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# Boron neutron capture therapy (BNCT) phase I clinical trial for newly diagnosed glioblastoma by newly developed accelerator at University of Tsukuba

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ABSTRACT

*Background:* Glioblastoma is unresectable and difficult to cure using surgery and chemoradiotherapy. New treatment strategies are needed, and our TB-GB-01 study aims to evaluate whether the combination of BNCT, external beam radiation, and temozolomide is a safe treatment for patients with newly diagnosed glioblastoma.
*Methods:* This is an interventional, open-label, non-randomized, single-center, single-arm, phase I physician-initiated trial designed and conducted by the University of Tsukuba. Eligible patients diagnosed with glioblastoma and selected according to inclusion and exclusion criteria will receive a combination of BNCT, external beam radiation, and temozolomide. Treatment includes BNCT, external-beam radiation (total dose 40 Gy, 20 cycles over 4 weeks), and chemotherapy (temozolomide in combination with x-ray therapy period, 75 mg/m$^2$/day). The first 3 patients will receive a BNCT normal brain maximum dose of 7 Gy at D2cc (mL) and will be moved to the next dose after adverse events are verified by the Safety monitoring committee and safety is ensured. The primary endpoint is the incidence of dose-limiting toxicities (DLT), and secondary endpoints include adverse event rates, treatment completion rate, response rate, progression-free survival, and overall survival. The target sample size is 12–18 patients.
*Discussion:* Study TB-GB-01 is the first trial to evaluate the safety of the combination of BNCT, external beam X-rays, and temozolomide for newly diagnosed glioblastoma at an accelerator neutron source.
*Ethics and dissemination:* This protocol was approved by the Institutional Review Board of Clinical Trials & Research Network, IBARAKI. Results will be presented at international meetings and published in peer-reviewed journals.

## 1. Introduction

Glioblastoma remains refractory. With the introduction of the concept of multimodality therapy, the combination of postoperative X-irradiation and temozolomide has become the standard of care, but cure is extremely rare, although survival has been slightly prolonged (Stupp

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et al., 2005). Despite advances in pathologic molecular diagnostics and various therapeutic approaches, no definitive new treatment has been found to date that is likely to be curative, as in other malignancies (Salvalaggio et al., 2024). BNCT has long been investigated for its efficacy in glioblastoma, but only in a small number of cases using reactor BNCT (Yamamoto et al., 2008; 2009 (Barth et al., 2005)Nakai et al., 2014). Since it is not practical to build a new nuclear reactor in a hospital, it was considered impossible to generalize BNCT as a medical device that can be reimbursed by insurance.

In the early 2010s, they succeeded in developing an accelerator-based neutron source that does not require a nuclear reactor and first conducted clinical trials in Japan ahead of the entire world using a cyclotron-based neutron source [Kanno et al., 2021]. As a result, national insurance started to cover the treatment of recurrent head and neck cancer in 2020 [Hirose et al., 2021]. Currently, BNCT is performed for recurrent or inoperable head and neck cancer as national insurance at two institutions in Japan[Sato M, 2024, Hirose and Sato, 2024]. These studies provided valuable insights into the early integration of BNCT into routine clinical practice, highlighting its efficacy and safety. Furthermore, several models of accelerator-based BNCT are under development, mainly in Asia, and clinical trials are underway or planning. At the National Cancer Center of Japan, a lithium-targeted accelerator-based neutron source is undergoing a phase 2 trial for skin cancer (angiosarcoma)[Igaki et al., 2022], and the same type of equipment has been used in a clinical study for breast cancer chest wall recurrence [Kurosaki et al., 2024]. A cyclotron-based neutron source has already been enrolled in a BNCT trial for recurrent glioblastoma and recurrent malignant meningiomas. [Miyatake et al., 2020, (Kawabata et al., 2021)]. The 1-year survival rate and median OS of the recurrent glioblastoma cases in this trial were 79.2 % and 18.9 months, respectively, the median PFS was 0.9 months. Clinical reports on accelerator BNCT to date have generally shown no safety issues, and further expansion of the indications for use of accelerator BNCT is desired[Matsumura et al., 2023].

We report that we have initiated an investigator-initiated clinical trial for newly diagnosed glioblastoma patients using our newly developed linear accelerator and beryllium-targeted neutron source, an associated treatment planning system, and a patient positioning system. [H. Kumada, K. Takata, 2021, H. Kumada, K. Takata, 2020]. These are clinical studies that have previously existed BNCT using nuclear reactors but have not been investigated in accelerators based BNCT. In addition, this protocol is a combination of X-rays and temozolomide, and is designed to allow comparison with standard treatment for glioblastoma. If its efficacy is proven after safety evaluation, it may be proposed as a new treatment protocol.

## 2. Materials and methods

This study is an interventional, open-label, non-randomized, single-center, single-arm Phase I clinical trial. It is investigator-initiated clinical trials conducted at the University of Tsukuba hospital. This research was supported by the Japan Agency for Medical Research and development (AMED) under Grant Number JP22ym0126086. Eligible patients diagnosed with newly diagnosed glioblastoma and selected according to the inclusion and exclusion criteria described below will receive BNCT and following X-ray and temozolomide.

### 2.1. Objectives and endpoints

#### 2.1.1. Objectives

The purpose of this study is to evaluate the safety and tolerability of boron neutron capture therapy (BNCT) in combination with sequential standard of care external beam radiation and temozolomide.

#### 2.1.2. Endpoints

The primary endpoint is the occurrence of dose-limiting toxicities (DLT) from BNCT to 91days (D91, safety evaluation period). Secondary endpoints are as follows.

1) Safety and tolerability from BNCT to day 7 (W1) (adverse events, serious adverse events, death, discontinuation due to adverse events)
2) Safety and tolerability from BNCT to 91days (safety evaluation period) (adverse events, serious adverse events, death, discontinuation due to adverse events)
3) Safety and tolerability (adverse events, serious adverse events, death, discontinuation due to adverse events) from BNCT to maximum 2years (efficacy evaluation period),
4) Measurements of clinical laboratory tests
5) Measurements of physical examination and other investigations

Efficacy endpoints - Overall survival - Progression-free survival - Local control at 90 days after BNCT - Karnofsky performance status (KPS) measurements and change from baseline - Neurological examination measurements and change from baseline - Tumor response evaluation - Duration of response.

