#8575

A pharmacokinetic comparison of the Marqibo® 3- and 5-vial injection kits in metastatic melanoma patients

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Updated Abstract

Introduction. In nonclinical and clinical studies, liposomal encapsulation of vincristine sulfate (VCR) increased the circulation time and accumulation of VCR at the tumor site, and improved antitumor efficacy in comparison to VCR. Marqibo® (vincristine sulfate liposomes injection) may be administered safely at doses exceeding that typically employed by VCR, with a manageable pattern of clinical toxicities consistent with VCR.

Methods. We conducted a phase 1, single-center, open-label, randomized, 2-arm crossover study designed to compare the pharmacokinetics (PK) of Marqibo utilizing the 3-vial and 5-vial kits. The 2.0 mg/m^2 dose (no dose capping) was administered by IV once every two (2) weeks in histologically confirmed, surgically nonresectable Stage III or IV metastatic melanoma patients. Patients randomized to receive the 3-vial kit at Cycle 1 were crossed over to receive the 5-vial kit at Cycle 2 or vice versa. During the third and subsequent cycles the 3-vial kit was used. Antitumor activity was assessed by CT scan every four (4) cycles. Blood samples for PK analysis were collected at pre-treatment, during infusion, end-of-infusion, and at various time points within 96 hours post end-of-infusion at Cycles 1 and 2. Total vincristine concentration and released vincristine concentration were measured using HPLC-MS/MS method.

Results. Fifteen (15) patients were enrolled and treated; eleven (11) were evaluable for the PK analysis. Median number of cycles received was four (4) (range, 1-24 cycles). The 90% CI (0.83-1.12) on the ratio of the means of the AUC_{Inf} of the 3- and 5-vial kits was within the interval of 0.80-1.25 confirming the bioequivalence of the two kits. Objective response was observed in 13% (1 CR, 1 PR) or stable disease in 20% (3 SD) as their best response. Seventy-three percent (73%) discontinued treatment due to disease progression and 13% discontinued due to adverse events. Adverse events included constipation, nausea, vomiting fatigue, pyrexia and anorexia.

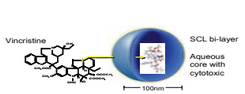
Conclusions. The 3- and 5-vial kits produced bioequivalent PK profiles. Single agent Marqibo demonstrated moderate activity in advanced Stage IV melanoma patients and was generally well tolerated with a similar adverse event profile to VCR.

Background

Marqibo is a novel formulation of vincristine encapsulated in the aqueous interior of proprietary liposomes composed of sphingomyelin-cholesterol (SCL), (OPTISOMES™). Optisomes are a new generation of nanoparticles that allow the principles of nanoparticle delivery technology to be applied to cell cycle specific drugs. The Optisomes unique (SCL) composition results in long circulation lifetimes, thereby enhancing accumulation at tumor sites and sustaining drug release at the tumor site. Optisomes represent an ideal marriage between the drugs and the nanoparticulate delivery system. Potential benefits are: 1) Increased efficacy - due to sustained release of cell cycle-specific drugs at tumor sites and higher active drug concentrations to the tumor; and 2) Increased efficacy and reduced toxicity - due to increased drug delivery to tumor sites compared to healthy tissue.

Encapsulation of vincristine protects the drug from the early phase of rapid elimination seen with conventional VCR resulting in increased circulation time and increased drug accumulating at the tumor site. In pre-clinical studies, it has been demonstrated that SCL encapsulation prolonged the plasma distribution half-life of the drug, increased the accumulation of drug at the tumor site and dramatically improved the anticancer efficacy of the drug in comparison to conventional VCR (1, 2) (Figure 1). Clinical experience from Phase 1 and 2 trials suggests that Marqibo may be administered safely at a dose of 2.0 mg/m^2, without dose capping, every two (2) weeks, exceeding the 2 mg cap typically employed for the conventional VCR. The toxicity profile in these studies was similar to that observed with conventional VCR (3). In this study, while determining the PK of Marqibo, we evaluated the safety and efficacy of this investigational agent in metastatic melanoma patients.

Figure 1. Vincristine Sulfate Injection, OPTISOMES



Characteristics of OPTISOMES (4):

- Particle diameter size of ~100 nm is small enough to escape tumor vasculature, which is somewhat "leaky," but too large to escape from blood vessel in normal tissue
- Tumor targeted therapy
- Prolonged circulation half-life
- Prolonged tumor drug exposure
- Sustained release of cycle-specific drug at tumor site

Study Objectives

Primary Objective: To compare the pharmacokinetics of Marqibo after administration of the 3-vial and 5-vial kits in patients with metastatic melanoma

Secondary Objective: To assess the safety and antitumor activity of Marqibo in this population

