

**MIYATAKE-1: Accelerator-based BNCT in rescue treatment of patients with recurrent GBM:
a multicenter phase II study**

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Background: Boron neutron capture therapy (BNCT) is tumor-selective particle radiation and theoretically efficacious especially for tumors with infiltrative nature, such as malignant gliomas, chiefly glioblastoma (GBM). The aim of this study is to assess safety and efficacy of accelerator-based BNCT (AB-BNCT) using cyclotron-based neutron generator, BNCT30, and ^{10}B -boronophenylalanine (borofalan(^{10}B)) agent, SPM-011, in patients with recurrent malignant gliomas, chiefly GBM.

Methods: The multi-institutional open-label, phase II clinical trial for recurrent 27 cases of malignant gliomas (MG) (24 cases were GBM) was conducted with above mentioned AB-BNCT system, using 500mg/kg of SPM-011. The study code of this trial is JG002. The patients were enrolled from February 2016 to June 2018. The inclusion criteria are bevacizumab-naïve MG, recurrent after standard treatment composed of X-ray treatment (50-65 Gy) and chemotherapy with temozolomide. Aged more than 20 years old and less than 75 years old, KPS should be more than 60%. SPM-011 was administrated 500mg/kg in 3 hours intravenously, 200 mg/kg an hour for 2 hours prior to neutron irradiation and 100mg/kg an hour during neutron irradiation. Neutronirradiation time were determined not to exceed to 8.5 Gy-Eq for scalp dose which was decided by preceding phase I trial. Primary endpoint was 1-year survival rate and secondary ones were median overall survival (mOS), median progression free survival (mPFS) and treatment-related adverse events. The results were compared to previous Japanese domestic bevacizumab trial for recurrent GBM (Study code: JO22506) which had the similar inclusion criteria with JG002.

Results: 1-year survival rate and mOS of recurrent GBM cases in JG002 was 79.2% (95% CI:57.0-90.8) and 18.7 months (95% CI:12.9-23.4) (data cutoff = 20 Jun 2019) respectively, while those of JO22506 was 34.5% (90% CI:20.0-49.0) and 10.5 months (95% CI:8.2-12.4), respectively. Median PFS of JG002 and JO22506 were 0.9 and 3.3 months, respectively. Most important adverse event in JG002 was brain edema. 21 out of 27 cases were treated with bevacizumab after progress disease.

Conclusions: AB-BNCT demonstrated acceptable safety and prolonged survival for recurrent MG chiefly GBM. Many cases showed brain swelling during the observation period after AB-BNCT. This seemed to be the reason of relatively short PFS instead of prolonged OS in this study, However brain swelling might be the unavoidable adverse event of re-irradiation for recurrent MG. This drawback seemed to be controlled well with bevacizumab, anti-angiogenic agent, approved for the treatment of malignant gliomas in Japan. On the other hand, bevacizumab alone is known to have no potency for survival prolongation not only for newly diagnosed but also recurrent GBM. Thus AB-BNCT seems to be potent treatment modality for recurrent malignant gliomas chiefly GBM. Now the combination of AB-BNCT system and SPM-011 is processing of application for new medical device and drug approval for recurrent malignant gliomas in Japan.