### 2.2. Patient registration

#### 2.2.1. Eligible criteria

Karnofsky Performance Status is greater than 50.

Histologically diagnosed glioblastoma (IDH-wild glioblastoma WHO grade 4 according to WHO, 2016 classification) (immunostaining negative for IDH-1).

Measurable target lesions by Response Assessment in Neuro-Oncology (RANO) criteria with the deepest portion of the contrast-enhanced lesion within 6 cm of the skin surface on postoperative contrast-enhanced MRI scan.

#### 2.2.2. Exclusion criteria

Multiple lesions, bilateral lesions, disseminated lesions on MRI images.

Significant postoperative symptoms of increased intracranial pressure.

Patients with severe systemic diseases.

Patients who have a history of radiotherapy to the brain.

Patients who meet the following criteria on clinical examination.

a) White blood cell counts less than 3,500/$mm^3$
b) Platelet count less than 7,5000/$mm^3$
c) AST and ALT are at least 2.5 times the upper limit of the institutional standard.
d) Total bilirubin is at least 1.5 times the upper limit of the institutional standard.
e) BUN is at least 2.5 times the upper limit of the institutional standard.
f) Creatinine is at least 1.5 times the upper limit of the institutional standard.
g) Patients for whom contrast-enhanced MRI cannot be performed
h) Patients who cannot administrate temozolomide
i) Patients with ongoing convulsive seizures
j) Patients with active multiple cancers other than the target diseaseit does not include patients with epithelial cancer or skin cancer that is considered curable with treatment, or with other cancers that have not recurred for at least 5 years.
k) Patients receiving or scheduled to receive bevacizumab
l) Pregnant women or patients who are unable to use contraception during the study period - Patients with phenylketonuria

### 2.3. Boron agents and neutron irradiation

Borofaran ($^{10}B$) was administered as a single intravenous dose at an infusion rate of 200 mg/kg per hour for the first 2 h, and at 100 mg/kg per hour during neutron irradiation. Neutron irradiation was performed

using a BNCT device, with D2cc in normal brain tissue defined as the maximum dose; 7 Gy-Eq (low dose) or 8 Gy-Eq (medium dose) or 9 Gy equivalent (high dose) was administered in a single dose within 60 min.

### 2.4. Neutron source and dose calculation

#### 2.4.1. Neutron source

The accelerator to be used in this clinical trial is a new one developed jointly by private and national laboratories. The code name is iBNCT001. It is developed by University of Tsukuba and KEK (High Energy Accelerator Research Organization). The RFQ and DTL Linac tube used inside is produced by Mitsubishi Heavy Industry. Protons with an average current of 2 mA are accelerated up to 8 MeV and irradiated to beryllium target to generate neutrons. Behind the beryllium target, a beam shaping assembly (BSA) is placed to adjust the generated neutrons into extra-thermal neutrons that can be used for therapy. Fig. 1 showed the schema of iBNCT. the generated neutrons are epi-thermal neutrons ($0.5<E<10$ keV), and the epi-thermal neutron flux under free beam conditions is about $7x10^8$ ($cm^2/s$) at the beam port. An extended collimator is also available for head and neck cancer (Kumada et al., 2020a).

#### 2.4.2. Dose calculation

BNCT is a radiation therapy that uses two highly linear energy transfer (LET) particles: alpha rays and lithium nuclei, produced by nuclear reactions between $^{10}B$ and thermal neutrons. BNCT includes not only $^{10}B$-derived doses that provide therapeutic effects, but also doses generated by nuclear reactions between neutrons and the elements that make up the body. The doses produced by the reactions of hydrogen and nitrogen are particularly large, and these two doses are called the hydrogen dose and the nitrogen dose. In addition, γ rays are also generated. These consist of γ rays generated by the reaction between the device and neutrons (primary γ rays) and γ rays generated by the reaction between neutrons incident on the living body and the elements that act on the living tissue (secondary γ rays). The main nuclear reactions that are the source of these four representative dose components are shown in Table 1. Of these, the boron dose varies in proportion to the concentration of boron in each tissue. If neutrons are given to tumor cells and normal cells in close proximity, the higher concentration of $^{10}B$ in the tumor will give a higher dose, even though the neutron intensity is the same, and the lower concentration of $^{10}B$ in the normal tissue will result in a lower average dose given to the normal tissue. The components other than the boron dose (hydrogen dose, nitrogen dose, and γ dose) are referred to as the "non-boron dose. These doses are proportional to the neutron intensity and the number of elements constituting the cell, regardless of the tissue type[Fukuda H, 2021].

#### 2.4.3. Absorbed dose

The dose delivered to each tissue or tumor in BNCT is ultimately evaluated as an equivalent dose. This equivalent dose is composed of the four dose components described above, each of which is first calculated in terms of absorbed dose.

#### 2.4.4. Equivalent dose, ED

The equivalent dose (Equivalent Dose, ED) given to the patient is further evaluated. The RBE for γ-rays is 1, while for boron doses, the RBE varies depending on the boron compound used and the cell to be treated. The RBE for γ-rays is 1, while for boron doses, the equivalent boron dose is calculated by multiplying the boron compound used and the loading factor (compound relative biological effectiveness, CBE), which varies for each target cell. The equations for obtaining the equivalent dose are shown in Equations

$$ED\ (Gy(RBE)) = C_B \cdot D_{B,ppm} \times CBE_B + D_N \times RBE_N + D_H \times RBE_H + D\gamma$$

Where $C_B$ is $^{10}B$ Concentration, $CBE_B$, $RBE_N$, $RBE_H$, and $RBE_\gamma$ are CBE and RBE for boron dose, nitrogen dose, and hydrogen dose, respectively. $D_{B,ppm}$ are the absorbed boron dose per μg/mL. The nitrogen dose is the dose resulting from the reaction of thermal neutrons with nitrogen and therefore varies little among BNCT instruments. On the other hand, the hydrogen dose is the dose resulting from the reaction of high-energy neutrons (fast neutrons) with neutrons, and therefore varies slightly depending on the ratio of fast neutrons in the neutron beam produced by each BNCT device. In addition, as mentioned above, the CBE value differs for each boron agent because each boron compound has different cellular accumulation properties. Table 2 shows the RBE of the iBNCT001 neutron beam. For the hydrogen dose, we conducted our own irradiation experiments with cells and found that the RBE of the fast neutron beam for cultured cells in iBNCT ranged from 1.96 to 2.72. We adopted an average value of 2.3 for the biological effectiveness ratio (RBE) of the fast neutron beam in iBNCT001(Kumada et al., 2020b). In addition, Table 3 shows the CBE values for each tissue and tumor for the boron investigational agent: SPM-011 used in the Phase I trials in iBNCT001.

