UPDATE ON A POTENTIALLY PIVOTAL TRIAL CNS-201: A RANDOMIZED, CONTROLLED TRIAL OF BERUBICIN VS. LOMUSTINE AFTER FIRST-LINE THERAPY FOR GLIOBLASTOMA MULTIFORME (GBM)

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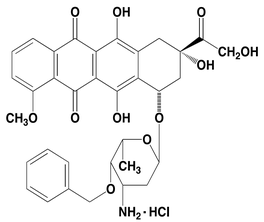
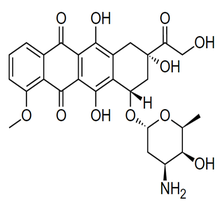
Abstract

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

Berubicin, derived from doxorubicin (Dox), appears to cross the BBB and has shown significant central nervous system (CNS) uptake and anti-tumor activity. A current, potentially pivotal trial for patients with recurrent GBM after first-line therapy has completed enrollment in the US and Europe: a total of 252 patients were randomized 2:1 (Berubicin:Lomustine) after failure of prior therapy. All patients had to have certification of progression by a central reader, were Grade 4 IDH WT, and were stratified by MGMT methylation status. The primary endpoint, overall survival (OS), is maturing in this blinded trial; however, data was compiled documenting the demographics of the Berubicin and Lomustine arms, allowing for a comparison of several parameters of this study.

Recently, a pre-planned non-binding futility analysis of the primary endpoint, OS, was evaluated when the trial reached ~30% of expected events (44 deaths). This interim analysis was performed by an independent biostatistician under the supervision of the Data Safety Monitoring Board (DSMB), which comprised two oncologists and the biostatistician. The DSMB's charter mandated that they review the primary endpoint, OS, as well as secondary endpoints and safety data to determine whether the risk-benefit profile warranted modification or discontinuation of the study. The DSMB recommended that the study continue as planned, with no modifications required, having met a pre-determined conditional endpoint. After the results of this interim analysis, CNS Pharmaceuticals continued the study and has now completed enrollment with 252 patients, having 239 evaluable for the current presentation.

The data herein include comparative demographics, disposition, and safety, showing a balance between the randomized arms. We also provide our recommendations and highlight our further drug development of Berubicin as a therapeutic option for patients with recurrent GBM and both primary and metastatic CNS malignancies.

Patient Demographics

Parameter	Berubicin[1] n=163	Lomustine[1] n=76	Overall[1] n=239
Age (years) Mean (SD)	56.9 (12.0)	58.8 (9.8)	57.5 (11.4)
Male n (%)	112 (68.7)	57 (75.0)	169 (70.7)
Female n (%)	51 (31.3)	19 (25.0)	70 (29.3)
Race n (%)			
White	128 (78.5)	58 (76.3)	186 (77.8)
Black or African American	4 (2.5)	1 (1.3)	5 (2.1)
Asian	6 (3.7)	2 (2.6)	8 (3.3)
Pacific Islander	1 (0.6)	0	1 (0.4)
Not Reported	20 (12.3)	9 (11.8)	29 (12.1)
Unknown	4 (2.5)	6 (7.9)	10 (4.2)
BSA (m^2) Mean (SD)	1.98 (0.23)	1.96 (0.23)	1.97 (0.23)
MGMT methylation n (%)	65 (39.9)	30 (39.5)	95 (39.7)
Baseline KPS Mean (SD)	85.3 (9.9)	83.6 (9.2)	84.7 (9.7)

Patient Disposition

Parameter	Berubicin[1] n=163	Lomustine[1] n=76	Overall n=239
Completed Study n (%)	138 (84.7)	60 (78.9)	198 (82.8)
Continuing on study n (%)	7 (4.3)	1 (1.3)	8 (3.3)
Withdrew from the study n (%)	18 (11.0)	15 (19.7)	33 (13.8)
Primary Reason for Withdrawing n (%)			
Adverse Event	5 (3.1)	2 (2.6)	7 (2.9)
Physician Decision	2 (1.2)	1 (1.3)	3 (1.3)
Withdrawal by Patient	8 (4.9)	7 (9.2)	15 (6.3)
Death	2 (1.2)	4 (5.3)	6 (2.5)
Other	1 (0.6)	1 (1.3)	2 (0.8)

Adverse Events (≥ 10%)

Preferred Term	Berubicin[1] n=163		Lomustine[1] n=76		Overall[1] n=239	
	All Grades	Grades 3-5	All Grades	Grades 3-5	All Grades	Grades 3-5
Any Reported	132 (81.0)	55 (33.7)	57 (75.0)	25 (32.9)	189 (79.1)	80 (33.5)
Anaemia	19 (11.7)	5 (3.1)	5 (6.6)	0	24 (10.0)	5 (2.1)
Asthenia	20 (12.3)	3 (1.8)	9 (11.8)	0	29 (12.1)	3 (1.3)
Diarrhea	7 (4.3)	0	3 (3.9)	0	10 (4.2)	0
Fatigue	40 (24.5)	1 (0.6)	11 (14.5)	0	51 (21.3)	1 (0.4)
Headache	15 (9.2)	3 (1.8)	2 (2.6)	0	17 (7.1)	3 (1.3)
Lymphocyte count decreased	18 (11.0)	10 (6.1)	10 (13.2)	6 (7.9)	28 (11.7)	16 (6.7)
Nausea	27 (16.6)	0	16 (21.1)	0	43 (18.0)	0
Neutrophil count decreased	29 (17.8)	16 (9.8)	9 (11.8)	5 (6.6)	38 (15.9)	21 (8.8)
Platelet count decreased	9 (5.5)	1 (0.6)	21 (27.6)	9 (11.8)	30 (12.6)	10 (4.2)
Seizure	18 (11.0)	9 (5.5)	11 (14.5)	6 (7.9)	29 (12.1)	15 (6.3)
Thrombocytopenia	5 (3.1)	2 (1.2)	15 (19.7)	4 (5.3)	20 (8.4)	6 (2.5)
White blood cell count decreased	20 (12.3)	10 (6.1)	12 (15.8)	4 (5.3)	32 (13.4)	14 (5.9)

Updated Results:

All patients enrolled show comparable demographics within each arm, including age, gender, race, BSA, and KPS. In addition, patients with unmethylated MGMT are approximately 39%, allowing for a reasonable comparison of efficacy irrespective of the arm of the study based on methylation status.

There is a slightly greater percentage of patients on the Berubicin arm that have completed the study, and a greater percentage of patients on the Lomustine arm that have withdrawn from the study, with patients on the Lomustine arm having withdrawn mostly due to patient preference and death.

All grades of any reported adverse events and those of Grade 3-5 in severity occurring in more than 10% of patients are shown to be relatively similar in the Berubicin and Lomustine arms. A slightly greater percentage of patients with all grades or Grades 3-5 with anaemia, headache, and decrease in neutrophil counts were shown in patients receiving Berubicin, while a significantly greater percentage of patients with a decrease in platelet counts and thrombocytopenia occurred in patients receiving Lomustine.

Although we have completed enrollment, we are following patients for the primary endpoint of overall survival between these treatment arms. The outcome of this trial is to potentially provide therapeutic options for patients after first-line therapy for GBM.

CNS would like to thank our investigators and their patients from the US, France, Italy, Spain, and Switzerland for their incredible efforts in the execution of this study.
The information provided is preliminary and has not been validated or certified for accuracy.