR	complete remission or response
CRp	CR without platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular or cell volume
D5W	5% dextrose in water
DBP	diastolic blood pressure
DLCO	lung diffusion capacity for carbon monoxide
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
FAB	French-American-British
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
g	gram
GI	gastrointestinal
GSH	glutathione
GSSG	oxidized glutathione
GST	glutathione-S-transferase
HCT-CI	Hematopoietic Cell Transplantation Comorbidity Index
HI	hematologic improvement
IPSS	International Prognostic Scoring System
ITT	intent-to-treat
IV	intravenous or intravenously
IWG	International Working Group
LDAC	low-dose ara-C
LFS	leukemia-free survival
MDR	multi-drug resistance
MDS	myelodysplastic syndrome

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mm Hg	millimeters of mercury
MPD	myeloproliferative disorder
MRC	Medical Research Council
MRP	multi-drug resistance associated protein
MTD	maximum tolerated dose
N	number
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	new drug application
NE	non-estimable
ORR	overall response rate (CR + CR_p)
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRBC	packed red blood cells
PS	performance score or status
RAEB	refractory anemia with excess blasts
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SWOG	Southwest Oncology Group
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
$V_{d,ss}$	volume of distribution at steady state
VOD	veno-occlusive disease
WBC	white blood cell
WHO	World Health Organization

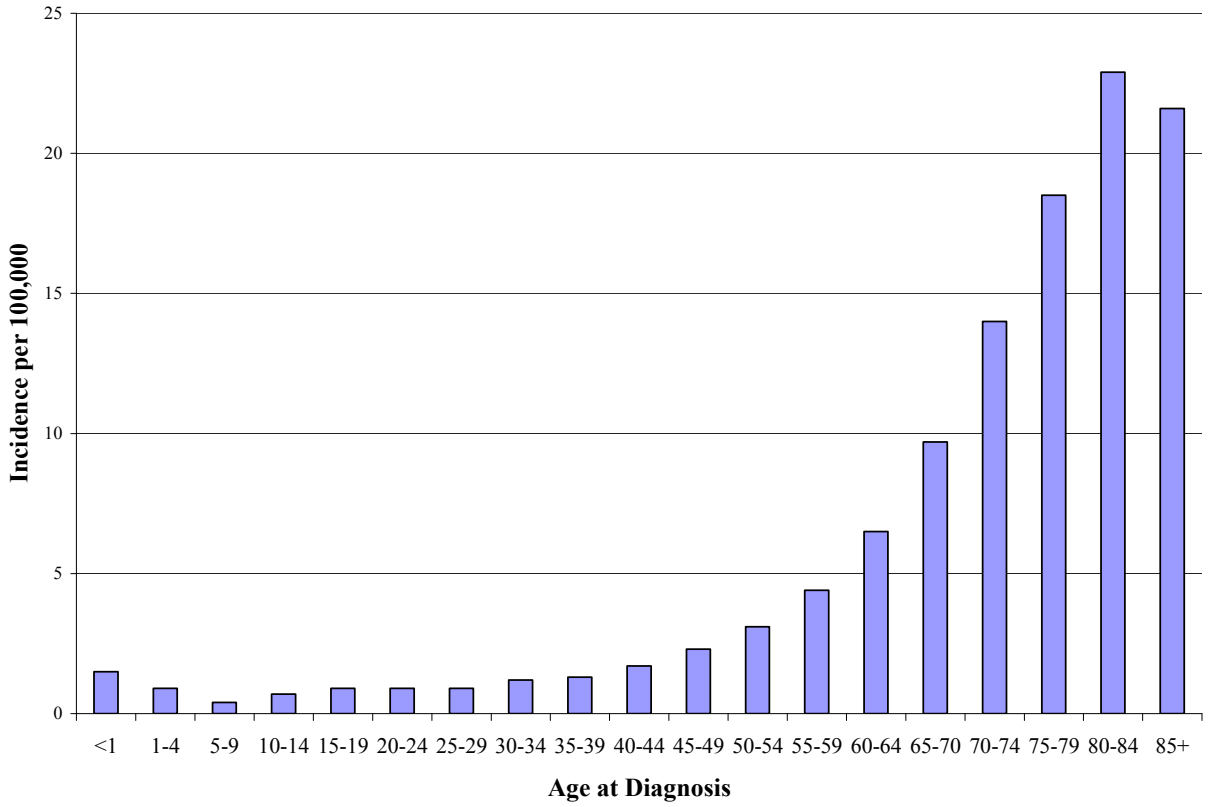
1. Introduction

1.1 Acute Myeloid Leukemia

1.1.1 Epidemiology

Acute myeloid leukemia (AML) is a rapidly progressive and uniformly fatal disease if left untreated. It is the most common type of acute leukemia seen in adults; approximately 13,000 cases are diagnosed annually in the United States (US). The median age at onset is approximately 67 years with an incidence increasing from 4 cases per 100,000 among individuals in the sixth decade of life to over 20 cases per 100,000 in patients in the ninth decade of life (2, 3) (Figure 2). The incidence of AML is almost 10 times greater in people ≥65 years of age than in younger patients (15.6 versus 1.7 per 100,000) (3, 4). More than two-thirds of patients with AML are over age 60. Based on the increase in AML incidence with age, the incidence of this hematologic malignancy can be expected to increase as the US population ages.

Figure 2: Incidence of AML by Age at Diagnosis



Reference: http://seer.cancer.gov/csr/1975_2006/results_merged/sect_13_leukemia.pdf (accessed 27 June 2009)

1.1.2 Disease Biology

AML comprises a group of well-characterized hematologic malignancies involving cells of the myeloid line of differentiation. It can be distinguished from other leukemic disorders by the

myeloid origin of the cells and, according to a recent World Health Organization (WHO) guidance, by the presence of more than 20% myeloblasts in the bone marrow (5).

The underlying pathophysiology of AML consists of a clonal maturational arrest, followed by uncontrolled growth of immature bone marrow cells. This causes impaired normal blood cell production and subsequent anemia, thrombocytopenia, and neutropenia, as well as an accumulation of leukemic blast cells in the bone marrow, spleen, and liver.

The subsets of AML vary in their cell population proportions, morphology, cytochemistry, chromosomal aberrations, and immunophenotypic markers (6). AML is classified as primary or secondary. Secondary AML is defined by the presence of a previous hematologic disorder, primarily myelodysplastic syndrome (MDS) or myeloproliferative disorder (MPD), or a history of treatment with leukemogenic chemotherapy or radiation. When such disorders or history do not precede the diagnosis of AML, the patient is considered to have *de novo* or primary disease.

Clinical symptoms of AML at presentation usually include multiple complications of pancytopenia, such as weakness and profound fatigue related to anemia; serious infections related to neutropenia, including pneumonia; fever; and hemorrhage.

1.1.3 Treatment of AML

The goal of treatment of AML is the same regardless of age at diagnosis: to achieve a complete remission (CR) by reducing the malignant clones and leukemic cells in order to allow recovery of normal peripheral blood production and re-population of the bone marrow with normal hematopoietic stem cells. In the treatment of AML, CR is considered the only clinically important form of response. The ability to achieve such a response has been directly correlated with survival and is a necessary first step in a curative treatment strategy (7). Further, obtaining durable CR is considered an indicator of clinical benefit (8). Patients in remission have absence of symptoms associated with leukemia and require less disease-directed intervention, e.g., transfusions.

Treatment paradigms for AML have remained the same for the last 30 to 40 years. AML treatment began in the 1950's with the introduction of the nitrogen mustards. In the 1960's, ara-C in combination with daunorubicin became the cornerstone of AML treatment. The current standard treatment for AML involves administration of systemic combination chemotherapy to induce remission, generally termed 7+3, which is 7 days of intravenous (IV) ara-C delivered by continuous infusion and 3 days of anthracycline or anthracenedione. Efforts to modify this therapy have been explored over the past 30 years. No treatment has emerged that is convincingly superior, despite intensifying the anthracycline dose, substituting an anthracenedione, increasing the ara-C dose, or adding growth factors or other agents, resulting in little change to this regimen (9).

While treatment is curative in some patients, most will either fail to respond to induction therapy or, after an initial CR, will experience disease recurrence. To prevent this, induction therapy is generally followed by a consolidation regimen to eliminate residual disease and prevent relapse. The vast majority of patients who fail to respond to initial treatment or relapse post-remission, will die from their disease. A small percentage of patients sustaining remissions for several years or undergoing successful consolidation via chemotherapy or bone marrow transplantation may be considered "cured" as measured by long-term disease-free survival.

No new agent has been approved for the induction of remission in previously untreated AML since 1987, and no agent has ever been approved for the induction treatment of elderly patients with poor-risk disease.

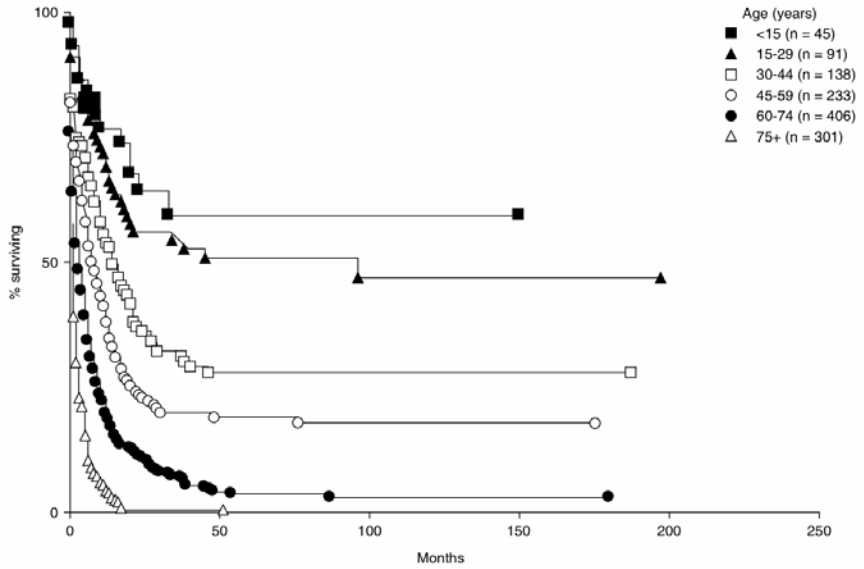
1.1.4 AML in the Elderly

Elderly patients with AML are biologically and clinically distinct from younger patients. These differences lead to poorer outcomes than in younger patients including lower response rates, increased treatment related-mortality, and shorter overall survival, and are attributed to poor-risk factors in the elderly patient. In general, older patients have an increased incidence of comorbidities (e.g., cardiac and pulmonary dysfunction), poor hematologic reserves, and worse ECOG performance scores that lead to lower tolerance for intensive therapies. This patient group also has a higher incidence of unfavorable cytogenetic profiles than younger patients, which is a known factor for poor outcomes (10). Additionally, AML in the elderly patient is more often associated with multi-drug resistance (MDR) expression; MDR-1 expression is detected in up to 71% of patients 65 years and older (1). This contributes to a lower response to a wide variety of agents.

Only 30% of older AML patients in the US received any form of chemotherapy and analysis from the SEER database from 1991-1996 revealed that when patients aged 65 years or older received currently available intensive chemotherapy, median overall survival was 7 months (33).

The life expectancy of patients with AML is worsens with increasing age (Figure 3) (11). Patients with AML who are 65 years of age or older, regardless of treatment, survive on average 2.4 months (11, 12). The most common cause of death is disease progression.

Figure 3: Overall Survival Rate According to Age for Patients with AML



Source: Jackson *Drugs Aging* 2002

Increasing age is a documented risk factor associated with poor outcome. In a retrospective assessment of AML patients in Sweden (13), irrespective of management of the disease, patients

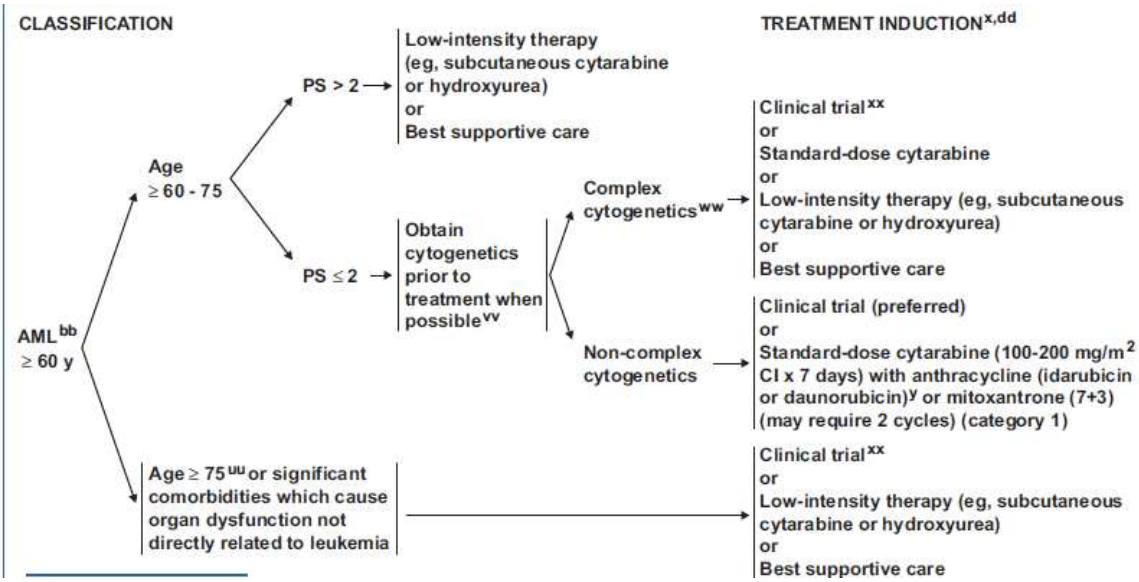
age 70 years and older had a 70% to nearly 100% mortality at 1 year following diagnosis. In comparison, patients younger than 70 years had 1-year mortality rates of 25% to 60%.

1.1.4.1 Treatment Considerations: Intensive Chemotherapy

There is currently no agreed upon standard for the treatment of older patients with AML; however, improved outcomes have been observed in older patients who undergo remission induction therapy (14). In general, physicians tend to stratify patients across several options based on age and their assessments as to whether or not a patient can tolerate intensive chemotherapy based on the presence of baseline risk factors such as comorbidities, age, performance status and unfavorable cytogenetics.

Figure 4 provides a description of 2009 National Comprehensive Cancer Network (NCCN) Guidelines (15). As evidenced by these guidelines, a minority of elderly patients with AML are candidates for 7+3 as induction treatment at presentation, and in the absence of other options for treatment, the majority of patients will receive palliation or best supportive care.

Figure 4: NCCN Treatment Algorithm for Induction Treatment of Elderly Patients with AML



Source: *2009 NCCN Clinical Practice Guidelines in Oncology, AML*

Table 2 lists the key study results from selected large clinical trials that investigated intensive treatment in elderly patients with AML. Regrettably, elderly patients are frequently not enrolled in phase 3 clinical trials for failure to meet eligibility criteria or for other reasons, making interpretation of outcomes data difficult (16).

Table 2: Cooperative Group Results of Intensive 7+3-Like Therapy, Age >55 Years*

Study	N	Median Age (yrs)	CR Rate	Early Death Rate	OS (months)
CALGB 8923	388	69	52%	25%	9.6
ECOG 3351	348	68	42%	17%	7.5
SWOG 9333	328	68	43%	18%	9
HOVON AML 9	539	68	42%	18%	9.5
MRC AML 14	1273	67	54%	18%	Not reported

*Patients deemed candidates for chemotherapy

Source: Stone *NEJM* 1995, Rowe *Blood* 2004, Anderson *Blood* 2002, Löwenberg *JCO* 1998, Burnett *BJH* 2009

To aid physicians in their decisions regarding which of their patients will likely respond to chemotherapy, multiple groups have attempted to define baseline factors that predict outcome in elderly AML patients treated with chemotherapy.

Appelbaum et al (10) conducted a retrospective analysis of 968 adults with AML enrolled in 5 Southwest Oncology Group (SWOG) trials to assess changes in the nature of AML with age. In this review, older patients with AML presented with poorer performance status, lower white blood cell counts, and a lower percentage of marrow blasts than younger patients. Multidrug resistance was found in 33% of younger patients compared with 57% of patients older than 75. The proportion of patients with unfavorable cytogenetics increased from 35% of patients younger than age 56 to 51% of patients older than 75. The increased incidence of unfavorable cytogenetics contributed to their poorer outcome, and, within each cytogenetic risk group, treatment outcome deteriorated markedly with age. Finally, the combination of a poor performance status and advanced age identified a group of patients with a very high likelihood of dying within 30 days of initiating induction therapy (Table 3).

Table 3: Mortality within 30 Days of Initiation of Induction

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	364	242	270	79
Early deaths* by performance status, no./no. total patients (%)				
0	3/129 (2)	8/72 (11)	9/73 (12)	2/14 (14)
1	6/180 (3)	6/112 (5)	20/126 (16)	7/40 (18)
2	1/46 (2)	6/34 (18)	16/52 (31)	7/14 (50)
3	0/9 (0)	7/24 (29)	9/19 (47)	9/11 (82)

Patients with known prestudy performance status are included.
*Within 30 days of registration to the trial.

Source: Appelbaum *Blood* 2006

Kantarjian and colleagues at MD Anderson Cancer Center reviewed results for 998 AML patients aged 65 years or over (range 65-89) treated with a variety of ara-C chemotherapy-based combinations from 1980-2004 (Table 4). Multivariate analysis identified several adverse prognostic factors including age ≥75 years, unfavorable cytogenetics, poor performance status, creatinine >1.3 mg/dL, duration of antecedent hematologic disorder >6 months, and treatment outside a laminar airflow room. Patients who had 3 or more of these risk factors had expected CR rates of less than 20%, 8-week mortality >50% and 1-year survival <10%. The authors concluded that patients with these multiple risk factors should not be treated with intensive chemotherapy. The analysis also showed that patients with zero or one adverse prognostic indicator were predicted to have CR rates greater than 60%, 8-week mortality of 10% and 1-year survival of >50%, from which the authors concluded that treatment of this patient group with an ara-C based regimen would be acceptable (17).

Table 4: Multivariate Analysis of Prognostic Factors Associated with Complete Response

Adverse Factor	*P-value*	Hazard Risk
Age ≥75 yrs	0.002	0.78
Prior therapy for other cancer	0.001	0.46
AHD ≥6 mos	<0.001	0.59
Treatment outside LAFR	<0.001	0.42
Unfavorable karyotype	<0.001	0.40
WBC ≥25 x 10^9/L	0.001	0.74
Hemoglobin ≤8 g/dL	0.006	0.82
Creatinine >1.3 mg/dL	0.003	0.77
Performance status >2 (ECOG)	0.046	0.60

No. Adverse Factors	No. Patients	CR n (%)	8-wk Mortality n (%)	Median Survival (months)	1-yr %
0-1	218	160 (73)	29 (13)	12	49
2-3	527	247 (47)	150 (28)	6	31
≥ 4	252	46 (18)	153 (61)	1	9

LAFR: laminar airflow room; CR: complete response; ECOG Eastern Cooperative Group

Source: Kantarjian *Cancer* 2006

The German-Austrian AML Study Group (AMLSG) evaluated 361 patients aged 60 years or older who received intensive treatment (18). This analysis identified 3 prognostic cytogenetic subgroups: low risk (t(15;17) and inv 16; standard risk (normal, t(8;21), t(11q23), +8 or 11 within a noncomplex karyotype, and high risk (all other aberrations). Patients aged 60 to 69 years without high-risk cytogenetics had a 62% CR rate with a median survival of 17.5 months, compared with a 21% CR rate and a median survival of 7.2 months in patients of the same age with high-risk cytogenetics. Additionally, patients older than 70 years without high-risk cytogenetics had a lower CR rate of 39% with a shorter median survival of 6.3 months compared to younger patients and further, the CR rate (15%) and median survival (3.1 months) in patients of the same age with high-risk cytogenetics was also lower than that of younger patients. These data support both 70 years of age and high-risk cytogenetics as prognostically important.

Table 5: CR Rates, Median OS, and 3-Year OS Rates Resulting from Cytogenetic Stratification of 361 Patients >60 years with AML

AMLSG score	No. of patients	CR, %	Median OS, mo	3-y OS (95% CI)
Younger than 70 y				
Not high risk	161	62	17.5	0.26 (0.20-0.33)
High risk	82	21	7.2	0.06 (0.02-0.13)
70 y or older				
Not high risk	72	39	6.3	0.06 (0.02-0.13)
High risk	46	15	3.1	0.02 (0.00-0.10)

Cytogenetic risk stratification according to the system proposed in this study.

Source: Froehling *Blood* 2006

A physician's assessment regarding type of treatment can include availability of family support or the presence of multiple comorbid conditions. To address the subjectivity and variability of comorbid conditions, there have been efforts to develop patient assessment scales in AML.

The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) is based on the Charlson Comorbidity Index and was developed by Sorror et al as a comorbidity index to predict non-relapse mortality for patients undergoing stem cell transplantation (19, 20). The HCT-CI includes 17 weighted conditions, including mild/moderate/severe pulmonary function, peptic ulcer disease, heart valve disease, mild/moderate/severe hepatic dysfunction, psychiatric disturbance, infection, and obesity. The HCT-CI has been validated in patients with hematologic malignancies undergoing stem cell transplantation (19). Baseline assessment of comorbidities predictive of outcome using an index such as HCT-CI can identify a population of "at risk" patients in need of alternative AML therapies. Giles et al demonstrated that the HCT-CI is predictive of early death and overall survival in 177 patients over 60 years receiving AML induction chemotherapy (21).

Other factors that complicate the decision to treat these patients include a reluctance of practitioners to treat older patients with intensive chemotherapy due to a reduced tolerance to such therapy, and difficulty finding bone marrow transplant donors following response. As a result, older AML patients are less likely to be offered chemotherapy and have a lower rate of remission (22-24).

Lang et al showed in a SEER-Medicare database analysis in 3439 elderly patients with AML that median survival decreases with age. In this study, median survival was 2.4 months. Table 6 presents median survival for patients ≥65 years who did and did not receive chemotherapy. As shown, median survival for treated patients survival decreases markedly with age.