Boron concentration values in each tissue and in the tumor are necessary for BNCT dosimetry. In actual treatment, the boron concentration in blood (μg/mL) is the only boron concentration that can be measured. Therefore, for dosimetry, the boron concentration in each tissue is calculated based on the ratio of the boron concentration in each tissue to the boron concentration in the blood. Table 4 shows the ratio of the blood concentration in each tissue used for dosimetry of iBNCT001.

### 2.5. Treatment Outlines of the clinical trial, BNCT combined with Xray radiotherapy and temozolomide

Treatment Outlines and standard treatment are shown in Fig.2.
Figure 2

After BNCT, combination therapy with temozolomide and X-ray therapy (20 fractions) is administered starting 7 days after BNCT.

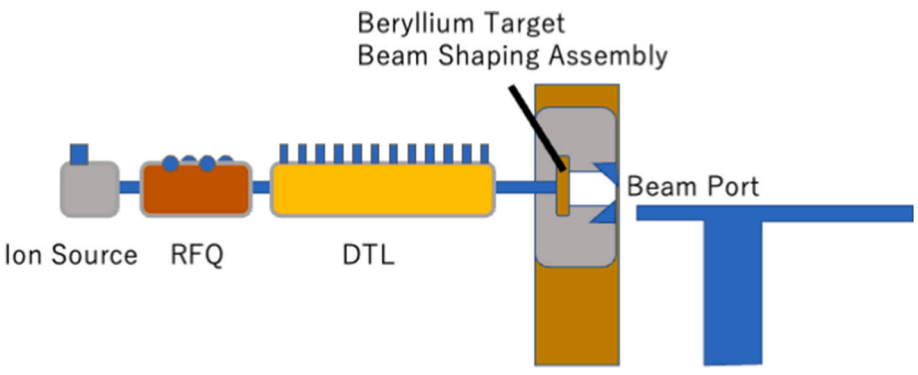


**Fig. 1.** Schematic Diagram of an Accelerator-Based Neutron Source. The Ion Source, RFQ and DTL linac tube generate protons with an average current of 2mA, accelerated up to 8MeV. A beam shaping assembly generate epi-thermal neutrons.

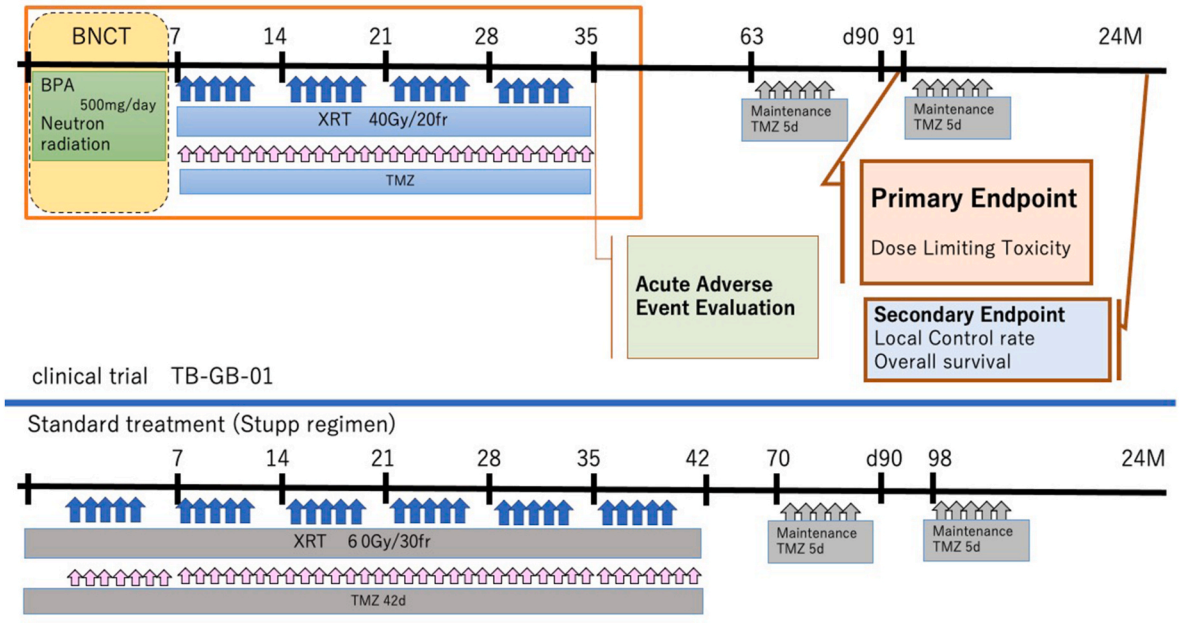


**Fig. 2.** Outline of the procedure. Schematic diagram of treatment under this protocol and standard treatment.

**Table 1**
Component of BNCT dose.

| Dose component | Reaction |
|---|---|
| Boron Dose、$D_B$ | $^{10}B\ (n,\alpha)^{7}Li$ |
| Fast neutron dose(Hydrogen dose)、$D_H$ | $^{1}H(n,n)p$ |
| Neutron dose (Nitrogen dose)、$D_N$ | $^{14}N(n,p)^{14}C$ |
| γ-ray dose, $D_\gamma$ | Primary γ-ray+ Secondary γ-ray from $^{1}H\ (n,\gamma)^{2}H$ |

**Table 2**
The RBE of the iBNCT001 neutron beam.

| Absorbed Dose | RBE | |
|---|---|---|
| Hydrogen dose | 2.3 | |
| Nitrogen Dose | 2.9 | Hiratsuka et al., 1991 |
| γ Dose | 1.0 | |

**Table 3**
The CBE values for each tissue and tumor for the boron investigational agent.

| Tissue | CBE | reference |
|---|---|---|
| Skin | 2.5 | Hiratsuka et al., 1991, Fukuda et al., 1994 |
| Normal Mucosa | 4.9 | Coderre et al., 1999, Morris et al., 2000 |
| Normal Brain | 1.34 | Morris et al., 1994 |
| Tumor | 4.0 | Davis et al., 1970, Coderre et al., 1993 |

**Table 4**
The ratio of the blood concentration in each tissue.

| Tissue | Blood B Concentration ratio |
|---|---|
| Normal Brain | 1.0 |
| Skin | 1.2 |
| Normal Mucosa | 1.0 |
| Tumor | 3.5 |

Temozolomide is administered at a dose of 75 mg/m2 (body surface area) once daily (during the x-ray treatment period).

