

## An early feasibility study of the Nativis Voyager<sup>®</sup> device in patients with recurrent glioblastoma: first cohort in US

Charles Cobbs<sup>\*1</sup>, Edward McClay<sup>2</sup>, J Paul Duic<sup>3</sup>, L Burt Nabors<sup>4</sup>, Donna Morgan Murray<sup>5</sup> & Santosh Kesari<sup>6</sup>

<sup>1</sup>Ben and Catherine Ivy Center for Advanced Brain Tumor Treatment, Swedish Medical Center, Seattle, WA 98122, USA

<sup>2</sup>Melanoma Research Center, California Cancer Associates for Research & Excellence (cCARE), San Marcos, CA 92024, USA

<sup>3</sup>Department of Neuro-oncology, New York University, Winthrop, Mineola, NY 11501, USA

<sup>4</sup>Division of Neuro-oncology, University of Alabama, Birmingham, AL 35294, USA

<sup>5</sup>Nativis, Inc., Seattle, WA 98109, USA

<sup>6</sup>Department of Translational Neuro-Oncology and Neurotherapeutics, John Wayne Cancer Institute & Pacific Neuroscience Institute, Santa Monica, CA 90404, USA

\*Author for correspondence: Tel.: 206 320 2300; Fax: 206 320 8149; [Charles.Cobbs@swedish.org](mailto:Charles.Cobbs@swedish.org)

**Aim:** Evaluation of the Nativis Voyager<sup>®</sup> device in patients with recurrent glioblastoma (rGBM). **Materials & methods:** Voyager is a noninvasive, nonthermal, nonionizing and portable investigational device which delivers ultra-low radio frequency energy ( $\mu$ RFE<sup>®</sup>) that uses a magnetic field to penetrate tissues to alter specific biologic functions within cells. Patients with rGBM were treated with Voyager alone (V) or Voyager in combination with standard of care (V + SoC). Safety and clinical utility were assessed every 2–4 months. **Results:** Data from the first 11 patients treated are reported here. Median progression-free survival was 10 weeks in the V arm and 16 weeks in the V + SoC arm. Median overall survival was 16 months in V arm and 11 months in the V + SoC arm. No serious adverse events associated with the device were reported. **Conclusion:** These data suggest that the Voyager is safe and feasible for the treatment of rGBM

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Glioblastoma (GBM) is the most malignant form of glioma and the most common primary intracranial neoplasm [1,2]. The incidence of GBM increases steadily above 45 years of age with an annual incidence of approximately 12,000 cases in the USA. Current standard therapy for the treatment of GBM includes surgical resection of the tumor, followed by concurrent radiation with temozolomide (TMZ), an oral alkylating chemotherapy agent, then adjuvant chemotherapy with TMZ [3,4]. GBM tumors are invasive and often located in areas of the brain that control motor function, speech and the senses making it difficult to completely resect the tumor with surgery. Due to the high degree of invasiveness, resection of the primary tumor is not curative and tumor cells undoubtedly remain within the surrounding tissue leading to disease progression and recurrence [5]. The prognosis for GBM patients remains poor, with a median survival of 15 months [3,6]. Approximately 70% of GBM patients will have disease progression within 1 year of diagnosis [7]. Median survival in patients with recurrent glioblastoma (rGBM) treated with standard of care (SoC) anticancer agents is 6 months [3,8].

The Nativis Voyager<sup>®</sup> is a nonsterile, noninvasive, nonthermal, nonionizing and portable investigational medical device that uses localized, ultra-low (0–22 kHz) radio frequency energy ( $\mu$ RFE<sup>®</sup>) for the treatment of malignant solid tumors, such as GBM. The  $\mu$ RFE is delivered to the patient by an electromagnetic coil worn externally on the head. The Voyager consists of only three components – a battery-operated controller, an electromagnetic coil and a battery charger. The electromagnetic coil is worn on the patient's head much like a crown and is connected to the controller (Figure 1). 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. The device



**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 overmolded in a medical-grade silicone designed to generate a nonlinear, oscillating magnetic field. The flexible headband is available in four sizes and includes a two-conductor cable with a latching connector for the Voyager controller. 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 LCD 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.