Table 6: Median Overall Survival of Elderly AML Patients Treated with Chemotherapy and Untreated

Patient Age (years)	OS, Treated (months)	N (%)	OS, Untreated (months)	N (%)
All patients ≥65	6.8	1164	1.7	2275
65-74	8.1	740 (64)	2.0	767 (34)
75-84	4.9	387 (33)	1.8	1020 (45)
≥85	2.5	37 (3)	1.3	488 (21)

Source: Lang *Drugs in Aging* 2005

Multiple studies have demonstrated that the majority of older patients with AML are not currently treated with induction chemotherapy.

In a retrospective analysis that included 705 patients ≥60 years with AML, 58% of patients younger than 65 years versus 24% of patients 70 to 74 years received intensive chemotherapy, and 89% of patients 75 years or older received only supportive care (25). Patients are even less likely to receive chemotherapy if they have comorbid conditions, poor performance status, unfavorable cytogenetics, and a history of prior MDS (all of which are more common features in elderly patients with AML) (25-27).

1.1.4.2 Treatment Considerations: Lower Intensity Therapy and Palliative Care

The UK Medical Research Council (MRC) completed a trial comparing low dose ara-C (LDAC; 20 mg administered twice daily subcutaneously for 10 days every 4-6 weeks) with hydroxyurea for older patients not considered for chemotherapy (28). Of the 217 patients randomized, 102 patients had data available from the LDAC arm. Both the rate of complete remission and overall survival were significantly improved over hydroxyurea. Eighteen percent (18%) of patients achieved a CR and median duration of response was 2.7 months in the LDAC arm compared with a 1% CR rate and median duration of response of 2.3 months with hydroxyurea. Early death rate was 26% and 28% in the LDAC and hydroxyurea arms, respectively. One-year survival was 25% and 8% in the LDAC and hydroxyurea arms, respectively.

Reductions in the dose and schedule of ara-C have not resulted in a reduction in treatment related mortality. In the MRC study, early death was consistent with the expected early death rate of 25% reported by Stone et al for patients receiving intensive induction treatment (24).

It is clear, given the 18% CR rate, including no remissions in patients with unfavorable cytogenetics, with no reduction in the early death rate, that LDAC does not fully address the needs of the elderly AML patient population and additional therapeutic options are needed.

Although complete remission is considered a requisite for long-term survival, approximately 65% of older patients with AML receive supportive care only rather than induction chemotherapy (12). Few studies have evaluated outcomes in patients who receive supportive care. The scarcity of studies in this area may be due to the absence of a widely accepted definition of supportive care.

One randomized trial that included 60 AML patients age 65 and older compared a "watch and wait" supportive care approach with intensive induction chemotherapy (ara-C, daunorubicin, and vincristine). Patients in the supportive care arm could receive mild cytoreductive chemotherapy [i.e., hydroxyurea (3 g orally on days 1 and 4) and ara-C (100 mg/m^2 subcutaneously) every 12

hours on days 2, 3, 5, and 6 of a 3 to 4 week cycle] for hyperleukocytosis and other leukemia-related symptoms. While the chemotherapy arm had significantly longer overall survival than the supportive care arm (4.8 versus 2.5 months), the 2 groups spent a similar amount of time in the hospital (23).

A second study randomized 550 older AML patients to chemotherapy, palliative therapy, or supportive care. Palliative treatment consisted of idarubicin (10 mg orally on day 1) combined with thioguanine (40 mg orally days 1-5), ara-C (80 mg subcutaneously days 1-5), or etoposide (100 mg orally days 1-5); supportive care included only transfusions. In this study, median overall survival was 1.8 months for the palliative treatment arm and 0.4 months for the supportive care arm (29).

Finally, a literature-based analysis of published trials encompassing 36 AML/MDS studies and over 12,000 patients reported median overall survival of 1.7 months in patients who received supportive care and 2.8 months in patients who received supportive care plus non-intensive treatment (30).

1.1.5 Discussion and Conclusions

AML, the most common type of acute leukemia in adults, is a rapidly progressive and uniformly fatal disease. It is largely a disease of older patients, and the incidence of AML is expected to increase with the aging population. The goal of treatment of AML is to achieve a complete remission in order to allow recovery and re-population of the bone marrow with normal hematopoietic stem cells. In the treatment of AML, complete remission is considered the only clinically important form of response. The ability to achieve such a response has been directly correlated with survival and is a necessary first step in a curative treatment strategy.

The challenges in treating older AML patients, including the presence of comorbidities, a higher incidence of MDR expression of the clonal line, and a higher incidence of unfavorable cytogenetics, make some physicians unwilling to treat such patients aggressively with high dose chemotherapy, thereby limiting the therapeutic options for such patients to investigational chemotherapy or relegating such patients to supportive care, with no hope for remission.

Since the best treatment for older AML patients remains undetermined, older patients with AML should be treated in clinical trials of investigational agents (31). Despite this, older, poor-risk AML patients are profoundly underrepresented in clinical trials (16, 32). This is related to exclusion of older patients due to poor performance status, the presence of comorbidities, and the frequently rapid clinical course of the disease which may not allow sufficient time for screening and enrollment of patients into clinical trials (31).

Only 30% of older AML patients in the US received any form of chemotherapy and analysis from the SEER database from 1991-1996 revealed that when patients aged 65 years or older received currently available intensive chemotherapy, median overall survival was 7 months (33). Additionally, patients experience treatment-related mortality of 25% (24).

Given that the majority of elderly patients with AML, especially those with poor-risk disease, remain untreated, there is clearly a need for new therapeutic options to induce remission for this patient group.

1.2 Development of Onrigin™ (laromustine) Injection

1.2.1 Background

Laromustine was selected as a candidate for clinical development based on its *in vitro* potency particularly against tumor cell lines that are resistant to currently approved alkylating agents (34), and its broad-spectrum *in vivo* anti-tumor efficacy (35, 36).

Laromustine is a novel alkylating agent from the sulfonylhydrazine prodrug class that spontaneously decomposes in an aqueous environment to yield VNP4090CE, which subsequently decomposes to produce a chloroethylating species that preferentially alkylates the O^6-position of guanine residues in DNA (34). If not repaired by alkylguanine-DNA alkyltransferase (AGT), the chloroethylated O^6-DNA guanine lesion progresses to form a G-C interstrand cross-link, a highly cytotoxic DNA lesion believed to be responsible for the therapeutic effectiveness of laromustine (37). The decomposition of laromustine also produces methyl isocyanate, a carbamoylating agent (38). Isocyanates are known to react with amino and thiol moieties of proteins, and have been shown to inhibit DNA polymerase, DNA ligase, and caspase activity. Methyl isocyanate has been shown to inhibit AGT activity and to enhance the cytotoxic effect of VNP4090CE and could contribute to the therapeutic, and potentially the toxic effects of laromustine (39).

Laromustine demonstrates broad spectrum anti-tumor efficacy against transplanted murine and human tumor models and is active against a variety of L1210 cell lines resistant to other alkylating agents including BCNU, cyclophosphamide and melphalan. In animal studies, laromustine was shown to be active against a BCNU-resistant L1210 cell line (L1210/BCNU) that had 3-fold elevations in AGT as well as increases in the levels of glutathione-S-transferase (GST), oxidized glutathione (GSSG) reductase activities, and glutathione (GSH) compared to parental L1210 cells. Laromustine can cross the blood brain barrier and kill intracranially-implanted leukemia cells (greater than 6-log kill) in mice. In addition to activity against murine leukemia models (L1210 and P388), laromustine demonstrates single-agent activity against many solid tumor models including the B16 murine melanoma, the C26 murine colon carcinoma, the U251 human glioma and the M109 murine lung carcinoma (35, 36).

Laromustine is not a substrate for the multidrug resistance proteins MDR-1 and MRP-1; cell lines overexpressing these proteins are less sensitive to anthracyclines such as doxorubicin but remain sensitive to laromustine. This is potentially an important attribute for the use of laromustine in elderly AML patients as MDR-1 expression is detected in 71% of patients 65 years and older (1).

1.2.2 Clinical Development of Onrigin™ in Hematologic Malignancies

The early clinical development program for Onrigin™ established the safety and tolerability profile of the chemotherapeutic at different doses and dose schedules in cancer patients with both hematologic malignancies and solid tumors when given as a single agent or in combination with other chemotherapeutic agents. The data from phase 1 studies was used to define a patient population in whom a reasonable safety profile was observed and who would be most likely to benefit from Onrigin™ therapy in later phase studies.

The phase 1 hematologic malignancy study, CLI-029, was initiated in 2002. The study was a single-agent phase 1 study designed to establish the safety profile and the maximum tolerated dose (MTD) of Onrigin™ in patients with relapsed or refractory leukemia or lymphoma. A

traditional dose-escalation scheme was utilized in which successive cohorts of patients received Onrigin™ by IV infusion on Day 1 of a 4-week schedule at doses ranging from 220 mg/m^2 to 708 mg/m^2. A total of 38 patients were treated in this study. Based on a dose-limiting toxicity (DLT) of prolonged myelosuppression occurring at 708 mg/m^2, the MTD of Onrigin™ was established as 600 mg/m^2. Eight patients were treated at the MTD of 600 mg/m^2 in this study. Although evaluation of response was not a primary objective of this study, activity in hematologic malignancies was observed in 2 patients, 1 patient with refractory anemia with excess blasts (RAEB) who responded after 1 cycle at 300 mg/m^2 and 1 patient with AML who responded after receiving 2 cycles at 600 mg/m^2. Both patients achieved a CR. The responses observed in this phase 1 trial provided preliminary evidence of the activity of Onrigin™ even in this heavily pretreated population. Based on the results of this study, the 600 mg/m^2 dose was selected as the dose for further examination in phase 2 trials in patients with hematologic malignancies (40).

The phase 2 clinical development program in patients with AML is comprised of 2 clinical studies. The first study, CLI-033, identified the efficacy signal in elderly patients with *de novo* AML. The second study, CLI-043, was prospectively designed to confirm the efficacy signal in elderly patients with *de novo* poor-risk AML. Details of the study designs for these 2 clinical trials are provided in Section 2.1.

The first phase 2 study CLI-033, which was initiated in March 2004, treated a total of 184 patients with AML or high risk MDS. These patients received IV induction treatment with Onrigin™ Injection at a dose of 600 mg/m^2. Study CLI-033 enrolled patients in 2 strata. Stratum A included patients with previously untreated *de novo* AML, secondary AML, or high-risk MDS. Stratum B included patients with AML in first relapse. During the conduct of the study and analysis of responses to Onrigin™ treatment, it was observed that a higher proportion of patients in Stratum A with *de novo* AML experienced CR and CRp with an overall response rate (ORR; CR+CRp) of 44% by investigator assessment (41).

The observations from Study CLI-033 led to the design of Study CLI-043, which was prospectively designed to confirm the efficacy of Onrigin™ in previously untreated elderly patients with *de novo* poor-risk AML. Data from Study CLI-043, which was initiated in May 2006, provide the primary evidence of the efficacy of Onrigin™ in patients with *de novo* poor-risk AML. Patients in Study CLI-043 were to be age 60 years or older, have AML confirmed histopathologically by WHO criteria, and have at least one of the following objectively defined poor-risk features: disease with unfavorable cytogenetics, ECOG PS of 2, age 70 years or older, cardiac dysfunction, pulmonary dysfunction assumed to be unrelated to AML, hepatic dysfunction related to chronic hepatitis or liver cirrhosis, or other organ dysfunction or comorbidity (see Section 2.1.4 for details on the study population). Each of the baseline risk factors has been identified in the literature as either a host or leukemic cell feature predicting for poor outcome based on either tolerability of therapy or lack of response to therapy. Patients received IV induction treatment with Onrigin™ Injection at a dose of 600 mg/m^2 over 60 minutes. A total of 85 patients were treated in this study.

1.2.3 Overview of Clinical Pharmacology

The pharmacokinetic (PK) parameters of laromustine were, in general, highly variable. Following an IV infusion of Onrigin™, the mean half-life of laromustine from 5 clinical studies (n=106 patients) ranged from 0.673 – 0.841 hours. Body surface area (BSA) normalized $V_{d,ss}$

ranged from 31.1 to 192 L/m^2 (% CV from 32 to 179), which exceeded the total body water and indicated extensive tissue distribution and binding. BSA normalized CL ranged from 48.0 to 181 L/hr/m^2 (% CV from 65 to 183), which equaled or exceeded cardiac output and was consistent with the rapid chemical decomposition of laromustine. There was no dose dependency of $V_{d,ss}$ and CL. C_{max} and AUC increased as the dose was increased.

Population PK analysis showed laromustine PK to be independent of dose and organ function, with no effect of subsequent dosing cycles, although inter-patient and inter-occasion variability was considerable. Covariates, including demographics, type of tumor, renal function and liver function, did not appear to explain any of the variability in laromustine PK parameters. The population PK analysis clearly demonstrates that dose individualization in patients with either solid or hematological tumors, or differences in liver/kidney function status, sex, race, or age is not indicated.

[^{14}C]-labeled Onrigin™ and its radioactive by-products were widely distributed to both well and poorly perfused tissues in rats. The highest concentrations of radioactivity were found in the small intestine contents at 0.5 hours and urinary bladder contents at 3 hours. The highest concentrations in specific organs were found in the renal cortex, small intestine, Harderian gland, and pancreas. Disappearance of total radioactivity from blood was slow, and concentrations were relatively unchanged from 0.5 to 8 hours post-dose. The calculated half life for the elimination of total radioactivity from tissues ranged from 51 hours for the Harderian gland to 262 hours for white adipose tissue, suggesting covalent linkage of the chloroethylating moiety to macromolecules.

Laromustine decomposed chemically in buffers and in incubation media with and without hepatic microsomes from rats, dogs, monkeys, and humans. The radiochromatographic profile was similar for all 4 species. Only one metabolite (C-7; VNP40107; 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-[(hydroxymethylamino)carbonyl]hydrazine) was formed by microsomes supplemented with NADPH from all species, and its formation was confirmed by incubation with human CYP2B6 and 3A4 enzymes. All other components in the radiochemical profile were decomposition products. Laromustine, C-7, and three other decomposition products were also identified from the plasma and urine of rats receiving an IV dose of laromustine. Two adducts originating from conjugation with glutathione, S-(carboxymethyl)cysteinylglycine (Cys(CH_2CO_2H)Gly) and S-(carboxymethyl)glutathione (GS(CH_2CO_2H)), were detected in bile collected from rats.

Renal excretion was the main route of elimination of laromustine and its metabolites/decomposition products. In rats receiving an IV dose of [^{14}C]-labeled Onrigin™, approximately 51% to 63% of the radioactivity was recovered from urine over 7 days. However, less than 5% of the radioactivity came from intact laromustine. Fecal excretion accounted for approximately 6%, whereas 11% of the radioactivity was recovered in expired air. Approximately 22% of the radioactivity remained in the carcass after 7 days. In human PK studies, <3% of the administered dose was recovered as intact laromustine in urine.

2. Design of Clinical Studies Conducted to Evaluate the Efficacy and Safety of Onrigin™ in Elderly Patients with *De novo* Poor-risk AML

2.1 Overview

The clinical development program was executed to evaluate the effectiveness and safety of Onrigin™ in the treatment of elderly patients with *de novo* poor-risk AML and includes two phase 2, open-label, multicenter, international studies. The primary study CLI-043 was conducted between 2006 and 2007 at 17 study sites in the US and Europe and treated 85 patients 60 years of age or older with *de novo* poor-risk AML. A supportive study CLI-033 was conducted between 2004 and 2006 at 14 study sites in the US and Europe. This study treated a total of 184 patients with AML and high-risk MDS and established the efficacy signal in the target population. From this supportive study, 55 patients were retrospectively determined to meet the criteria established in Study CLI-043 for elderly patients with *de novo* poor-risk AML. These two phase 2 studies which support the efficacy claim of Onrigin™ in the target population had the same primary endpoint, utilized the same dose of Onrigin™, and assessed disease response using the same criteria.

2.1.1 Study CLI-043: Design

The primary study designed to assess the efficacy and safety of Onrigin™ as induction therapy for elderly patients with *de novo* poor-risk AML, Study CLI-043, was an open-label, international, multicenter, phase 2 study. The primary objective of the study was to determine ORR, defined as proportion of patients who achieved CR or CRp using definitions from the International Working Group (IWG) (42).

Secondary objectives included estimation of the probability of overall survival, duration of response (i.e., leukemia-free survival; LFS), and progression-free survival (PFS), and determination of the toxicity profile of Onrigin™ in the target population.

The study was designed as a 2-stage optimal minimax design with responses required in 9 or more of the first 42 patients enrolled in the study for accrual to continue. This response criterion was met and accrual continued to stage 2. The study enrolled 86 patients at 17 sites in the US and Europe under the original protocol design, with the first patient enrolled on 18 May 2006 and last patient completing the study on 19 December 2007.

Patients received Onrigin™ 600 mg/m^2 induction therapy on study Day 1 by IV infusion over 60 minutes in a total volume of 500 mL of dextrose in 5% water (D5W). All patients were premedicated with an antiemetic and an antihistamine prior to dosing. Following treatment, patients were seen at least twice weekly until they attained CR or CRp or discontinued study.

Patients with evidence of clinical progression were removed from the study and considered treatment failures. These patients continued to be followed for survival. Patients without evidence of clinical progression underwent bone marrow biopsy and aspiration 4 to 6 weeks after dosing. Patients with hematologic improvement and residual AML or partial response (PR) were eligible for a second induction cycle of Onrigin™ 600 mg/m^2.

Patients who achieved CR or CRp after the first or second induction cycle, or PR after the second induction cycle, were eligible to receive consolidation with moderate dose continuous infusion ara-C at 400 mg/m^2/day for 5 days. Following the first consolidation cycle, a second cycle of the

same dose of ara-C could be administered at the discretion of the investigator. The administration of consolidation treatment was to occur no earlier than 45 days after induction in patients with CR, no earlier than 60 days in patients with CRp and no later than 90 days from Day 1 of the last induction cycle. The later consolidation start in patients with CRp was chosen to allow for maximum platelet recovery.

Following consolidation therapy, maintenance therapy could have been administered at the discretion of the investigator.

Patients who achieved CR, CRp, or PR after completion of all treatment were followed until the initiation of anti-leukemic therapy for progression/relapse. Patients were seen as clinically indicated but at least monthly for 6 months, every 2 months for the next 6 months, and then every 3 months for the next 6 months. A bone marrow biopsy and/or aspirate were to be performed if there was clinical or complete blood count evidence of disease progression. Patients receiving non-protocol consolidation, maintenance, or intensification also were followed until progression of leukemia.

After disease progression, all patients were followed for survival every 3 months for up to 36 months after the date of first infusion of study drug.

2.1.2 Study CLI-043: Patient Population

In Study CLI-043, men and women 60 years or older with pathologically confirmed *de novo* AML based on WHO criteria (excluding those patients with favorable cytogenetics [t(15;17), t(8;21) or inv16] were candidates for the study. Patients were required to have no prior history of chemotherapy with or without irradiation and no prior history of an antecedent hematologic disorder (MDS or MPS). In addition, patients must not have received a standard induction regimen containing cytotoxic agents (regimens containing ara-C or other nucleoside analogues ± an anthracycline) nor a regimen containing a low-dose single agent cytotoxic chemotherapy (e.g., ara-C, decitabine, 5-azacytidine). Prior treatment with gemtuzumab ozogamycin was also excluded.

In addition, patients were required to have <u>at least one</u> additional poor-risk feature:

- Unfavorable cytogenetics, defined as del (5q)/-5q; -7/del(7q); abnormal 3q, 9q, 11q, 20q, 21q or 17p; t(6;9); t(9;22); trisomy 8; complex karyotypes (>3 unrelated abnormalities),
- ECOG PS of 2,
- Age >70 years,
- Cardiac dysfunction as defined by any one of the following:
  - An ejection fraction ≤50%, or
  - A history of significant coronary artery disease (one or more vessel stenosis requiring medical treatment, stent placement or surgical bypass graft), or
  - A history of congestive heart failure or myocardial infarction, or
  - A significant arrhythmia including atrial flutter, sick sinus syndrome, or ventricular arrhythmia, or
  - Heart valve disease (excluding mitral valve prolapse), or
  - Other heart disease (with sponsor approval). Patients with a history of heart disease as defined above were to be on appropriate medication(s) and have their disease under control.

- Pulmonary dysfunction assumed to be unrelated to the patient's AML, as defined by carbon monoxide diffusing capacity (DLCO) and/or forced expiratory volume in the first second (FEV_1) <80% or dyspnea on slight activity or at rest, or requiring oxygen
- Hepatic dysfunction related to chronic hepatitis or liver cirrhosis
- Other organ dysfunction or comorbidity

In addition, patients were required to meet the following clinical laboratory values within 24 hours prior to beginning protocol treatment:

- Serum creatinine ≤2.0 mg/dL
- Total bilirubin ≤2.0 mg/dL
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤5 times the upper limit of normal

Patients with uncontrolled active infection, concurrently receiving any other standard or investigational treatment for their leukemia (with the exception of hydroxyurea), with clinical evidence of an ongoing second malignancy unrelated to AML or MDS, or, since the formulation contained 30% ethanol, being treated with disulfiram (Antabuse®), were excluded from the study.

2.1.3 Study CLI-033: Design

The supportive study, Study CLI-033, was an open-label, international, multi-center, phase 2 study conducted in patients with AML or high-risk MDS. The primary objective of the study was to determine the ORR (CR+CRp) following treatment with Onrigin™. Secondary objectives included evaluation of PK and the toxicity profile of Onrigin™ in this population. Subsequent analysis of the data from this study provided initial evidence of compelling anti-leukemic activity (as measured by CR and CRp) in elderly *de novo* poor-risk AML patients, which led to the design of Study CLI-043.

Study CLI-033 enrolled a total of 188 patients at 14 sites in the US and Europe, 184 of the 188 patients were treated in two strata. Stratum A included 131 poor-risk patients at least 60 years of age with AML or high risk MDS. Stratum B was comprised of 53 patients at least 18 years of age with AML in first relapse following a prior CR.