The following conditions must be met before starting temozolomide administration:

Neutrophil count: ≥1,500/mm$^3$

Platelet count: ≥100,000/mm$^3$

In addition, blood tests should be performed at least once a week to determine if the drug should be continued. If any of the following adverse reactions occur, the dosage should not be increased or decreased, and the drug should be withdrawn or discontinued.

### 2.6. Data analysis

This study will use a three-cohort method (algorithm-based design) with three cases (+3 cases) as one cohort to determine the Maximum Tolerated Dose (MTD)Figure 3a. This method is the usual procedure used to determine drug capacity and allows for a DLT of up to 1 out of 6 cases at each dose. At the recommended dose, 6 cases should be treated and less than 1 DLT should be observed. Therefore, 12 to a maximum of 18 patients will be enrolled.

1) If no DLT is observed in any of the 3 cases in any cohort, the dose is increased to the next dose group.
2) If DLT is observed in 1 of the 3 cases in any cohort, the dose is not increased and the same dose is given to the additional 3 cases.

If DLT develops in 1 of the 6 cases, the dose is increased to the next dose group.

If DLT develops in 2 or more cases out of 6 cases, the dose is reduced to the previous dose.

3) If 2 or more cases of DLT occur among 3 cases in any cohort, the dose should be reduced to the previous dose.

If the number of cases at the previous dose is 6, then this dose is the MTD. If there were only 3 cases at the previous dose, another 3 cases are added and irradiated with the same dose.

If DLT develops in 1 of the 6 cases, the dose is increased to the next dose.

If DLT develops in more than 1 of the 6 cases, the dose is reduced to the previous dose.

The second case of each cohort will be included if DLT develops before the examination (35 days after D1) after the completion of the

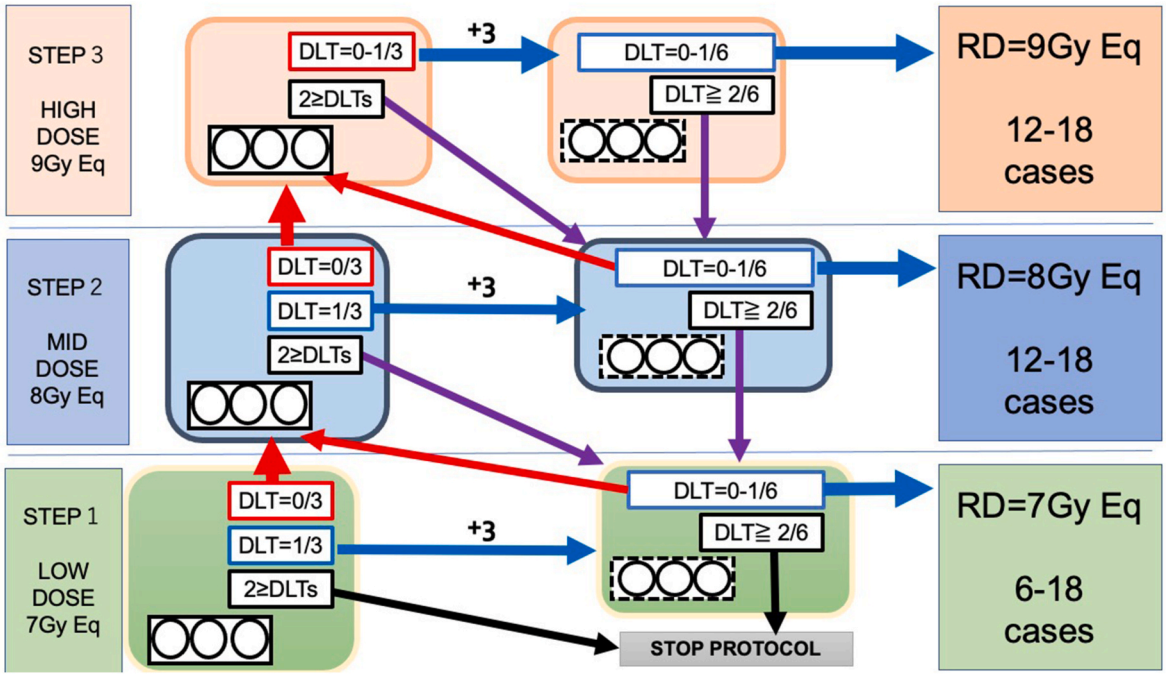


**Fig. 3a.** Algorithm of dose escalation with three-cohort methods.
This study will use a three-cohort method (algorithm-based design) with 3 cases (+3 cases) as one cohort to determine the Maximum Tolerated Dose (MTD).
1) If no DLT is observed in any of the 3 cases in any cohort, the dose is increased to the next dose group.
2) If DLT is observed in 1 of the 3 cases in any cohort, the dose is not increased and the same dose is given to the additional three cases.If DLT develops in 1 of the 6 cases, the dose is increased to the next dose group. If DLT develops in 2 or more cases out of 6 cases, the dose is reduced to the previous dose.
3) If 2 or more cases of DLT occur among 3 cases in any cohort, the dose should be reduced to the previous dose. If the number of cases at the previous dose is 6, then this dose is the MTD. If there were only 3 cases at the previous dose, another 3 cases are added and irradiated with the same dose. If DLT develops in 1 of the 6 cases, the dose is increased to the next dose. If DLT develops in more than 1 of the 6 cases, the dose is reduced to the previous dose.

first case of X-ray radiotherapy, and if the Safety Evaluation Committee evaluates that there is no problemFigure 3b. If one or more DLTs occur in the first 3 cases of each cohort, the Safety Evaluation Committee will evaluate the DLTs that do occur in order to determine whether to add three more cases in that cohort or to move to a cohort with one lower dose level.