is simply removed for personal hygiene or medical procedures and repositioned on the head afterwards. The coil comes in a range of sizes to comfortably fit a patient's head. A cap or headband may be worn over the coil to hide it from view or to hold it in place as needed or as desired. The device does not require the patient to shave his or her head or any other special preparation for use. Each controller has a battery-life of approximately 16 h. The patient is provided with two controllers so that one unit may be charged using the battery charger (like a cell phone charger) while the other controller is in use. Recharging takes less than 2 h. The controller weighs only 2.7 ounces and is approximately the size of a pager. It is intended to be clipped to a belt or an arm band worn by the patient.

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 (Lorentz Force). It is a fundamental principle of modern physics with application in biology and medicine [9]. Molecular signals are obtained from solvated molecules using a direct-current super-conducting quantum interference device coupled to a second derivative gradiometer operating in a highly shielded magnetic environment. The apparatus is used to generate a  $\mu$ RFE cognate by placing a sample of the solvated molecule of interest within a magnetically shielded Faraday cage, centered within the gradiometer. The Voyager produces  $\mu$ RFE that induces a biologic response in malignant solid tumors [10]. The encrypted time-series data used to generate the  $\mu$ RFE cognate is embedded in the firmware of the Voyager controller during manufacturing and cannot be altered or copied after release for clinical use. The  $\mu$ RFE cognate A1A, is theorized to act on the distribution of charge within the  $\beta$ -tubulin monomer through magnetic induction, thereby forcing a conformational change that strengthens bonds between monomers and dimers, leading to multinucleation and disruption of mitotic spindle activity during cell division at metaphase [11]. The  $\mu$ RFE produced by the Voyager readily penetrates the brain tissue thereby delivering therapy across the blood-brain barrier to the entire volume

Table 1. Patient disposition (safety population).

Reasons	n (%)
<b>Off treatment reasons</b>	
Completed treatment schedule	8 (73%)
Documented disease progression	9 (82%)
Treatment-related toxicity	0 (0.0%)
Nontreatment-related toxicity	0 (0.0%)
Patient requested early discontinuation of study but still followed	0 (0%)
Physician requested early discontinuation of study for reasons not related to toxicity	2 (18%)
Death	8 (73%)
Noncompliance	0 (0.0%)
Other	0 (0%)
<b>Off study reasons</b>	
Completed treatment schedule	0 (0.0%)
Documented disease progression	0 (0.0%)
Patient requested early discontinuation of study but still followed	0 (0.0%)
Lost to follow-up	0 (0.0%)
Death	8 (73%)
Other	2 (18%)

Note: One patient is still on treatment, as of data cutoff of 10 July 2018.

of the brain. The electromagnetic field consists of two components, the electric field and magnetic field, each occurring perpendicular to the other. Extremely low frequency magnetic fields easily penetrate the human body without any significant attenuation [12,13]. This is in contrast to electric fields that can be highly attenuated by human tissue [12,13]. The objective of this study was to assess whether the Voyager  $\mu$ RFE therapy is a safe and feasible treatment for recurrent GBM.

## Materials & methods

### Patient selection & study design

Patients were eligible to participate in the study if they had a histologically confirmed diagnosis of GBM, failed or were intolerant to radiotherapy, failed or were intolerant to TMZ therapy, had progressive disease with at least one measurable lesion on MRI or CT, were at least 18 years of age, had a Karnofsky Performance Score  $\geq 60$ , had adequate organ and marrow function, and provided signed, informed consent.

The Nativis Voyager is an investigational medical device consisting of only three components – a battery-operated controller, an electromagnetic coil and a battery charger. Patients were provided two controller units to make a fully charged unit always available. No special alignment of the coil on the head was necessary. Treatment 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 MRI were performed at baseline and at each visit.

