

# A Pivotal Study of Marqibo® in Adults With Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia in Second Relapse: Preliminary Results of an Interim Analysis of the rALLY Study

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## Abstract\*

\*The poster presents more recent data available since submission of the abstract

**Background:** VLSI (Marqibo®) is a nanoparticle formulation of vincristine sulfate (VCR) encapsulated in sphingomyelin/cholesterol liposomes called Optisomes®. The optional formulation lends itself to an improved pharmacokinetic profile and enhanced tumor penetration and concentration. Preclinical studies of VLSI showed enhanced efficacy versus standard VCR in a variety of solid and hematologic malignancies. VLSI has a maximum tolerated dose of 2.25 mg/m<sup>2</sup> with no dose cap, while conventional VCR is dosed at 1.4 mg/m<sup>2</sup> with a 2 mg dose cap. A previous study in relapsed ALL showed a complete response rate of 19%, warranting further study.

**Methods:** Eligible adult subjects received single agent intravenous VLSI at a dose of 2.25 mg/m<sup>2</sup> weekly with no dose cap. This international, multicenter, single arm study will enroll approximately 56 subjects. Major endpoints include response rate and overall survival (OS). An interim analysis was planned following enrollment of 29 evaluable subjects.

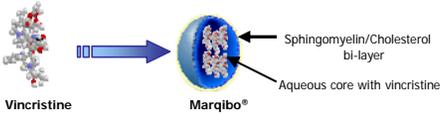
**Results:** 29 heavily pretreated subjects received ≥ 1 dose of VLSI. To date, at least 9 of 29 subjects had clearing of leukemic blasts and achievement of an M1 bone marrow. Based on preliminary data, the median OS is estimated to be 7.5 months (95% CI: 4.7-10.5) using the Kaplan-Meier method. The most frequent related adverse event (AE) was peripheral neuropathy (PN) (48%), half of which was Grade 3. No Grade 4 PN was reported. Six subjects had 8 treatment associated Grade 4 AEs of neutropenia (4), thrombocytopenia (2), anemia (1), and inappropriate antidiuretic hormone secretion (1).

**Conclusions:** These results are encouraging, as VLSI was given as a single agent to a heavily pretreated patient population who nearly universally received prior VCR. This population typically has a very low response rate to anti-leukemia therapies. Early OS data compares favorably to an historical median OS of ~ 2 months (8.7 weeks) in a second salvage population (data on file, M.D. Anderson). VLSI was well tolerated in these patients in the context of universal prior vincristine treatment.

## Background

- A majority of adults with Ph- ALL will relapse following successful initial induction therapy
- Prognosis at the time of second relapse or relapse following a stem cell transplant (SCT) performed in first remission is grim with SCT offering one of the key therapeutic options with the potential for long-term survival
- Approved and standard-of-care treatments are lacking for the second salvage setting
- A new, potent, and minimally myelosuppressive second salvage therapeutic is needed to re-induce complete remission and facilitate survival until a possible SCT
- Vincristine sulfate liposomes injection (VLSI, Marqibo) has the potential to provide targeted, dose-intensified, effective, single-agent therapy for adults with Ph- ALL in second relapse

## Benefits of Optisome® Technology



- Optisomes permit high concentration drug loading: ~10,000 moieties per optisome
- Optisomes allow for first-order drug release over several days
- Optisomes allow for prolonged circulation times with human plasma half-life of ~16 hr
- Optisome mean diameter of ~100nm facilitates extravasation through fenestrated tumor vasculature
- Optisomes result in improved drug penetration and accumulation in cancerous tissues

## Study Design and Objectives

- Phase 2, international, multicenter, open-label, single-arm trial
- Eligible subjects receive 2.25 mg/m<sup>2</sup> Marqibo, with no dose cap, i.v. once weekly for 4 weeks per cycle
- Subjects who attain CR, CRi, PR, HI (hematologic improvement) or SD are treated until stem cell transplant, disease progression, toxicity or physician determination of no further benefit

