

Survival after Complete Response to Treatment with Laromustine (Onrigin™, formerly Cloretazine®) in Elderly Patients with *De Novo* Poor Risk Acute Myelogenous Leukemia (AML)

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Objective

- To present survival data for a combined group of *de novo* poor risk AML patients age 60 or older who achieved a response (CR/CRp by IWG criteria¹) to laromustine

¹ Appelbaum. *Blood*. 2007

Background: Elderly AML

- Effective treatment options for patients with AML are limited
- Increasing age, decreasing performance status, unfavorable cytogenetics, and the presence of comorbid conditions are common and associated with poor outcomes
- Induction mortality for elderly patients with AML ranges from 12-82% depending on age and performance status¹
- Patients ≥ 65 years with AML, regardless of treatment, have a short survival (median 2.4 months)²
- For elderly patients who receive treatment, 1-year survival ranges from 5-25%^{3,4}
- Complete remission is a desired outcome from induction treatment and a requisite for meaningful survival

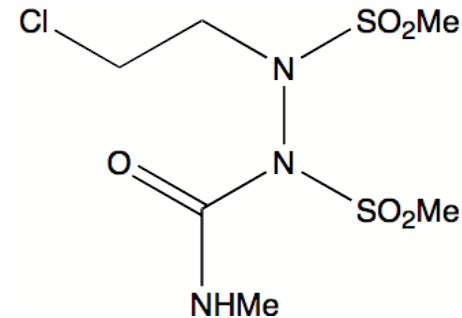
¹ Appelbaum. *Blood*. 2006

² Lang. *Drugs Aging*. 2005

³ Menzin. *Arch Intern Med*. 2002

⁴ Burnett. *Cancer*. 2007

Background: Laromustine



- Sulfonylhydrazine alkylating agent
- Prodrug activated to
 - 90CE (1,2 Bis(methylsulfonyl)-1-(2-chloroethyl)hydrazine)
 - Generates cationic chloroethylating species that preferentially targets the O^6 position of guanine
 - Methyl isocyanate
 - Carbonylating species
 - Inhibits alkylguanine alkyltransferase (AGT), a DNA repair enzyme
 - Active in L1210 cell lines (BCNU, cyclophosphamide, and melphalan resistant)
- Crosses blood-brain barrier
- Not a substrate for MDR

Methods

- A total of 140 patients were analyzed for response and survival
 - 85 patients in study CLI-043
 - 55 patients from a retrospectively identified *de novo* subset of study CLI-033 who reasonably met the eligibility criteria for CLI-043

CLI-033 and CLI-043: Study Overview

	CLI-033	CLI-043
Phase	Phase II, open label	Phase II, open label
Enrollment Period	Mar 2004 - Jun 2006	May 2006 - Aug 2007
Patient Population	<p>Prospectively enrolled AML/MDS patients by FAB criteria. Retrospectively identified 55 enrolled patients who were age ≥ 60 years with <i>de novo</i> AML by WHO criteria with at least one poor risk factor:</p> <ul style="list-style-type: none"> • Age ≥ 70 • Unfavorable cytogenetics • ECOG PS 2 • Cardiac, pulmonary, or hepatic dysfunction 	<p>Prospectively enrolled 85 patients age ≥ 60 with <i>de novo</i> AML by WHO criteria with at least one poor risk factor:</p> <ul style="list-style-type: none"> • Age ≥ 70 • Unfavorable cytogenetics • ECOG PS 2 • Cardiac, pulmonary, or hepatic dysfunction
Induction	Laromustine 600 mg/m ² *	Laromustine 600 mg/m ²
Consolidation	Laromustine 400 mg/m ²	AraC 400 mg/m ² /day x 5 days
Primary objective	Complete Response (CR and CRp)	Complete Response (CR and CRp)
Secondary objectives	Toxicity Spectrum Pharmacokinetics	Progression-free survival Leukemia-free survival Overall survival Toxicity Spectrum

*45 of 55 patients also received hydroxyurea 30 mg/kg po q12 h x 6 doses (day 1-3)

Treatment Administered and Risk Factors

Treatment	Total N=140
Received Induction 1	140 (100%)
Received Induction 2	23 (16%)
Received Consolidation	33 (24%)

Type of Risk Factor	Total N=140
Age \geq 70	105 (75%)
Unfavorable Cytogenetics	63 (45%)
ECOG PS	51 (36%)
Cardiac Dysfunction	85 (61%)
Pulmonary Dysfunction	81 (58%)
Hepatic Dysfunction	3 (2%)

