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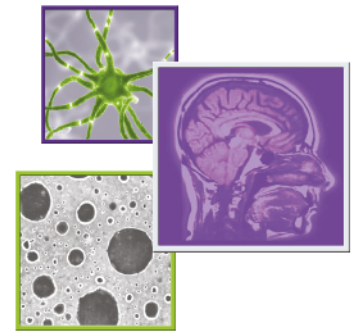

A feasibility study of the Nativis Voyager® device in patients with recurrent glioblastoma in Australia

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Aim: Evaluation of the Nativis Voyager®, an investigational medical device, as monotherapy for recurrent glioblastoma (rGBM). **Materials & methods:** A total of 15 patients with rGBM were treated with one of two Voyager ultra-low radio frequency energy cognates: A1A or A2HU. Safety and clinical utility were assessed every 2–4 months. **Results:** Median overall survival was 8.04 months in the A1A arm and 6.89 months in the A2HU arm. No serious adverse events associated with Voyager were reported. No clinically relevant trends were noted in clinical laboratory parameters or physical exams. **Conclusion:** The data suggest that the Voyager is safe and feasible for the treatment of rGBM.

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Keywords: brain cancer • clinical trial • electromagnetic fields • glioblastoma • medical device • Nativis Voyager • recurrent GBM

Glioblastoma (GBM) is an aggressive and common malignant brain tumor [1,2]. Despite treatment including surgical resection of the tumor, followed by concurrent radiation with temozolomide, the prognosis for GBM patients remains poor, with a median survival of 15 months [3–8]. There is a need for new treatment modalities to improve overall survival.

The Nativis Voyager® is an investigational medical device that uses localized, ultra-low radio frequency energy (*ul*RFE®), in the range of 0–22 kHz, for the treatment of malignant solid tumors including GBM [9]. The *ul*RFE signal, referred to as a cognate, is obtained from solvated molecules using a direct-current super-conducting quantum interference device [9]. The device has been designed to be easily and comfortably used in a home or office environment so that a patient can carry on with daily activities without any disruption from the device (Figure 1).

Voyager therapy is based on the ability of a time-varying magnetic field to exert force on point charge through a process known as magnetic induction, which is a fundamental principle of modern physics with application in biology and medicine [10]. The Voyager induces a biologic response *in vitro* and *in vivo* [11].

In this clinical trial, two *ul*RFE cognates were studied. The *ul*RFE cognate A1A is theorized to disrupt mitotic spindle activity during cell division [9,12]. The *ul*RFE cognate A2HU was derived from small interfering RNA (siRNA) sequences known to inhibit expression of CTLA-4 and PD-1 [13,14], with the intent of creating a magnetic field that would reduce the expression of these proteins; the detailed mechanism of action of A2HU is unknown and studies are underway to explore the basis for its effects.

Electromagnetic fields, such as those produced by the Voyager, easily penetrate the human body without any significant attenuation [15]. As such, the cognates penetrate bone and other tissues as easily as they penetrate air.

