

A Phase 2 Study Of Marqibo® In Patients with Metastatic Uveal Melanoma

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Abstract*

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

Background: Pre-clinical and clinical studies showed that liposomal encapsulation of vincristine sulfate (VCR) results in increased drug circulation time and accumulation of VCR at the tumor site. Marqibo has been administered safely at 2.25 mg/m², a dose exceeding that typically employed for VCR (dose capped at 2 mg), with tolerable clinical toxicities consistent with VCR. Of the 27 previously treated patients with metastatic melanoma in the Marqibo pharmacokinetic studies, 3 patients had a tumor response, including one patient with uveal melanoma metastatic to the lung that experienced a complete response.

Methods: Patients with metastatic uveal melanoma with no more than one prior systemic therapy were enrolled. Patients with controlled brain metastases were allowed. Marqibo (2.25 mg/m² by 1-hour intravenous infusion, no dose capping) was administered every 14 days until tumor progression. Responses were assessed every 6 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST). Toxicity was assessed at least as frequently as before each dose.

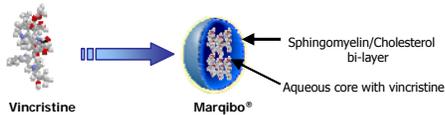
Results: Preliminary data is available for 22 enrolled patients (73% female). Median age was 65 years (range 38-79), 23% were previously treated with systemic chemotherapy, 86% had liver metastasis and 96% had M1c disease. Baseline serum LDH levels were elevated in 73% and were more than 2 x ULN in 37% of the patients. Twenty-one patients were evaluable for response; one patient discontinued the treatment after a single dose of therapy for toxicity without tumor progression. No patients died of drug toxicity while on the study. Twelve patients (57%) had stable disease. Estimated median survival is 6.4 months. Fourteen patients are alive, 2 for more than 12 months. Treatment related side effects were mostly grade 1 or 2; peripheral neuropathy was the only grade 3 toxicity, seen in 18% of the patients. The hematologic toxicities were minor; no neutropenia or thrombocytopenia was seen.

Conclusion: Marqibo is well tolerated as single agent therapy in patients with advanced stage IV uveal melanoma. Its impact on the progression-free and overall survival of these critically ill patients will be presented.

Background

Marqibo is a novel formulation of vincristine encapsulated in the aqueous interior of proprietary liposomes (OPTISOMES[®]) composed of sphingomyelin/cholesterol (55%/45%). Clinical experience from Phase 1 and 2 trials suggests that Marqibo may be administered safely at a dose of 2.25 mg/m² weekly without dose capping, exceeding the doses typically employed for conventional VCR. The toxicity profile was similar to that observed with conventional VCR. In previous Marqibo studies, 27 patients with metastatic melanoma were treated, three (3) patients had a tumor response including one (1) patient with metastatic uveal melanoma metastatic to the lung that experienced a complete response that is still maintained 48 months after discontinuation of therapy. In this study, we are evaluating the safety and efficacy of Marqibo in both newly diagnosed and previously treated patients with metastatic uveal melanoma.

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 prolonged human plasma half-life to ~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 Objectives

- Primary Objective**
- Efficacy of Marqibo as determined by the disease control rate (CR, PR or durable SD) in patients with metastatic malignant uveal melanoma
- Secondary Objectives**
- Overall response rate (CR+PR)
 - Progression-free survival
 - Overall survival
 - Safety of Marqibo in this patient population

Study Design

- Open label, multi-center, single-arm study
- Marqibo 2.25 mg/m² (with no dose cap) intravenous infusion over 1 hour once every 2 weeks (equals 1 cycle)
- Objective tumor response evaluated by MRI/CT scan using RECIST response criteria performed following every three (3) cycles of Marqibo administration (6 weeks)
- Safety assessments:
 - Neurological exam prior to each cycle
 - Weekly laboratory assessments
 - Adverse event assessment prior to each dose

Main Eligibility Criteria

- Age ≥18 years
- Must have uveal melanoma and histologic/cytologic confirmation of metastatic disease when possible
- At least one unidimensionally measurable lesion
- May be previously untreated or may have received one prior systemic chemotherapy
- Adequate liver, renal and bone marrow function
- ECOG performance status of 0-2
- Asymptomatic metastatic CNS disease allowable if clinically stable for at least six weeks prior to study entry

Patient Characteristics*

* N=30 unless otherwise stated

Median Age (years)	60 [range, 28-76]
Men/Women	7 / 23
Baseline Performance Status (n=29)	
0	17 [59%]
1	9 [31%]
2	3 [10%]
Baseline LDH Levels (n=29)	
Not Elevated	10 [34%]
1 x ULN [†]	11 [38%]
2 x ULN	4 [14%]
3 x ULN	4 [14%]

[†]Upper limit of normal

Types of Prior Therapy for Metastasis	
No Prior Chemotherapy or Radiation	19 [63%]
Chemotherapy	
Chemotherapy	9 [30%]
Radiation	1 [3%]
Chemotherapy and Radiation	1 [3%]
Site of Metastatic Disease (n=29)	
Liver	18 [62%]
Lung	2 [7%]
Liver and Lung	7 [24%]
Other	2 [7%]

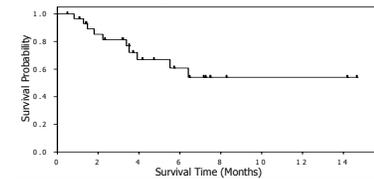
Results**

**Response data available as of April 29, 2009

Preliminary Efficacy Results (n=30)	
Median Number of Cycles Received	4 [range, 1-15]
Median Cumulative Dose Vincristine Received (mg)	17.0 [range, 4.1-51.7]
Disease Control Rate ¹	9 [30%]
Overall Response Rate ²	0
Stable Disease	15 [50%]
Progressive Disease	11 [37%]
Not Evaluable	4 [13%] ³

¹Disease Control Rate = CR+PR+durable SD (Durable SD ≥ 12wks based on patient's best documented response during the study)
²Overall Response Rate = CR+PR based on the patient's best documented response during the study
³Patients discontinued study prior to follow-up response assessment for the following: withdrew consent (n=2); adverse event (n=2)

Preliminary Kaplan-Meier Survival Plot



- 19 patients continue to be followed for survival
- 3 patients have been followed for >12 months
- 11 patients have died
- 10 due to disease progression
- 1 due to an unknown cause

Adverse Events Occurring in ≥30% of Patients***

*** N=18 patients for whom safety data are available

Term	All Grades	Grade 3	Grade 4	Grade 3/4 Assessed as Related to Marqibo
Anorexia	12 (67%)	1 (6%)	0	0
Constipation	11 (61%)	0	0	0
Dyspnea	10 (56%)	2 (11%)	0	2 (11%)
Fatigue	13 (72%)	5 (28%)	0	4 (22%)
Nausea	10 (56%)	0	0	0
Neuropathy (including peripheral, motor and sensory)	14 (78%)	4 (22%)	1 (6%)	5 (28%)
Pain	9 (50%)	1 (6%)	0	1 (6%)

Discussion

- Optisome encapsulation has the potential to preferentially deliver and facilitate vincristine accumulation in the liver
- Marqibo represents a convenient and generally well-tolerated therapy for metastatic uveal melanoma
- Achievement of stable disease in this patient population, who typically succumb to rapidly progressive disease, likely contributed to enhanced survival duration
- Weekly dosing, which is being used in the ongoing rALLY (adult ALL) trial, may provide greater efficacy than bi-weekly dosing in metastatic uveal melanoma

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