A RANDOMIZED, CONTROLLED TRIAL OF BERUBICIN, A NOVEL TOPOISOMERASE II INHIBITOR, AFTER FIRST-LINE THERAPY FOR GLIOBLASTOMA MULTIFORME (GBM): PRELIMINARY RESULTS

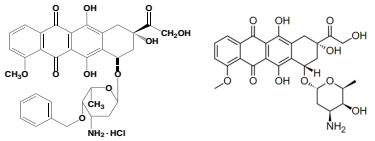
S. Silberman[1], S. Hsu[2], Z. Muzyczenko[1], D. Picker[1], S. Bisdas[3], O. Kubassova[4], J. O'Lynn[4], W. Priebe[5]

[1]CNS Pharmaceuticals, Houston, TX, [2]Memorial Hermann Texas Medical Center, Houston, TX, [3]UCL Hospitals NHS Trust, London, UK, [4] IAG, Image Analysis Group, London, UK, [5] MD Anderson Cancer Center, Houston, TX

Abstract # 383142

Abstract

Berubicin is a doxorubicin (Dox) analog with significant central nervous system (CNS) uptake. Berubicin prolongs survival in orthotopic mouse intracranial models with greater infiltration of the tumor compared to normal tissue.



Berubicin

Doxorubicin

A Phase 1 dose-escalation enrolled thirty-five patients with recurrent or refractory GBM or other primary brain cancers to receive 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, more specifically neutropenia. Minimal nonhematological toxicities were observed, no neurotoxicity or cardiotoxicity was noted. The maximum tolerated dose (MTD) was 7.5 mg/m^2/day.

Of 25 patients evaluable for efficacy, one patient demonstrated a Complete Response (CR) and is in remission >15 years; 2 patients had partial/minor responses; 9 patients had stable disease leading to an overall 48% clinical benefit rate.

Multicenter, Open-Label Study with a Randomized Control Arm of the Efficacy, Safety, and Pharmacokinetics of Intravenously Infused Berubicin in Adult Patients with Recurrent GBM (WHO Grade IV) After Failure of Standard First Line Therapy

A trial of Berubicin vs Lomustine in patients with recurrent GBM (IDH WT) after first-line therapy in the US and EU is enrolling patients in a 2:1 randomization design of Berubicin:Lomustine. Patients will be stratified by MGMT methylation status. The primary objective is to assess the effect of Berubicin compared with Lomustine on the primary endpoint of overall survival (OS) in adult patients with GBM after standard initial therapy. An interim futility analysis to explore the relative efficacy between these drugs will be conducted after up to half of the patients have reached 6 months of therapy.

As of the data cutoff of 17October2022, 49 patients have been enrolled; 35 on Berubicin and 14 on Lomustine.

Patient Demographics*

Parameter	Berubicin n=35	Lomustine n=14	Total n=49
Age (years) Mean (SD)	52.9 (15.0)	56.5 (10.3)	54.0 (13.8)
Gender (M/F) n(%)	23 (65.7)/12 (34.3)	9 (64.3)/5 (35.7)	32 (65.3)/17 (34.7)
Race^ (White/Black/Asian) n%	31 (89)/3 (.09)/1 (.03)	10 (71)/1 (.07)/2 (.14)	41 (84)/4 (.08)/3 (.06)
BSA (m^2) Mean (SD)	2.0 (0.23)	1.98 (0.27)	2.0 (0.24)
MGMT Methylation * n (%)	13 (37.1)	6 (42.9)	19 (38.8)
Baseline KPS Mean (SD)	85.3 (9.6)	83.6 (7.5)	84.8 (9.0)

* Data cutoff date 17October2022
^ No other Races were reported at this time

Patient Disposition

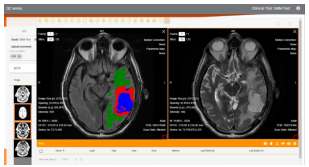
Parameter	Berubicin n=35	Lomustine n=14	Total n=49
Currently on study n (%)	7 (20.0)	3 (21.4)	10 (20.4)
Withdrew from study n (%)	16 (45.7)	8 (57.1)	24 (49.0)
Primary Reason for Withdrawal			
Adverse Event	1 (2.9)	0	1 (2.0)
Physician Decision	3 (8.6)	2 (14.3)	5 (10.2)
Withdrawal by Patient	4 (11.4)	2 (14.3)	6 (12.2)
Other	8 (22.9)	4 (28.6)	12 (24.5)

Adverse Events (≥ 5%)

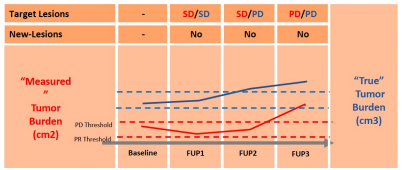
Parameter	Berubicin n=35		Lomustine n=14		Total n=49	
	All Grades	Grades 3-5	All Grades	Grades 3-5	All Grades	Grades 3-5
Anemia n (%)	4 (11.4)	1 (2.9)	1 (7.1)	0	5 (10.2)	1 (2.0)
Constipation n (%)	3 (8.6)	0	2 (14.3)	0	5 (10.2)	0
Fatigue n (%)	13 (37.1)	0	6 (42.9)	0	19 (38.8)	0
Hyperglycemia	4 (11.4)	0	1 (7.1)	0	5 (10.2)	0
Neutrophil count decrease	9 (25.7)	4 (11.4)	3 (21.4)	1 (7.1)	12 (24.5)	5 (10.2)
Seizure	3 (8.6)	1 (2.9)	4 (28.6)	2 (14.3)	7 (14.3)	3 (6.1)
WBC count decrease	5 (14.3)	4 (11.4)	3 (21.4)	2 (14.3)	8 (16.3)	6 (12.2)

Advanced Imaging Assessments

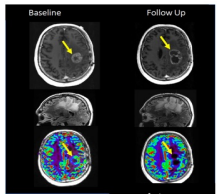
VOLUMETRIC ASSESSMENT

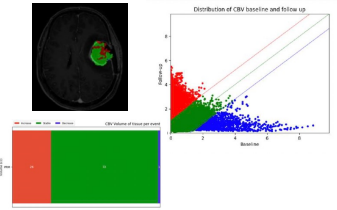


RANO vs. VOLUMETRIC ASSESSMENT



LOW PERFUSION SUGGESTS PSEUDOPROGRESSION





Decreased CBV: Blue
Stable CBV: Green
Increased CBV : Red
Parametric response mapping of CBV

Preliminary Results:

At present patients show comparable demographics, with age, gender, race, BSA and KPS reasonably balanced. In addition, the unmethylated MGMT population is approximately 40% in both arms. The percentage of patients that are currently continuing on study or having withdrawn is also comparable between arms.

All grades of adverse events occurring in more than 5% of patients, as well as Grade 3-5 events, were also similar in the Berubicin and Lomustine arms.

Use of advanced imaging technology will provide additional insights into the treatment effects of this novel anthracycline with activity against tumors in the brain, both preclinically and clinically.

Although this data is early. we are continuing our evaluation of safety and will provide an assessment of efficacy at an interim analysis of overall survival between these treatment arms when 30-50% of patients have been on the study for at least 6 months. The ultimate outcome of this trial is to potentially provide therapeutic options for patients after first-line therapy.

Information provided is preliminary and has not been validated or certified