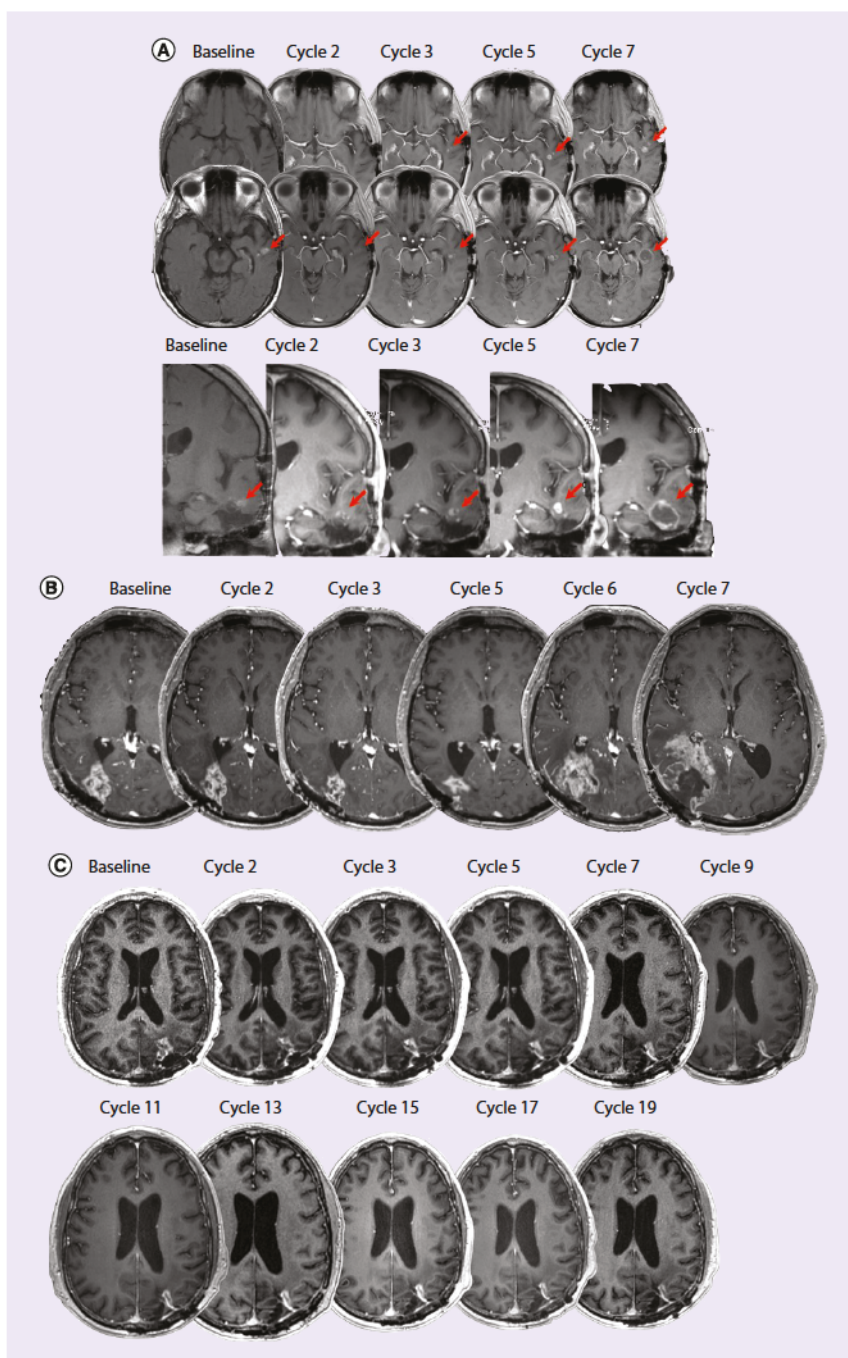
In this study, patients received treatment with A1A, a  $\mu$ RFE cognate that mimics the action of paclitaxel by inhibiting microtubule function [11]. Investigators were given the choice to treat patients with Voyager alone or to treat with Voyager plus SoC anticancer agents. The treatment arms were not intended for comparison.

The study protocol and subsequent amendments as well as the patient informed consent form were reviewed and approved by the Western institutional review board.