### 2.7. To enroll the second case

If DLT develops between the BNCT irradiation of the first case and the post-treatment X-ray examination, a safety evaluation committee will be convened to evaluate whether the second case in each cohort can be enrolled or not. If one or more dose-limiting toxicities occur in one to three cases in each cohort, the dose-limiting toxicities that occur will be evaluated to determine whether three additional cases should be

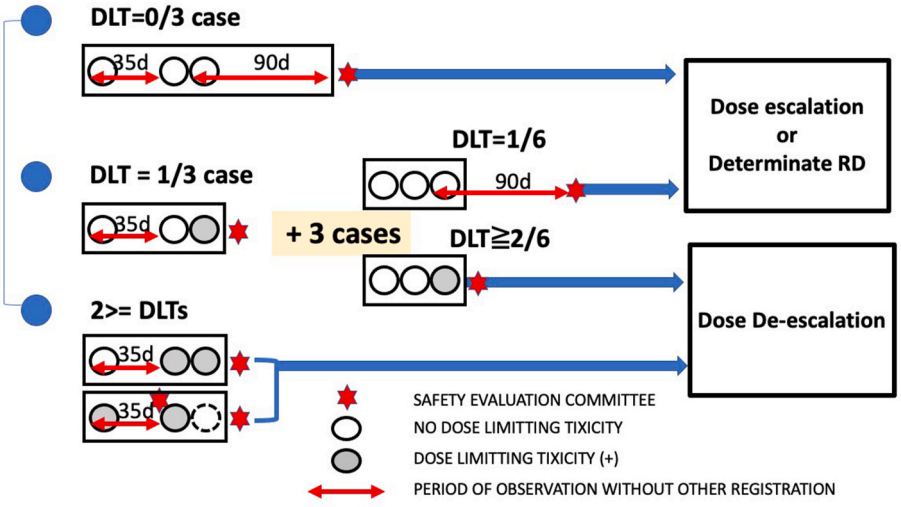


**Fig. 3b.** The second case of each cohort will be included if DLT develops before the examination (35 days after D1) after the completion of the first case of X-ray treatment, and if the Safety Evaluation Committee evaluates that there is no problem.
If 1 or more DLTs occur in the first 3 cases of each cohort, the Safety Evaluation Committee will evaluate the DLTs that do occur in order to determine whether to add three more cases in that cohort or to move to a cohort with one lower dose level.

performed in that cohort or whether the cohort should be moved to a cohort with one lower dose level. If dose-limiting toxicity is observed only in the first case, it has already been reviewed, so evaluation is not required when the post-treatment examination of the third case is completed.

### 2.8. Dose-limiting toxicity criteria

Dose-limiting toxicity is defined as the following adverse events for which a causal relationship with BNCT cannot be ruled out.

- Non-hematologic toxicities that are Grade 3 or higher of CTCAE version 5.0
- Hematologic toxicities that are Grade 4 or higher of CTCAE version 5.0

  Feverish neutropenia, anemia requiring red blood cell transfusion, and thrombocytopenia requiring platelet transfusion are considered dose-limiting toxicities regardless of the CTCAE version 5.0 grade.

### 2.9. Events not defined as dose-limiting toxicities

The following events shall not be considered dose-limiting toxicities.

- Nonhematologic toxicities of Grade 3 or less observed in conventional radiotherapy
- Events that can be controlled

#### 2.9.1. Cerebral edema and radiation dermatitis

Cerebral edema and radiodermatitis are treatment-related adverse events that are frequently observed in conventional radiotherapy for glioma.

- Evaluation of cerebral edema will be based on the following symptoms of cerebral edema. Headache, vomiting, seizures, floating dizziness, Decreased level of consciousness, Optic papillary edema, visual loss, Floating dizziness: If symptoms are present prior to BNCT, they shall not be considered dose-limiting toxicities even if they worsen after BNCT.

Radiation dermatitis (erythema, wet desquamation, necrotic ulceration of skin), eczema.

### 2.10. Other toxicities

Other non-hematologic toxicities expected with conventional radiation therapy shall be defined as follows.

Fatigue, anorexia, headache, otalgia, rotatory dizziness, nausea, vomiting, blepharoconjunctivitis, sinusitis, otitis media (mastoiditis), etc.

The definition of controllable is as follows.

- Adverse events resolved with no treatment.
- Adverse events resolved with treatment (excluding surgical procedures).

### 2.11. Treatment protocol and algorithm of dose escalation

[Tables 5 and 6].

The following items will be documented in the medical record and case report form.

All adverse events occurring during the observation and evaluation periods since the start of the investigational drug administration.

- KPS: The Karnofsky Performance Status should be investigated and the results should be documented in the medical record and case report.
- NANO scale: The NANO (The Neurologic Assessment in Neuro-Oncology) scale is investigated and the results are documented in the medical record and case report form.
- MMSE: The MMSE (Mini Mental State Examination) should be investigated and the results should be documented in the medical record and case report form.
- Information collected from MRI examinations: distance from skin surface to deepest contrast-enhanced lesion, presence of postoperative bleeding, presence of postoperative infection, special postoperative notes, T1-weighted gadolinium-enhanced areas (long and short diameters), T2-weighted image high signal areas, presence of new lesions, response judgment (W1, after completion of X-ray therapy, TW1, D91 ≈ TW5, If the overall evaluation was PD at W1, TW1, D91 ≈ TW5, the evaluation of pseudo-progression was also included).

Response Assessment (RANO criteria: Response Assessment in Neuro-Oncology): In this study, the RANO criteria will be used to determine response; The RANO criteria will be used to determine clinical symptoms by KPS, but the final decision will be based on the physician's evaluation. After completion of W1 and X-rays, if the overall evaluation is PD at TW1, D91 ≈ TW5, the physician should evaluate whether or not pseudo-progression is present. As a general rule, PD is considered to have occurred less than 12 weeks after BNCT is performed only when there is a new lesion in the irradiated field or when pathological diagnosis of progression is confirmed. In this study, RANO criteria based on initial version that described in Neuro Oncology working group (Wen et al., 2010).

