DESIGN AND INITIATION OF PIVOTAL STUDIES FOR BERUBICIN, A NOVEL, POTENT TOPOISOMERASE II POISON FOR THE TREATMENT OF RECURRENT GLIOBLASTOMA MULTIFORME (GBM)

S. Silberman[1], S. Hsu[2], Z. Muczyczenko[1], D. Picker[1], M. Sipowicz[3], E. Żak[3], A. Buczyńska[3], M. Olejniczak[3], W. Priebe[4]

[1]CNS Pharmaceuticals, Houston, TX, [2]Memorial Hermann Texas Medical Center, Houston, TX [3]WPD Pharmaceuticals, Warszawa, Poland [4]The University of Texas M. D. Anderson Cancer Center, Houston, TX

Abstract

Berubicin (WP744/RTA744) is a doxorubicin analog that crosses the blood-brain barrier (BBB), shows significant CNS uptake, and induces more DNA damage but lower lethality than doxorubicin at equivalent doses. Berubicin also prolongs the survival time of intracranial orthotopic glioma models in mice compared to temozolomide, currently the standard of care in GBM.

A Phase 1 study at MD Anderson in patients with recurrent glioma treated with escalating doses of Berubicin administered qdx3 repeated q21 days showed that it was well tolerated, with myelosuppression (neutropenia and thrombocytopenia) as the dose-limiting toxicity. Of 25 patients evaluable for efficacy, there was 1 complete response (13+ years), 1 partial response, and 10 patients with stable disease for a clinical benefit rate of 48%.

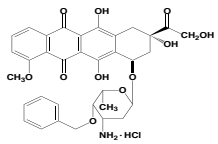
To assure a rapid and economically practicable development program, two companies have collaborated to conduct trials in the US and EU, leading to a potentially more rapid evaluation and approval of Berubicin for treating GBM in patients with limited options for this disease.

CNS Pharmaceuticals, Inc. has initiated a randomized, controlled clinical trial of Berubicin vs. Lomustine in adults with recurrent GBM. WPD Pharmaceuticals has sub-licensed Berubicin to also study recurrent GBM in adults in an open-label trial. This is a unique collaboration in which the same overall design, eligibility criteria, procedures, and database for patients receiving Berubicin are used by both companies, ensuring that there will be a more robust and substantial data set for evaluation of activity and safety. The primary endpoint of the CNS study, to be conducted in the US and Europe, is overall survival (OS). The WPD study conducted in the EU has a primary endpoint of overall response rate (ORR).

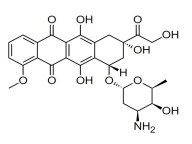
The data from these two trials are expected to provide substantial and sufficient information to support a potential registration program in both the US and EU for the treatment of patients with glioblastoma.

Educational Objectives

1. Acquire information about the first effective anthracycline that crosses the BBB with efficacy in glioblastoma
2. Understand the value of biopharmaceutical companies' use of global cooperation and collaboration in coordinating and performing potentially pivotal clinical trials with promising new drugs for unmet medical needs



Berubicin



Doxorubicin

Berubicin is more potent than Doxorubicin in Solid Tumors and Lymphomas

Cell Line	Tumor Type	Berubicin IC_{50} (nM)	Doxorubicin IC_{50} (nM)	Ratio
MCF-7	Breast	0.72	4.02	5.6
NCI-H522	Lung	3.40	8.32	2.4
A549	Lung	1.07	4.68	4.4
SW480	Colon	2.99	8.26	2.8
HT-29	Colon	3.66	23.40	6.4
AsPC-1	Pancreas	5.62	80.50	14.3
BxPC-3	Pancreas	4.05	15.70	3.9
Capan-1	Pancreas	5.30	30.75	5.8
OVCAR-3	Ovarian	5.31	11.53	2.2

Cell line	Tumor Type	Berubicin IC_{50} (nM)	Doxorubicin IC_{50} (nM)	Ratio
Toledo	B cell lymphoma	3.1	24.5	7.9
HD4	Hodgkin's B cell lymphoma	4.0	43.0	10.7
HD2	Hodgkin's T cell lymphoma	5.2	53.0	10.1
HH	Cutaneous T cell lymphoma	11.6	57.4	4.9
MJ	Cutaneous T cell lymphoma	10.0	40.0	4.0
Daudi	Burkitt lymphoma	3.4	12.2	3.6

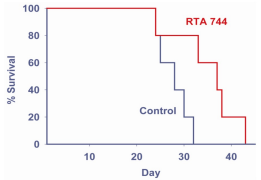
Comparison of IC_{50} values for Berubicin and doxorubicin (Ratio = Dox/Berubicin)