### 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, progression-free survival (PFS) at 6 months, median PFS, overall survival (OS) at several intervals and median OS. The radiological response of the tumor was assessed by MRI



**Figure 2.** Examples of MRI responses on study. All patients were treated continuously with the Voyager. Investigators were given the choice to treat patients with Voyager alone or to treat with Voyager plus anticancer agents of their choice. (A) 55-year-old female with GBM at first recurrence (methylation status unknown) treated with Voyager alone arm. Serial axial and coronal T1 postgadolinium images show PR at cycle 2 and eventual progression at cycle 7. (B) 54-year-old male with GBM at second recurrence (methylation status unknown) treated with Voyager plus temozolomide. Serial axial T1 postgadolinium images show PR at cycle 3 and eventual progression at cycle 6. (C) 55-year-old male with GBM at first recurrence (methylated) treated with Voyager plus lomustine. Serial axial T1 postgadolinium images show PR at cycle 5. GBM: Glioblastoma; PR: Partial response.

Characteristic	Treatment arms	
	Voyager alone (n = 4)	Voyager + SoC (n = 7)
<b>Age (years):</b>		
– Median (min, max)	56.5 (33, 60)	54.5 (38, 64)
<b>Gender, n (%):</b>		
– Female	2 (50%)	2 (29%)
– Male	2 (50%)	5 (71%)
<b>Race, n (%):</b>		
– Caucasian	4 (100%)	7 (100%)
<b>Ethnicity, n (%):</b>		
– Not Hispanic or Latino	4 (100%)	7 (100%)
<b>KPS, n (%):</b>		
– 100%	1 (25%)	1 (13%)
– 90%	2 (50%)	2 (29%)
– 80%	1 (25%)	2 (29%)
– 70%	0 (0%)	2 (29%)
– 60%	0 (0%)	0 (0%)
– <60%	0 (0%)	0 (0%)
<b>Number of recurrences, n (%):</b>		
– 1	1 (25%)	2 (29%)
– 2	2 (50%)	2 (29%)
– 3 or more	1 (25%)	3 (42%)
<b>Days from GBM diagnosis to enrollment:</b>		
– Median (min, max)	1545 (417, 5055)	335 (187, 991)
<b>Days from last radiotherapy to enrollment:</b>		
– Median (min, max)	686 (618, 770)	288 (69, 841)
<b>Days from last temozolomide dose to enrollment:</b>		
– Median (min, max)	578 (509, 4942)	143 (1, 757)

GBM: Glioblastoma; KPS: Karnofsky Performance Score; SoC: Standard of care.

studies according to RANO criteria [14]. All patients had their tumor measurements recorded at baseline and at the time of each MRI scan. The dose and type of contrast agent was held constant from scan to scan for each patient. Images were assessed by the investigators as well as an independent radiology review team.

### Statistical analysis

The Voyager alone and Voyager + SoC arms were evaluated separately. Data from patients who were enrolled and treated for at least 1 month were included in the analysis of safety and feasibility in the first cohort.

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 Karnofsky Performance Score) were summarized via counts and percentages.

AEs were graded according to the NCI Common Terminology Criteria for Adverse Event Version 3.0 (CTCAE V3.0) and were also coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Treatment-emergent adverse events (TEAEs), defined as any AE that occurred after a subject 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 (TESAEs) were tabulated by MedDRA preferred term within SOC.

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

Table 3. Clinical utility end points.

End point	Treatment arms	
	Voyager alone (n = 4)	Voyager + SoC (n = 7)
Days on treatment:		
– Median (min, max)	134 (27, 222)	242 (29, >1000)
PFS:		
– Median (weeks)	10	16
PFS-6:		
– n (%)	0 (0%)	3 (43%)
OS:		
– Median (months)	16	11
OS-6:		
– n (%)	4 (100%)	7 (100%)
OS-12:		
– n (%)	2 (50%)	3 (43%)
OS-18:		
– n (%)	2 (50%)	2 (29%)
OS-24:		
– n (%)	2 (50%)	2 (29%)
OS-36:		
– n (%)	0 (0%)	1 (14%)
Tumor response after 2 months (by investigator), n:		
– Disease controlled	2	5
– CR	0	0
– PR	1	1
– SD	1	4
– PD	2	2

CR: Complete response; OS: Overall survival; PD: Progressive disease; PFS: Progression free survival; PR: Partial response; SD: Stable disease; SoC: Standard of care.

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.

