A RANDOMIZED, CONTROLLED TRIAL OF BERUBICIN VS. LOMUSTINE AFTER FIRST-LINE THERAPY FOR GLIOBLASTOMA MULTIFORME (GBM): INTERIM RESULTS

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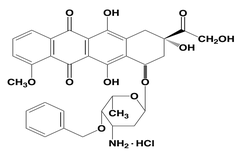
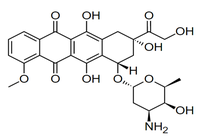
Abstract

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

***Phase 1 Trial*:**
Dose-escalation in 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 and ranged from 1.2 to 9.6 mg/m²/day. The most common dose-limiting toxicity (DLT) was myelosuppression, Minimal nonhematological toxicities were observed, and no neurotoxicity or cardiotoxicity was noted. The maximum tolerated dose (MTD) was 7.5 mg/m²/day. Of 25 patients evaluable for efficacy, there was one Complete Response (15+ years); 2 patients had partial/minor responses; 9 patients had stable disease. The overall clinical benefit rate was 48%.

A 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

Current Trial:
Berubicin vs Lomustine in patients with recurrent GBM (IDH WT) after first-line therapy (US + EU) in a 2:1 randomization design of Berubicin:Lomustine and patients stratified by MGMT methylation status. The primary objective is the overall survival of Berubicin compared with Lomustine in adult patients with GBM after failure of standard initial therapy. An interim futility analysis is planned to explore the relative efficacy of Berubicin compared to Lomustine, data that will include progression-free and overall survival. This is to take place after 44 events (deaths) have occurred in the patient population, evaluated by an independent Data Safety Monitoring Board (DSMB), which will recommend continuing the study if Berubicin is considered non-inferior to Lomustine based on these parameters. As of the data cutoff of 08 September 2023, 196 patients have been randomized; 133 on Berubicin and 63 on Lomustine. Target enrollment of patients in the per-protocol population (having received at least one dose of study drug) is 210 patients. Data presented here show the comparability of the two arms of the study, as well as the safety demonstrated by these therapeutic modalities for the treatment of recurrent GBM.

Patient Demographics

Parameter	Berubicin (n=133)	Lomustine (n=63)	Overall (n=196)
Age (years) Mean (SD)	56.7 (12.48)	58.9(10.18)	57.4(11.81)
Male n (%)	88 (66.2)	46 (73.0)	134 (68.4)
Female n (%)	45 (33.8)	17 (27.0)	62 (31.6)
Race n (%)			
Hispanic or Latino	7 (5.3)	4 (6.3)	11 (5.6)
White	105 (78.9)	49 (77.8)	154 (78.6)
Black or African American	3 (2.3)	1 (1.6)	4 (2.0)
Asian	5 (3.8)	2 (3.2)	7 (3.6)
Native Hawaiian or Pacific Islander	1 (0.8)	0	1 (0.5)
Not Reported	14 (10.5)	5 (7.9)	19 (9.7)
Unknown	4 (3.0)	6 (9.5)	10 (5.1)
BSA (m²) Mean (SD)	1.98 (0.23)	1.98 (0.25)	1.98 (0.24)
MGMT methylation n (%)	54 (40.6)	24 (38.1)	78 (39.8)
Baseline KPS Mean (SD)	85.6 (9.98)	83.8 (9.41)	85.0 (9.81)

Patient Disposition

Parameter	Berubicin (n=133)	Lomustine (n=63)	Overall (n=196)
Completed Study n (%)	76 (57.1)	32 (50.8)	108 (55.1)
On-going on study n (%)	46 (34.6)	24 (38.1)	70 (35.7)
Withdrew from the study n (%)	11 (8.3)	7 (11.1)	18 (9.2)
Primary Reason for Withdrawing n (%)			
Adverse Event	3 (2.3)	2 (3.2)	5 (2.6)
Physician Decision	1 (0.8)	0	1 (0.5)
Withdrawal by Patient	5 (3.8)	5 (7.9)	10 (5.1)
Death	2 (1.5)	0	2 (1.0)

Adverse Events (Treatment-Related and/or ≥ 10%)

Preferred Term	Number (%) of Subjects Reporting					
	Berubicin (n=133)		Lomustine (n=63)		Overall (n=196)	
	All Grades	Grades 3-5	All Grades	Grades 3-5	All Grades	Grades 3-5
Any Reported^	93 (69.9)	30 (22.6)	34 (54.0)	14 (22.2)	127 (64.8)	44 (22.4)
Anaemia	13 (9.8)	2 (1.5)	4 (6.3)	0	17 (8.7)	2 (1.0)
Asthenia	12 (9.0)	1 (0.8)	4 (6.3)	0	16 (8.2)	1 (0.5)
Fatigue	30 (22.6)	0	9 (14.3)	0	39 (19.9)	0
Febrile neutropenia	1 (0.8)	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Headache	11 (8.3)	3 (2.3)	1 (1.6)	0	12 (6.1)	3 (1.5)
Leukopenia	3 (2.3)	1 (0.8)	1 (1.6)	0	4 (2.0)	1 (0.5)
Lymphopenia/Lymphocyte count decreased*	18 (13.5)	8 (6.0)	8 (12.7)	5 (7.9)	26 (13.2)	13 (6.6)
Nausea	24 (18.0)	1 (0.8)	13 (20.6)	0	37 (18.9)	1 (0.5)
Neutropenia/Neutrophil count decreased*	31 (23.3)	14 (10.5)	10 (15.9)	5 (7.9)	41 (20.9)	19 (9.7)
Seizure	4 (3.0)	2 (1.5)	0	0	4 (2.0)	2 (1.0)
Thrombocytopenia/Platelet count decreased*	4 (3.0)	1 (0.8)	18 (28.6)	6 (9.5)	22 (11.2)	7 (3.6)
Tumour haemorrhage	1 (0.8)	0	0	0	1 (0.5)	0
Vomiting/Vomit	5 (3.8)	0	3 (4.8)	0	8 (4.1)	0
White blood cell count decreased	14 (10.5)	8 (6.0)	8 (12.7)	3 (4.8)	22 (11.2)	11 (5.6)

^ this includes adverse events not delineated in this chart
**these include verbatim terms and composite values for similar preferred terms*

Updated Results:

All patients enrolled show comparable demographics between each arm, including age, gender, race, BSA, and KPS. In addition, patients with unmethylated MGMT comprise approximately 40% of each arm, allowing for comparison irrespective of the molecular profile that might influence the efficacy of the therapy administered. Although there are a higher number of patients who withdrew from the Lomustine arm during the study there are too few patients to make any definitive conclusions about whether this will affect the outcome.

All reported adverse events for both arms are shown for all grades and grades 3-5. These were similar, including the more severe events in the higher grades. The adverse events occurring in more than 10% of patients and/or that were considered treatment-related, are shown for all grades as well as grades 3-5, and overall were relatively similar in the Berubicin and Lomustine arms. In terms of myelosuppression (lymphocyte, neutrophil/white blood cell count or red blood cell [anemia] reductions), there is no significant difference between the therapeutic arms, although thrombocytopenia (platelet count decrease) appears to be slightly greater with Lomustine for both all grades of severity as well as grades 3-5.

We will be evaluating efficacy, including overall survival, in an interim analysis and will use a futility score to ensure that Berubicin is at least as effective as Lomustine to be able to continue enrolling patients in this study. The ultimate outcome of this trial is to potentially provide a safe and effective therapeutic option for patients after first-line therapy for high grade glioma (GBM).

Information provided is preliminary and has not been validated or certified