**Primary Objective:**  
CR/CRi rate

**Secondary Objectives:**  
Duration of CR/CRi  
Overall Survival  
Safety and Tolerability

## Main Eligibility Criteria

- Adults (age ≥18 years) with confirmed Ph- ALL or lymphoblastic lymphoma in second relapse, or adults with Ph- ALL who failed two treatment lines of anti-leukemia chemotherapy
- Histologically proven ALL and ≥10% bone marrow blasts, confirmed by central pathology review
- Responsive to a prior anti-leukemia therapy as defined by a leukemia-free interval of ≥3 months
- ECOG performance status 0-3 and lack of evidence of active CNS leukemia
- Eligible subjects must be tapered off of any corticosteroids by Day 5 of Course 1 of study drug
- Patients with up to Grade 1 neuropathy at screening were allowed on study

## Subject Demographics\*

\*N=33 subjects in updated data analysis

Median age, yrs (range)	31 (19 - 77)
Sex	20 M/13 F
Median baseline BSA	1.9 m <sup>2</sup>
Prior stem cell transplant	No 19 (58%) Yes 14 (42%)
Prior vincristine exposure	33 (100%)
ECOG performance status	0 or 1 29 (88%) 2 or 3 4 (12%)

## Adverse Events Occurring in ≥ 30% of subjects\*\*

\*\* Safety data were not available for 2 subjects

Adverse Event	Any Grade	Grade 3	Grade 4	Grade 3 / 4 Assessed Related to Marqibo
Neuropathy (all)	28 (85%)	10 (30%)	0	10 (30%)
Nausea	17 (51%)	0	0	0
Constipation	14 (42%)	1 (3%)	0	1 (3%)
Fatigue	11 (33%)	2 (6%)	0	1 (3%)
Pyrexia	11 (33%)	3 (9%)	0	0
Anemia	10 (30%)	3 (9%)	2 (6%)	3 (9%)
Febrile neutropenia	10 (30%)	8 (24%)	1 (3%)	2 (6%)

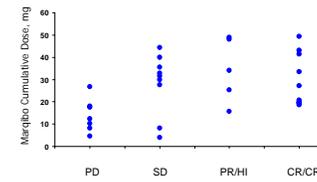
## Efficacy Results\*

\*N=31 subjects for whom response data were available as of April 3, 2009. Two patients were not assessable as they went off study prior to Cycle 1 disease evaluation

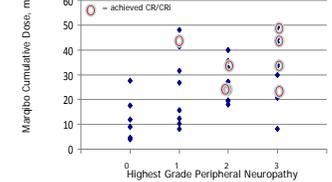
Median number of cycles received	6 (Range: 1 - 13)
Median cumulative vincristine dose received (mg)	25.2 (Range: 4.0 - 49.3)
Complete remission and complete remission with incomplete hematologic recovery (CR/CRi)	10 (30.3%)
Hematologic improvement (HI)	1 (3.0%)
Partial Remission (PR)	4 (12.1%)
Overall Response Rate (ORR)	15 (45%)
Stable Disease (SD)	9 (27.3%)
Progressive Disease (PD)	7 (21.2%)
Patients Receiving Subsequent Stem Cell Transplant	4 (12.9%)
Median CR/CRi duration (months)	3.7 (95% CI: 2.4 - 5.8)*

\*3 patients remain in remission with a short follow up to date

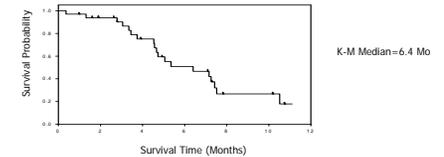
## Efficacy in the Context of Drug Exposure



## Efficacy in the Context of Safety



## Kaplan-Meier Survival Plot



## Discussion and Future Directions

- Marqibo enabled dose-intensified delivery of vincristine with a predictable safety profile
- Marqibo therapy resulted in CR/CRi in ~ 30% of this heavily pre-treated, second relapsed ALL population
- Marqibo demonstrated encouraging single-agent, anti-leukemic activity despite universal prior vincristine exposure and leukemic relapse following stem cell transplant in 42% of subjects
- Estimated median progression free survival of 4.5 months and median overall survival of 6.4 months compare favorably to historical control data

This poster can be found at <http://ir.hanabiosciences.com/presentations.cfm>