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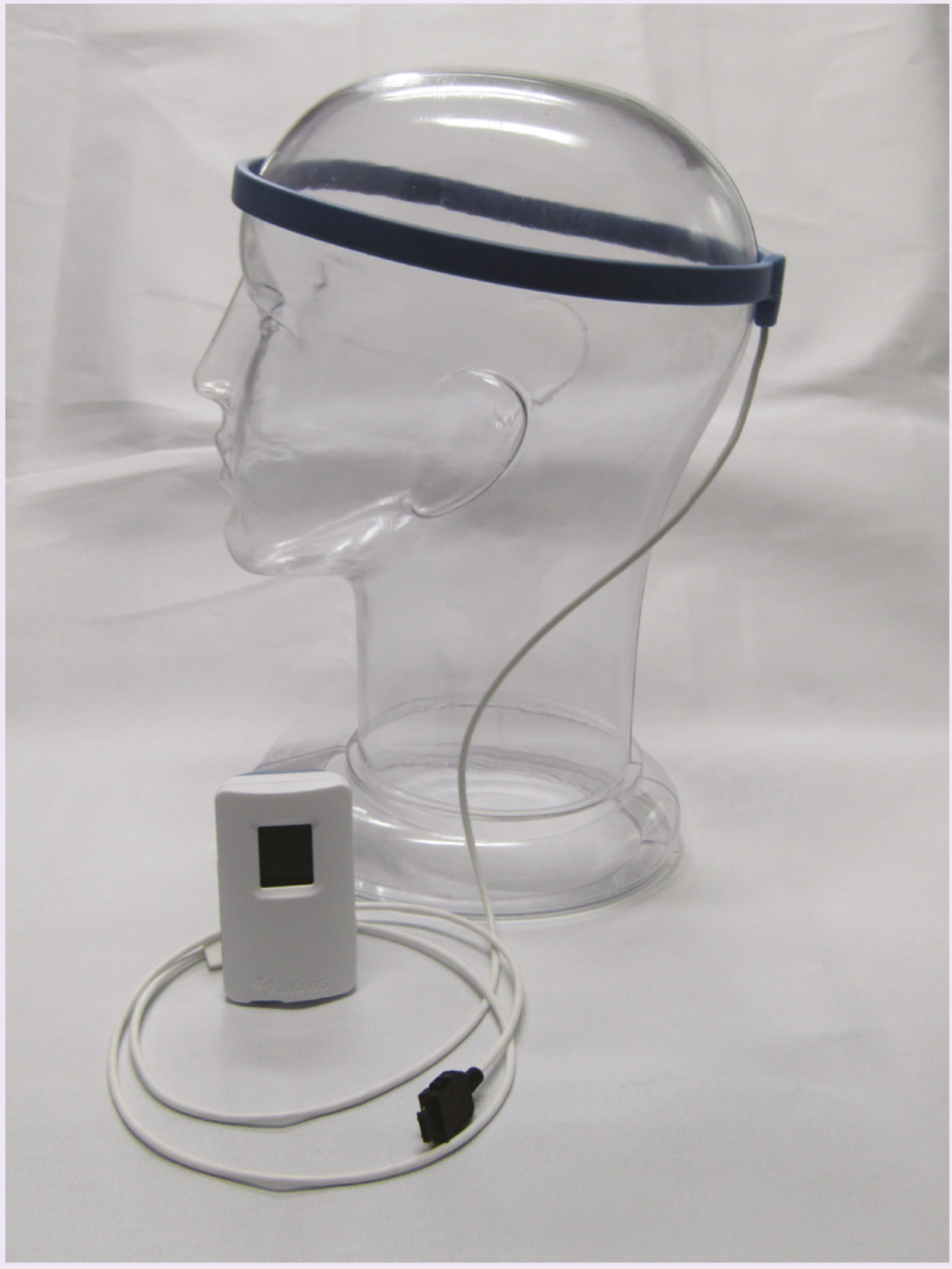

Figure 1. Nativis Voyager device as worn by a patient. The Voyager headband is placed on the patient's head and connected to the controller. It is a closed-loop solenoid coil over-molded in a medical-grade silicone designed to generate a nonlinear and oscillating magnetic field. The flexible headband is available in four sizes and includes a 2-conductor cable with a latching connector for the Voyager controller, which weighs only 2.7 ounces and is approximately the size of a pager. The Voyager controller is clipped to the patient's pocket, belt or armband. It is a software-controlled amplifier powered by a rechargeable lithium-ion battery that delivers a cognate to the patient via the Voyager headband. The small, lightweight device includes a single recessed power button and an liquid crystal display that enables the user to read the device status. There is no user-programming required, and there is no personal health information stored within the device. The device does not require the patient to shave his or her head or any other special preparation for use.
Reproduced with permission from [9].

The field is essentially perpendicular to the plane of the headband coil. The Voyager delivers 25–40 mGauss to the entire brain. These levels are tenfold below safety guidelines [16].

The objective of this study was to assess whether the Voyager *ul*RFE therapy is a safe and feasible treatment for recurrent GBM (rGBM).

Materials & methods

Patient selection & study design

Patients were eligible to participate in the study if they had a histologically confirmed diagnosis of GBM, who failed or intolerant to radiotherapy, failed or intolerant to temozolomide therapy, had progressive disease with at least one measurable lesion on imaging, were at least 18 years of age, had Karnofsky performance score ≥60, had adequate organ and marrow function, and provided signed, informed consent.