On study Day 1, patients received Onrigin™ 600 mg/m^2 by IV infusion over 30 minutes in a total volume of 500 mL D5W. All patients were premedicated with an antiemetic and an antihistamine prior to dosing. Prior to Amendment 2, patients also received hydroxyurea 30 mg/kg orally every 12 hours, from 2 to 3 hours before Onrigin™ infusion for a total of 6 doses. After Amendment 2, hydroxyurea could be administered at the investigator's discretion. Following treatment, patients were to be seen at least twice weekly until they attained a CR or CRp or discontinued study.

Patients with evidence of clinical progression were removed from the study and considered treatment failures. These patients continued to be followed for safety and survival. Patients without evidence of clinical progression underwent bone marrow biopsy and aspiration 4 to 5 weeks after dosing. Patients with hematologic improvement and residual AML or PR were eligible for a second induction cycle of Onrigin™ 600 mg/m^2.

For patients achieving CR or CRp after the first or second induction cycle, one cycle of consolidation with Onrigin™ 400 mg/m^2 or an alternate treatment could be administered at the discretion of the investigator.

Each patient was to be followed for survival for at least 36 months after his or her last dose of study drug. Patients who achieved a response were also to be followed for response status during this time interval until disease progression or death.

To confirm the outcome of treatment in *de novo* poor-risk AML patients at least 60 years old in Study CLI-033 with the outcome in the same population in Study CLI-043, the Sponsor undertook a *post hoc* analysis of a subset of patients in Study CLI-033. For entry into Study CLI-033, the AML diagnosis was based on the French–American–British (FAB) classification system. The WHO classification system for AML was used in Study CLI-043. Patients in Study CLI-033 were reclassified according to the WHO classification system.

After reclassification by WHO, the inclusion and exclusion criteria from Study CLI-043 pertaining to age and disease status, including poor-risk factors, were applied to the Study CLI-033 population. For this, medical history, physical exam and concomitant medication data available on patient listings and tables included in the CLI-033 Clinical Study Report were reviewed. The identification of patients was done without considering treatment outcomes. Fifty-five patients from Stratum A of Study CLI-033 were found to meet the Study CLI-043 eligibility criteria.

In order to support the efficacy claim of Onrigin™ in the target population, data from these 55 elderly *de novo* poor-risk AML patients from Study CLI-033 are presented with the data from the 85 patients enrolled in Study CLI-043. Response data from the subset of the 55 patients in CLI-033 is presented in Table 13. Response data for the entire study population is presented in Appendix A.

2.1.4 Study CLI-033: Patient Population

Men or women with pathologically confirmed AML (FAB type M0, M1, M2, M4-7, excluding acute promyelocytic leukemia) and high-risk MDS (International Prognosis Scoring System [IPSS] score ≥1.5), ≥18 years of age and with ECOG PS of 0 to 2 were candidates for enrollment in Study CLI-033.

Patients were enrolled in 2 strata:

Stratum A:

- Patients ≥60 years of age with AML or high-risk MDS who had received no prior cytotoxic treatment were enrolled. Low-dose single-agent ara-C, decitabine, or 5-azacytidine regimens were not considered prior cytotoxic treatment for the purpose of this study. Patients who had received prior cytotoxic treatment for an antecedent pre-leukemic condition (for example, MDS) or as curative/adjuvant treatment for another malignancy, were eligible, provided the chemotherapy was completed >6 months prior to enrollment in the present trial.

Stratum B:

- Patients ≥18 years of age with AML in first relapse, who had not yet received treatment (other than hydroxyurea) for first relapse, and duration of first CR had been < 12 months. High-risk MDS patients, who had achieved CR with an intensive AML-like cytotoxic regimen within the previous 6 months, and relapsing with AML, were eligible for this stratum.

The entrance criteria from the primary efficacy Study CLI-043, including the WHO classification of *de novo* AML, were applied to the patient population enrolled in Stratum A of

Study CLI-033. A total of 55 of the 131 patients treated under Stratum A met the criteria for inclusion in Study CLI-043 and are included in the Onrigin™ efficacy evaluations to support the indication of induction therapy for patients 60 years or older with *de novo* poor-risk AML.

2.2 Efficacy Considerations

2.2.1 Efficacy Evaluations Conducted during the Studies

The efficacy evaluations conducted during the phase 2 studies were standard for the evaluation of response to treatment in patients with AML and were consistent across the studies.

A thorough medical history, including date of initial diagnosis of AML and AML classification, was obtained prior to entry into the study.

A complete blood count (CBC) with differential and platelet count was obtained within 24 hours prior to each dose (all cycles) and was repeated on Days 2 and 3, weekly thereafter, and at treatment assessment of each cycle; hematology assessments were repeated at each follow-up visit and at the off-study visit.

Bone marrow biopsy and/or aspirate were obtained within 14 days prior to the first dose of Onrigin™. The bone marrow biopsy and/or aspirate were repeated at Weeks 4 to 6 after treatment, and as required to document response and/or progression.

As prospectively defined in the protocol for Study CLI-043, 6 unstained bone marrow smears from each bone marrow procedure were submitted for independent review; if insufficient material was available, submission of at least 1 Wright-stained slide was required. The screening bone marrow sample was submitted for independent confirmation of the AML diagnosis; this was not required to be available prior to study enrollment. For Study CLI-033, bone marrow slides were submitted for independent review for patients in the *de novo* poor-risk AML subgroup who were determined to be responders (CR or CRp) by the investigators.

Immunophenotype and cytogenetics were performed on the baseline bone marrow aspirate; this may have been done on peripheral blood if there were sufficient circulating blasts. Cytogenetics, immunophenotype, and CBC reports were included with the submission of the Wright-stained slide for independent review.

As detailed above, patients who achieved CR, CRp or PR after completion of all treatment were followed until the initiation of anti-leukemic therapy for progression/relapse. Patients were seen as clinically indicated but at least monthly for 6 months, every 2 months for the next 6 months, and then every 3 months for the next 6 months. After disease progression, all patients were followed for survival every 3 months for up to 36 months after the date of first infusion of study drug.

2.2.2 Independent Evaluation of Diagnosis and Response

The protocol design of Study CLI-043 required bone marrow samples to be independently reviewed. This independent review of bone marrow slides and peripheral blood data were conducted to confirm response to treatment and the diagnosis of AML. The review was performed at Quest Diagnostics Laboratory, Van Nuys, CA by an experienced board certified pathologist, with subspecialty in hematopathology. The purpose of this independent review was to provide an unbiased and consistent review of all bone marrow slides across the multicenter study.

Bone marrow slides for those patients enrolled in Stratum A of Study CLI-033 who achieved a response following treatment with Onrigin™ as determined by the investigator were also submitted to independent review for evaluation of response to provide a consistent assessment across the data from the 2 studies.

2.2.3 Disease Response Criteria

The following definitions, based on the International Working Group (IWG) criteria (42), were used to determine response to treatment:

- Complete Response (CR): The absence of leukemic blasts in the peripheral blood and a bone marrow with < 5% blasts as measured by morphology studies in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells; absence of blasts with Auer rods; no extramedullary disease; an absolute granulocyte count of at least 1,000/mm^3; and a platelet count of at least 100,000/mm^3.
- Complete Response without full platelet recovery (CRp): Defined as for CR but allows a platelet count < 100,000/mm^3. Patients must be transfusion independent, defined as able to maintain a platelet count of ≥20,000/mm^3; however, patients can meet the criteria for CRp if platelet transfusions are required in the presence of infection, bleeding, or medical/surgical conditions predisposing to bleeding.
- Partial Response (PR): Defined as for CR with the exception that leukemic blasts in the bone marrow may range from 5% to 25%, provided the count has decreased by at least 50% from baseline.
- Hematologic Improvement (HI): Defined as the reduction of blasts based on total cellularity and percent of leukemic blasts.
- Morphologic Leukemia Free: Defined as <5% blasts in an aspirate sample. There should be no blasts with Auer rods or persistence of extramedullary disease.
- Sustained Disease/Treatment Failure: Patients who do not meet any of the above criteria.
- Relapse (or recurrence) following CR or CRp: defined as reappearance of leukemic blasts in peripheral blood or presence of ≥5% blasts in a marrow aspirate and/or biopsy not attributable to any other cause. The appearance of new dysplastic changes in the bone marrow should also be considered relapse. If there are no circulating blasts and the marrow aspirate and/or biopsy demonstrates 5-20% blasts, a repeat bone marrow exam is required ≥1 week later documenting ≥5% blasts.
- Disease progression: leukemic blasts in peripheral blood or presence of ≥5% blasts in a marrow aspirate and/or biopsy not attributable to any other cause.

2.2.4 Efficacy Endpoints and Analysis Populations

The primary analysis set for evaluation of efficacy data in both Studies CLI-043 and CLI-033 was the ITT analysis set; defined as all patients who were enrolled into the study and received at least 1 dose of study drug. Efficacy analyses provided in this summary for Study CLI-033 were performed on the subset of patients at least 60 years of age with *de novo* poor-risk AML in the ITT Analysis Set defined for that study.

The primary efficacy endpoint in both Studies CLI-043 and CLI-033 was ORR, defined as the proportion of patients who achieved CR or CRp (see Section 2.2.3). Patients not achieving CR or CRp were considered non-responders. ORR was selected as the primary measure of efficacy for Studies CLI-043 and CLI-033. In the treatment of AML complete remission is the only clinically significant form of response. The ability to achieve such a response has been directly correlated with survival and is a necessary first step in a curative treatment strategy (7). CRp describes a subgroup of responders, wherein patients fulfill all criteria for CR except that platelet counts are less than $100x10^9$/L. As published by Estey (43), patients achieving CRp live significantly longer than non-responders and therefore CRp has relevance in untreated AML. Additionally, CRp has been included as an endpoint in past regulatory approvals.

The primary analysis was based on the independent review of response; the investigator assessments were considered secondary. Point estimates and 95% exact binomial confidence intervals (CI) are presented for the proportion of patients with CR, CRp, and ORR in each study, as well as overall.

The number and percentage of patients who achieved a CR or CRp, as well as the ORR, were summarized separately for each of the following patient subgroups: age category (60 to <70 years and ≥70 years), baseline ECOG performance status (0, 1, and 2), baseline cytogenetics category (intermediate, unfavorable, and unknown), and presence or absence of cardiac and pulmonary dysfunction. No formal subgroup analyses were performed for patients with hepatic dysfunction.

Secondary endpoints included duration of response (CR/CRp) based on LFS, OS, and PFS as defined below.

All time to event analysis, including LFS, OS and PFS, are summarized descriptively using Kaplan-Meier product-limit estimates. The proportion of patients alive and/or disease free at 6, 9 and 12 months are also provided.

LFS measures response duration and was calculated from the date that objective criteria for a CRp or CR were first met until the date of a bone marrow or CBC assessment indicating recurrence of leukemia or date of death (from any cause). Date of recurrence is the earliest date in which ≥5% blasts were observed in bone marrow or leukemic blasts reappear in the peripheral blood. LFS was calculated using independently confirmed response.

Patients not experiencing a recurrence of leukemia or death had their observation times censored at the latest date at which valid assessments of disease confirmed the patient's status either by CBC and/or bone marrow aspirate. One day was added to the calculation to ensure both event endpoint days were properly taken into account.

OS was calculated from the date of first dose of Onrigin™ to the date of death (from any cause). Patients who did not die had their survival times censored on the last date of contact. One day was added to the calculation to ensure both event endpoint days were properly taken into account.

PFS was calculated from the date of first dose of Onrigin™ to the date that objective criteria were met for progressive disease (PD) or death (from any cause). Date of recurrence is the earliest date in which ≥5% blasts were observed in bone marrow or leukemic blasts reappear in the peripheral blood.

Patients not experiencing disease progression or death had their observation times censored at the latest date at which valid assessments of disease confirmed the patient's status. One day was added to the calculation to ensure both event endpoint days were properly taken into account.

2.3 Safety Evaluations

2.3.1 Safety Evaluations Conducted During the Studies

Standard safety evaluations were conducted in Studies CLI-043 and CLI-033, including monitoring for adverse events and concomitant medications, clinical laboratory evaluations, vital signs, and performance status.

Grading of adverse events was to be performed using the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 3.0. Adverse events were recorded for 42 days after each treatment.

Clinical laboratory assessments, including hematology, liver function tests, serum chemistry and coagulation parameters, were conducted prior to the first dose, weekly during each cycle, at each follow-up visit and at the off-study visit.

Vital signs measurements were obtained prior to and immediately after dosing and every 30 minutes through 2 hours post-dose. The assessments were repeated at Weeks 4 to 5 and at the follow-up and off-study visits.

ECOG PS was assessed prior to study treatment, at Weeks 4 to 5, at each follow-up visit and at the off-study visit.

All patients in both studies, and, at the request of FDA, 8 patients in Study CLI-029 who received the induction dose of 600 mg/m^2 Onrigin™, are included in the population of 277 patients with hematologic malignancies assessed for safety.

Tabulations include patient accountability and disposition, overall extent of exposure to active drug, patient demographics, AEs, clinical laboratory evaluations, vital signs, and ECOG performance status.

For presentation of safety data across studies, the AEs in each study were recoded to comply with the Medical Dictionary for Drug Regulatory Affairs (MedDRA) Version 10.0 dictionary. Overall treatment-emergent AE (TEAE) incidences are summarized by MedDRA system organ class (SOC) and preferred term. All TEAEs and drug-related TEAEs are tabulated as are TEAEs by maximum severity (grade). A tabulation of the subset of TEAEs that occurred during the first cycle, i.e., following Onrigin™ infusion on day 1 of induction 1 and prior to the next protocol or non-protocol treatment is also presented.

Laboratory results were graded according to the NCI CTCAE v3.0. For each parameter with toxicity grade criteria available, the maximum toxicity grade per patient for each cycle in which Onrigin™ was received and across all cycles is summarized as the number and percentage of patients within each toxicity grade (0 through 4).

Changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) from baseline to pre-infusion, end of infusion, and 60 and 120 minutes post-infusion during each Onrigin™ cycle are summarized descriptively. In addition, the number and percentage of patients with increases and decreases in systolic and diastolic blood pressure of at least

20 mm Hg from pre-infusion to end of infusion and 60 and 120 minutes post-infusion is tabulated.

3. Disposition and Baseline Characteristics of the Elderly *De novo* Poor-Risk AML Population

3.1 Disposition and Exposure

3.1.1 Disposition

Table 7 displays the treatment cycles received and disposition of the elderly patients with *de novo* poor-risk AML included in the efficacy analyses across the primary and supportive studies.

The efficacy of Onrigin™ Injection is examined in 140 patients, 85 from Study CLI-043 and 55 from Study CLI-033, with *de novo* poor-risk AML, who were at least 60 years old. All 140 patients received at least one induction cycle with 600 mg/m^2 Onrigin™. A second induction cycle was administered to 23 (16.4%) patients overall. The proportion of patients in each study who received a second induction cycle was similar.

As detailed in Table 7, patient disposition and exposure were similar in Studies CLI-033 and CLI-043. As the definition of study completion required patients to receive all study treatment, achieve CR or CRp and not relapse prior to final evaluation, the most common reasons for early study termination were disease progression, reported in 32.9% of all 140 patients, and death reported in 32.1% of all patients. Only 2 patients (1.4%) were reported to have terminated the study due to adverse events.

Table 7: Patient Disposition (Elderly *De novo* Poor-Risk AML Population)

Disposition:	Study CLI-043 N=85 n (%)	Study CLI-033 N=55 n (%)	Total N=140 n (%)
Cycles Received			
First Induction	85 (100)	55 (100)	140 (100)
Second Induction	14 (16.5)	9 (16.4)	23 (16.4)
First Consolidation[a]	18 (21.2)	15 (27.3)	33 (23.6)
Second Consolidation[a]	4 (4.7)	NA	4 (2.9)
Discontinued from the Study	71 (83.5)	41 (74.5)	112 (80.0)
Reasons for Discontinuation			
Disease Progression/Relapse	27 (31.8)	19 (34.5)	46 (32.9)
Death	32 (37.6)	13 (23.6)	45 (32.1)
Physician Request	8 (9.4)	0	8 (5.7)
Withdrew Consent	2 (2.4)	3 (5.5)	5 (3.6)
Sponsor Request	0	4 (7.3)	4 (2.9)
Adverse Event	2 (2.4)	0	2 (1.4)
Other	0	2 (3.6)	2 (1.4)

Note that study completion was defined as completing all per-protocol treatment, achieving a CR or CRp, not receiving any non-protocol treatment for consolidation or maintenance, and not relapsing prior to final study evaluation.

[a] Patients in CLI-033 could receive 1 optional consolidation with 400 mg/m^2 Onrigin™. Patients in CLI-043 received at least 1 consolidation cycle with ara-C and could receive a second, optional consolidation with ara-C.

3.1.2 Exposure to Study Treatment

A summary of exposure to Onrigin™ Injection is provided in Table 8. Among the 140 patients, 104 (74.3%) received only one cycle of Onrigin™ treatment (Induction 1 only), 34 (24.3%) patients received 2 cycles (Inductions 1 and 2, or Induction 1 and Consolidation 1), and 2 (1.4%) patients in Study CLI-033 received 3 cycles (Inductions 1 and 2 and Consolidation 1).

The dose for remission induction is given in one hour on Day 1. Median duration of infusion across all 140 patients was 60 minutes in Inductions 1 and 2.

The infusion of Onrigin™ was well tolerated; infusion interruptions were uncommon during Onrigin™ administration.

Table 8: Exposure to Onrigin™ Injection, All Cycles (Elderly *De novo* Poor-Risk AML Population)

Exposure	Induction Cycle 1 N=140	Induction Cycle 2 N=23	Consolidation Cycle 1[d] N=15
Dose Received (mg/m^2)[a]	600	600	400
Duration of Onrigin™ Infusion (min)[b]			
Mean (SD)	58.6 (33.53)	57.1 (23.63)	47.7 (35.84)
Median	60.0	60.0	30.0
Range	30-310	30-135	25-140
Patients w/Infusion Interruptions (n [%])[c]	3 (2.1)	2 (8.7)	0
AE	3 (2.1)	2 (8.7)	0
Other	0	1 (4.3)	0

[a] Patients could receive up to 2 induction cycles with 600 mg/m^2 Onrigin™. Patients in CLI-033 could receive one consolidation cycle with 400 mg/m^2 Onrigin™.
[b] If start or end time was missing, duration was set to the scheduled infusion duration for the given study. Planned duration was 60 minutes in Study CLI-043 and 30 minutes in Study CLI-033.
[c] Patients may have had more than one reason for dose interruption.
[d] Study CLI-033 only.

Patients in Study CLI-033 who achieved CR or CRp received consolidation with Onrigin™ 400 mg/m^2 (Table 8).

3.2 Demographics, Baseline, and Patient Characteristics

3.2.1 Demographics and Baseline Characteristics

The demographics and baseline characteristics of 140 elderly *de novo* poor-risk AML patients from CLI-033 and CLI-043 are provided in Table 9.

The demographic characteristics were similar across the primary and supportive studies. The majority of 140 patients in the 2 clinical trials were Caucasian males, which is consistent with the general demographics of AML patients in the US. Overall, 57.1% of patients were men and 90.0% were Caucasian.

Mean age of all 140 patients was 73.6 years and ranged from 60 to 88 years. Seventy-five percent of patients were at least 70 years old. A slightly higher percentage of patients in Study CLI-043 (77.6%) were 70 years or older compared with patients in Study CLI-033 (70.9%).

A higher proportion of patients in Study CLI-043 entered the study with ECOG PS of 2 (41.2%) compared to Study CLI-033 (29.1%). The higher level of poor PS seen in Study CLI-043 is related to the prospective selection of poor-risk patients.

Table 9: Patient Demographics and Baseline Characteristics (Elderly *De novo* Poor-Risk AML Population)

Demographic Characteristic	Study CLI-043 N=85	Study CLI-033 N=55	Total N=140
Age (years)			
N	85	55	140
Mean (SD)	73.4 (6.33)	73.8 (6.70)	73.6 (6.46)
Median	72.0	75.0	74.0
Range	60-87	60-88	60-88
Age by Category [n (%)]			
<70 years	19 (22.4)	16 (29.1)	35 (25.0)
≥70 years	66 (77.6)	39 (70.9)	105 (75.0)
Sex [n (%)]			
Male	50 (58.8)	30 (54.5)	80 (57.1)
Female	35 (41.2)	25 (45.5)	60 (42.9)
Race [n (%)]			
Caucasian	76 (89.4)	50 (90.9)	126 (90.0)
Hispanic	4 (4.7)	3 (5.5)	7 (5.0)
Black	5 (5.9)	2 (3.6)	7 (5.0)
Body Surface Area (m^2)			
N	85	55	140
Mean (SD)	1.84 (0.211)	1.86 (0.228)	1.84 (0.217)
Median	1.85	1.88	1.87
Range	1.34-2.33	1.45-2.36	1.34-2.36
ECOG Performance Status [n (%)]			
0	23 (27.1)	12 (21.8)	35 (25.0)
1	27 (31.8)	27 (49.1)	54 (38.6)
2	35 (41.2)	16 (29.1)	51 (36.4)

3.2.2 Patient Characteristics

Each of the baseline risk factors identified in these patients has been reported in the literature as either a host or leukemic cell feature predicting for poor outcome based on either tolerability of therapy or response to therapy. Results are summarized in Table 10.

Across all 140 patients, 75.0% were age 70 or older, 60.7% had cardiac dysfunction, 57.9% had pulmonary dysfunction, 45.0% had unfavorable cytogenetics, and 36.4% had ECOG PS of 2. Over 86% of the 140 patients had at least 2 poor-risk factors with 58% having 3 or more factors. Notably more patients in Study CLI-043 had cardiac or pulmonary dysfunction (72.9% and 76.5%, respectively) than did patients in Study CLI-033 (41.8% and 29.1%, respectively). Generally, patients in Study CLI-043 had more risk factors than patients in Study CLI-033. This profile is expected because the patients admitted to Study CLI-043 were prospectively selected for their poor-risk status.