Berubicin is more potent than Doxorubicin in Primary CNS Tumor Cell Lines

Cell Line	Tumor Type	Berubicin (nM)	Doxorubicin (nM)	Ratio
D556	Human Medulloblastoma	5.1	36.0	7.0
DAOY-WT	Human Medulloblastoma	13.0	47.0	3.6
GL261	Murine Glioma	11.5	46.2	4.0
U-251	Glioblastoma	4.7	62.3	13.3
U-87	Glioblastoma	50.3	163.8	3.3
BT-58	Ependymoma	36.5	124.0	3.4

Comparison of IC_{50} values for Berubicin and doxorubicin

Berubicin Increases Survival in U-87 Mouse Orthotopic Glioma Model



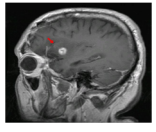
U-87 MG (human glioblastoma) cells implanted into the right hemisphere of the brain in *nu/nu* mice. Day 1 and Day 10. 10 mg/kg berubicin or vehicle were delivered by i.p. injection.

Phase 1 Clinical Trial

Thirty-five patients with recurrent or refractory GBM or other primary brain cancers received IV Berubicin over 2 hours for 3 consecutive days (one cycle) every 21 days. Doses were escalated using an accelerated titration design and ranged from 1.2 to 9.6 mg/m^2/day.

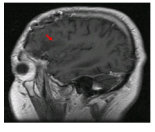
The most common dose limiting toxicity (DLT) was myelosuppression, specifically neutropenia. Minimal nonhematological toxicities were observed, no neurotoxicity or cardiotoxicity was noted. The maximum tolerated dose (MTD) of Berubicin was determined to be 7.5 mg/m^2/day.

Of 25 patients evaluable for efficacy, one patient demonstrated a Complete Response (CR) and is in remission >13 years; 2 patients had partial/minor responses; 9 patients had stable disease; with an overall 48% clinical benefit rate.



Baseline

- MRI scan of GBM (confirmed) patient at baseline, then after 7 cycles of Berubicin
- The patient had a complete response (CR) to treatment with Berubicin
- The patient remains in remission 13 years later despite no additional therapy



After 7 Cycles

Design of Clinical Trials for Pivotal Studies of Berubicin in GBM

	CNS-201	WPD-201
Protocol Title	Multicenter, Open-Label Study with a Randomized Control Arm of the Efficacy, Safety, and Pharmacokinetics of Intravenously Infused Berubicin in Adult Patients with Recurrent Glioblastoma Multiforme (WHO Grade IV) After Failure of Standard First Line Therapy	Multicenter, Open-Label Study of the Efficacy, Safety, and Pharmacokinetics of Intravenously Infused Berubicin in Adult Patients with Recurrent Glioblastoma Multiforme (WHO Grade IV) After Failure of Standard First Line Therapy
Indication	Recurrent Glioblastoma Multiforme (GBM) after failure of first line therapy	
Primary Objective	To assess the effect of Berubicin compared with Lomustine on overall survival (OS) in adult patients with GBM (WHO Grade IV) after standard initial therapy	To confirm efficacy of Berubicin treatment on objective response rate (ORR) per modified Response Assessment in Neuro-Oncology (mRANO) criteria in patients with GBM (WHO Grade IV) that has recurred after standard initial therapy, based on Simon's 2-stage design
Primary Endpoint	Overall Survival	Overall Response Rate
Number of Patients	210 2:1 randomization (Berubicin:Lomustine)	Up to 61
Interim Analysis	Comparative interim analysis: ~ 30 % of all patients at 6 months for futility	2-stage design: 18 patients @ 6-month time point evaluated for safety, efficacy and pharmacokinetics
Berubicin Administration	7.5 mg/m^2 as a 2-hr infusion Days 1-3 every 21 days	
MRI scans	Every 6 weeks	
Vendors	Same Drug supply, CRO, Database, and Imaging Company for Central Read	
Eligibility Criteria	Only one prior therapy for disease with documented recurrence; no prior lomustine; stratified by MGMT status	Any number of prior therapies after documented recurrence of disease
Countries	US, France, Germany, Italy, Spain, Switzerland	Poland, Czech Republic

Advantage of Conducting Clinical Trials with Corporate Collaboration

1. Generates additional data about Berubicin in a larger number of patients simultaneously
2. Has the potential to use these trials as pivotal for registration based on an overall survival endpoint in a randomized, controlled trial (CNS) with substantial supportive data of the same patient population (WPD)
3. Could encourage Biopharmaceutical companies to use global cooperation and collaboration to harmonize studies for promising new drugs in an orphan designation with unmet medical needs