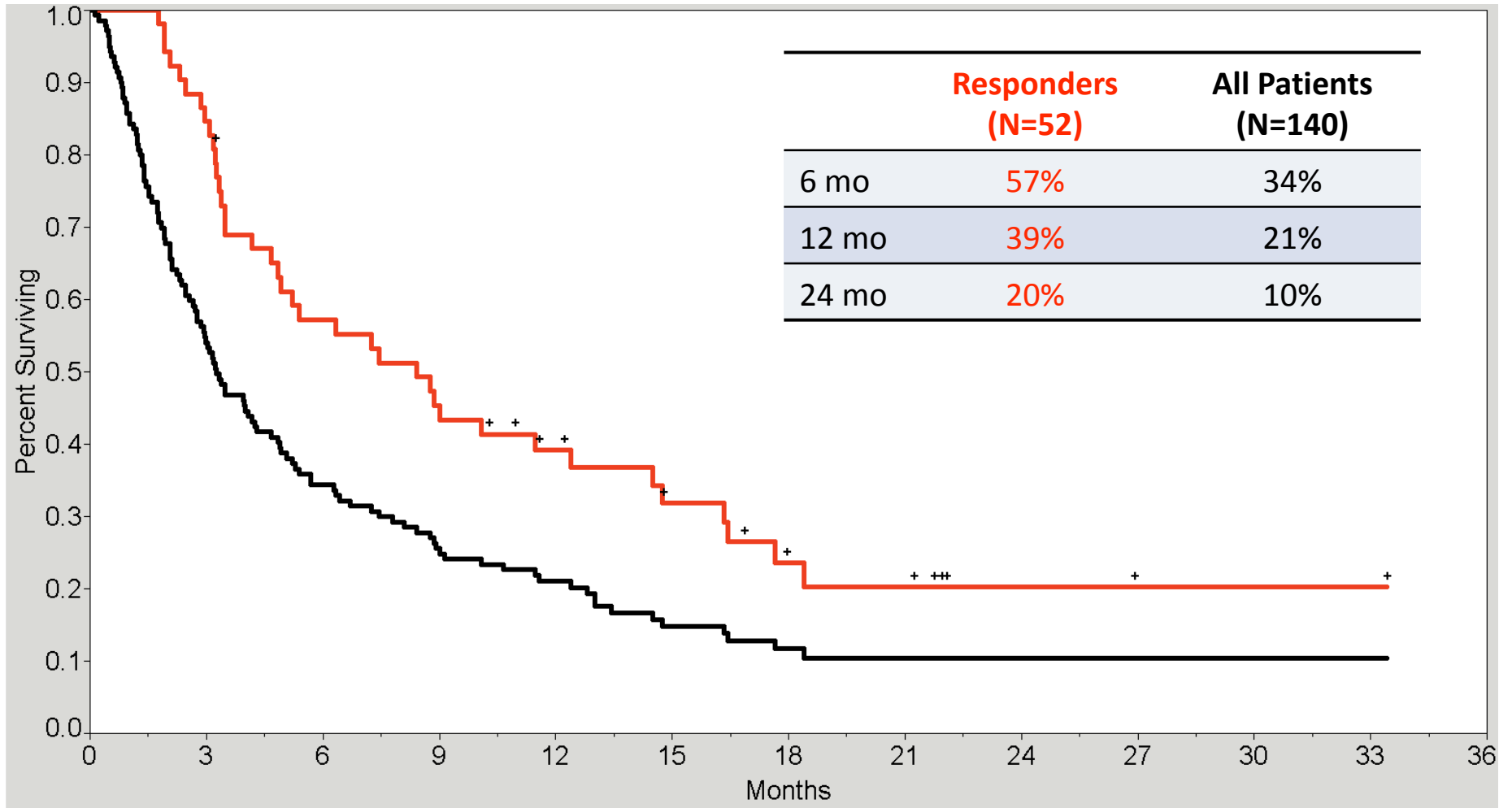
- 86% of patients had 2 or more risk factors
- 72% of patients had 3 or more risk factors