Table 10: Baseline Risk Factors (Elderly *De novo* Poor-Risk AML Population)

Risk Factors	Study CLI-043 N=85 n (%)	Study CLI-033 N=55 n (%)	Total N=140 n (%)
Age 70 Years or Greater	66 (77.6)	39 (70.9)	105 (75.0)
ECOG Performance Status of 2	35 (41.2)	16 (29.1)	51 (36.4)
Unfavorable Cytogenetics	40 (47.1)	23 (41.8)	63 (45.0)
Cardiac Dysfunction	62 (72.9)	23 (41.8)	85 (60.7)
Pulmonary Dysfunction	65 (76.5)	16 (29.1)	81 (57.9)
Hepatic Dysfunction	3 (3.5)	0	3 (2.1)
Total Number of Risk Factors			
1	3 (3.5)	16 (29.1)	19 (13.6)
2	18 (21.2)	21 (38.2)	39 (27.9)
3	31 (36.5)	14 (25.5)	45 (32.1)
4	26 (30.6)	3 (5.5)	29 (20.7)
5 or more	7 (8.2)	1 (1.8)	8 (5.7)

Comorbidities present at baseline were prospectively defined and recorded in Study CLI-043 based on definitions from HCT-CI (19-21, 44). Results are summarized in Table 11 across both studies and for all 140 *de novo* poor-risk AML patients. The representation of significant baseline comorbidity in patients enrolled to this study suggests a population often not treated with standard induction chemotherapy due to poor tolerability. In general, older patients with comorbid medical illnesses which result in limited cardiac, pulmonary, renal and/or hepatic functional reserve may be less able to tolerate intensive cytotoxic induction with standard regimens (45).

Most patients treated in Study CLI-043 had pulmonary comorbidities at study entry, with 50.6% having severe pulmonary conditions defined as DLCO and/or FEV_1 values ≤65%, or with dyspnea at rest or requiring oxygen. Conditions related to the cardiovascular system were also frequent for patients in Study CLI-043. Arrhythmia (42.4%), coronary artery disease (30.6%), heart valve disease (20.0%), myocardial infarction (16.5%), and congestive heart failure (14.1%) were recorded and are expected conditions in this population.

Table 11 provides a detailed listing of the comorbidities in patients which meet the eligibility requirements according to the HCT-CI for Study CLI-043.

To delineate the poor baseline health status of patients enrolled to Study CLI-043, a more detailed list of **all** comorbidities is provided in Table 12.

Table 11: Baseline Cardiac, Pulmonary and Hepatic Comorbidity Meeting Eligibility Criteria (Elderly *De novo* Poor-Risk AML Population)

Comorbidity	CLI-043 N=85 n (%)	CLI-033 N=55 n (%)	Total N=140 n (%)
Pulmonary Comorbidity	**65 (76.5)**	**16 (29.1)**	**81 (57.9)**
Severe Pulmonary	43 (50.6)	12 (21.8)	55 (39.3)
DLCO and/or FEV ≤ 65%	33 (38.8)	3 (5.5)	36 (25.7)
Dyspnea at rest or requiring oxygen	10 (11.8)	10 (18.2)	20 (14.3)
Moderate Pulmonary	22 (25.9)	4 (7.3)	26 (18.6)
DLCO and/or FEV > 65% to 80%	15 (17.6)	3 (5.5)	18 (12.9)
Dyspnea w/ slight activity or w/ moderate activity despite treatment	7 (8.2)	6 (10.9)	13 (9.3)
Cardiac Comorbidity	**62 (72.9)**	**23 (41.8)**	**85 (60.7)**
Arrhythmia (atrial fibrillation, flutter, sick sinus syndrome, or ventricular arrhythmia)	36 (42.4)	7 (12.7)	43 (30.7)
Coronary Artery Disease requiring treatment, stent or bypass graft in ≥ 1 vessel	26 (30.6)	15 (27.3)	41 (29.3)
Ejection Fraction ≤ 50%	6 (7.1)	0	6 (7.1)
Myocardial Infarction	14 (16.5)	11 (20.0)	25 (17.9)
Heart Valve Disease	17 (20.0)	5 (9.1)	22 (15.7)
Congestive Heart Failure	12 (14.1)	3 (5.5)	15 (10.7)
Hepatic Comorbidity	**3 (3.5)**	**0**	**3 (2.1)**
Moderate/severe liver disease	3 (3.5)	0	3 (2.1)

Note: Patients could have had multiple cardiac or pulmonary conditions.

Table 12: Baseline Comorbidities in ≥ 10% of Patients (Study CLI-043, Elderly *De novo* Poor-Risk AML Population)

Comorbidity	N=85 n (%)
Severe Pulmonary, including	**43 (50.6)**
DLCO and/or FEV ≤ 65%	33 (38.8)
Dyspnea at rest or requiring oxygen	10 (11.8)
Arrhythmia (Atrial fibrillation, flutter, sick sinus syndrome, or ventricular arrhythmia)	**36 (42.4)**
Coronary Artery Disease	**32 (37.6)**
Coronary artery stenosis requiring treatment, stent, or bypass graft in ≥1 vessel	26 (30.6)
Ejection fraction ≤50%	6 (7.1)
Infection (On anti-microbial treatment after Day 10)	**31 (36.5)**
Moderate Pulmonary	**22 (25.9)**
DLCO and/or FEV >65% to 80%	15 (17.6)
Dyspnea w/ slight activity or w/ moderate activity despite treatment	7 (8.2)
Mild Diabetes (On insulin or oral hypoglycemic)	**20 (23.5)**
Psychiatric Disturbances (Depression or anxiety requiring psychiatric consult or treatment)	**18 (21.2)**
Heart Valve Disease	**17 (20.0)**
Myocardial Infarction	**14 (16.5)**
≥1 MI resulting in hospitalization and w/ ECG and/or enzyme changes	7 (8.2)
≥1 MI	7 (8.2)
Mild Liver Disease (Bilirubin >ULN to 1.5xULN or AST or ALT >ULN to 2.5xULN)	**14 (16.5)**
Obesity (BMI >35 kg/m^2)	**13 (15.3)**
Congestive Heart Failure	**12 (14.1)**
Exertional or paroxysmal nocturnal dyspnea and response to digitalis, diuretics, or afterload-reducing agents	7 (8.2)
History of congestive heart failure	5 (5.9)
Prior Solid Tumor	**12 (14.1)**
Treated at any time	8 (9.4)
Non-metastatic treated in last 5 years	4 (4.7)
Peripheral Vascular Disease	**9 (10.6)**
Intermittent claudication	3 (3.5)
Bypass for atrial insufficiency	3 (3.5)
Acute arterial insufficiency	2 (2.4)
Untreated thoracic or abdominal aneurysm ≥ 6 cm	1 (1.2)

4. Efficacy Results in the Elderly *De novo* Poor-risk AML Population

Treatment with Onrigin™ led to durable complete remissions in an elderly patient population with *de novo* poor-risk AML. Clinical benefit was observed in responding patients based on durable responses and increased overall survival. Similar responses rates were observed across patient subgroups often associated with poor outcomes, including patients 70 years of age or older, patients with ECOG PS of 2, patients with cardiac and pulmonary dysfunction, and patients with unfavorable cytogenetics.

4.1 Primary Efficacy Endpoint: Overall Response Rate Based on Independent Review

ORR defined as the percentage of patients who achieved a best response of CR or CRp as determined by independent review for the ITT population, is the primary efficacy endpoint; results are presented in Table 13. The NDA noted 15 samples were not available for independent review. Subsequent to filing the NDA and at FDA request, the Sponsor obtained missing samples from 14 patients, which were submitted for review. The ORR reported in Table 13 represents the completed independent review in this briefing document.

The ORR in Study CLI-043 based on independent review was 31.8% (27 of 85 patients). CR was achieved by 20 (23.5%) patients and CRp was achieved by 7 (8.2%) patients. The ORR in Study CLI-033 was 38.2% based on independent review, including 32.7% of patients achieving CR and 5.5% achieving CRp.

Across all 140 elderly *de novo* poor-risk AML patients, ORR was 34.3% based on independent review.

Table 13: Overall Response Rate Based on Independent Review (Elderly *De novo* Poor-Risk AML Population)

Response	CLI-043 N=85		CLI-033 N=55		Total N=140	
	n (%)	[95% CI]	n (%)	[95% CI]	n (%)	[95% CI]
ORR (CR+CRp)	27 (31.8)	[22.1, 42.8]	21 (38.2)	[25.4, 52.3]	48 (34.3)	[26.5, 42.8]
CR	20 (23.5)	[15.0, 34.0]	18 (32.7)	[20.7, 46.7]	38 (27.1)	[20.0, 35.3]
CRp	7 (8.2)	[3.4, 16.2]	3 (5.5)	[1.1, 15.1]	10 (7.1)	[3.5, 12.7]

Eighty eight percent (88%, 42 of 48 patients) responded following treatment with the first induction cycle. In Study CLI-043, 23 (85.1%) of the 27 patients who achieved CR or CRp responded following the first induction cycle as did 19 (90.5%) of 21 responders in Study CLI-033.

A discussion of ORR by patient subgroups is provided in Section 4.6.

4.2 Overall Response Rate Based on Investigator Assessment

Table 14 provides a summary of ORR based on the investigator assessment of response. As shown, these results were consistent with those reported based on independent review. The ORR in Study CLI-043 was 31.8% (27 of 85 patients) with 23.5% achieving CR and 8.2% achieving CRp. The concordance rate between independent and investigator assessment was 88%.

Table 14: Overall Response Rate Based on Investigator Assessment (Elderly *De novo* Poor-Risk AML Population)

Response	CLI-043 N=85		CLI-033 N=55		Total N=140	
	n (%)	[95% CI]	n (%)	[95% CI]	n (%)	[95% CI]
ORR (CR+CRp)	27 (31.8)	[22.1, 42.8]	24 (43.6)	[30.3, 57.7]	51 (36.4)	[28.5, 45.0]
CR	20 (23.5)	[15.0, 34.0]	20 (36.4)	[23.8, 50.4]	40 (28.6)	[21.3, 36.8]
CRp	7 (8.2)	[3.4, 16.2]	4 (7.3)	[2.0, 17.6]	11 (7.9)	[4.0, 13.6]

4.3 Duration of Response: Leukemia-Free Survival

Leukemia-free survival is a measure of clinical benefit as it reflects duration of remission in responding patients (CR/CRp). It is defined as the interval from time of remission to relapse of disease or death. For those patients achieving a CR or CRp, time spent in a leukemia-free interval translates to freedom from disease-related symptoms and freedom from the need for either supportive or disease-directed therapy.

Table 15 presents Kaplan-Meier estimates of LFS in patients with CR or CRp by independent review for each study; the Kaplan-Meier curves for these analyses are presented in Figure 5 and Figure 6 for Studies CLI-043 and CLI-033, respectively.

In Study CLI-043, median duration of response was 183 days (6.0 months) with 7 (25.9%) of the 27 patients with CR or CRp in continued remission at the point of last contact. The Kaplan-Meier probability of LFS to 3, 6, 9, 12 months is 62.5%, 53.2%, 38.7%, and 27.6%, respectively. Maximum duration of response in this study was 581 days (19.1 months) in a patient who remained in continuous complete remission at last contact.

In Study CLI-033, median duration of response was 150 days (4.9 months) with 4 (19.0%) of 21 patients with CR or CRp in continued remission at the point of last contact. The Kaplan-Meier probabilities of LFS to 3, 6, 9 and 12 months were similar to those reported in Study CLI-043 (70.0%, 40.0%, 40.0%, and 28.6%, respectively). Maximum duration of response in this study was 981 days (32.3 months) in a patient who remained in a continuous complete remission at last contact.

Across responding *de novo* poor-risk AML patients, median LFS was 165 days (5.4 months).

Table 15: Duration of Response: Cumulative Probability of Leukemia-Free Survival (Elderly *De novo* Poor-Risk AML Patients With CR/CRp)

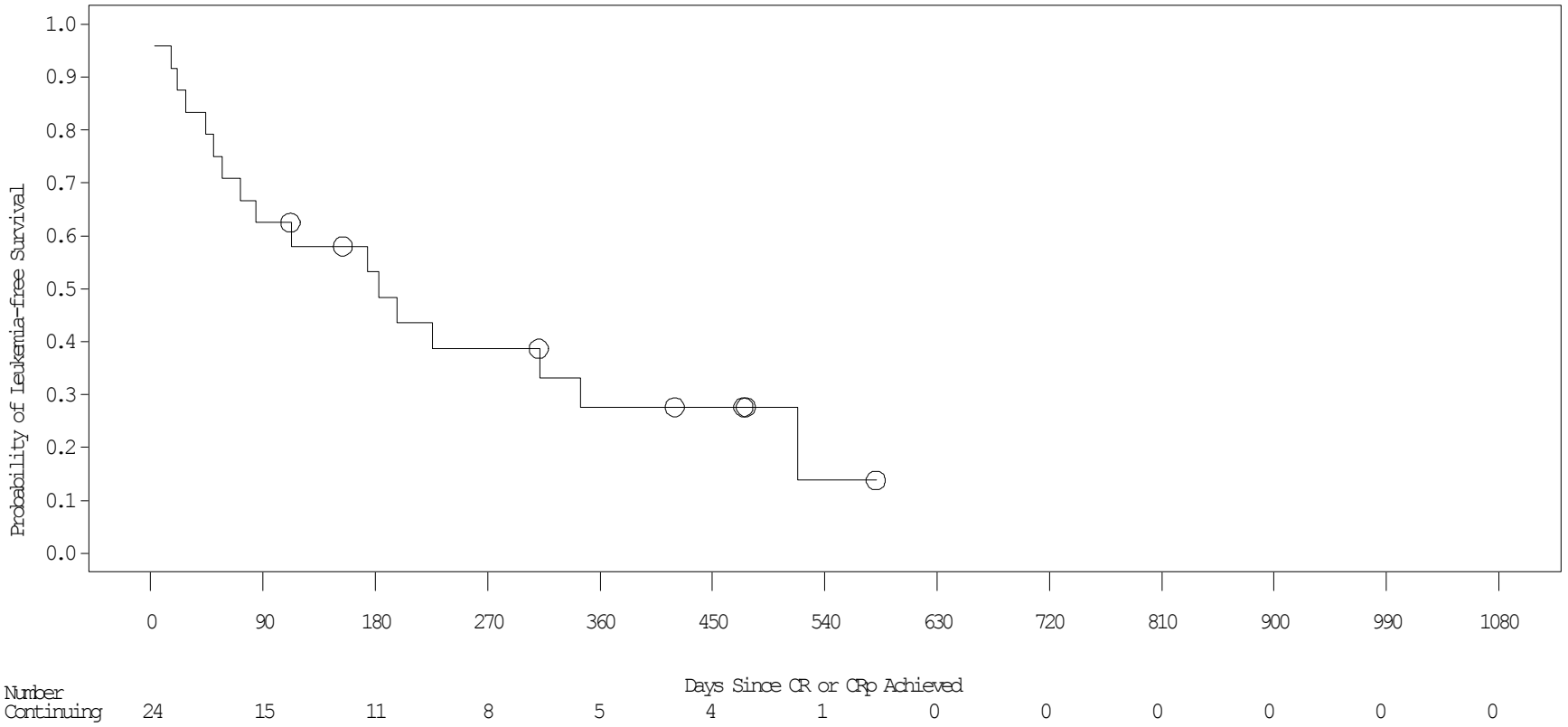
Parameter	CLI-043 N=27	CLI-033 N=21	Total N=48
LFS Status (n [%])			
Alive and did not progress	7 (25.9)	4 (19.0)	11 (22.9)
Met progression criteria or died	17 (63.0)	16 (76.2)	33 (68.8)
Missing	3 (11.1)	1 (4.8)	4 (8.3)
Kaplan-Meier Estimate of LFS (days)[a]			
Median (95% CI)	183.0 (72.0, 344.0)	150.0 (74.0, 349.0)	165.0 (108.0, 312.0)
Minimum, maximum	3, 581+	15, 981+	3, 981+
Kaplan-Meier Probability of LFS[b]			
3 months (90 days)	62.5%	70.0%	65.9%
6 months (180 days)	53.2%	40.0%	47.0%
9 months (270 days)	38.7%	40.0%	39.5%
12 months (360 days)	27.6%	28.6%	28.4%

[a] Patients without disease progression as of the date of last follow-up had their response duration censored at the last date of known favorable status.

[b] Kaplan-Meier estimate of the probability of LFS to the indicated time point.

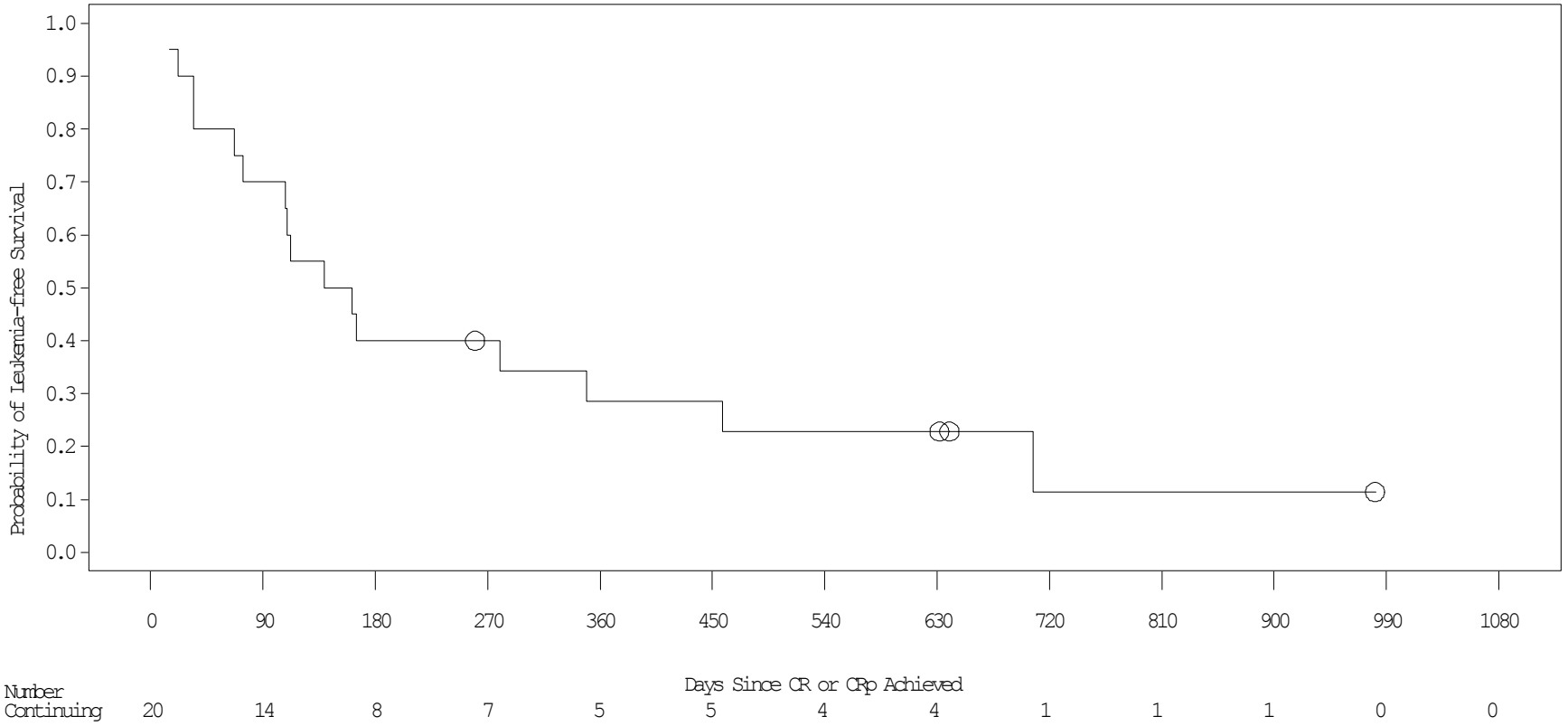
NE=not estimable

Figure 5: Kaplan-Meier Curve of the Cumulative Probability of LFS (Study CLI-043, Elderly *De novo* Poor-Risk AML (Patients With CR/CRp Based on Independent Review, N=27)



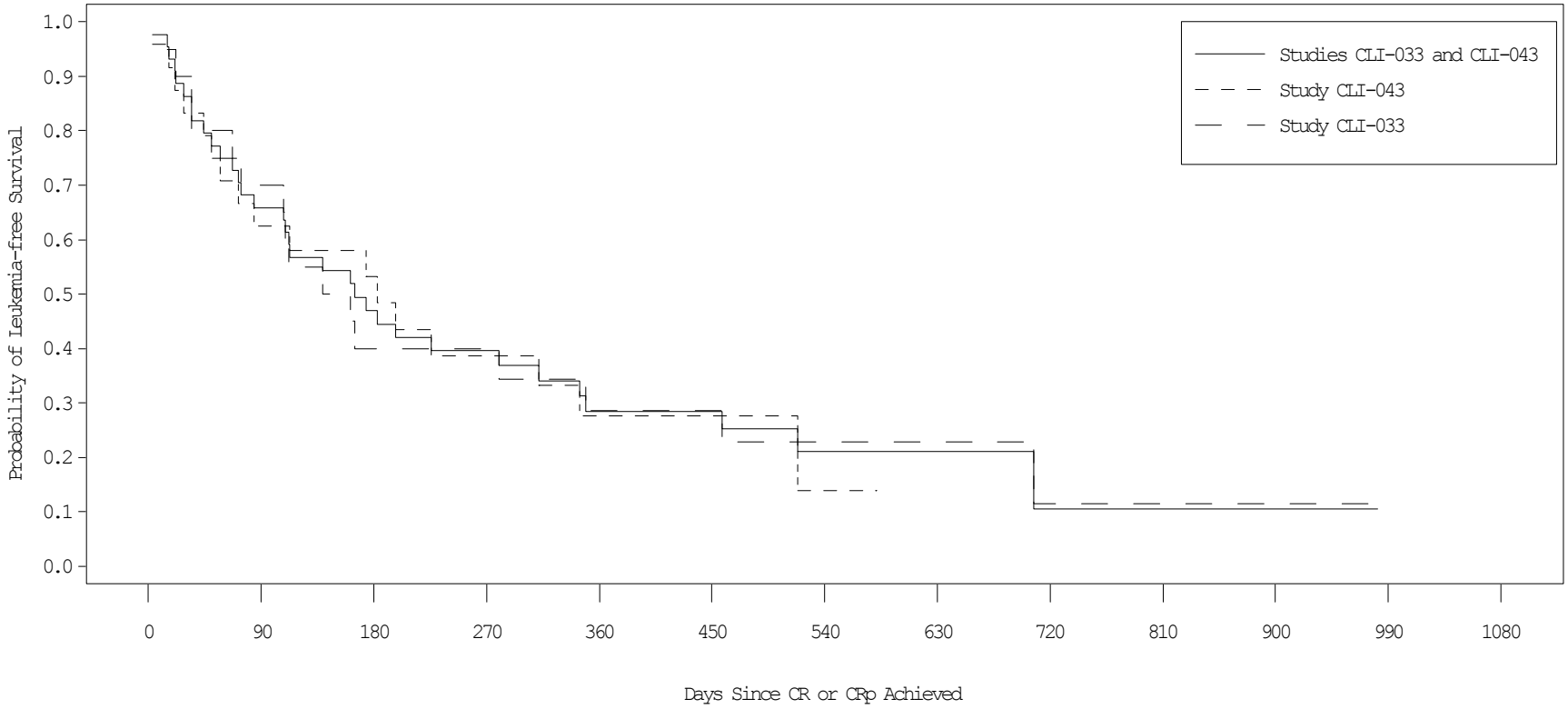
Note: Patients without disease progression as of the date of last follow-up had their response duration censored at the last date of known favorable status. Circles indicate censored observations.