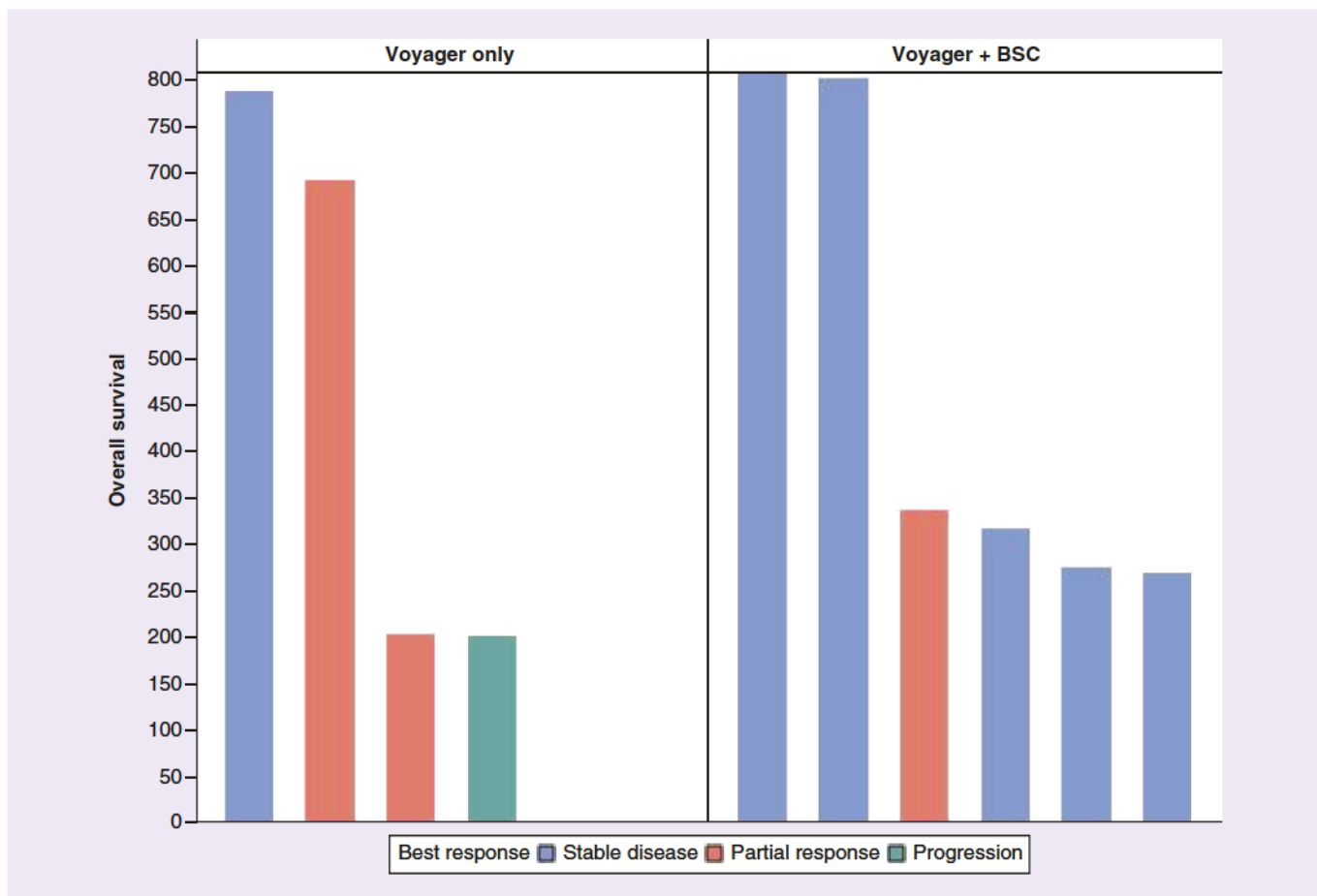
Tumor response was assessed by the RANO criteria from MRI conducted at each post-treatment visit. A copy of each scan was submitted to two independent radiology reviewers and outcomes were compared. Patients with unknown status for tumor response at the time point were excluded from the analysis.

