

Safety and Efficacy of Marqibo (Vincristine Sulfate Liposomes Injection, OPTISOME™) for the Treatment of Adults with Relapsed or Refractory Acute Lymphocytic Leukemia (ALL)

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Abstract

Introduction: Vincristine sulfate (VCR) is a lipophilic, cell-cycle specific, antineoplastic agent that inhibits cell division by specifically binding to tubulin in mitotic spindles. The activity of VCR is dose and time-dependent, but central and peripheral neuropathy prohibits its use beyond doses of 1.4 mg/m² (capped at 2 mg). Marqibo is a formulation of VCR encapsulated in a sphingomyelin-cholesterol liposome (OPTISOME) with a longer half-life than VCR. In murine models using L1210 or P388 lymphoid leukemia cell lines, Marqibo demonstrated greater anti-tumor activity compared with VCR. Marqibo was therefore an appropriate agent to study in relapsed or refractory ALL.

Methods: Two clinical trials have been completed. First, a phase II trial of single agent Marqibo given at 2 mg/m² (no dose capping) every 2 weeks enrolled 16 patients (pts) [Thomas et al, Cancer 106:120, 2006]. A multicenter dose escalation phase I trial using weekly Marqibo (1.5, 1.825, 2.0, 2.25, 2.4 mg/m²) in combination with pulse dexamethasone followed. There were no restrictions on the number of prior therapies. Subjects with grade 2 or greater central or peripheral neuropathy were ineligible.

Results: In total, 52 pts with relapsed or refractory ALL were treated in the two studies combined. Median age was 34 years (range, 19-77), 31 males/21 females, with a median number of prior salvage regimens of 2 (range, 1-3). Nine pts had confirmed Philadelphia positive disease (8 in the pre-imatinib era, 1 resistant to tyrosine kinase inhibitor therapy). All pts had previously received conventional VCR therapy. There were 8 complete remissions and 3 partial remissions for an overall response rate of 21% [95% CI, 11, 35]. An additional 12 pts (23%) achieved hematological improvements (e.g., clearance of marrow blasts, platelet transfusion independence). Five responders were able to undergo allogeneic stem cell transplantation following therapy with Marqibo. The maximum tolerated dose in the phase I trial was 2.25 mg/m² owing to grade 3 motor neuropathy, grade 4 seizure, and grade 4 hepatotoxicity observed in 1 patient each at the 2.4 mg/m² dose level. Grade 1-2 peripheral neuropathy was manageable with dose modifications and anti-neuralgia agents such as gabapentin. Commonly observed toxicities included febrile neutropenia, myelosuppression, abdominal pain, nausea, constipation, diarrhea, fatigue, and infusion-related pyrexia.

Background

Relapsed/Refractory Adult ALL

Salvage CR rates 20-30%, median survival 2-6 months

Age, duration of first CR & disease burden influence outcome with salvage therapy.¹

Novel agents needed to overcome resistance mechanisms

VSLI: Rationale for Development^{2,3}

- Efficacy of VCR dose and time-dependent
- Sphingoliposomal encapsulation of free VCR
- ↑ tumor exposure with liposomal delivery
- ↑ PK of VCR governed by PK of liposome
- Slow release VCR (50% at 24 hours)
- Higher tumor C_{max} and AUC than free VCR

Phase I Clinical Trial in Solid Tumors⁴

- Previously treated refractory patients with various malignancies (n=25)
- VSLI dose 0.5 to 2.8 mg/m² q3 weeks
- DLT at 2.8 mg/m² with myalgias, constipation and peripheral neuropathy
- Grade 3-4 constipation (12%), fatigue (8%), alopecia (8%), and anemia (8%)
- Recommended Phase II dosing 2 mg/m²

Study Design & Eligibility

Congregate data of 2 clinical trials (n=52)

Phase II Marqibo 2 mg/m² q2 wks⁵ (n=16)

- Component pivotal NHL lymphoma trial

Phase I Marqibo weekly + dexamethasone (n=36)

- Marqibo 1.5, 1.825, 2, 2.25 or 2.4 mg/m²
- Dexamethasone 40 mg days 1-4 & 11-14

No dose capping of Marqibo as with free VCR

Eligibility

Previously treated ALL, Burkitt leukemia or lymphoma, lymphoblastic lymphoma

Performance status 3 or better

No restrictions in # of prior therapies (21 days elapsed unless PD with resolution toxicity)