Figure 6: Kaplan-Meier Curve of the Cumulative Probability of LFS (Study CLI-033, Elderly *De novo* Poor-Risk AML (Patients With CR/CRp Based on Independent Review, N=21)



Note: Patients without disease progression as of the date of last follow-up had their response duration censored at the last date of known favorable status. Circles indicate censored observations.

Figure 7: Kaplan-Meier Curve of the Cumulative Probability of LFS (Studies CLI-043 and CLI-033, Elderly *De novo* Poor-Risk AML (Patients With CR/CRp Based on Independent Review, N=48)



4.4 Progression-Free Survival

Table 16 presents Kaplan-Meier estimates of PFS; results are presented separately for each study and across all 140 *de novo* poor-risk AML patients. PFS was defined as the time from first dose of Onrigin™ to the date that objective criteria were met for disease progression or date of death from any cause.

Median PFS was 56 days in Study CLI-043 and 50 days in Study CLI-033; maximum progression-free survival was 1017 days (2.8 years) reported in a patient in Study CLI-033 who experienced complete response.

Table 16: Cumulative Probability of Progression-Free Survival (Elderly *De novo* Poor-Risk AML Patients)

Statistic	CLI-043 N=85	CLI-033 N=55	Total N=140
PFS Status (n [%])			
Alive and did not progress	8 (9.4)	4 (7.3)	12 (8.6)
Met progression criteria or died	77 (90.6)	51 (92.7)	128 (91.4)
Kaplan-Meier Estimate of PFS (days)[a]			
Median (95% CI)	56.0 (36.0, 78.0)	50.0 (38.0, 79.0)	53.0 (39.0, 70.0)
Minimum, maximum	1, 614+	13, 1017+	1, 1017+
Kaplan-Meier Probability of PFS[b]			
3 months (90 days)	36.5%	36.4%	36.7%
6 months (180 days)	21.6%	23.6%	22.9%
9 months (270 days)	14.1%	16.4%	15.6%
12 months (360 days)	10.9%	14.3%	12.2%

[a] Patients who did not progress as their last disease assessment but who died within 180 days of that disease assessment have their date of death used as the (uncensored) date of progression. Patients who died more than 180 days after their last disease assessment are counted in the "Met progression criteria or died" row of this summary but have censored PFS values using the date of their last disease assessment in the Kaplan-Meier analyses.

[b] Kaplan-Meier estimate of the probability of PFS to the indicated time point.

4.5 Overall Survival

Results of the analysis of overall survival are provided in Table 17 for Studies CLI-043 and CLI-033, as well as across all 140 *de novo* poor-risk AML patients; the Kaplan-Meier curve for OS for Study CLI-043 is provided in Figure 8.

Median OS was 98 days (3.2 months) in Study CLI-043 and 103 days (3.4 months) in Study CLI-033, with ~13 to 15% of patients alive at last follow-up in each study. The cumulative probability of survival at 3, 6, 9 and 12 months was also similar in the 2 studies. Maximum overall survival time was 1017 days (2.8 years) in a patient in Study CLI-033 who was alive and in remission at last contact. Across all 140 elderly *de novo* poor-risk AML patients, median OS was 99 days (3.3 months).

Table 17: Cumulative Probability of Overall Survival (Elderly *De novo* Poor-Risk AML Patients)

Statistic	CLI-043 N=85	CLI-033 N=55	Total N=140
Overall Survival Status (n [%])			
Alive	11 (12.9)	8 (14.5)	19 (13.6)
Dead	74 (87.1)	47 (85.5)	121 (86.4)
Kaplan-Meier Estimate of OS (days)[a]			
Median (95% CI)	98.0 (68.0, 159.0)	103.0 (81.0, 154.0)	99.0 (84.0, 131.0)
Minimum, Maximum	4, 668+	13, 1017+	4, 1017+
Kaplan-Meier Probability of Overall Survival[b]			
3 months (90 days)	54.1%	55.8%	54.8%
6 months (180 days)	35.3%	33.5%	34.6%
9 months (270 days)	28.2%	24.2%	26.7%
12 months (360 days)	21.1%	22.1%	21.5%

[a] Patients alive as of the date of last follow-up have their survival time censored at the last date of known survival status.

[b] Kaplan-Meier estimate of the probability of overall survival to the indicated time point.

It is reported in the literature that remission is associated with prolonged survival (7). OS was examined for the subgroup of patients who achieved CR or CRp based on independent review in the primary and supportive studies. Results are provided in Table 18 and the Kaplan-Meier curve of OS for the primary study in this subgroup of patients is provided in Figure 9.

Median OS was substantially longer in patients who achieved CR or CRp in both studies compared to the overall population. In Study CLI-043, median OS among the 27 patients who achieved remission based on independent review was 377 days (12.4 months) and in 21 patients in Study CLI-033 was 221.0 days (7.3 months). Across all 48 patients who achieved response, median OS was 272 days (8.9 months). Notably, the probability of survival at 12 months in this group of responders was 47.9%.

Among the 48 patients who achieved CR or CRp based on independent review, 30 (62.5%) were alive at 6 months after first induction treatment, including 18 (66.7%) of 27 responders in Study CLI-043 and 12 (57.1%) of 21 responders in Study CLI-033. Overall, 20 (41.7%) of 48 responders were alive 1 year after first treatment, including 12 (44.4%) of 27 and 8 (38.1%) of 21 responders in Studies CLI-043 and CLI-033, respectively.

Figure 10 displays the OS Kaplan-Meier curve across all 140 patients in Studies CLI-043 and CLI-033; results are presented for the total population and separately based on response to treatment. As displayed, the clinical benefit of achieving a response to treatment based on prolonged survival is evident compared to patients who do not achieve a response.

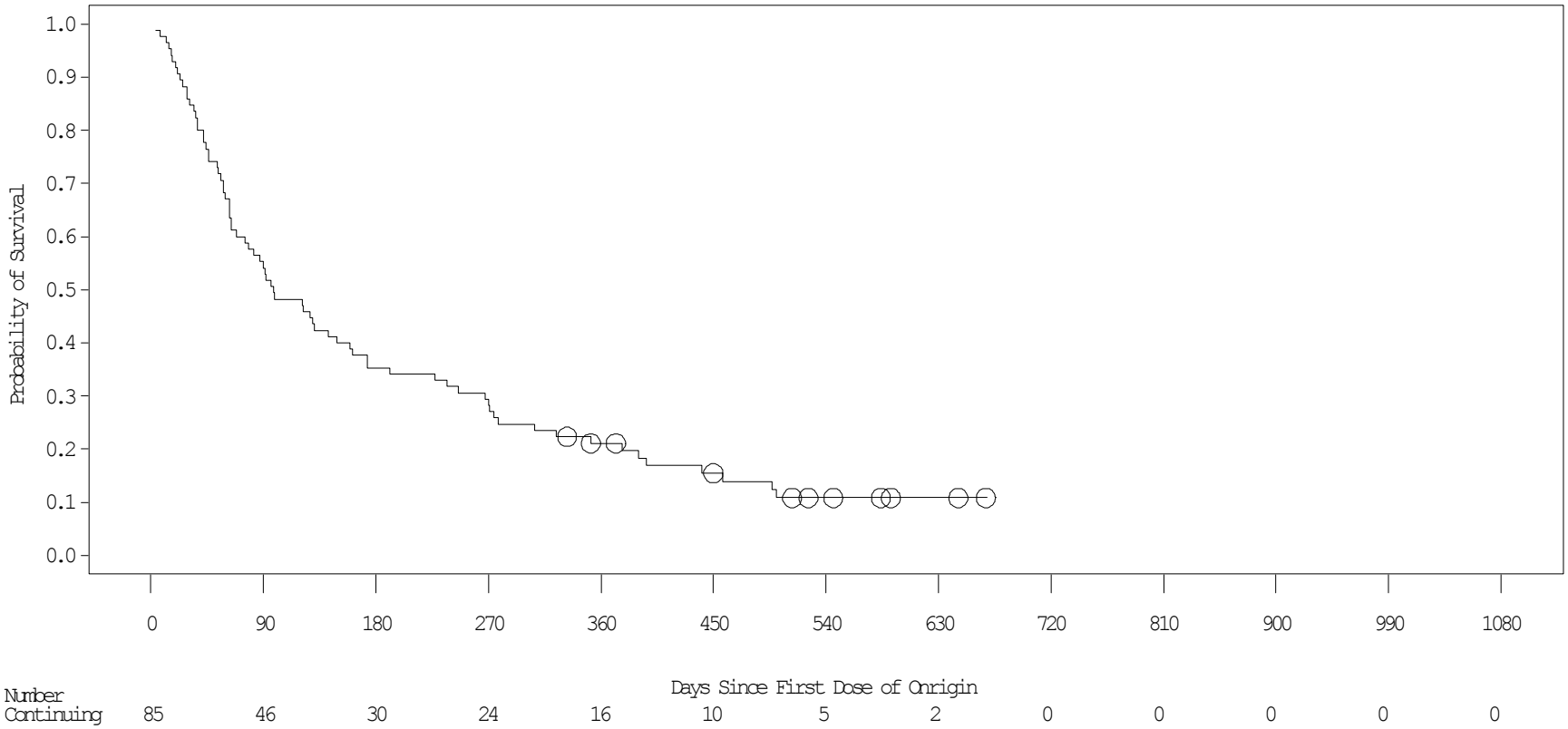
Table 18: Cumulative Probability of Overall Survival (Elderly *De novo* Poor-Risk AML Patients with CR/CRp Based on Independent Review)

Statistic	CLI-043 N=27	CLI-033 N=21	Total N=48
Overall Survival Status (n [%])			
Alive	9 (33.3)	5 (23.8)	14 (29.2)
Dead	18 (66.7)	16 (76.2)	34 (70.8)
Kaplan-Meier Estimate of OS (days)[a]			
Median (95% CI)	377.0 (142.0, 497.0)	221.0 (147.0, 537.0)	272.0 (164.0, 449.0)
Minimum, Maximum	58, 668+	54, 1017+	54, 1017+
Kaplan-Meier Probability of Overall Survival[b]			
3 months (90 days)	85.2%	95.2%	89.6%
6 months (180 days)	66.7%	57.1%	62.5%
9 months (270 days)	55.6%	42.9%	50.0%
12 months (360 days)	51.9%	42.9%	47.9%

[a] Patients alive as of the date of last follow-up have their survival time censored at the last date of known mortality status.

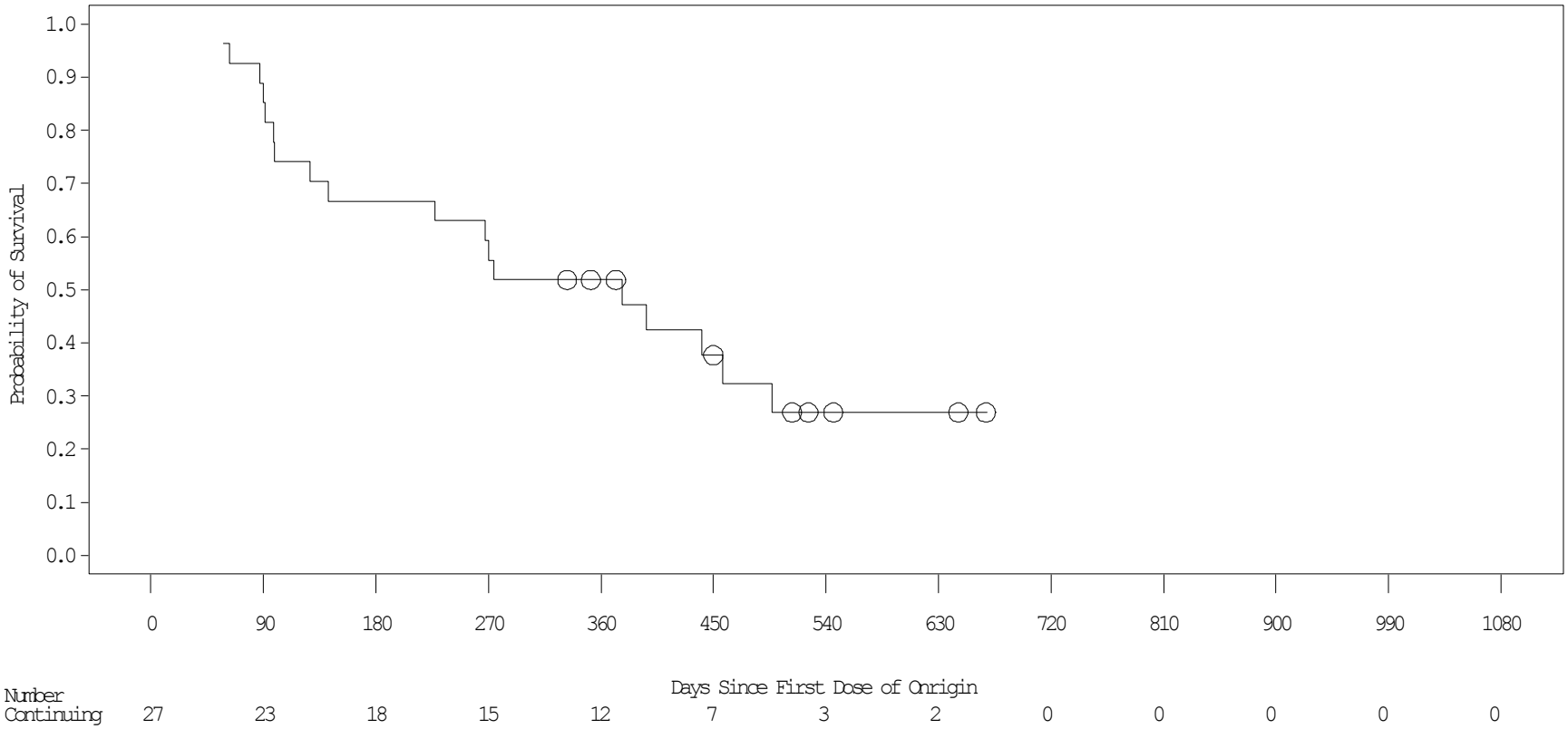
[b] Kaplan-Meier estimate of the probability of overall survival to the indicated time point.

Figure 8: Kaplan-Meier Curve of the Cumulative Probability of OS (Study CLI-043, Elderly *De novo* Poor-Risk AML Patients, N=85)



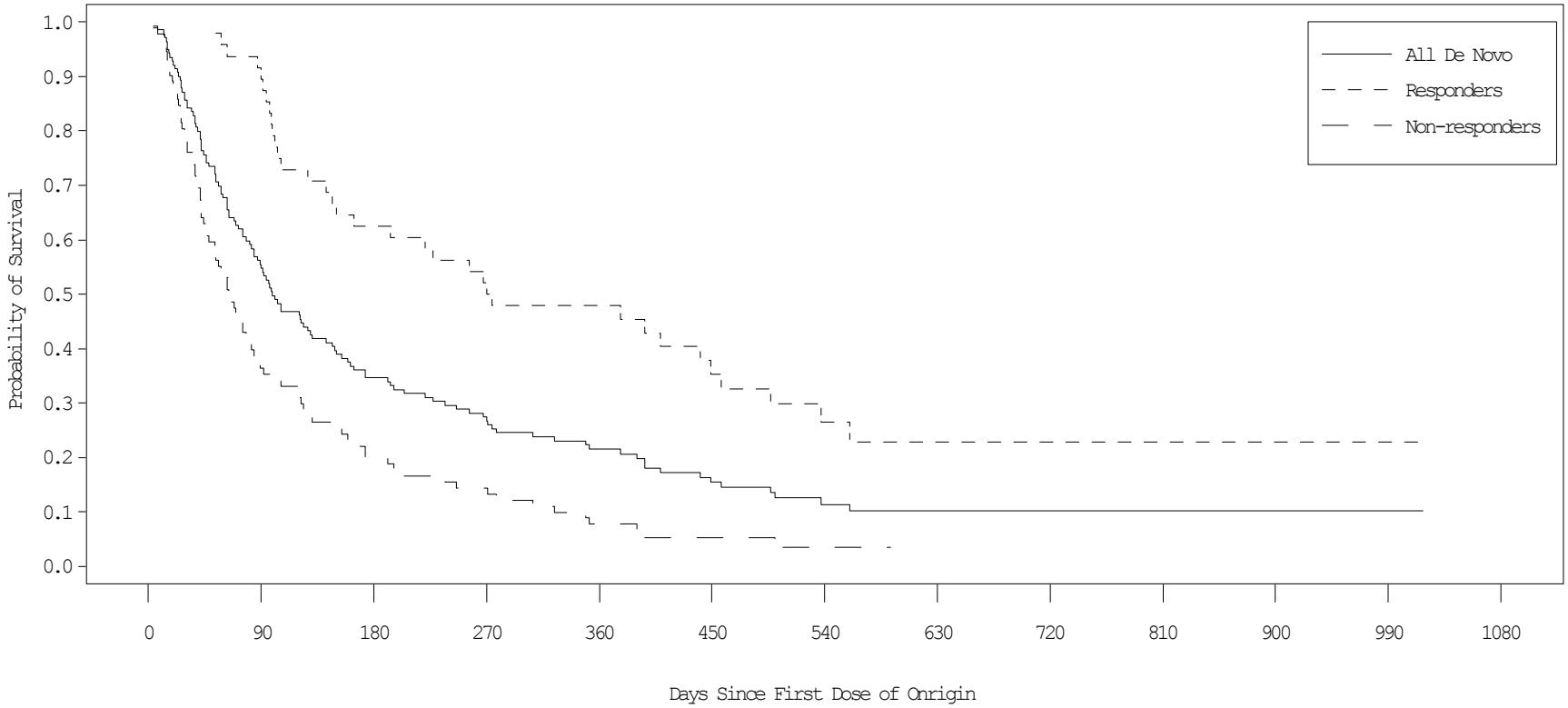
Note: Patients alive as of the date of last follow-up have their survival time censored at the last date of known mortality status. Circles indicate censored observations.

Figure 9: Kaplan-Meier Curve of the Cumulative Probability of OS (Study CLI-043, Elderly *De novo* Poor-Risk AML Patients With CR/CRp Based on Independent Review, N=27)



Note: Patients alive as of the date of last follow-up have their survival time censored at the last date of known mortality status. Circles indicate censored observations.

Figure 10: Kaplan-Meier Curve of the Cumulative Probability of OS: Comparison of Responders to Non-responders (Studies CLI-043 and CLI-033 Based on Independent Review, N=140)



Note: Patients alive as of the date of last follow-up have their survival time censored at the last date of known mortality status. Circles indicate censored observations.

4.6 Evaluation of Response in Specific Patient Subgroups

Overall response rate in Studies CLI-043 and CLI-033 and across all 140 elderly patients with *de novo* poor-risk AML was assessed across patients subgroups based on age, gender, ECOG PS, cytogenetics and cardiac and pulmonary function. Results of response assessment based on independent review are presented in Table 19. Note that a subgroup analysis of response rates by hepatic function was not conducted because fewer than 20% of patients in either study had this organ dysfunction at study entry.

Table 19: Overall Response Rate in Patient Subgroups Based on Independent Review (Elderly *De novo* Poor-Risk AML Population, N=140)

	Study CLI-043 (N=85)			Study CLI-033 (N=55)			Total (N=140)		
Subgroup	**N**	**n (%)**	**[95% CI][a]**	**N**	**n (%)**	**[95% CI][a]**	**N**	**n (%)**	**[95% CI][a]**
Age									
60-<70 years	19	6 (31.6)	[12.6, 56.6]	16	7 (43.8)	[19.8, 70.1]	35	13 (37.1)	(21.5, 55.1)
≥70 years	66	21 (31.8)	[20.9, 44.4]	39	14 (35.9)	[21.2, 52.8]	105	35 (33.3)	(24.4, 43.2)
Gender									
Male	50	15 (30.0)	[17.9, 44.6]	30	10 (33.3)	[17.3, 52.8]	80	25 (31.3)	[21.4, 42.6]
Female	35	12 (34.3)	[19.1, 52.2]	25	11 (44.0)	[21.1, 61.3]	60	23 (38.3)	[26.1, 51.8]
ECOG PS									
0, 1	50	16 (32.0)	(19.5, 46.7)	39	13 (33.3)	(19.1, 50.2)	89	29 (32.6)	(23.0, 43.3)
2	35	11 (31.4)	(16.9, 49.3)	16	8 (50.0)	(24.7, 75.4)	51	19 (37.3)	(24.1, 51.9)
Cytogenetic Profile									
Intermediate	41	19 (46.3)	(30.7, 62.6)	28	11 (39.3)	(21.5, 59.4)	69	30 (43.5)	(31.6, 56.0)
Unfavorable	40	7 (17.5)	(7.3, 32.8)	23	9 (39.1)	(19.7, 61.5)	63	16 (25.4)	(15.3, 37.9)
Cardiac Function									
No dysfunction	23	6 (26.1)	(10.2, 48.4)	32	13 (40.6)	(23.7, 59.4)	55	19 (34.5)	(22.2, 48.6)
Dysfunction	62	21 (33.9)	(22.3, 47.0)	23	8 (34.8)	(16.4, 57.3)	85	29 (34.1)	(24.2, 45.2)
Pulmonary Function									
No dysfunction	20	7 (35.0)	(15.4, 59.2)	39	14 (35.9)	(21.2, 52.8)	59	21 (35.6)	(23.6, 49.1)
Dysfunction	65	20 (30.8)	(19.9, 43.5)	16	7 (43.8)	(19.8, 70.1)	81	27 (33.3)	(23.2, 44.7)
Risk Factors									
1	3	1 (33.3)	(0.8, 90.6)	16	6 (37.5)	(15.2, 64.6)	19	7 (36.8)	(16.3, 61.6)
2	18	8 (44.4)	(21.5, 69.2)	21	7 (33.3)	(14.6, 57.0)	39	15 (38.5)	(23.4, 55.4)
3	31	10 (32.3)	(16.7, 51.4)	14	6 (42.9)	(17.7, 71.1)	45	16 (35.6)	(21.9, 51.2)
4 or more	33	8 (24.2)	(11.1, 42.3)	4	2 (50.0)	(6.8, 93.2)	37	10 (27.0)	(13.8, 44.1)

[a] Exact interval based on binomial distribution

Overall Response Rate by Age

Age is an important prognostic indicator for response and tolerability of induction chemotherapy for patients with AML with the ability to attain a complete remission with induction therapy decreasing with increasing age.