Table 7 showed the RANO criteria.

### 2.12. Validity of safety (dose-limiting toxicity) assessment

After the completion of D91 evaluation of all patients (3–6 patients) in each cohort, the possibility of transfer to the next cohort will be evaluated. If dose-limiting toxicities are observed after D91 before the assessment of transfer to the next cohort, such information will be included in the evaluation. If dose-limiting toxicities are observed after transfer to the next cohort, the possibility of continuation in the cohort will be evaluated.Figure 3a and 3b

### 2.13. Trial resources

This clinical trial will be supported by the Japan Agency for Medical Research and Development, Bridging Research Program "Safety Study of Boron Neutron Supplementation Therapy Using a Novel High Power Neutron Source for Primary Malignant Glioma" (Principal Investigator: Hideyuki Sakurai, University of Tsukuba, Japan).

#### 2.13.1. Provision of investigational drug

The investigational drug (SPM-011) for this study will be provided free of charge by Stella Pharma Corporation. Safety information on SPM-011 will also be provided by Stella Pharma Corporation. (SPM-011).

## 3. Ethics and dissemination

This study was approved by the Institutional Review Board of Clinical Trial & Research Network IBARAKI, Act of Japan and the Declaration of Helsinki or its equivalents. This trial is registered in the Japan Registry of Clinical Trials (jRCT, 2032230554, 5th Jan,2024). The results from this study will be analyzed and published in peer-reviewed journals.

**Table 5**
Schedule of the treatment and observation [1].

| | | Screening Period | Safety Evaluation Period | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Acute adverse event evaluation | | | | | | | | | |
| | | | Efficacy Evaluation Period | | | | | | | | | |
| Time period<br>D: Days later, W: Weeks later<br>M: after a month,<br>T: maintenance therapy | | D-28<br>～<br>D-1 | D1 | D4 | W1 | W2 | W3 | W4 | (W5, W6) | | TW1 | D91<br>≒<br>TW5 |
| Base date (days later) | | | | 3 | 7 | 14 | 21 | 28 | | 35 | last day of XRT+28 | 90 |
| Allowance (days) | | | | | +2 | ±2 | ±2 | ±2 | ±2 | +14 | +7 | ±7 |
| Consent Obtained | | ● | | | | | | | | | | |
| Background Check | | ● | | | | | | | | | | |
| Eligibility Determination | | ● | | | | | | | | | | |
| Case Registration | | ● | | | | | | | | | | |
| CT scan for Planning | | ● | | | | | | | | | | |
| Treatment Plan | | ● | | | | | | | | | | |
| Clinical Trial | Boron administration<br>Blood B concentration | | ●<br>● | | | | | | | | | |
| | BNCT | | ● | | | | | | | | | |
| | Temozolomide<br>X ray radiotherapy | | | | XRT and TMZ | | | | | | | |
| TMZ maintenance therapy | | | | | | | | | | | | |
| Physical Examination and Other Surveys*. | | ● | ● | | ● | ● | ● | ● | ● | ● | ●† | ● |
| Vision/hearing test** | | ● | | | | | | | | | | ● |
| KPS・NANO scale | | ● | | | ● | | | | | ● | ●† | ● |
| MMSE | | ● | | | | | | | | | | ● |
| Laboratory tests *** | | ● | | | ● | ● | ● | ● | ● | ● | ●† | ● |
| Diagnostic Imaging **** | | ● | | | ● | | | | | ● | ●† | ● |
| AE/medications/adjunctive therapy | | ●†† | | | | | | | | | | |
| Survival observation | | | | | | | | | | | | |

In case of discontinuation after BNCT is performed, evaluation at the time of discontinuation will be conducted. Subjects who have completed the safety and efficacy evaluation period/discontinued will be moved to the follow-up period and will be observed for survival until the end of the last case observation.
Temozolomide X-Ray Therapy: Temozolomide will be administered at a dose of 75 mg/m2 (body surface area) once daily from W1 until the end of X-Ray therapy. W (42 ± 2 days) only if X-ray therapy is not completed in 4 weeks.
Temozolomide maintenance therapy: After approximately 4 weeks off temozolomide X-rays, maintenance therapy consists of 150 mg/m2 of temozolomide once daily for 5 consecutive days, followed by a 23-day rest period. In principle, 6 courses of 28 days each are administered, but the patient may continue receiving temozolomide at the physician's discretion after that. If temozolomide is discontinued, patients should visit the hospital only at TW17 (≈6M), TW41 (≈12M), TW65 (≈18M), and TW89 (≈24M) after D91 evaluation.
**: Body weight, systolic blood pressure, diastolic blood pressure, pulse rate, and temperature.
**: Visual examination should be done by fundoscopy if necessary, and auditory examination should be done by examination.
***: Hematological, blood biochemical, and virological tests (performed only during the screening period; use of data prior to obtaining consent is allowed), and urinalysis should be performed. Women of childbearing potential should also undergo a pregnancy test (not required for W1-TW1).
****: If a postoperative MRI scan has already been performed prior to obtaining consent, it is not required in the

screening period; if MRI imaging is not available after BNCT irradiation, CT imaging may be substituted.
††:Allowance should be ±7 days.
†††: Only concomitant medications and concomitant therapies should be collected.