Patients were instructed to wear the device continuously, removing it for personal hygiene or medical procedures. Treatment with the Nativis Voyager was administered continuously until unequivocal disease progression, occurrence of a device-related clinically significant adverse event (AE), unacceptable adverse reactions or removal from the study. At the discretion of the investigator, patients could remain on treatment postprogression. Patient visits occurred at least every 8 weeks during the first 6 months and every 4 months thereafter. Routine hematology and chemistry assessments, physical exam (including vital signs and neurological exam), and imaging were performed at baseline and regular intervals as per standard of care.

In this study, two cognates were used. The first cohort of patients received treatment with A1A, a *ul*RFE cognate derived from paclitaxel [9], and the second cohort received treatment with A2HU, a *ul*RFE cognate derived from the siRNA against CTLA-4 and programmed death-1 [13,14]. All patients were treated with Voyager as monotherapy. The treatment arms were not intended for comparison.

The study protocol and subsequent amendments as well as the patient informed consent form were reviewed and approved by the Human Research Ethics Committee at St Vincent's Hospital, in Melbourne, Australia, where the study was conducted.

Safety & clinical utility measurements

Safety was assessed by incidence and evaluation of any AEs associated with the investigational therapy, abnormal laboratory findings and abnormal physical exam findings (including neurological exam and vital signs).

Clinical utility was assessed by tumor response after 2 months, progression-free survival (PFS) at 6 months, median PFS, overall survival (OS) at 6 and 12 months and median OS. The radiological response of the tumor was assessed by imaging studies according to Response Assessment in Neuroonocology (RANO) or Immunotherapy RANO (iRANO) criteria. Patients in the A1A arm were assessed for PFS using the RANO criteria [17], while patients in the A2HU arm were assessed using the iRANO criteria [18]. All patients had their tumor measurements recorded at baseline and at the time of each scan. The dose and type of contrast agent were held constant from scan to scan for each patient.

Statistical analysis

The A1A and A2HU treatment arms were analyzed separately. Data from patients, who were enrolled and treated for at least 1 day, were included in the safety analysis, and patients who were enrolled and treated for at least 1 month were included in the feasibility analysis.

The data analyses were conducted using SAS® Software, version 9.4 or later. Baseline and demographic characteristics of the safety population were summarized. Continuous variables (age, baseline height) were summarized via mean, standard deviation, median, range and number of nonmissing responses. Categorical variables (gender, race, ethnicity and KPS) were summarized via counts and percentages.

The AEs were graded according to the NCI Common Terminology Criteria for Adverse Event Version 3.0 (CTCAE V3.0) and also coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Treatment-emergent AEs (TEAEs), defined as any AE that occurred after a patient received the assigned study treatment, were summarized by the number and proportion of patients reporting at least one occurrence of the AE. Frequencies of each TEAE were summarized by MedDRA preferred term within system organ class (SOC), by severity grade and relation to study device. Treatment emergent serious adverse events were tabulated by MedDRA preferred term within SOC.

Table 1. Patient disposition (safety population).

Reasons	N = 15
Off treatment reasons, n (%)	
Documented disease progression	5 (33%)
Treatment related toxicity	0 (0%)
Nontreatment related toxicity	0 (0%)
Patient requested early discontinuation of study but still followed	4 (27%)
Physician requested early discontinuation of treatment for reasons not related to toxicity	0 (0%)
Death	3 (20%)
Noncompliance	0 (0%)
Other/unknown	3 (20%)
Off study reasons, n (%)	
Documented disease progression	0 (0%)
Patient requested early discontinuation of study but still followed	0 (0%)
Lost to follow-up	0 (0%)
Death	15 (100%)
Other	0 (0%)

The two patients enrolled sequentially in both treatment arms are counted once for disposition.

Clinical laboratory tests were performed at prestudy (baseline) and at all visits. For each panel (hematology, biochemistry and coagulation), the study results were summarized in shift tables from baseline using the categories normal, abnormal (not clinically significant) and abnormal (clinically significant). All clinically significant abnormal findings were reported as AEs.

Physical exams, including vital signs and neurological exams, were performed at prestudy (baseline) and at all patient visits. Physical exam shift tables were constructed to summarize the changes in each body system from baseline for each assessed cycle.