Survival rates were estimated: PFS rate at 6 months (PFS-6), OS at 6 months (OS-6), OS at 12 months (OS-12), OS at 18 months (OS-18), OS at 24 months (OS-24), and OS at 36 months (OS-36). 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. OS was assessed using death as the end point. PFS was determined using RANO criteria. A plot for each treatment arm was produced, displaying survival time and best overall tumor response for each patient.

## Results

Eighteen patients were screened and 15 were enrolled and received at least 1 day of treatment with the investigational device alone in or combination with SoC. Of these 15 treated patients, 11 were treated for at least 1 month and were the basis of the safety and feasibility analysis in this first cohort. All patients are followed on study until death (Table 1). The patient population is typical of those with rGBM (Table 2).



**Figure 3.** The relationship between survival and tumor response in Voyager alone and Voyager + standard of care treatment arms. All patients were treated continuously with the Voyager. Investigators were given the choice to treat patients with Voyager alone or to treat with Voyager plus anticancer agents of their choice. Tumor response was determined via MRI every 2–4 months, according to the modified RANO criteria. This modified waterfall plot illustrates the relationship overall survival (in months) and the best overall tumor response.

#### Summary of safety

There were no clinically significant changes on physical exams (including changes in vital signs and neurological exams) or in laboratory findings at any timepoint (data not shown). A total of 55 TEAEs were reported. All patients reported at least one TEAE; none were related to the investigational device. One patient reported a serious AE, which was an infection of the ankle and not related to the investigational device. The most commonly reported TEAE was seizure. None of the patients stopped treatment or withdrew from the study due to TEAEs.

#### Summary of clinical utility

The median day on treatment were 134 days in the Voyager alone treatment arm and 242 days in the Voyager + SoC treatment arm (Table 3). The longest treatment duration occurred in a patient in the Voyager + SoC, with treatment ongoing at >1000 days. PFS was longer in the Voyager + SOC treatment arm and OS was longer in the Voyager alone treatment arm (Table 3). The most frequently documented response by investigators was stable disease. Figure 2 shows examples of objective MRI responses. Figure 3 displays the relationship between survival (in months) and tumor response. Overall, seven (64%) patients had stable disease at first response assessment.

#### Discussion

The Nativis Voyager is a nonsterile, noninvasive, nonthermal, nonionizing, battery-operated, portable and investigational medical device. The aim of this clinical study was to assess if the Voyager is a safe and feasible treatment for recurrent GBM. Overall, treatment with the Voyager was safe. No device-related serious AEs were reported. Of

the 55 TEAEs reported during the study, none were related to the investigational device. The deaths that occurred on study were expected outcomes of recurrent GBM and not associated with use of the investigational device.

The majority of patients in this study achieved a best overall response of either stable disease or partial response, providing preliminary evidence for the clinical utility of this investigational medical device. When combined with concurrent anticancer therapies, the data further suggest an OS rate in patients with rGBM that exceeds that expected with anticancer therapies alone [4,8]. Although the number of patients was small in this early feasibility cohort, safety data, tumor response and survival outcomes supported expanding both treatment arms in this study to further investigate the safety and clinical utility of this Nativis Voyager in adults with recurrent GBM.

Based on these data, the current study in rGBM was expanded. The study is ongoing and the data will be reported separately. In addition, a study was initiated in patients with newly diagnosed GBM (NAT-109, NCT03276286).

Although this study is conducted in adults with GBM, the safety and clinical utility of the Nativis Voyager device could be relevant to other high-grade gliomas. For example, diffuse midline glioma (DMG) is an aggressive and lethal brain tumor in young children, adolescents and young adults [1,2]. DMG, including diffuse intrinsic pontine glioma, is characterized by a distinctive H3 K27M histone mutation, which is associated with poor prognosis and is mutually exclusive of favorable prognostic molecular markers in other gliomas such as methylation, isocitrate dehydrogenase, and epidermal growth factor receptor amplification [2]. Pediatric patients are currently being treated under a compassionate use program. Most of these children have been diagnosed with diffuse midline glioma or diffuse intrinsic pontine glioma.

## 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, additional patients were enrolled in both treatment arms and will be reported separately.