**Table 6**
Schedule of the treatment and observation [2].

| | Efficacy Evaluation Period (continue) | | | | | | | | | Not specified††† | Follow-up period |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Time<br>D: Days later,<br>W: Weeks later<br>M: after a month,<br>T: maintenance therapy | TW9<br>**(4M)** | TW13<br>**(5M)** | TW17<br>**(6M)** | TW21<br>TW25<br>TW29<br>TW33<br>TW37<br>**(7M To 11M)** | TW41<br>**(12M)** | TW45<br>TW49<br>TW53<br>TW57<br>TW61<br>**(13M to 17M)** | TW65<br>**(18M)** | TW69<br>TW73<br>TW77<br>TW81<br>TW85<br>**(19M to 22M)** | TW89<br>**(24M)**/<br>Discontinue | | Every 12W |
| Base date<br>(Days later) | TW1<br>+56 | TW1<br>+84 | TW1<br>+112 | TW1<br>+140<br>+168<br>+196<br>+224<br>+252 | TW1<br>+280 | TW1<br>+308<br>+336<br>+364<br>+392<br>+420 | TW1<br>+448 | TW1<br>+476<br>+504<br>+532<br>+560<br>+588 | TW1<br>+616 | | |
| Allowance (days) | ±7 | ±14 | ±14 | ±14 | ±14 | ±14 | ±14 | ±14 | ±14 | | ±28 |
| temozolomide Maintenance Therapy | | | | | | | | | | | |
| Physical Examination and Other Surveys*. | | | ● | | ● | | ● | | ● | | |
| Vision/hearing test** | | | ● | | ● | | ● | | ● | | |
| KPS | ● | ● | ● | ● | ● | ● | ● | ● | ● | | |
| NANO scale | | | ● | | ● | | | | ● | | |
| MMSE | | | | | | | | | ● | | |
| Laboratory tests *** | | | ● | | ● | | | | ● | | |
| Laboratory tests (hematology only) | ● | ● | | ● | | ● | ● | ● | | | |
| diagnostic Imaging **** | | | ● | | ● | | | | ● | ● | |
| medications/adjunctive therapy | | | | | | | | | | ● | |
| Survival observation | | | | | | | | | | | ● |

One month is defined as 28 days.
In case of discontinuation after BNCT, evaluation at the time of discontinuation will be conducted.
Subjects who have completed the safety and efficacy evaluation period/discontinued will be moved to the follow-up period and will be observed for survival until the end of the last case observation.
Temozolomide maintenance therapy: After approximately a 4-week pause following the completion of temozolomide X-ray therapy, maintenance therapy consists of temozolomide at 150 mg/m2 once daily for 5 consecutive days, followed by a 23-day pause. In principle, 6 courses of 28 days each are administered, but the patient may continue receiving temozolomide at the physician's discretion after that. If temozolomide is discontinued, patients should visit the hospital only at TW17 (≈6M), TW41 (≈12M), TW65 (≈18M), and TW89 (≈24M) after D91 evaluation.
**: Body weight, systolic blood pressure, diastolic blood pressure, pulse rate, and temperature.
**: Visual examination should be done by fundoscopy if necessary, and auditory examination should be done by examination.
***: Hematology, blood biochemistry, and urinalysis should be performed. Women of childbearing potential should also undergo a pregnancy test.
****: If MRI imaging is not available after BNCT irradiation, CT imaging may be substituted.

**Table 7**
Summary of the proposed RANO response criteria.

| Criterion | CR | PR | SD | PD |
|---|---|---|---|---|
| T1 gadolinium enhancing disease | None | ≥50 % ↓ | <50 % ↓ but <25 % ↑ | ≥25 % ↑[a] |
| T2/FLAIR | Stable or ↓ | Stable or ↓ | Stable or ↓ | ↑[a] |
| New lesion | None | None | None | Present[a] |
| Corticosteroids | None | Stable or ↓ | Stable or ↓ | NA[b] |
| Clinical status | Stable or ↑ | Stable or ↑ | Stable or ↑ | ↓[a] |
| Requirement for response | All | All | All | Any[a] |

RANO:Response Assessment in Neuro-Oncology、.
CR:Complete response、PR:Partial response、SD:Stable disease、.
PD:Progressive disease、FLAIR:Fluid-attenuated inversion recovery、.
NA; Not applicable.
[a] Progression occurs when this criterion is present.
[b] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

## 4. Discussion

The following three points were taken into consideration at the start of this clinical trial.

(1) The study should be conducted in patients with newly diagnosed glioblastoma. It is difficult to evaluate efficacy in recurrent cases, and a large number of cases are required to prove superiority in survival, which is not realistic. By targeting first-onset cases, recent molecular diagnoses can be taken into account, and by targeting IDH wild type, factors of local control can be examined from images for diseases that are difficult to cure.
(2) To partially combine standard treatment with X-rays and temozolomide. Although previous reactor clinical studies have suggested prolonged survival, recurrence within the irradiated field has also been observed in many cases. The use of borocaptate sodium in combination with BPA required the approval of a new drug, and the concept of using X-rays to replace the diffusion-distributed neutron dose to the normal brain with extra-radiation was initiated. At the time, the study was conducted before the launch of temozolomide, and the concomitant drug was ACNU, which was approved only in Japan and was not the global standard. Therefore, in the current combination protocol, it was decided to start with a dose with a peak normal brain dose of no less than 60 Gy of the standard treatment, and to determine the recommended dose by means of dose escalation studies. The dose of the drug for head and neck cancer was controlled by the irradiation time, since a dose that maintains a stable blood concentration had already been established.
(3) Cases with residual tumor should be targeted. The course and process of changes in medical images are expected to differ from those seen with spatial local therapy radiotherapy, which places an upper limit on the conventional useful dose. We aim to be able to construct reliable data on how the images of glioblastoma in almost naïve areas change while producing changes.

### 4.1. Treatment concept

The concept of this study is to replace boosted irradiation of the tumor area in conventional X-ray therapy (contrast-enhanced area = tumor area with a dose aiming at a maximum of 60 Gy) with BNCT. The so-called target volume (defined as the area containing the tumor invasion. Usually, this is a 2 cm extension from the T2 high-signal region on MRI to the periphery) is guaranteed 40 Gy with X-rays, as is the standard prescription for X-rays. Local irradiation or dose escalation after fractionated x-ray irradiation has not been shown to be effective when the total local dose exceeds 60 Gy, either by adding stereotactic radiation or by increasing the tumor dose itself, and also increases the risk of radiation brain necrosis and higher brain dysfunction. Therefore, we judged that treatment within the standard range of 60 Gy could be expected to be tolerated, and designed the study to titrate within that range as much as possible. When considering the assumption that X-rays are prescribed to the target volume after BNCT, the peak biological total dose (expressed here as a single 2 Gy equivalent, or EQD2 equivalent) should be set to be equivalent to the normal tissue dose (EQD2 maximum 60 Gy) in the standard treatment of X-ray therapy to ensure safety. The irradiation dose should be set to be equivalent to the normal tissue dose (EQD2 up to 60 Gy) in the standard treatment of X-ray therapy to ensure safety. Assuming that 40 Gy of the target volume prescription is directly delivered by X-rays, the normal tissue dose allowed for BNCT is the EQD2 equivalent of 20 Gy (2 Gy per dose, 10 cycles) because 40 Gy of the EQD2 equivalent (2 Gy per dose, 20 cycles) is delivered by X-ray therapy after BNCT.