The ORR was 37.1% in the 35 patients 60 to 69 years of age and 33.3% in the 105 patients 70 years or older indicating that Onrigin™ has similar efficacy across age categories, and in particular induces remissions in patients 70 years of age or older. Results for patients 70 years of age or older were similar in Study CLI-043 (31.8%) and Study CLI-033 (35.9%).

Overall Response Rate by Gender

Based on the independent assessment of best response, the ORR was 31.3% in the 80 male patients and higher at 38.3% in the 60 female patients. A comparable trend was seen in both Study CLI-043 and Study CLI-033 (ORR of 30.0% and 33.3% in males, respectively, and 34.3% and 44.0% in females, respectively).

Overall Response Rate by ECOG PS

Performance status (PS) has been a factor used to determine the course of treatment in AML patients. Due to advancing age and increasing comorbidities, ECOG PS scores are often higher (worse) in elderly patients.

The ORR was 32.6% in the 89 patients with a baseline ECOG PS of 0 or 1 and 37.3% in the 51 patients with a baseline ECOG PS of 2. Significantly, response to Onrigin™ treatment in this patient population did not appear to be affected by increasing PS. In the pivotal study, results were also similar across PS categories with ORR of 32.0% and 31.4% in patients with PS 0 or 1 and PS 2, respectively.

Overall Response Rate by Cytogenetic Profile and Conversion of Karyotype

An unfavorable cytogenetic profile is an independent poor prognostic feature in patients with AML (46). Treatment with Onrigin™ as induction chemotherapy in *de novo* poor-risk AML patients resulted in complete remissions for a subset of patients with unfavorable cytogenetics.

The ORR was 43.5% in the 69 patients with intermediate cytogenetics and 25.4% in the 63 patients with unfavorable cytogenetics at baseline.

In the primary Study CLI-043 cytogenetic profiles in the bone marrow cells were to be obtained pre- and post-treatment. A total of 40 patients presented with an unfavorable cytogenetic profile at baseline; 7 of these patients achieved a remission following Onrigin™ treatment. In 5 of these 7 patients cytogenetic karyotyping was repeated after Onrigin™ induction.

In 3 of the 5 responders with repeat karyotyping post-treatment, conversion to a normal diploid karyotype was detected. The conversion to normal karyotype was reported at approximately 5 weeks (36 to 43 days) after treatment with Onrigin™. The overall survival in these patients was 3.3, 16.9 and 22.0 months. These data indicate that in some patients with unfavorable cytogenetics, treatment with Onrigin™ can induce cytogenetic remissions, which can be associated with prolonged survival.

Overall Response Rate by Cardiac Function

Baseline cardiac dysfunction can be a contraindication to induction with standard chemotherapy based on a patient's ability to tolerate known treatment toxicities. Patients with cardiac comorbidities were enrolled in Studies CLI-033 and CLI-043 and were able to achieve a response rate similar to the response rate for the total population.

The ORR was 34.5% in the 55 patients without cardiac dysfunction and 34.1% in the 85 patients with cardiac dysfunction at baseline.

Overall Response Rate by Pulmonary Function

Baseline pulmonary dysfunction can be another contraindication to induction with standard chemotherapy based on a patient's ability to tolerate treatment toxicities. Patients with pulmonary comorbidities at baseline were enrolled to Studies CLI-033 and CLI-043 and were able to achieve a response rate similar to the response rate for the total population.

The ORR was 35.6% in the 59 patients without pulmonary dysfunction and 33.3% in the 81 patients with pulmonary dysfunction at baseline.

4.7 Historical Context

The patients enrolled to the two phase 2 clinical trials of Onrigin™ had multiple poor-risk factors predicting for poor outcome and represent an unmet clinical need. A review of the available published literature on the treatment of elderly AML patients did not reveal an appropriate comparator for this population. However, the patients enrolled to the non-intensive arm of the MRC AML14 were sufficiently similar to provide context for the Onrigin™ data.

A total of 1485 elderly patients with AML were included in the AML14 trial and received treatment between December 1998 and November 2003 (28). Patients were initially enrolled to receive either intensive or non-intensive therapy as determined by the local investigator.

Demographics of 1273 patients treated with daunorubicin and ara-C on AML14 demonstrated that patients who received intensive induction treatment are younger and have better performance status (median age 67, PS 2 6%). Therefore, these patients would not align with the Onrigin population. In contrast, the demographics of 212 patients treated non-intensively with LDAC or palliatively with hydroxyurea in AML14 were similar to the demographics of the Onrigin™ population (median age 74, PS 2 17%).

Subsequently, 121 patients from the non-intensive arm of AML-14 were selected based on the CLI-043 entry criteria (diagnosis, age 60+, cytogenetics, risk factors). Treatment outcomes were compared between 121 AML14 patients and 140 patients ≥60 years old with *de novo* poor-risk AML treated in Studies CLI-043 and CLI-033.

The following parameters were compared:

- Demographics
- ORR (CR and CRp) as determined by central review
- Mortality rates at 30 days
- Overall survival (OS) Kaplan-Meier estimates

4.7.1 Results of Historical Comparison

The comparison of demographic parameters demonstrated that the patients enrolled in the Vion and AML14 studies were comparable (Table 20). There were no significant differences in age, performance status, cytogenetic profile, or number of risk factors. Patients in the AML14 trial were slightly older than those in the CLI-043 study, although differences are relatively small with a median difference of only 1 year.

Statistically significant differences were noted in the number of patients with cardiac and/or pulmonary comorbidities; 61% of patients treated with Onrigin™ had cardiac comorbidities, as opposed to only 14% of those in AML14. This is mainly due to different reporting methods used to capture medical comorbidities at baseline.

Table 20: Comparison of Demographics in Onrigin™ and AML14 Populations

Demographics	AML14 Non-Intensive n=121	Onrigin n=140	p-values
Median Age (range)	75 (61-90)	74 (60-88)	0.05
Performance Status			
0	29 (24%)	35 (25%)	
1	49 (40%)	54 (39%)	1.0
2	43 (36%)	51 (36%)	
Cytogenetics			
Intermediate	52 (43%)	76 (54%)	1.0
Unfavorable	42 (35%)	63 (45%)	
Abnl 5,7	23 (19%)	23 (16%)	0.14
No. of Risk Factors[a]			
0	5 (4%)	6 (4%)	
1	58 (48%)	64 (46%)	1.0
2	43 (35%)	56 (40%)	
3	15 (12%)	14 (10%)	

[a] Risk factor analysis includes: age 70+ years, PS 2, unfavorable cytogenetics.

Patients treated with Onrigin™ had a higher ORR (34%) in comparison to patients receiving hydroxyurea (2%) and LDAC (23%). The difference in ORR was statistically significant when Onrigin™ is compared to hydroxyurea or the pooled non-intensive arm. Even when adjusted for known prognostic variables, the difference remains statistically significant.

Higher response rates were observed with Onrigin™ (26%) in patients with unfavorable cytogenetics compared to LDAC (10%). This difference is pronounced in patients with 5,7 genetic abnormalities indicating that Onrigin™ is able to induce remissions in these difficult to treat patients with poor prognosis, whereas LDAC does not. In patients with 5,7 abnormalities Onrigin™ treatment resulted in better OS than treatment with LDAC.

Table 21: Comparison of Response Rates in Onrigin™ and AML14 Populations

Comparison	Result %	95% CI	p-value (comparison to Onrigin™)
ORR			
Onrigin™ (n=140)	34	(26; 43)	---
Hydroxyurea (n=60)	2	(0.04; 9)	<0.00001
LDAC (n=61)	23	(13; 36)	0.1
Non-intensive (n=121)	12	(7; 20)	0.00004
ORR – unfavorable cytogenetics			
Onrigin™ (n=63)	26	(16; 39)	0.14
LDAC (n=20)	10	(1; 32)	
ORR – abn 5,7			
Onrigin™ (n=23)	26	(10; 48)	0.07
LDAC (n=11)	0		

The 30-day mortality rates tended to be lower in Onrigin™ treated patients (14%) in comparison to patients treated with hydroxyurea (28%), LDAC (26%) or all patients in the AML14 non-intensive arm (27%) (Table 22). The difference at 30 days is statistically significant when Onrigin™ is compared to any of the non-intensive arms in AML14.

Onrigin™ had significantly improved OS in comparison to hydroxyurea (22% vs 8% at 1 year). Even when adjusted for known prognostic variables, the survival benefit obtained with Onrigin™ compared to hydroxyurea remains significant.

Overall survival at 1 year was not significantly different between Onrigin™ and LDAC, or between Onrigin™ and all non-intensive patients, although the numbers are relatively small as indicated by wide confidence intervals.

Table 22: Comparison of Mortality and Survival in Onrigin™ and AML14 Populations

Comparison	Result %	95% CI	p-value (comparison to Onrigin™)
30-day Mortality			
Onrigin™ (n=140)	14%	(9; 21)	---
Hydroxyurea (n=60)	28%	(19; 42)	0.02
LDAC (n=61)	26%	(17; 39)	0.03
Non-intensive (n=121)	27%	(20; 34)	0.008
1-year Survival			
Onrigin™ (n=140)	22%	(15; 29)	---
Hydroxyurea (n=60)	8%	(3; 17)	0.001
LDAC (n=61)	25%	(15; 36)	1.0
Non-intensive (n=121)	17%	(11; 24)	0.08

4.7.2 Discussion of Historical Comparison

While no exact match for the Vion study population could be found in the available published literature, Vion identified a dataset, which provides a reasonable context for interpretation of the data from Studies CLI-043 and CLI-033.

Considering the early mortality and survival results, this comparison supports that Onrigin™ does not cause excess mortality in comparison to LDAC and improves survival in comparison to hydroxyurea. It is important to note that OS is not adversely affected by Onrigin™ in comparison to hydroxyurea or LDAC.

In the context of currently available treatments for elderly poor-risk AML patients, the historical control data presented support Onrigin™ as a therapeutic option.

4.8 Efficacy Summary and Conclusions

Induction therapy with Onrigin™ led to durable complete remissions in a meaningful proportion of patients 60 years of age or older with *de novo* poor-risk AML.

- The ORR based on independent review was consistent across the primary and supportive studies with ORR of 31.8% and 38.2% in Study CLI-043 and Study CLI-033, respectively. Across all 140 patients enrolled in the 2 clinical trials ORR was 34.3%.
- Results of the independent review were consistent with results reported by the site investigators. The ORR across all 140 patients based on investigator assessment was 36.4%.
- Median duration of response in Study CLI-043 was 6.0 months with Kaplan-Meier estimates of remaining leukemia free at 6 months of 53.2%. Maximum duration of response in this study was 19.1 months in a patient who remained in remission at last contact.
- Median duration of response in Study CLI-033 was 4.9 months with Kaplan-Meier estimates of remaining leukemia free at 6 months of 40.0%. Maximum duration of response in this study was 32.3 months in a patient who remained in remission at last contact.

A majority of the responses occurred after a single dose.

- Eighty eight percent (88%, 42 of 48 patients) responded following treatment with the first induction cycle and 6 responded following a second induction cycle.

ORR was consistent across patient subgroups regardless of type and number of risk factors.

- Across all 140 patients enrolled in the 2 clinical trials, ORR was 34.3%.
- ORR was 33.3% among those 70 years of age or older.
- ORR was 37.3% for patients with ECOG PS of 2 at study entry.
- ORR was 25.4% among patients with unfavorable cytogenetic profiles.
- ORR was 34.1% and 33.3% in patients with cardiac or pulmonary dysfunction at baseline.
- ORR was 38.5% in patients with 2 risk factors, 35.6% in patients with 3 risk factors, and 27.0% in patients with 4 or more risk factors.

A survival benefit was observed in patients who achieved complete remission.

- Among patients who achieved CR or CRp median OS was 12.4 months in Study CLI-043 and 7.3 months in Study CLI-033. Notably, the probability of survival at 12 months in across all responders was 47.9%.
- Median OS across all patients regardless of response to treatment was 3.2 months in Study CLI-043 and 3.4 months in Study CLI-033.
- Among the 48 patients who achieved CR or CRp based on independent review across both studies, 62.5% were alive at 6 months after first induction treatment and 47.9% were alive at 1 year.

In the context of currently available treatments for elderly poor-risk AML patients, the data presented in the 2 Onrigin™ clinical trials demonstrate its role as a therapeutic option.

5. Safety and Tolerability of Onrigin™

5.1 Impact of the Disease and Adverse Effects Characteristic of the Pharmacologic Class

Onrigin™ belongs to a class of alkylating agents with known toxicities. Organ systems frequently affected by treatment with alkylating agents include the bone marrow, gastrointestinal tract, gonads, lungs, bladder, and liver.

The primary DLT of alkylating agents is their effect on bone marrow cells. In the majority of cases, acute suppression of the marrow results in decreased granulocyte count. However, most alkylating agents depress all blood elements, presumably through their impact on progenitor stem cells, so that both cellular and humoral immunity are suppressed. This intended antitumor effect in the treatment of patients with AML has both desirable and undesirable clinical consequences.

Pulmonary infection, e.g., pneumonia, in the setting of leukemia and bone marrow hypoplasia is of concern. The appearance of pulmonary changes due to possible toxic injury can be difficult to differentiate from tumor progression or infection.

Alkylating agents, including BCNU, CCNU and procarbazine, as well as asparaginase, bleomycin, methotrexate, cytarabine and many newer targeted agents (47) have been associated with non-infectious pulmonary toxicity.

AML patients who experience neutropenic infections from either the underlying disease or from the myelosuppressive effects of treatment are inevitably at risk for renal impairment. Acute renal failure occurs in approximately 19% of patients with moderate sepsis, 23% with severe sepsis, and 51% with septic shock when blood cultures are positive.

Tumor lysis syndrome, which is associated with a high morbidity and mortality, is a well-recognized consequence of treatment in AML.

5.2 Overview of Studies included in the Safety Evaluation

The full safety dataset for Onrigin™ presented in the NDA includes data on a total of 818 adults and pediatric patients with hematologic malignancies and solid tumors who received single or multiple Onrigin™ doses ranging from 3 to 800 mg/m^2 in both Vion-sponsored and investigator-sponsored clinical studies. The safety profile in the larger patient population is consistent with the subset of patients with hematologic malignancies treated with single agent Onrigin™ at the dose of 600 mg/m^2 (n=277).

The integrated safety dataset in support of the 600 mg/m^2 dose in patients aged 60 years or older with *de novo* poor-risk AML is derived from 3 Vion-sponsored clinical studies. In these 3 studies, 277 patients with hematologic malignancies were treated at the dose of 600 mg/m^2 including 85 patients in Study CLI-043, 184 patients in Study CLI-033 and 8 patients treated in the dose-escalation Phase 1 Study CLI-029 who received the proposed dose of 600 mg/m^2.

The Safety population (N=277) was comprised of patients ranging in age from 15 to 88 years with a median age of 71 years. More than half of the population (59.2%) was 70 years or older. The patients were mostly Caucasian (approximately 90%) and there were more males (61.4%)

than females (38.6%), reflecting the general population of AML patients. ECOG PS was 0 or 1 in 71.8% of patients and PS was 2 in 27.9%.

5.3 Safety Results

5.3.1 Overview

Table 23 presents the most common AEs, i.e., those reported in 10% or more of the 277 patients in the Safety population, including events Grade 3 or greater in severity.

The most commonly reported AEs following treatment with Onrigin™ were gastrointestinal disturbances, myelosuppression or the consequences of myelosuppression, and respiratory events. Events of Grade 3 to 5 severity were most commonly associated with myelosuppression. These types of events are expected due to the known effects of alkylating agents.

Myelosuppression events or the consequences of myelosuppression included cytopenias (febrile neutropenia [37.2%], neutropenia [21.3%], thrombocytopenia [20.2%] and anemia [13.0%]), infections (pneumonia [19.5%]) and pyrexia (46.6%). Overall, hematopoietic cytopenias were reported in 63.5% of the 277 patients; hematologic abnormalities were reported as Grade ≥3 in severity in 54.9% of patients. Infections occurred in 62.1% of patients and were the second most commonly reported type of event assessed as Grade ≥3 in severity (35.4% of patients). For further details on myelosuppression, see Section 5.3.2.1.

Gastrointestinal disorders occurred in 83.8% of patients and included reports of nausea (52.3%) and vomiting (25.3%) which are frequent and likely related to administration of Onrigin™. The majority of GI events were Grade 1 or 2 in severity; GI events Grade ≥3 in severity occurred in 10.8% of patients. Diarrhea (41.2%), constipation (34.7%), and abdominal pain (11.6%) were also frequently reported. These are common events in cancer patients undergoing chemotherapy and can be related to underlying gastrointestinal complications (e.g., colitis due to *C. difficile* [2.2%]) from chemotherapy or to concomitant medications. For further details on GI events, see Section 5.3.2.2.

Respiratory AEs were also among the most frequently reported events, and primarily included reports of dyspnea (32.1%) and cough (23.5%). These were generally a consequence of myelosuppression and infection. There was a delayed pattern of pulmonary events observed in 9.0% of Onrigin™ treated patients that is consistent with those observed following treatment with BCNU (events occurring between 30 and 60 days after therapy, with bilateral pulmonary infiltrates, with or without pleural effusions, and with no obvious alternative explanations). For further details on respiratory events, see Section 5.3.2.3.

Because there is a known pattern of Onrigin™ infusion-related AEs, including headache, nausea, vomiting, myalgia/cramps, facial flushing, dizziness, tachycardia, and hypotension, an analysis of overall events and events occurring within one day of infusion was conducted. Within 1 day of the first Onrigin™ infusion, the most commonly reported AEs were nausea (20.2%), hypotension (19.9%), pyrexia (13.4%), and headache (11.9%); all other events reported in this time period occurred in <10% of patients. For further details on infusion-related events, see Section 5.3.3.1.

Table 23: Adverse Events Reported in 10% or More of Patients, Overall and for Events Grade 3, 4 or 5 in Severity (Safety Population, N=277)

MedDRA System Organ Class / Preferred Term	All AEs n (%)	Grade ≥3 AEs n (%)
Gastrointestinal Disorders	**232 (83.8)**	**30 (10.8)**
Nausea	145 (52.3)	5 (1.8)
Diarrhea	114 (41.2)	6 (2.2)
Constipation	96 (34.7)	0
Vomiting	70 (25.3)	2 (0.7)
Abdominal pain	32 (11.6)	3 (1.1)
General Disorders, Administration Site Conditions	**230 (83.0)**	**58 (20.9)**
Pyrexia	129 (46.6)	26 (9.4)
Edema peripheral	70 (25.3)	2 (0.7)
Fatigue	65 (23.5)	8 (2.9)
Chills	35 (12.6)	0
Chest pain	34 (12.3)	2 (0.7)
Edema	33 (11.9)	1 (0.4)
Mucosal inflammation	30 (10.8)	2 (0.7)
Asthenia	28 (10.1)	6 (2.2)
Respiratory, Thoracic and Mediastinal Disorders	**199 (71.8)**	**72 (26.0)**
Dyspnea	89 (32.1)	29 (10.5)
Cough	65 (23.5)	0
Epistaxis	47 (17.0)	2 (0.7)
Pleural effusion	39 (14.1)	12 (4.3)
Hypoxia	28 (10.1)	19 (6.9)
Blood and Lymphatic System Disorders	**179 (64.6)**	**152 (54.9)**
Febrile neutropenia	103 (37.2)	78 (28.2)
Neutropenia	59 (21.3)	49 (17.7)
Thrombocytopenia	56 (20.2)	46 (16.6)
Anemia	36 (13.0)	19 (6.9)
Infections and Infestations	**172 (62.1)**	**98 (35.4)**
Pneumonia	54 (19.5)	30 (10.8)
Metabolism and Nutrition Disorders	**162 (58.5)**	**33 (11.9)**
Hypokalemia	70 (25.3)	13 (4.7)
Hypomagnesemia	37 (13.4)	1 (0.4)
Anorexia	32 (11.6)	3 (1.1)
Decreased appetite	29 (10.5)	1 (0.4)
Nervous System Disorders	**145 (52.3)**	**23 (8.3)**
Headache	71 (25.6)	1 (0.4)
Dizziness	30 (10.8)	1 (0.4)
Skin and Subcutaneous Tissue Disorders	**139 (50.2)**	**9 (3.2)**
Rash	62 (22.4)	3 (1.1)
Petechiae	39 (14.1)	0
Vascular Disorders	**126 (45.5)**	**18 (6.5)**
Hypotension	78 (28.2)	8 (2.9)
Psychiatric Disorders	**124 (44.8)**	**18 (6.5)**
Confusional state	49 (17.7)	10 (3.6)
Insomnia	47 (17.0)	1 (0.4)
Anxiety	45 (16.2)	2 (0.7)
Cardiac Disorders	**104 (37.5)**	**33 (11.9)**
Tachycardia	47 (17.0)	2 (0.7)

5.3.2 Common Adverse Events

5.3.2.1 Myelosuppression

Hematological toxicity can be difficult to assess in this patient population because most patients present with abnormal bone marrow function, particularly cytopenias, at baseline. Furthermore, myelosuppression is required for anti-tumor activity in the treatment of patients with AML, and as such, has both desirable and undesirable clinical consequences. Onrigin™ appears to have a significant effect on hematopoietic stem cells, based on the observed clinical effects. The clinical picture following exposure to 600 mg/m^2 of Onrigin™ is consistent with substantial effects on bone marrow cells.