## Future perspective

Treatment of brain cancer is likely to continue to include a multimodality approach. However, multiple cognates can be delivered via the Voyager. As such, there is the possibility to use a 'cocktail' of cognates either alone or in combination with drug therapy. Beyond brain cancer in adults and children, the Voyager technology could be applied to other tumor types as well as nononcology and nonmedical uses. For example, the Voyager technology is being explored for treatment of lung cancer, management of pain and applications in veterinary medicine.

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## Financial & competing interests disclosure

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### Summary points

- The Nativis Voyager is a noninvasive, nonthermal, nonionizing, battery-operated and portable investigational medical device that uses ultra-low radio frequency energy (*u*/RFE®) to treat cancer.
- *u*/RFE technology is theorized to act on the distribution of charge within the  $\beta$ -tubulin monomer through a process known as magnetic induction (Lorentz Force), thereby forcing a conformational change that strengthens bonds between monomers and dimers.
- NAT-101 (NCTC02296580) is a multisite, prospective, open-label and early feasibility study intended to assess the safety and feasibility of the Voyager as a treatment for recurrent glioblastoma (GBM), using the *u*/RFE cognate A1A.
- Investigators assigned patients to a Voyager alone treatment arm or Voyager plus standard of care (SoC) treatment arm.
- There were no treatment-emergent serious AEs 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 either stable disease or partial response.
- The data suggest that the Nativis Voyager is safe for the treatment of recurrent GBM and has clinical utility for the treatment of recurrent GBM.

### References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Ostrom QT, Gittleman H, Liao P *et al*. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro-oncology* 19(5), 1–88 (2017).
2. Louis DN, Perry A, Reifenberger G *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 131(6), 803–820 (2016).
3. Stupp R, Taillibert S, Kanner A *et al*. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA* 318(23), 2306–2316 (2017).
4. Sim HW, Morgan ER, Mason WP. Contemporary management of high-grade gliomas. *CNS Oncol.* 7(1), 51–65 (2018).
5. Wilson TA, Karajannis MA, Harter DH. Glioblastoma multiforme: state of the art and future therapeutics. *Surg. Neurol. Int.* 5, 64–62 (2014).
6. Thakkar JP, Dolecek TA, Horbinski C *et al*. Epidemiologic and molecular prognostic review of glioblastoma. *Cancer Epidemiol. Biomark. Prev.* 23, 1985–1996 (2014).
7. Stupp R, Hegi ME, Mason WP *et al*. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised Phase III study: 5-year analysis of the EORTCNCIC trial. *Lancet Oncol.* 10, 459–466 (2009).
8. Stupp R1, Wong ET, Kanner AA *et al*. TTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur. J. Cancer* 48(14), 2192–202 (2012).
9. Hunt RW, Zavalin A, Bhatnaga AR, Chinnasamy S, Das KC. Electromagnetic biostimulation of living cultures for biotechnology, biofuel and bioenergy application. *Int. J. Mol. Sci.* 10, 4515–4558 (2009).
10. Ulasov IV, Foster H, Butters M *et al*. Precision knockdown of EGFR gene expression using radio frequency electromagnetic energy. *J. Neurooncol.* 133(2), 257–264 (2017).
- **Demonstrates *in vitro* and *in vivo* activity of the technology.**
11. Butters JT, Figueroa XA, Butters BM. Non-thermal radio frequency stimulation of tubulin polymerization *in vitro*: a potential therapy for cancer treatment. *Biophys. J.* 4, 147–168 (2014).
- **Demonstrates effect of the technology on tubulin (i.e., mechanism of action).**
12. Barnes SF, Greenebaum B. In: *Biological and Medical Aspects of Electromagnetic Fields*. CRC Press, Boca Raton, FL, USA (2007).
- **Describes biological activity of electromagnetic fields.**
13. International Commission on Non-ionizing Radiation Protection (ICNIRP). ICNIRP Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300GHz). *Health Phys.* 74(4), 494–522 (1998).
- **Describes safety and activity of electric versus electromagnetic fields.**
14. Wen PY, Macdonald DR, Reardon DA *et al*. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J. Clin. Oncol.* 28(11), 1963–1972 (2010).