Tumor response was assessed by the RANO or iRANO criteria (as appropriate to the treatment arm) at each post-treatment visit. Patients with unknown status for tumor response at the time point were excluded from the analysis.

Survival rates were estimated: PFS rate at 6 months (PFS-6), OS at 6 months (OS-6) and OS at 12 months (OS-12). Survival rates were summarized by counts (n) and rates (percent surviving to time point) by treatment arm.

For the median survival end points – in other words, OS (in months) and PFS (in weeks) – patients were followed until death. The start of the efficacy period for all analyses in this study was date of treatment initiation, day 1. The OS was assessed using death as the end point. The PFS was determined using RANO or iRANO criteria, as appropriate to the treatment arm. A plot of survival for each treatment arm was produced, displaying survival time and tumor response after 2 months of treatment for each patient.

Results

A total of 28 patients were screened, and 17 were enrolled and received at least 1 day of treatment with the investigational device (i.e., the safety population). In the A1A treatment arm, five of the six treated patients received at least one 28-day treatment cycle and were imaged; the sixth patient was treated for only 1 week. In the A2HU treatment arm, ten of the 11 treated patients received at least one 28-day treatment cycle and were imaged; the eleventh patient was treated for 3 weeks. As such, there were a total of 15 patients in treated population, with a median treatment time of 6 months. Two patients crossed over from the A1A treatment arm into the A2HU treatment arm after progression, so these patients are counted twice. All patients were followed on study until death (Table 1). A total of 16 of the 17 patients died from disease progression; the remaining patient died from a myocardial infarction. The patient population is typical of those with rGBM (Table 2).

Summary of safety

There were no clinically significant changes on physical exams (including changes in vital signs and neurological exams) or in laboratory findings (data not shown). A total of 193 TEAEs were reported – 74 from patients in the

Table 2. Demographics and baseline characteristics (safety population).

Characteristic	Treatment arms	
	A1A (N = 6)	A2HU (N = 11)
Age (years), n		
Mean (SD)	62.8 (5.78)	53.1 (11.85)
Median (min, max)	62.5 (55, 70)	55 (37, 68)
Gender, n (%)		
Female	4 (67%)	5 (46%)
Male	2 (33%)	6 (54%)
Race, n (%)		
White	6 (100%)	11 (100%)
Ethnicity, n (%)		
Not Hispanic or Latino	6 (100%)	11 (100%)
Karnofsky performance score, n (%)		
100%	3 (50%)	1 (10%)
90%	1 (17%)	3 (27%)
80%	0 (0%)	2 (18%)
70%	2 (33%)	3 (27%)
60%	0 (0%)	2 (18%)
Number of recurrences, n (%)		
1	1 (17%)	5 (46%)
2	5 (83%)	6 (54%)
3 or more	0 (0%)	0 (0%)
Days from GBM diagnosis to enrollment		
Median (min, max)	493 (189, 1098)	467 (235, 2872)
Days from last radiotherapy to enrollment		
Median (min, max)	431 (111, 1022)	386 (264, 1364)
Days from last temozolomide dose to enrollment		
Median (min, max)	267 (39, 1022)	386 (82, 1364)

GBM: Glioblastoma; Max: Maximum; Min: Minimum; SD: Standard deviation.

A1A treatment arm and 119 from patients in the A2HU treatment arm. All patients reported at least TEAE, and most were reported as unlikely or unrelated to Voyager therapy. Only one patient (in the A2HU treatment arm) reported a TEAE that was possibly related to Voyager therapy. This TEAE was an unresolved increase in headaches with no action taken. In the A2HU treatment arm, the most frequently reported TEAEs were headache and seizure. In the A1A treatment arm, the most frequently reported TEAEs were amnesia and aphasia. Four patients in the A1A treatment arm and 12 patients in the A2HU treatment arm reported serious AEs; none were related to the study device. There were no reports of dermatologic AEs such as rash or abrasion at locations in contact with the device.