Study Design & Methodology

- Open label, single center, single dose level, randomized, 2-arm crossover study
- Marqibo 2.0 mg/m^2 intravenous infusion over 1 hour once every 2 weeks (equals 1 cycle). Patients were randomized to receive the 3-vial kit at Cycle 1 then the 5-vial kit at Cycle 2 or vice versa
- During the third and subsequent cycles the 3-vial kit was used
- Blood samples were collected for analysis of total and released vincristine levels at pre-treatment, during infusion, end-of-infusion, and at various timepoints within 96 hours post end-of-infusion at Cycles 1 and 2
- HPLC-MS/MS was used for determination of total and released vincristine in plasma
- Pharmacokinetic parameters were determined by WinNonLin
- Objective tumor response was evaluated by computed tomography using WHO response criteria following every four (4) cycles of Marqibo administration

5-vial Kit Components		
Components	No. of Vials/Kit	Description
Active	2	Vincristine Sulfate Injection, USP (1 mg/mL, 2 mL)
Liposomes	1	Sphingomyelin/Cholesterol Liposomes Injection (100 mg/mL, 1 mL)
Buffer	1	Sodium Phosphate Injection (14.2 mg/mL, 20 mL)
Empty Vial	1	Sterile empty vial (30 mL)
3-vial Kit Components		
Components	No. of Vials/Kit	Description
Active	1	Vincristine Sulfate Injection, USP (1 mg/mL, 5 mL)
Liposomes	1	Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL, 1 mL)
Buffer	1	Sodium Phosphate Injection (14.2 mg/mL, 25 mL)

Eligibility Criteria

- Age ≥ 18 years
- Histologically confirmed, surgically nonresectable Stage III or IV metastatic cutaneous, mucosal or choroidal melanoma
- Bidimensionally measurable disease
- Zubrod performance status of 2 or better
- Life expectancy > 8 weeks
- Adequate hematologic, renal and hepatic function
- No concurrent treatment with drugs known to inhibit or induce hepatic drug metabolism by cytochrome P450-3A4 isoenzymes and/or p-glycoprotein within one (1) week of study enrollment (prohibited until completion of Cycle 2 PK sample collection period)
- Signed informed consent

Results

Table 1. Patient Characteristics

Characteristics	n=15 (ITT)[1]
Median age (years)	57 (range, 41–80)
Men/Women	12/3
Median number of prior chemo/immunotherapy regimens	3 (range, 0-5)
Types of prior therapy (n [%])	
Chemotherapy	13 [86.7]
Immunotherapy	8 [53.3]
Radiation	9 [60.0]
Surgery	14 [93.3]
Zubrod Performance Status (n [%])	
0 / 1 / 2	8 [53.3] / 5 [33.3] / 2 [13.3]
AJCC at Baseline – Stage IV (n [%])	15 [100]

[1] ITT = Intent to treat

Figure 2. Mean Plasma Concentration of Total Vincristine Following Administration of the 3-vial or 5-vial Kit

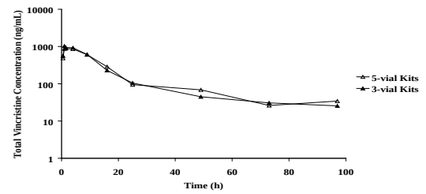


Table 2. Plasma PK Parameters of Total Vincristine for 3-vial and 5-vial Marqibo Kits

Treatment	Statistical parameter	C_{max} (ng/mL)	$T_{1/2Ke}$ (h)	$T_{1/2\lambda1}$ (h)	MRT_{Inf} (h)	AUC_{Inf} (h •ng/mL)	V_{ss} (mL)	CL (mL/h)
5-vial n=11	Mean ± SD	982 ± 244	2.6 ± 0.9	14.4 ± 7.3	12.1 ± 12.7	14557 ± 8547	3024 ± 1229	362 ± 236
	Median	922	2.6	13.9	8.1	13279	2621	301
	Range	529 - 1490	1.3 – 4.2	4.8 – 32.5	3.8 – 47.4	4333 - 31435	1740 - 5975	126 - 909
	%CV	25	35	51	105	59	41	62
3-vial n=11	Mean ± SD	1068 ± 351	2.5 ± 0.5	15.5 ± 7.9	10.1 ± 8.4	14386 ± 10855	2934 ± 1081	404 ± 233
	Median	981	2.5	13.7	7.4	12490	2658	299
	Range	661 - 1990	1.9 - 3.1	7.4 - 35.1	3.8 - 32.1	5139 - 43287	1869 - 5494	91 - 746
	%CV	33	18	51	83	75	37	58

C_{max}=Observed maximum concentration; $T_{1/2Ke}$=Initial phase half-life calculated as ln2/λ0 in biexponential profile; $T_{1/2\lambda1}$=Circulation half-life calculated as ln2/λ1; MRT_{Inf}=Mean residence time from 0 h to infinity; AUC_{Inf}=Area under the plasma concentration time curve, from 0 h to infinity; V_{ss}=Apparent volume at steady state; CL=Total clearance