If the LQ model is applied ($\alpha/\beta = 3$) and the BNCT single irradiation dose to the normal brain is converted using EQD2, 20 Gy (2 Gy per dose, 10 cycles) is roughly equivalent to 9 Gy (RBE) (single irradiation).

- 7 Gy (single irradiation) = equivalent to 14 Gy in EQD2
- 8 Gy (single irradiation) = equivalent to 17.6 Gy in EQD2
- 9 Gy (single irradiation) = equivalent to 21.6 Gy in EQD2

The worst-case scenario, a condition under which normal brain doses can be excessive, is the respective 2 Gy equivalent doses of 18.7, 24, and 30Gy, assuming $\alpha/\beta = 1$, respectively, with the initial dose not exceeding the standard treatment dose of 60 Gy.

Thus, the maximum BNCT dose that can be achieved in combination with 40 Gy of X-rays and in the range where the total dose in terms of divided irradiation of 2 Gy at a time does not exceed 60 Gy of standard treatment is considered to be 8 Gy (RBE). After confirming that no adverse events occurred, it was considered appropriate to evaluate the high-dose group as well.

### 4.2. Combination with X-ray radiotherapy, temozolomide (TMZ)

Combination therapy with temozolomide and X-ray therapy is currently considered the standard of care as chemoradiotherapy for first-episode malignant gliomas, and in the Guidelines for Glioblastoma in Adults (GBM) (Japanese Brain Tumor Society), chemoradiotherapy with temozolomide is recommended as a postoperative treatment for first-episode glioblastoma in elderly patients (Brandes et al., 2003).

In an attempt to further increase the radiation dose, a total dose of 81.6 Gy using the hyperfractionation method was used, but none of these doses was found to be effective. On the other hand, further attempts to increase the dose have been made using the hyperfractionation method, with total doses of 81.6 Gy, etc., but none of them have shown any advantage in median survival compared to existing treatments. Currently, 60 Gy/30 fraction is the standard postoperative radiation therapy. In actual clinical practice, x-ray therapy is usually given in 30 fractions, but since it takes as long as 6 weeks and most patients are hospitalized, hypofractionated irradiation may be used to shorten the treatment period for elderly patients, patients with poor prognosis and inactive patients. The results of past clinical studies have shown that the current standard irradiation dose prolongs survival, but during the course of treatment, a high rate of local recurrence occurs within the irradiated field or from the margins, indicating that the dose is not sufficient for tumor control, but rather is defined by the tolerable dose for normal brain, which also indicates the limitations of external irradiation.

The prognostic significance of MGMT promoter methylation in glioblastoma patients treated with Temozolomide is well established (Hegi ME et al., 2005; Brawanski LR et al., 2023), highlighting the

potential value of molecular markers in optimizing future therapeutic strategies. Although the primary objective of this Phase I study is to assess safety and determine the recommended dose of BNCT, we will explore the feasibility of incorporating a tissue banking protocol or molecular marker diagnostic results to collect and store tumor samples for future molecular analysis, including MGMT promoter methylation status. This will enable retrospective studies to identify prognostic factors and improve clinical outcomes in subsequent trials.

### *4.3. Rationale for BNCT to precede X-irradiation*

In BNCT, the boron compound must reach the tumor in advance. Since the boron compound is administered intravenously on the day of irradiation, if irradiation is preceded by X-ray irradiation, blood flow in the tumor area may be altered and the degree of boron accumulation may be reduced. Therefore, we considered it necessary to precede BNCT. The fact that the evaluation lesion, i.e., the area contrasted by MRI, remains in the patient after surgery can be interpreted as having blood flow that allows the contrast agent to at least reach the residual tumor after surgery.

### *4.4. Comparison with short-term irradiation for elderly patients*

Regarding shortening regimens for the elderly.

We also consider shortening protocols for the elderly. The so-called standard of care, the stupp regimen, prolonged the prognosis with the combination of temozolomide compared to conventional postoperative radiotherapy alone. In the elderly, shortening the duration of treatment is being considered. We understand that the reason for this is that in many cases, if cure is not achieved and survival is comparable or non-inferior in adverse events, a shortened regimen is acceptable.

Our proposed protocol also includes patients who would not be champion data in the current standard of care, i.e., those who cannot undergo total resection, do not have good ADL, and are elderly. And if these patients were to achieve a significant prolongation of survival and complete local control, i.e., cure, then the protocol would be adopted to achieve cure even with a prolonged treatment period.

## 5. Conclusion

The BNCT investigator-initiated clinical trial for newly diagnosed glioblastoma at our hospital was outlined.

It is a phase I trial for newly diagnosed glioblastoma, preceded by BNCT in combination with X-rays and temozolomide, and with a recommended starting dose set equal to that of the standard of care.

## CRediT authorship contribution statement

**Kei Nakai:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Hiroaki Kumada:** Validation, Software, Methodology, Investigation. **Yoshitaka Matsumoto:** Resources, Methodology, Investigation. **Keiichiro Baba:** Investigation. **Motohiro Murakami:** Investigation. **Toshiki Ishida:** Investigation. **Takashi Saito:** Project administration, Conceptualization, Resources, Methodology, Investigation. **Masatoshi Nakamura:** Supervision, Project administration, Methodology, Investigation, Conceptualization. **Haruko Numajiri:** Supervision, Methodology, Investigation, Conceptualization. **Masashi Mizumoto:** Supervision, Project administration, Methodology, Investigation. **Narushi Sugii:** Methodology, Investigation, Conceptualization. **Shunichiro Miki:** Methodology, Investigation, Conceptualization. **Eiichi Ishikawa:** Supervision, Project administration, Methodology, Conceptualization. **Kazushi Maruo:** Validation, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Masae Takemura:** Visualization, Validation, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Koichi Hashimoto:** Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Tomomi Takahashi:** Supervision, Methodology, Formal analysis, Conceptualization. **Toshimitsu Hayashi:** Resources, Methodology, Formal analysis, Conceptualization, Validation, Supervision. **Hideyuki Sakurai:** Investigation, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability

No data was used for the research described in the article.

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