Results

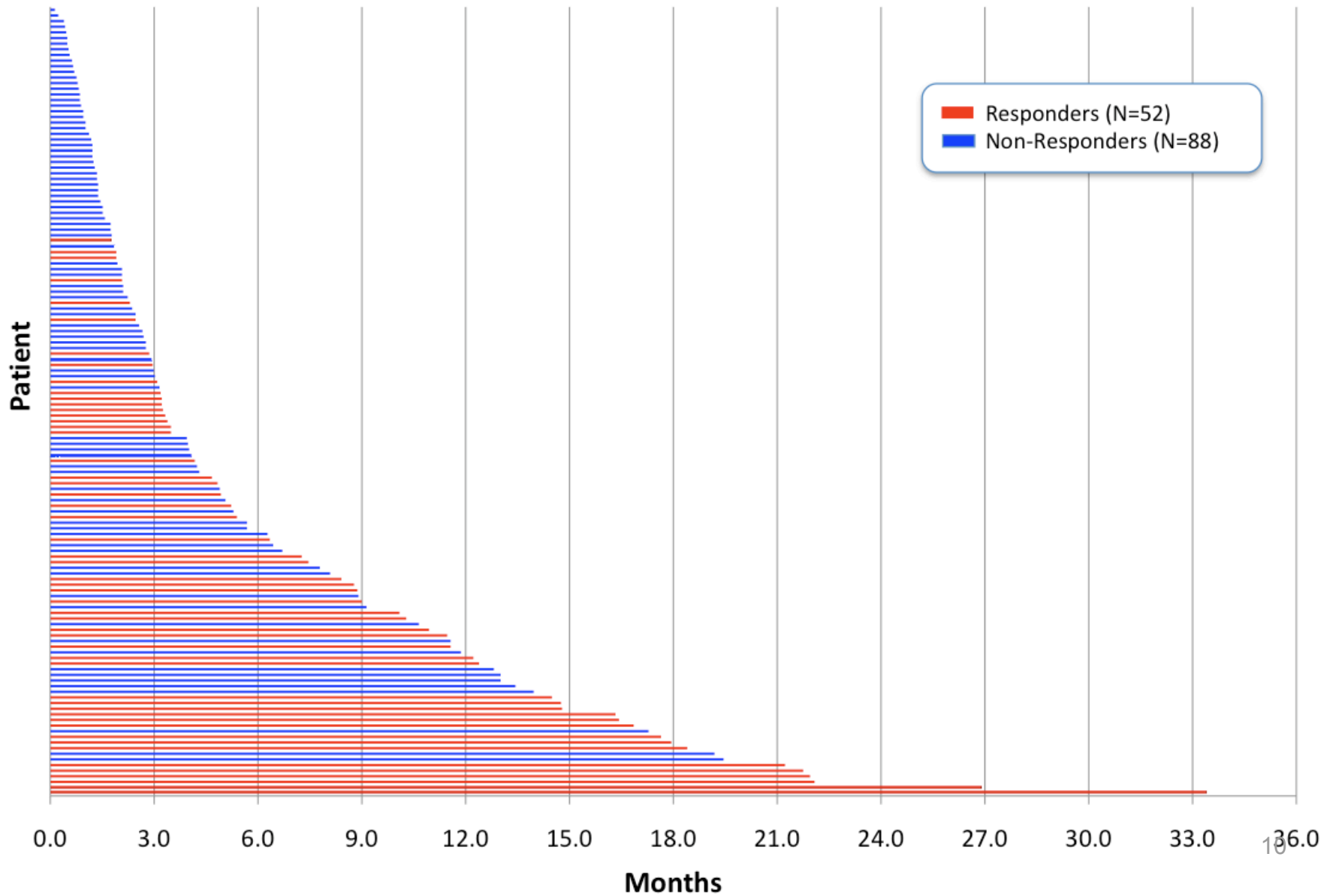
	Total N=140
ORR (CR and CRp)	52 (37%)
95% CI	29.1% - 45.1%
CR	40 (29%)
CRp	12 (9%)
All cause induction mortality	20 (14%)

- 94% of patients achieved CR/CRp following first induction
- The most common serious adverse events were in the following system organ classes: infections and infestations (34%); blood and lymphatic system disorders (24%); and respiratory, thoracic and mediastinal disorders (22%)

Overall Survival



Overall Survival



Conclusions

- Of 140 *de novo* poor risk AML patients age 60 or older, 37% of patients responded to laromustine (Onrigin™, formerly Cloretazine®).
- In this analysis, clinical benefit is achieved in elderly AML patients who respond to laromustine, as demonstrated by 6 and 12 month survival of 57% and 39%, respectively.