Table 24 presents the most commonly reported hematologic, infection and hemorrhagic adverse events reported for the 277 patients included in the Safety population.

AEs related to cytopenias, primarily neutropenia and thrombocytopenia, were frequently reported (63.5%) in the Safety population. Febrile neutropenia, neutropenia and thrombocytopenia were reported in 37.2%, 21.3% and 20.2% of patients, respectively; the reported incidence of Grade 3 or 4 events was 28.2%, 17.7% and 16.6%, respectively.

Other AEs that may be related to myelosuppression, including infections (62.1%), primarily reports of pneumonia (19.5%), and hemorrhagic events (46.9%), primarily reports of epistaxis (17.0%). The incidence of Grade 3 to 5 infections was 35.4%; the most common type of infection of this severity was pneumonia (10.8% Grade 3 to 5 severity). Overall, sepsis was reported in 12 patients (4.3%); all reports of sepsis were Grade 3 to 5 in severity. Most hemorrhagic events were Grade 1 or 2 in severity.

Table 24: Myelosuppression, Infection and Hemorrhagic Adverse Events Reported in ≥2% of Patients Overall and Grade ≥3 in Severity (Safety Population, N=277)

Adverse Events	All Events n (%)	Grades 3 to 5 n (%)
Blood and Lymphatic System Events	**179 (64.6)**	**152 (54.9)**
Febrile neutropenia	103 (37.2)	78 (28.2)
Neutropenia	59 (21.3)	49 (17.7)
Thrombocytopenia	56 (20.2)	46 (16.6)
Anemia	36 (13.0)	19 (6.9)
Pancytopenia	12 (4.3)	10 (3.6)
Leukopenia	11 (4.0)	7 (2.5)
Febrile bone marrow aplasia	6 (2.2)	6 (2.2)
Infections	**172 (62.1)**	**98 (35.4)**
Pneumonia	54 (19.5)	30 (10.8)
Cellulitis	17 (6.1)	4 (1.4)
Sepsis	12 (4.3)	12 (4.3)
Bacteremia	12 (4.3)	8 (2.9)
Fungal infection	8 (2.9)	6 (2.2)
Neutropenic infection	6 (2.2)	6 (2.2)
Septic shock	6 (2.2)	6 (2.2)
Hemorrhagic Event	**130 (46.9)**	**NA**
Epistaxis	47 (17.0)	2 (0.7)
Petechiae	39 (14.1)	0
Hematuria	14 (5.1)	1 (0.4)
Ecchymosis	10 (3.6)	1 (0.4)
Hematoma	8 (2.9)	0
Mouth hemorrhage	8 (2.9)	1 (0.4)
Gingival bleeding	8 (2.9)	0
Prothrombin time prolonged	8 (2.9)	0

Table 25 presents maximum CTCAE severity grade for hematology parameters at baseline and as a worst value following Induction Cycle 1; results are displayed for all 277 patients in the Safety population. As expected, cytopenias were observed with Onrigin™ administration. Most patients had Grade 4 decreases in WBC (78.7%), neutrophils (85.8%), and platelets (87.0%), Grade 3 or 4 decreases in lymphocytes (76.5%), and Grade 2 or 3 decreases in hemoglobin (92.1%) following the first induction cycle with Onrigin™.

Table 25: Maximum CTCAE Severity by Cycle for Hematology Parameters (Safety Population, N=277)

Parameter		Maximum Toxicity Grade[a] (n=277)				
Time point	n[b]	0	1	2	3	4
WBC						
Baseline	277	131 (47.3)	21 (7.6)	42 (15.2)	60 (21.7)	23 (8.3)
Induction 1	277	13 (4.7)	4 (1.4)	9 (3.2)	33 (11.9)	218 (78.7)
Neutrophils (ANC)						
Baseline	255	65 (25.5)	15 (5.9)	30 (11.8)	42 (16.5)	103 (40.4)
Induction 1	267	7 (2.6)	3 (1.1)	5 (1.9)	23 (8.6)	229 (85.8)
Lymphocytes (ALC)						
Baseline	253	98 (38.7)	94 (37.2)	33 (13.0)	24 (9.5)	4 (1.6)
Induction 1	268	6 (2.2)	23 (8.6)	34 (12.7)	117 (43.7)	88 (32.8)
Hemoglobin						
Baseline	277	10 (3.6)	78 (28.2)	152 (54.9)	36 (13.0)	1 (0.4)
Induction 1	277	0	8 (2.9)	167 (60.3)	88 (31.8)	14 (5.1)
Platelet Count						
Baseline	277	26 (9.4)	45 (16.2)	61 (22.0)	78 (28.2)	67 (24.2)
Induction 1	277	0	1 (0.4)	8 (2.9)	27 (9.7)	241 (87.0)

a Patients are counted only once for each parameter, under the maximum severity grade observed during the period.

b Includes only patients that were treated with Onrigin™ during the cycle and had the assessment performed.

In order to assess the timing of myelosuppression and recovery of cell counts, clinical laboratory data were analyzed for nadir and recovery values as well as time to nadir and recovery. Table 26 presents the myelosuppression (nadir) and recovery data for absolute neutrophil count (ANC) and platelet count for the Safety population and for patients achieving a CR, CRp or PR. The analysis includes all patients with baseline and follow-up laboratory values.

Following the first induction cycle with Onrigin™, the median time to reach an ANC nadir of <500/µL was 15.0 days and the median time to recovery (first value of 500/µL after nadir) was 14.0 days. A total of 118 (51.5%) of 229 patients with available data recovered ANC following Induction Cycle 1. Following treatment with a second induction cycle, the median time to reach an ANC nadir of <500/µL was 20.0 days and the median time to recovery was 13.0 days. Fifteen (53.5%) of 28 patients recovered following Induction Cycle 2. Similar results were observed for an ANC nadir of <1000/µL.

Following first induction with Onrigin™, the median time to reach a platelet nadir of < 50,000/µL was 16.0 days, and the median time to recovery (first value ≥ 50,000/µL after nadir) was 14.0 days. A total of 108 (40.0%) of 270 patients recovered platelet counts following Induction Cycle 1. For patients receiving a second induction cycle, the median time to reach a nadir of < 50,000/µL was 18.0 days and the median time to recovery was 17.5 days. Twelve (30.8%) of 39 patients recovered following Induction Cycle 2. Similar results were observed for platelet count nadir of < 100,000/µL.

Table 26: Myelosuppression by Onrigin™ Induction Cycles

Parameter / Treatment Cycle	Total Patients (N = 277)					Total CR, CRp or PR Patients (N = 76)				
	Precycle Value[a]	Nadir Value	Cycle Day of Nadir	Recovery Value[b]	Duration (days)[a]	Precycle Value[a]	Nadir Value	Cycle Day of Nadir	Recovery Value[b]	Duration (days)[a]
ANC – Recovery value of ≥500/µL (/µL)										
Induction 1										
n[c]	215	229	229	118	118	62	66	66	61	61
Median	660.0	40.0	**15.0**	1394.5	**14.0**	387.0	43.0	**15.0**	1890.0	**18.0**
Range	0, 41720	0, 480	2, 49	500, 29000	1, 61	0, 41720	0, 471	2, 40	530, 20000	6, 58
Induction 2										
n[c]	28	28	28	15	15	11	11	11	9	9
Median	800.0	53.0	**20.0**	1140.0	**13.0**	1456.0	42.0	**22.0**	1309.0	**9.0**
Range	25, 3780	0, 470	7, 74	571, 7600	4, 45	51, 3780	0, 415	7, 74	755, 6910	4, 22
ANC – Recovery value of ≥1000/µL (/µL)										
Induction 1										
n[c]	237	252	252	110	110	65	69	69	64	64
Median	735.0	50.0	**15.0**	2274.0	**16.0**	400.0	46.0	**15.0**	2350.0	**21.0**
Range	0, 41720	0, 920	2, 49	1000, 29000	1, 87	0, 41720	0, 920	2, 40	1000, 20000	5, 76
Induction 2										
n[c]	33	33	33	15	15	13	13	13	9	9
Median	635.0	91.0	**20.0**	1857.0	**13.0**	1456.0	140.0	**23.0**	1349.0	**12.0**
Range	0, 5950	0, 840	7, 74	1000, 7600	4, 56	51, 5950	0, 670	7, 74	1000, 6910	4, 22
Platelet Count - Recovery value of ≥50,000/µL (/µL)										
Induction 1										
n[c]	270	270	270	108	108	74	74	74	65	65
Median	46000.0	11000.0	**16.0**	91000.0	**14.0**	56500.0	13000.0	**15.0**	121000.0	**18.0**
Range	2000, 762000	0, 48000	2, 91	50000, 475000	1, 54	5000, 233000	0, 45000	2, 52	50000, 475000	5, 54
Induction 2										
n[c]	39	39	39	12	12	13	13	13	9	9
Median	42000.0	10000.0	**18.0**	93000.0	**17.5**	170000.0	12000.0	**18.0**	91000.0	**15.0**
Range	6000, 604000	1000, 39000	3, 57	55000, 292000	4, 26	19000, 604000	6000, 24000	14, 37	55000, 292000	4, 26
Platelet Count - Recovery value of ≥100,000/µL (/µL)										
Induction 1										
n[c]	276	276	276	72	72	76	76	76	61	61
Median	48000.0	11000.0	**16.0**	175000.0	**18.0**	57500.0	13000.0	**15.0**	178000.0	**19.0**
Range	2000, 762000	0, 70000	2, 91	100000, 480000	1, 54	5000, 233000	0, 55000	2, 52	100000, 480000	6, 54
Induction 2										
n[c]	39	39	39	10	10	13	13	13	8	8
Median	42000.0	10000.0	**18.0**	188500.0	**20.0**	170000.0	12000.0	**18.0**	203500.0	**20.0**
Range	6000, 604000	1000, 39000	3, 57	100000, 373000	6, 27	19000, 604000	6000, 24000	14, 37	110000, 373000	6, 27

a Precycle value is the last value obtained prior to infusion of study drug for the cycle. Duration = day of recovery – day of nadir.
b Recovery value for ANC is the first value ≥500/µL or ≥1000/µL following observation of nadir; recovery value for platelet count is the first value ≥50,000/µL or ≥100,000/µL.
c Includes only patients whose nadir value is less than the recovery value for the parameter being summarized.

The median duration of neutropenia and thrombocytopenia as measured from study day 1 to ANC recovery to ≥500/μL and platelet recovery to ≥50,000/μL was 30 days and 31 days, respectively. For ANC recovery to ≥1000 cells/μL, the median duration of neutropenia was 32 days. For platelet recovery to ≥100,000 cells/μL, the median duration of thrombocytopenia was 34 days.

Patients who did not respond continued to have low ANC values, likely due to persistent leukemia. Sixty (17%) of the 277 patients were alive without ANC recovery to >500/μL by day 42; of these 47 (78%) were found to have persistent leukemia. Three (5%) of the 60 patients remained neutropenic without leukemia and without the myelosuppressive effects of intervening cytotoxic treatment. For these 3 patients with prolonged myelosuppression, defined as an ANC <500/uL in the absence of leukemic blasts in the bone marrow or peripheral blood for more than 42 days, platelet values remained less than 10,000/uL.

Patients with myelosuppression, due to either disease or treatment, may require transfusion. Almost all patients in the Safety population received transfusions of PRBCs and platelets.

5.3.2.2 Gastrointestinal Adverse Events

Gastrointestinal disturbance was one of the most commonly reported types of events (83.8%) of patients and primarily included reports of nausea (52.3%), diarrhea (41.2%), constipation (34.7%), vomiting (25.3%) and abdominal pain (11.6%). The majority of these events were Grade 1 or 2 in severity; Grade ≥3 GI events were reported in 10.8% of patients. The most commonly reported Grade ≥3 GI events were diarrhea (2.2%), nausea (1.8%), and abdominal pain (1.1%); all other severe GI events were reported in <1% of patients.

The incidence of GI events within one day of the initial Onrigin™ infusion was 30.7% of patients; nausea, vomiting, constipation and diarrhea were reported in 20.2%, 8.3%, 4.7% and 4.0% of patients during this time period.

Table 27: Gastrointestinal Adverse Events Reported in ≥5% of Patients Overall and Grade ≥3 in Severity (Safety Population, N=277)

MedDRA System Organ Class/ Preferred Term	All Events n (%)	Grades 3 to 5 n (%)
Gastrointestinal Disorders	**232 (83.8)**	**30 (10.8)**
Nausea	145 (52.3)	5 (1.8)
Diarrhea	114 (41.2)	6 (2.2)
Constipation	96 (34.7)	0
Vomiting	70 (25.3)	2 (0.7)
Abdominal pain	32 (11.6)	3 (1.1)
Abdominal pain upper	24 (8.7)	2 (0.7)
Dyspepsia	18 (6.5)	1 (0.4)

Events presented include those with overall incidence of at least 5% or that were reported as Grade ≥3 in severity in >2% of patients

The primary GI events were emesis (nausea and vomiting), which was common, but mild in intensity. Given the frequency of antiemetic use (42% received glucocorticoids and 40%

received serotonin (5HT3) antagonists, including ondansetron [22%]), these results are consistent with Onrigin™ as a mild to moderate emetogenic chemotherapy agent.

Constipation and diarrhea were commonly reported following Onrigin™ therapy. Most reports of diarrhea were Grade 1 or 2 (95%). Similarly all constipation events were Grade 1 or 2.

5.3.2.3 Pulmonary Adverse Events

An overview of pulmonary adverse events is provided in Table 28. In the Safety population of 277 patients, respiratory AEs were observed in 71.8% of patients; in 26.0%, the respiratory events were rated ≥Grade 3 in severity. The most commonly reported events were dyspnea and cough. Grade 3 or 4 dyspnea was reported in 21 (7.6%) and 8 (2.9%) patients, respectively; all reports of cough were Grade 1 or 2 in severity.

Pleural effusions were reported in 39 patients (14.1%) and in 12 patients (4.3%) the events were reported as Grade 3 to 5 in severity. Hypoxia was reported in 28 patients (10.1%) with 19 patients (6.9%) having hypoxia reported as Grade 3 to 5.

Table 28: Respiratory Adverse Events Reported in ≥5% of Patients Overall and Grade ≥3 in Severity (Safety Population, N=277)

MedDRA System Organ Class/ Preferred Term	All Events n (%)	Grades 3 to 5 n (%)
Respiratory, Thoracic and Mediastinal Disorders	**199 (71.8)**	**72 (26.0)**
Dyspnea	89 (32.1)	29 (10.5)
Cough	65 (23.5)	0
Epistaxis	47 (17.0)	2 (0.7)
Pleural effusion	39 (14.1)	12 (4.3)
Hypoxia	28 (10.1)	19 (6.9)
Pharyngolaryngeal pain	23 (8.3)	0
Pulmonary edema	21 (7.6)	4 (1.4)
Rales	19 (6.9)	0
Respiratory failure	15 (5.4)	13 (4.7)

Events presented include those with overall incidence of at least 5% or that were reported as Grade ≥3 in severity in >2% of patients

In the Safety population of 277 patients, 25 patients (9.0% of the 277 patients) had clinical presentations described as subacute or symptomatic diffuse bilateral pulmonary infiltrates, often associated with bilateral pleural effusion, occurring from day 21 to day 60 after study drug treatment. Treatment of the conditions was evaluated for these 25 patients. A total of 13 of the patients received supportive care with antibiotics and oxygen; 3 (23.1%) of these patients had symptoms which resolved. The remaining 12 patients received supportive care with antibiotics, steroids and oxygen; 6 (50.0%) of these patients had resolution of symptoms.

As a further evaluation, the incidence of respiratory adverse events was assessed for the 140 elderly patients with *de novo* AML based on the presence or absence of pulmonary dysfunction at baseline. The incidence of respiratory adverse events was higher among patients with pulmonary dysfunction at baseline (80.2%) compared to patients without pulmonary dysfunction

(66.1%). In particular, reports of dyspnea (42.0% vs 23.7%), cough (25.9% vs 15.3%), hypoxia (17.3% vs 6.8%), and wheezing (8.6% vs 0%) were higher among patients with pulmonary dysfunction at study entry.

5.3.3 Other Adverse Events of Interest

5.3.3.1 Infusion Reactions

Adverse events related to the Onrigin™ infusion were first noted in a single-agent phase 1 study (40). An infusion-related syndrome was described as occurring during or immediately after the infusion. The symptoms were facial flushing, headache, nausea, vomiting, dizziness, leg cramps, syncope, tachycardia and/or hypotension. Subsequent clinical protocols with Onrigin™, including Studies CLI-043, CLI-033 and CLI-029, included pre-treatment with antihistamines and antiemetics prior to the infusion.

The symptoms of the infusion reaction were usually mild and transient (resolve within 24 hours) and likely due to the presence of ethanol in the formulation (30%). An infusion of 600 mg/m^2 in the average sized person would contain approximately 33 mL ethanol. Ethanol is known to cause hypotension due to peripheral vasodilatory effects with other associated symptoms (e.g., dizziness, syncope, tachycardia, flushing).

Table 29 presents these events that occurred on the day of or the following day from Onrigin™ treatment in comparison to the incidence of each event over the course of the study. The relatively frequent occurrence of hypotension, flushing and nausea during this period, when compared to the same events overall, is consistent with the known infusion-related reaction effects.

Table 29: Infusion-Related Reactions Reported in Patients (Safety Population, N=277)

Adverse Event	Following Induction 1 n (%)	Within 1 Day of Infusion n (%)
Headache	63 (22.7)	33 (11.9)
Tachycardia	32 (11.6)	11 (5.1)
Hypotension	72 (26.0)	55 (19.9)
Flushing	20 (7.2)	18 (6.5)
Nausea	131 (47.3)	56 (20.2)
Vomiting	53 (19.1)	23 (8.3)
Dizziness	24 (8.7)	12 (4.3)
Syncope	3 (1.1)	2 (0.7)

This section describes the AEs and vital sign changes observed during the day of and the full day following the infusion of Onrigin™ in patients with hematologic malignancies who received 600 mg/m^2 administered as a 30 to 60 minute IV infusion.

Hypotension Adverse Events, Including Vital Signs Evaluations

Hypotension as an adverse event, and decreases in blood pressure readings during and immediately following treatment, occur commonly following treatment with Onrigin™.

Overall, hypotension was reported as an adverse event in 78 (28.2%) of the 277 patients included in the Safety population; the events were assessed as Grades 3 or 4 in severity in 8 patients (2.9%). Most reports of hypotension occurred within 1 day of the first infusion of Onrigin™ (55 patients, 19.9%).

No deaths occurred during the day of infusion or the following day. In 3 patients, hypotension was associated with syncope occurring within 9 hours of the infusion of Onrigin™.

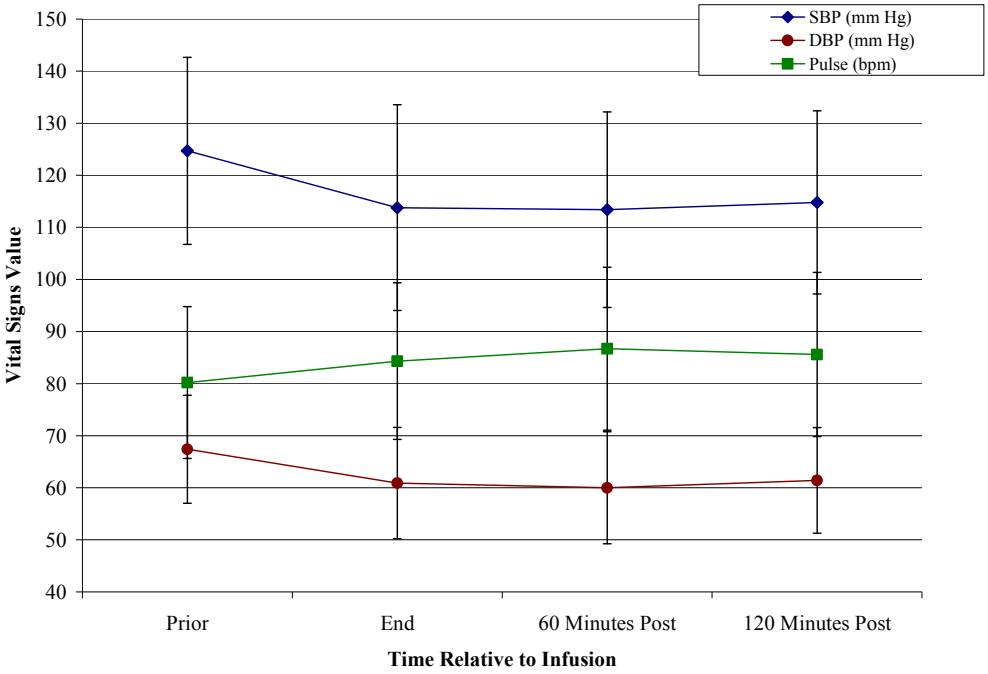
The events of hypotension are consistent with a drug or vehicle effect following the infusion of Onrigin™. The hypotensive episodes, while important, appeared to be transient and, in the majority of the cases, low grade.

Vital signs, including blood pressure, and pulse rate were measured before, at the end of infusion, and at multiple time points after the infusion of Onrigin™ in Studies CLI-033 and CLI-043. In Study CLI-029, vital signs were only collected at screening.

Median systolic and diastolic blood pressure and pulse over time relative to the Onrigin™ infusion during the first induction cycle is displayed graphically in Figure 11. Median systolic and diastolic blood pressures decreased during infusion and remained below baseline for the 2-hour post-infusion observation period in both Induction 1 and Induction 2 cycles.

Median pulse rates generally increased during infusion, consistent with the observed decreases in systolic and diastolic blood pressure, and did not return to baseline during the observation period. At 120 minutes post-infusion in all cycles, median pulse rates remained elevated.