Summary of clinical utility

The median days on treatment were 168 days in the A1A treatment arm and 202 days in the A2HU treatment arm (Table 3). The longest treatment duration occurred in a patient in the A1A arm, with treatment spanning 342 days. The most frequently documented response was stable disease. Figure 2 shows a patient who experienced a partial response. Figure 3 displays the relationship between survival (in months) and tumor responses. At the first response assessment at 2 months, four patients in the A1A treatment arm and eight patients in the A2HU treatment arms had disease controlled.

Discussion

The aim of the current clinical study was to assess if the Voyager is a safe and feasible treatment for rGBM. In contrast to the first study in which patients were treated with Voyager as monotherapy or in combination with standard chemotherapeutic agents [9], all patients in the current study received treatment with Voyager alone. Safety

Table 3. Summary of clinical utility (treated population).

End point	Treatment arms	
	A1A (N = 5)	A2HU (N = 10)
Days on treatment		
Median (min, max)	168 (34, 342)	202 (54, 266)
PFS		
Median (weeks)	16	12
PFS-6		
n (%)	1 (20%)	3 (30%)
OS		
Median (months)	8	7
OS-6		
n (%)	3 (60%)	6 (60%)
OS-12		
n (%)	2 (40%)	3 (30%)
Tumor response after 2 months (by investigator), n		
Disease controlled (CR, PR and SD)	4	8
CR	0	0
PR	0	2
SD	4	6
PD	0	2
Unknown/unreported	1	0

CR: Complete response; Max: Maximum; Min: Minimum; OS: Overall survival; PD: Progressive disease; PGS: Progression free survival; PR: Partial response; SD: Stable disease.

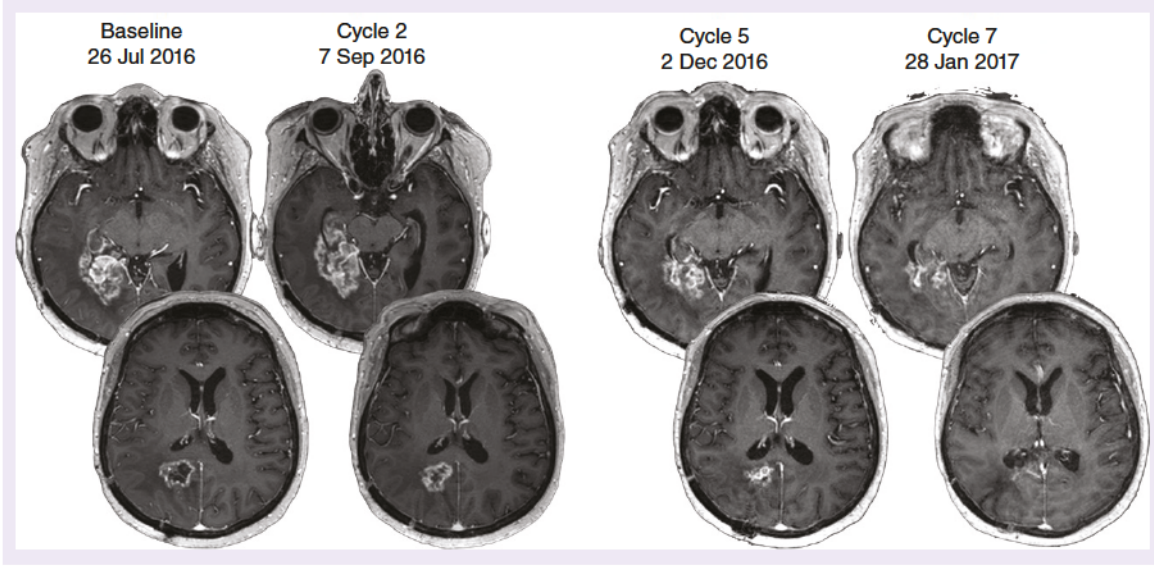

Figure 2. Example of image response on study. All patients were treated continuously with the Voyager as monotherapy. These images are from a 53 yo female with GBM at first recurrence (methylation status unknown) treated with Voyager in the A2HU treatment arm. Serial axial and coronal T1 postgadolinium images show partial response at cycles 5 and 7 (cycles were 28 days in duration).
GBM: Glioblastoma.

results were similar in both studies. No device-related serious AEs were reported in either study. Of the 193 TEAEs reported during the current study, only one event was reported as possibly related to the device. All other TEAEs were either not related or unlikely related to the device. The deaths that occurred on study were expected outcomes of rGBM and not associated with use of the device.