No CNS disease or neurological disorder

Adequate hepatorenal function

No active uncontrolled infection

Treatment Delivery of Marqibo

Phase II

- Median no. doses 2 (range, 1-5)
- Median dose 3.8 mg (range, 2.9 - 4.2)
- Limited by progression of disease

Phase I

- Course defined as 4 weekly doses (replaced if < 4 doses in absence of DLT)
- Median no. doses 4 (range, 2-11)
- Median cumulative dose 9 mg/m² (range, 4.5 to 19.7 mg/m²)

Table 1: Pretreatment Characteristics

Parameter	No. (%)	
	Phase II (n=16)	Phase I (n=36)
Age (yrs)		
< 40	8 (50)	25 (69)
41-59	4 (25)	19 (53)
> 60	4 (25)	1 (3)
1 st CR Duration (mos)		
0	3 (19)	8 (22)
1-5.9	6 (28)	5 (14)
6-11.9	3 (19)	7 (19)
≥ 12	4 (25)	16 (44)
Circulating blasts (%)	Y 11 (69)	23 (64)
Karyotype	Ph+ 8 (50)	1 (3)
Leukocyte (× 10 ⁹ /L)		
< 25	10 (63)	32 (89)
25-49.9	4 (25)	3 (8)
≥ 50	2 (12)	1 (3)
Hemoglobin (g/dL)	< 10 7 (44)	14 (39)
Platelet (× 10 ⁹ /L)	< 100 13 (81)	24 (67)
Salvage attempt no.	1 11 (69)	12 (33)
2	3 (19)	14 (39)
≥ 3	2 (12)	9 (25)

Toxicity Attributed to Marqibo

- Phase II
 - Grade 1 peripheral neuropathy (n=2)
- Phase I
 - Dose-limiting toxicities at 2.4 mg/m²
 - Grade 4 seizure (subdural)
 - Grade 4 hepatotoxicity
 - Grade 3 motor neuropathy
 - Grade 1-2 peripheral neuropathy, bone pain, constipation not uncommon

Response

Phase II
• 1 CR, 1 PR (12%)

Phase I

Dose level Total No. No. Response (%)

Dose level	Total No.	No. Response (%)
1.5	5	2 CR (40)
1.825	3	1 CR (33)
2	3	---
2.25	18	3 CR, 2 PR (28)
2.4	7	1 CR (14)

Phase II + I Overall

CR 8
PR 3

Note: Standard 3 + 3 design. Replaced if course not completed in absence of DLT. Expanded at MTD.

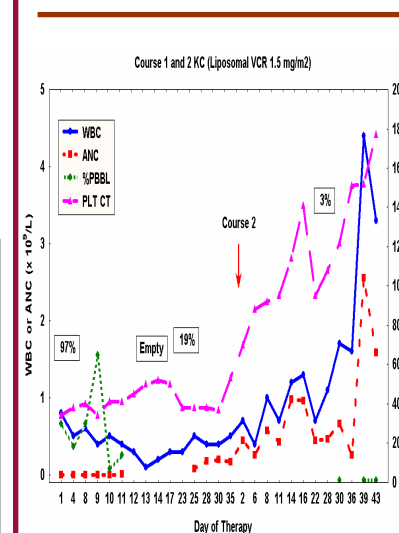


Figure 1. Refractory T-cell ALL achieving CR after 2 courses of Marqibo 1.5 mg/m² IV weekly concurrently with oral dexamethasone. HLA-identical allogeneic SCT followed. Note boxes represent bone marrow blasts.

Summary of Responders

- Objective responses in 21%
- Hematological improvements observed
 - Clearance marrow blasts
 - Platelet transfusion independence
- Five responders (including HI) underwent allogeneic SCT after Marqibo therapy

Conclusions

Marqibo with or without pulse dexamethasone appears to have clinically meaningful activity in heavily pre-treated adults with ALL.

A multicenter phase II trial of single agent Marqibo 2.25 mg/m² weekly as second salvage therapy for adults with relapsed ALL is now underway.

A phase III multicenter trial of Marqibo in combination with standard chemotherapy for de novo elderly ALL is in the planning phase.

References

1. Thomas DA et al, Cancer 86:1216, 1999
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AT, BL, SRD employed by Hana Biosciences, Inc (SRD has stock options); DAT, SOB, HMK, WS are/have been consultants; SOB, WS, LH have received research funding; DAT, SOB, HMK have received honoraria; DAT, HMK, SOB, WS, LH have participated in Advisory Boards