Figure 11: Median (±SD) Vital Signs Values Prior to, at the End of, and Post-Infusion during Induction Cycle 1



a Includes only patients that were treated with Onrigin™ in the given cycle.

Decreases in systolic blood pressure of at least 20 mm Hg occurred in 43.3% of patients following infusion in Induction Cycle 1 and increases of at least 20 mm Hg occurred in 8.1%. The percentage of patients with these changes was similar at the end of infusion and 60 and 120 minutes post-infusion. Decreases in diastolic blood pressure of at least 20 mm Hg occurred in 23.6% of patients and increases occurred in 2.8% of patients.

5.3.3.2 Renal Adverse Events and Tumor Lysis Syndrome

AML patients who experience neutropenic infections from either the underlying disease or from the myelosuppressive effects of treatment, especially those who develop sepsis or septic shock, are at risk for renal impairment. Concomitant use of a variety of medications as prophylaxis against or treatment of bacterial, viral and fungal infections imposes additional intrinsic potential to damage the kidneys.

An overview of adverse events reported in the renal and urinary system is provided in Table 30. Overall 71 (25.6%) of the 277 patients experienced renal events. Most events were Grade 1 or 2 in severity; 6.5% of patients had a Grade ≥3 renal event. The most commonly reported Grade ≥3 events were renal failure and acute renal failure reported in 16 patients (5.8%) overall. Most patients with renal complications appeared to have concurrent septic events or tumor lysis syndrome. However, a possible contribution of Onrigin™ cannot be excluded.

Based on the types and incidence of renal adverse events, treatment with Onrigin™ does not appear to be associated with a significantly increased risk of renal adverse events.

Table 30: Renal Adverse Events Reported in ≥5% of Patients Overall and Grade ≥3 in Severity (Safety Population, N=277)

MedDRA System Organ Class/ Preferred Term	All Events n (%)	Grades 3 to 5 n (%)
Renal and Urinary Disorders	**71 (25.6)**	**18 (6.5)**
Renal failure	23 (8.3)	6 (2.2)[a]
Renal failure acute	14 (5.1)	11 (4.0)[a]
Hematuria	14 (5.1)	1 (0.4)

Events presented include those with overall incidence of at least 5% or that were reported as Grade ≥3 in severity in >2% of patients

a One patient had both Grade ≥3 renal failure and acute renal failure reported.

Tumor lysis syndrome occurs following treatment with Onrigin™. Tumor lysis syndrome was reported as an adverse event in 5 (1.8%) of the 277 patients; in 3 patients (1.1%) the events was Grade ≥3 in severity.

5.3.3.3 Cardiac Adverse Events

Cardiac events are expected in a population that includes elderly patients, many of whom have underlying cardiac disease.

In the Safety population, 37.5% of the 277 patients experienced cardiac events, with 11.9% experiencing events which were Grade 3 or higher. Arrhythmias in general accounted for the vast majority of patient events. The most common arrhythmia was tachycardia (17.0%) likely related to infusion reactions, hypotension or sepsis, followed by atrial fibrillation (9%).

The most serious medical consequence of any potential arrhythmia is sudden death. The potential for Torsades des Pointes, an uncommon variant of ventricular tachycardia, was not observed. A specific study to investigate the effect of Onrigin™ on the QT-interval in cancer patients is complete and data analysis is on-going.

Congestive cardiac failure was reported in 4.3% of patients with 7 patients experiencing this event at a severity of Grade 3 or higher. Other medically important events, such as myocardial infarction, cardio-respiratory arrest, and cardiac failure, occurred in <2% of patients.

Table 31: Cardiac Adverse Events in ≥5% of Patients Overall or Grade ≥3 in Severity in ≥2% of Patients (Safety Population, N=277)

MedDRA System Organ Class/ Preferred Term	All Events n (%)	Grades 3 to 5 n (%)
Cardiac Disorders	**104 (37.5)**	**33 (11.9)**
Tachycardia	47 (17.0)	2 (0.7)
Atrial fibrillation	25 (9.0)	7 (2.5)
Cardiac failure congestive	12 (4.3)	7 (2.5)

Events presented include those with overall incidence of at least 5% or that were reported as Grade ≥3 in severity in >2% of patients

Cardiac events of Grade 3 or 4 severity were reported more frequently in patients with baseline cardiac dysfunction (15.3%) compared to patients without cardiac dysfunction (7.3%) at baseline in *de novo* population (n=140).

5.3.3.4 Hepatic Adverse Events

No AEs were reported at an incidence of 5% or higher in the hepatobiliary disorders SOC and none were rated as Grade 3 to 5 at an incidence of 2% or higher. Three AEs rated as Grade 3 to 5 reported each in 1 patient included acute cholecystitis, hepatic failure, and hepatorenal failure.

The liver is not a target organ of treatment with Onrigin™, and the metabolic profile of the drug does not appear to be mediated substantially by the liver. The incidence of hepatic AEs was low, and veno-occlusive disease (VOD) was not observed in the Safety population.

An evaluation of liver function tests is provided in Section 5.3.6.

5.3.4 Deaths and Other Serious Adverse Events

5.3.4.1 Deaths

A total of 42 of 277 patients (15.2%) died within 30 days of first induction. Induction mortality within 30 days was 14.1% (12 of 85 patients) in Study CLI-043. The causes of death within 30 days of Induction cycle 1 are presented in Table 32. The most common cause was progression of the patient's underlying leukemia, reported for 16 patients (5.8%) occurring within 30 days. Infection was also commonly reported as the cause of death in this time period (11 patients, 4.0%).

Table 32: Causes of Death within 30 Days Following Induction Cycle 1 (Safety Population, N=277)

Parameter	N (%)
Died Within Given Days of Last Dose n (%)	**42 (15.2)**
Cause of Death[a]	
AML, Disease Progression	16 (5.8)
Adverse Event/Toxicity	22 (7.9)
Infection	11 (4.0)
Hemorrhage	3 (1.1)
Acute Renal Failure	2 (0.7)
Multi-organ Failure	2 (0.7)
Acute Respiratory Distress	2 (0.7)
Cardiac Arrest	1 (0.4)
Tumor Lysis Syndrome	1 (0.4)
Not reported/Unknown	4 (1.4)

a As reported by the investigator

This mortality profile is consistent with that of older individuals undergoing induction treatment for AML and appears to be consistent with the literature for induction-related mortality (10, 46, 48).

5.3.4.2 Serious Adverse Events

All SAEs that occurred in 2% or more of patients are summarized in Table 33. Most patients (205 patients, 74.0%) experienced at least one SAE and the incidence was similar across the 3 studies. The high percentage of patients experiencing SAEs reflects the patient population and the intention to achieve bone marrow ablation.

The SAE profile mirrors the AE profile, primarily reflecting myelosuppression and the consequences of myelosuppression. There are also respiratory effects of myelosuppression (e.g., pneumonia, sepsis, acute respiratory distress syndrome). Specific SAEs that occurred in more than 5% of patients were febrile neutropenia (21.3%), pneumonia (8.7%), thrombocytopenia (5.4%), dyspnea (6.5%), and pyrexia (9.0%). Nausea, diarrhea, constipation, and vomiting occurred as SAEs in fewer than 3% of patients.

Table 33: Serious Adverse Events in 2% or More of Patients (Safety Population)

MedDRA System Organ Class/ Preferred Term	Total (n = 277) n (%)
At Least One Serious Adverse Event	***205 (74.0)***
Blood and Lymphatic System Disorders	**80 (28.9)**
Febrile neutropenia	59 (21.3)
Thrombocytopenia	15 (5.4)
Anemia	9 (3.2)
Infections and Infestations	**73 (26.4)**
Pneumonia	24 (8.7)
Sepsis	9 (3.2)
Septic shock	6 (2.2)
Respiratory, Thoracic and Mediastinal Disorders	**52 (18.8)**
Dyspnea	18 (6.5)
Respiratory failure	9 (3.2)
Pleural effusion	8 (2.9)
Hypoxia	6 (2.2)
General Disorders, Administration Site Conditions	**49 (17.7)**
Pyrexia	25 (9.0)
Death	10 (3.6)
Cardiac Disorders	**27 (9.7)**
Atrial fibrillation	8 (2.9)
Neoplasms Benign, Malignant and Unspecified	**21 (7.6)**
Acute myeloid leukemia	16 (5.8)
Gastrointestinal Disorders	**21 (7.6)**
Nausea	6 (2.2)
Renal and Urinary Disorders	**12 (4.3)**
Renal failure acute	7 (2.5)
Vascular Disorders	**11 (4.0)**
Hypotension	7 (2.5)
Psychiatric Disorders	**10 (3.6)**
Confusional state	10 (3.6)

5.3.5 Adverse Events Leading to Study Discontinuation

Nine (3.2%) of 277 patients in the Safety population experienced at least one AE that led to discontinuation from the study in which they were enrolled. These AEs occurred most frequently in the Blood and Lymphatic System Disorders SOC (3 patients, 1.1%), Infections and Infestations SOC (2 patients, 0.7%) and General Disorders SOC (2 patients, 0.7%). No individual AE that led to discontinuation occurred in more than 1 patient (0.4%) each. Adverse events leading to discontinuation included febrile neutropenia, pancytopenia, thrombocytopenia, endocarditis, bacterial sepsis, staphylococcal infection, disease progression, mucosal inflammation, leukemia cutis, grand mal convulsion, cardiac failure, hypoxia, acute renal failure and decreased ejection fraction.

5.3.6 Clinical Laboratory Evaluation

A discussion of hematologic changes associated with myelosuppression is provided in Section 5.3.2.1.

Table 34 presents the maximum CTCAE severity grade for serum chemistry parameters, including liver and renal function tests, and electrolytes.

There was a low incidence of patients with a maximum severity of Grade 4 reported following induction cycle 1 (for those clinical parameters where CTCAE grades were available).

Table 34: Maximum CTCAE Severity by Onrigin™ Cycle for Chemistry Parameters (Safety Population)

Parameter		Maximum Toxicity Grade[a] (n=277)				
Time point	n[b]	0	1	2	3	4
Albumin						
Baseline	254	122 (48.0)	86 (33.9)	44 (17.3)	2 (0.8)	0
Induction 1	250	47 (18.8)	77 (30.8)	108 (43.2)	18 (7.2)	0
Alkaline Phosphatase						
Baseline	267	221 (82.8)	39 (14.6)	7 (2.6)	0	0
Induction 1	270	172 (63.7)	79 (29.3)	17 (6.3)	2 (0.7)	0
ALT (SGPT)						
Baseline	252	223 (88.5)	24 (9.5)	5 (2.0)	0	0
Induction 1	258	214 (82.9)	30 (11.6)	9 (3.5)	5 (1.9)	0
AST (SGOT)						
Baseline	212	184 (86.8)	26 (12.3)	2 (0.9)	0	0
Induction 1	231	162 (70.1)	59 (25.5)	5 (2.2)	4 (1.7)	1 (0.4)
Total bilirubin						
Baseline	269	237 (88.1)	20 (7.4)	11 (4.1)	1 (0.4)	0
Induction 1	274	147 (53.6)	72 (26.3)	42 (15.3)	12 (4.4)	1 (0.4)
Creatinine						
Baseline	277	237 (85.6)	37 (13.4)	3 (1.1)	0	0
Induction 1	272	202 (74.3)	47 (17.3)	17 (6.3)	4 (1.5)	2 (0.7)
Glucose						
Baseline	209	103 (49.3)	72 (34.4)	29 (13.9)	5 (2.4)	0
Induction 1	216	47 (21.8)	108 (50.0)	48 (22.2)	11 (5.1)	2 (0.9)
Sodium						
Baseline	274	247 (90.1)	24 (8.8)	0	3 (1.1)	0
Induction 1	270	165 (61.1)	88 (32.6)	4 (1.5)	13 (4.8)	0
Potassium						
Baseline	275	238 (86.5)	32 (11.6)	0	5 (1.8)	0
Induction 1	272	152 (55.9)	88 (32.4)	3 (1.1)	25 (9.2)	4 (1.5)
Magnesium						
Baseline	235	195 (83.0)	37 (15.7)	1 (0.4)	2 (0.9)	0
Induction 1	248	156 (62.9)	80 (32.3)	5 (2.0)	6 (2.4)	1 (0.4)
Calcium						
Baseline	266	177 (66.5)	58 (21.8)	30 (11.3)	1 (0.4)	0
Induction 1	265	102 (38.5)	81 (30.6)	72 (27.2)	8 (3.0)	2 (0.8)
Phosphate						
Baseline	258	220 (85.3)	8 (3.1)	24 (9.3)	6 (2.3)	0
Induction 1	255	173 (67.8)	6 (2.4)	48 (18.8)	28 (11.0)	0

a Patients are counted only once for each parameter, under the maximum severity grade observed during the period.

b Includes only patients that were treated with Onrigin™ during the cycle and had the assessment performed.

5.4 Extent of Exposure

Extent of exposure to Onrigin™ for the Safety population is summarized in Table 35. In Studies CLI-043 and CLI-033, 204 patients (75.8%) received only 1 induction cycle; 63 patients (23.4%) received 2 cycles, and 2 patients (0.7%) received 3 cycles (2 induction, 1 consolidation). Similarly, 5 patients (62.5%) in Study CLI-029 also received only 1 cycle.

Median total dose of Onrigin™ administered was 600 mg/m^2. Maximum dose that could be administered was 1600 mg/m^2 (2 induction cycles of 600 mg/m^2 and 1 consolidation cycle of 400 mg/m^2 in Study CLI-033).

Table 35: Exposure to Onrigin™ Injection, All Cycles (Safety Population)

All Cycles[a]	CLI-043 n = 85	CLI-033 n = 184	CLI-029 n = 8	Total for CLI-043 and CLI-033 n = 269[a]
No. of Cycles Received, n (%)				
1 Cycle	71 (83.5)	133 (72.3)	5 (62.5)	204 (75.8)
2 Cycles	14 (16.5)	49 (26.6)	3 (37.5)	63 (23.4)
3 Cycles	NA	2 (1.1)	NA	2 (0.7)
Total Duration of Infusion (min)				
N	85	184	8	269
Mean (SD)	74.3 (27.59)	61.9 (48.94)	70.6 (28.59)	65.8 (43.68)
Median	61.0	45.0	75.0	60.0
Minimum, Maximum	30, 195	25, 370	20, 100	25, 370
Total Dose (mg/m²)				
N	85	184	8	269
Mean (SD)	698.8 (223.87)	740.2 (238.65)	825.0 (310.53)	727.1 (234.46)
Median	600.0	600.0	600.0	600.0
Minimum, Maximum	600, 1200	600, 1600	600, 1200	600, 1600
Pts w/ Interruptions, n (%)				
Induction Cycle 1	1 (1.2)	7 (3.8)	NA	8 (3.0)
AE	1 (1.2)	7 (3.8)	NA	8 (3.0)
Induction Cycle 2	2 (14.3)	0	NA	2(5.4)
AE	2 (14.3)	0	NA	2 (5.4)
Other	1 (7.1)	0	NA	1 (2.7)

NA=not applicable

a All 277 patients received study drug at the assigned dose; 8 patients in Study CLI-029 had incomplete information for infusions and were not included in the total.

Patients in the Safety population received multiple concomitant medications, reflecting the general standard of care for induction chemotherapy and baseline health status of older patients

enrolled to the Onrigin™ studies. As expected in a myelosuppressed population, the classes of medications most frequently administered included antibiotics, antifungals, or antivirals given prophylactically or for active infections.

Other common medications were for conditions that frequently accompany aging and for the side effects of leukemia and chemotherapy. In addition, as the protocols required patients to receive antiemetics and antihistamines prior to each dose, these classes of drugs were also frequently administered. The most frequently administered medications were acetaminophen (paracetamol) (81.9%), allopurinol (70.0%), vancomycin (60.3%), potassium chloride (59.9%), furosemide (57.8%), levofloxacin (41.5%), fluconazole (40.4%), diphenhydramine (39.0%), lorazepam (36.1%), and pantoprazole (32.5%).

5.5 Safety Summary and Conclusions

The safety profile associated with Onrigin is consistent and predictable. Adverse events, including SAEs are predominantly related to myelosuppression. Commonly occurring gastroinstestinal and infusion-related adverse events are low grade and transient and easily managed.

The safety profile of Onrigin™ is primarily characterized by myelosuppression and the consequences of myelosuppression, infusion-related reactions, and pulmonary complications. AEs occurring most frequently ≥Grade 3 were febrile neutropenia, neutropenia, thrombocytopenia, pneumonia, and dyspnea.

Myelosuppression and the consequences of myelosuppression included cytopenias (febrile neutropenia [37.2%], neutropenia [21.3%], thrombocytopenia [20.2%] and anemia [13.0%]), infections (pneumonia [19.5%]) and pyrexia (46.6%). Overall, hematopoietic cytopenias were reported in 63.5% of the 277 patients; hematologic abnormalities were reported as Grade ≥3 in severity in 54.9% of patients. Infections occurred in 62.1% of patients and were the second most commonly reported type of event assessed as Grade ≥3 in severity (35.4% of patients).

There is a known pattern of Onrigin™ infusion-related AEs, including headache, nausea, vomiting, myalgia/cramps, facial flushing, dizziness, tachycardia, and hypotension. Within 1 day of the first Onrigin™ infusion, the most commonly reported AEs were nausea (20.2%), hypotension (19.9%), pyrexia (13.4%), and headache (11.9%); all other events reported in this time period occurred in <10% of patients.

Respiratory AEs were among the most frequently reported events, and primarily included reports of dyspnea (32.1%) and cough (23.5%). These usually presented as a consequence of myelosuppression and infection. There was a delayed pattern of pulmonary events observed in 9.0% of patients treated with Onrigin™ with bilateral pulmonary infiltrates, with or without pleural effusions, and with no obvious alternative explanations.

Gastrointestinal disorders occurred in 83.8% of patients and included reports of nausea (52.3%) and vomiting (25.3%) which are likely related to administration of Onrigin™. The majority of GI events were Grade 1 or 2 in severity; GI events Grade ≥3 in severity occurred in 10.8% of patients. Diarrhea (41.2%), constipation (34.7%), and abdominal pain (11.6%) were also frequently reported.

The SAE profile of Onrigin™ mirrors the AE profile, reflecting myelosuppression and the consequences of myelosuppression. The most commonly reported SAEs were febrile neutropenia (21.3%), pneumonia (8.7%), thrombocytopenia (5.4%), dyspnea (6.5%), and pyrexia (9.0%).

A total of 42 patients (15.2%) died within 30 days of first infusion. This mortality profile is consistent with that for induction treatment of older patients with AML and is consistent with the literature for induction-related mortality.

The safety analyses demonstrate that Onrigin™ Injection at a dose of 600 mg/m^2 is well characterized and predictable. Onrigin™ can be safely administered to a population 60 years or older with *de novo* AML and poor-risk features.

6. Benefit/Risk Conclusions

AML is a rapidly progressive and fatal disease. Approximately two-thirds of elderly patients go untreated and, if left untreated, they will die of their disease in 1.7 months.

Elderly patients with AML are biologically and clinically distinct from younger patients and have an increased incidence of comorbidities, poor hematologic reserves, and worse ECOG performance scores, which lead to lower tolerance for intensive therapies. This patient population also has a higher incidence of unfavorable cytogenetic profiles than younger patients, which is a known factor for poor outcomes. Furthermore, AML in the elderly is more often associated with multi-drug resistance (MDR) expression, which contributes to a lower response to a wide variety of agents.

These characteristics make elderly patients difficult to treat and unlikely to respond to or tolerate therapy, and also make some physicians less willing to treat such patients aggressively with high dose chemotherapy.

Onrigin™ is a novel alkylating agent with demonstrated antileukemic activity in this patient population with significant unmet medical need. The patients enrolled to the two Onrigin™ Phase 2 clinical trials in AML demonstrated significant comorbidities and poor-risk factors at baseline. Of the 140 patients presented here, 75% were age 70 or older, 61% had cardiac dysfunction, 58% had pulmonary dysfunction, 45% had unfavorable cytogenetics and 36% had ECOG PS of 2. Over 86% of the 140 patients had at least 2 of these poor-risk factors and 59% had 3 or more risk factors.

Elderly AML patients with multiple poor-risk factors have been shown to have poor outcomes. In one major analysis by Kantarjian et al, patients who had 3 or more risk factors had expected CR rates of less than 20%, an 8-week mortality > 50% and a 1-year survival of < 10%. The authors conclude that patients with these multiple risk factors should not be treated with intensive chemotherapy.

Induction therapy with Onrigin™ induced remissions in 34.3% of these elderly, poor-risk AML patients, with a substantial proportion of patients experiencing lasting remissions. Thirty-seven percent (37%) of patients achieving a complete remission had a duration of response lasting 6 months or longer. Twenty percent (20%) of patients achieving a complete remission had a duration of response lasting a year or longer.

In Study CLI-043, median OS among the 27 patients who achieved remission based on independent review was 12.4 months.

Additionally, induction therapy with Onrigin™ in this patient population demonstrated an acceptable safety profile and induction mortality rate. The 30-day mortality rate was 15.2% and the discontinuation rate due to adverse events was 1.4%. The safety profile associated with Onrigin™ is consistent and predictable. Adverse events, including SAEs are predominantly related to myelosuppression. Commonly occurring gastrointestinal and infusion-related adverse events are low grade and transient and easily managed.

In the context of currently available treatments for elderly poor-risk AML patients, the data presented demonstrate the role of Onrigin™ as a therapeutic option.

The totality of the evidence support a positive benefit risk profile for Onrigin™ when used as single agent induction treatment at a dose of 600 mg/m^2 for patients 60 years or older with *de novo* poor-risk AML.

Onrigin™ addresses an unmet medical need for the population of AML patients who are elderly and poor-risk and should be made available as a therapeutic option to treat this underserved patient population.

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Appendix A

Overall Response Rate in Study CLI-033

Stratum	Diagnostic Group	N	No. of Pts with CR+CRp	ORR	95% CI
A	All	130	40	30.8%	23.0-39.5
	De novo	53	24	45.3%	31.6-59.6
	Secondary AML	51	6	11.8%	4.4-23.9
	High-risk MDS	26	10	38.5%	20.2-59.4
B	All	53	2	3.8%	0.5-13.0