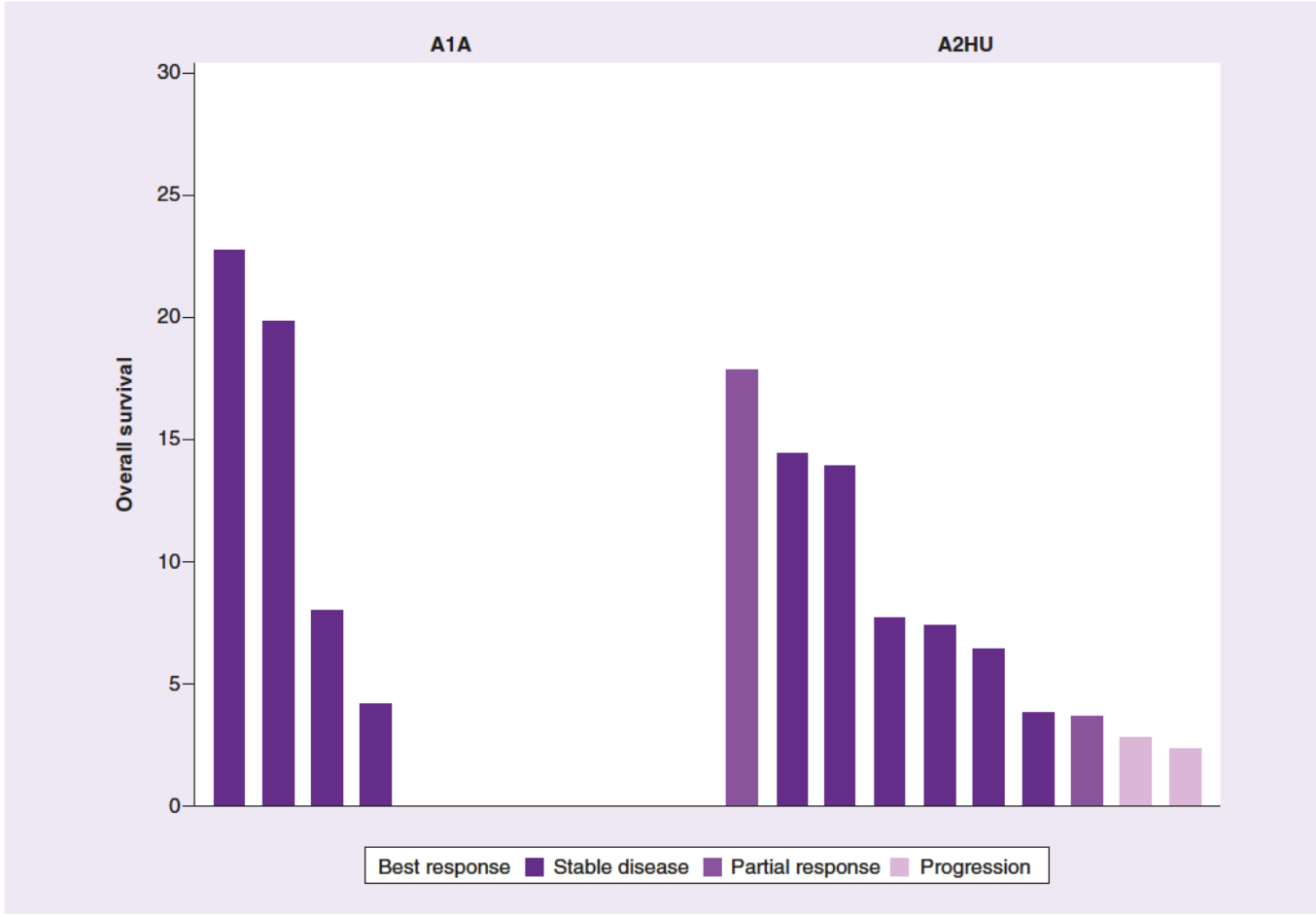

Figure 3. The relationship between survival (in months) and tumor response in A1A treatment arm and A2HU treatment arm. All patients were treated continuously with the Voyager as monotherapy. Tumor response was determined via imaging every 2–4 months, according to the modified RANO criteria (for the A1A arm) or iRANO criteria (for the A2HU arm). This modified waterfall plot illustrates the relationship overall survival (in months) and the best overall tumor response.
iRANO: Immunotherapy Response Assessment in Neuro-onocology.