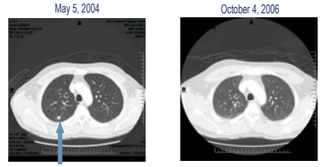
Table 3. Efficacy

Median number of cycles received was 4 (range, 1-24)

Best Response to Treatment	
Best Confirmed Response	Number (%) of patients ITT population n=15 [95% Confidence Interval][2]
Objective Response[1]	2 (13.3) [1.66, 40.46]
Complete Response	1 (6.7) [0.17, 31.95]
Partial Response	1 (6.7) [0.17, 31.95]
Stable Disease	3 (20)
Progressive Disease	9 (60)
Not evaluable	1 (6.7)

[1]The objective response rate = CR + PR based on patient's best documented response during the study
[2]The 95% confidence interval for the proportion of responders is based on the normal approximation to the binomial distribution

Figure 3. Complete Response



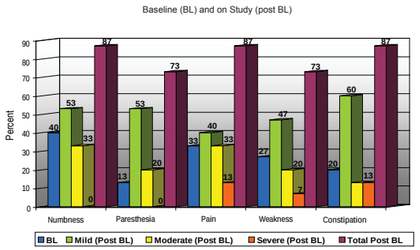
A 45 year-old man with a history of choroidal melanoma of the right eye diagnosed in 1997. Patient was treated with radioactive I-125 brachytherapy. Local recurrence in July, 2000 with a maximum tumor height of approximately 6.1 mm. On July 11, 2000 he underwent enucleation of the right eye confirmed with choroidal melanoma. The patient did well until he was found to have bilateral pulmonary metastases on February 4, 2004. On March 8, 2004, the patient was evaluated at MDACC at which time systemic treatment was recommended in view of his pulmonary disease. He was initiated on Marqibo on March 8, 2004. On August 25, 2004 a CT scan of the chest showed regression of the metastases. The CT scan on December 15, 2004 failed to show any pulmonary metastases. Patient received 24 courses of Marqibo. The treatment was discontinued on February 27, 2005, two (2) months post CR. At last follow-up date of October 4, 2006, the patient remained in CR.

Table 4. Safety

Adverse Events Reported ≥ 20% of Patients

	Number of Patients (n=15)		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Gastrointestinal Disorders			
Abdominal Pain	3 (20)	1 (7)	0 (0)
Constipation	8 (53)	4 (27)	0 (0)
Nausea	10 (67)	0 (0)	0 (0)
Vomiting	6 (40)	0 (0)	0 (0)
General Disorders & Administration Site Conditions			
Fatigue	10 (67)	0 (0)	0 (0)
Pain	5 (33)	0 (0)	0 (0)
Pyrexia	6 (40)	0 (0)	0 (0)
Metabolism & Nutritional Disorders			
Anorexia	8 (53)	0 (0)	0 (0)
Musculoskeletal & Connective Tissue Disorders			
Arthralgia	3 (20)	1 (7)	0 (0)
Back Pain	3 (20)	0 (0)	0 (0)
Myalgia	4 (27)	0 (0)	0 (0)
Nervous System Disorders			
Headache	4 (27)	0 (0)	0 (0)
Hypoesthesia	3 (20)	0 (0)	0 (0)
Psychiatric Disorders			
Insomnia	3 (20)	0 (0)	0 (0)
Respiratory, Thoracic & Mediastinal Disorders			
Cough	5 (33)	0 (0)	0 (0)
Dyspnea	3 (20)	0 (0)	0 (0)

Figure 4. Neurologic Symptoms (Sensory, Motor and Autonomic Function)



Conclusions

- The 5-vial and 3-vial kits produced similar PK profiles and were considered bioequivalent
  - Current clincial trials use 3-vial kit configuration
  - The preparation procedure for the Marqibo 3-vial kit can be reliably performed with a high degree of confidence (5), with small variations having minimal or no effect on product quality and performance
- Marqibo was generally well tolerated in metastatic melanoma patients with an adverse event profile similar to conventional vincristine
- Marqibo showed promising single agent activity against Stage IV metastatic melanoma
- Marqibo is currently being further investigated in metastatic melanoma patients in a phase 2, open-label, single center study at UTMDACC

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Acknowledgments

- Melissa Santory, Emiko Miyamoto, William Bleker and Lucy Prasad, Hana Biosciences, Inc. South San Francisco, CA
- This study was sponsored by Inex Pharmaceuticals Corporation, Vancouver, British Columbia, Canada.
- Hana Biosciences, Inc. acquired Marqibo in May 2006.
- Presented at the American Society of Clinical Oncology 2007 Annual Meeting, June 1-5, 2007, Chicago, Illinois, USA.

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