Most patients achieved a best overall response of stable disease. Two patients had a partial response. The median survival times were 8.04 months for patients in the A1A arm and 6.89 months for patients in the A2HU arm. Median times to progression were 16.14 weeks for patients in the A1A arm and 11.93 weeks for patients in the A2HU arm. Although the number of patients was small in this early feasibility study, the safety data, tumor response and survival outcomes show promising results.

The current generation of the Voyager does not have the ability to track compliance with the protocol requirement for continuous use. Anecdotal data from the clinical sites (i.e., patient diaries and interviews) suggests that patients are highly compliant because they are motivated to fight the disease and the device is easy to use. The next generation of the Voyager is planned to include real-time compliance tracking. In a larger study with the next generation device, minimum effective treatment time could be investigated.

The data from the first feasibility study (NAT-101, NCT02296580), in which patients with rGBM were treated with Voyager alone or Voyager in combination with anticancer therapies, suggest improved clinical utility when Voyager is combined with other anticancer therapies [9]. Therefore, that study in rGBM (NAT-101, NCT02296580) was expanded to evaluate the safety and feasibility of Voyager with concurrent treatment with lomustine, with or without concurrent treatment with bevacizumab. In addition, a study is underway using the Voyager in with the treatment of newly diagnosed GBM (NAT-109, NCT03276286).

Conclusion

These data suggest that the Voyager is safe and feasible for the treatment of rGBM. Given that therapy is delivered noninvasively, and no serious AEs attributed to the investigational therapy were reported, further study of this device in a larger prospective, feasibility study in patients with rGBM is warranted.

Future perspective

In the current study, we demonstrated that multiple cognates (e.g., A2HU which contains the cognates for siRNA from both CTLA-4 and PD-1) can be delivered via the Voyager. When multiple cognates are deployed, they are delivered in a continuous loop of sequential and specific electromagnetic signals. Cognates potentially can be generated from any solvated molecule, and hundreds of cognates are currently available. Therefore, a virtually unlimited combination of cognates potentially can be derived from standard chemotherapeutic agents as well as immunotherapy agents and specific tumor biomarkers or antigens. For example, the Voyager could be programmed to deliver cognates derived from paclitaxel, siRNA of EGFR and an inhibitor of P13 kinase. Today, the Voyager contains a fixed cognate or set of cognates that cannot be altered by the patient or the physician. Theoretically, in the future, a physician could select from a library of cognates to deliver one or more specific cognates targeted for a given patient's tumor.

Summary points

- The Nativis Voyager is a noninvasive, nonthermal, nonionizing, battery-operated, portable investigational medical device that uses ultra-low radiofrequency energy to treat cancer.
- This device delivers one or more specific oscillating magnetic fields to the patient via a headband. This magnetic field, derived by capturing the electrostatic surface potential of solvated molecules, is hypothesized to interact with cellular targets and disrupt their actions.
- NAT-105 (NCT02507102) was a single-site, prospective, open-label, early feasibility study intended to assess the safety and feasibility of the Voyager as a treatment for recurrent glioblastoma.
- All patients were treated with Voyager as monotherapy. Two distinct ultra-low radiofrequency energy cognates were studied: A1A (derived from paclitaxel) and A2HU (derived from small interfering RNA targeting CTLA-4 + PD-1).
- There were no treatment-emergent serious adverse events reported related to the study device, and no clinically relevant trends were noted in clinical laboratory parameters, vital signs or physical exams.
- The majority of patients achieved disease control, with a best overall response of stable disease. Two of 15 patients had a partial response.
- The data suggest that the Nativis Voyager is safe and has clinical utility for the treatment of recurrent glioblastoma.

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Disclosure

Portions of these data were presented at the 2017 Cooperative Trials Group for Neuro-Oncology Annual Scientific Meeting in Melbourne, Australia.

Financial & competing interest disclosures

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No writing assistance was utilized in the production of thismanuscript.

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