Short Communication

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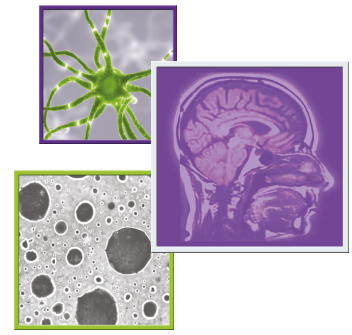

An expanded safety/feasibility study of the EMulate Therapeutics Voyager™ System in patients with recurrent glioblastoma

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Aim: The EMulate Therapeutics Voyager™ is a simple, wearable, home-use device that uses an alternating electromagnetic field to alter biologic signaling within cells. **Objective:** To assess the safety/feasibility of the Voyager in the treatment of recurrent glioblastoma (rGBM). **Methods:** In this study, patients with rGBM were treated with Voyager as monotherapy or in combination with standard chemotherapy at the Investigator's discretion. Safety was assessed by incidence of adverse events associated with the Voyager. Patients were followed until death. **Results:** A total of 75 patients were enrolled and treated for at least one day with the Voyager (safety population). Device-related adverse events were uncommon and generally did not result in interruption or withdrawal from treatment. There were no serious adverse events associated with Voyager. A total of 60 patients were treated for at least one month (clinical utility population). The median progression-free survival (PFS) was 17 weeks (4.3 months) in the Voyager only group (n = 24) and 21 weeks (5.3 months) in the Voyager + concurrent therapy group (n = 36). The median overall survival (OS) was 7 months in the Voyager only group and 9 months in the Voyager + concurrent therapy group. In patients treated with Voyager + concurrent therapy, the median OS for patients enrolled with their 1st or 2nd recurrence (n = 26) was 10 months, while in patients enrolled with their 3rd or 4th recurrence (n = 10) OS was 7 months. **Conclusion:** The data support the safety and feasibility of the Voyager for the treatment of rGBM. Further prospective study of the device is warranted.

Trial Registration Number: NCT02296580 (ClinicalTrials.gov).

First draft submitted: 3 October 2022; Accepted for publication: 6 July 2023; Published online: 18 July 2023

Keywords: brain tumor • clinical trial • electromagnetic field • GBM • medical device • novel therapy • recurrent glioblastoma

Glioblastoma (GBM) is the most malignant of astrocytomas and the most common primary malignant intracranial neoplasm [1,2]. With current standard of care (SoC), the median survival in patients with newly diagnosed GBM is 15 months and in recurrent GBM is 6 months [3–9]. The SoC for newly diagnosed GBM is considered maximal safe resection of the tumor, followed by concurrent radiotherapy with temozolomide and subsequent

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adjuvant temozolomide. Resection of the primary tumor is not curative, and disease progression and recurrence generally occur within a year. Upon recurrence, patients are treated with a wide range of chemotherapeutic agents; the most common are lomustine and bevacizumab. Novocure's Optune™ system is an electric field therapy device approved for patients with rGBM patients after the completion of radiotherapy [4,8]. Unfortunately, GBMs develop chemoresistance due to various mechanisms, such as angiogenesis, immune escape, and hypoxic tumor microenvironment and acidosis. The blood brain barrier limits or blocks the efficient delivery of chemotherapy agents which contributes to chemoresistance. As a result, finding strategies to improve outcomes in GBM is an urgent issue.

The Emulate Therapeutics™ Voyager is a non-sterile, wearable, non-thermal, non-ionizing, portable, battery-operated, home-use medical device that delivers a defined, localized ultra-low radio frequency energy (*ul*RFE®) signal, referred to as the A1A cognate or A1A, for treatment of malignant solid tumors. The Voyager System uses a low-frequency magnetic field. The effects of the A1A WAV signal produce an increase in the tubulin polymerization rate, emulating the mechanism of action of paclitaxel (Supplementary Figure 1), inhibiting the disassembly of the spindles, and leading to an increase in cell-cycle aberrations. The A1A signal is delivered to the patient by an electromagnetic coil worn externally on the top of the head, much like a headband. The coil is connected to a small controller device and is clipped to a patient's pocket or belt. It was designed to be worn continuously, without the need for shaving the head, and can be easily removed when a patient showers. The magnetic field is attenuated by approximately 0.1 to 0.05% and the field extends up to 6 inches from the center of the head coil. Only ferro-magnetic materials alter of block the propagation of the magnetic field. Hair, wigs or cloth are transparent to the magnetic field. Nonclinical studies demonstrated that the device has cancer cell anti-proliferative activity *in vitro* and *in vivo* [9,10]. Early feasibility studies in patients with recurrent GBM demonstrated that the device is safe and suggested that the device provides a clinical benefit [11,12].

The closest comparable device for GBM treatment is Novocure's, Optune™ system whose mechanism of action differs from that of Emulate Therapeutics A1A signal. Optune applies a voltage gradient across two electrodes at a frequency of 200 kHz. The charge on the electrodes switches from positive to negative 200,000-times per second and has been given the moniker "Tumor Treatment Field" (TTF) [13]. This fast switching of charge across the axis of the tumor disrupts cell division by disrupting the spindle formation of the dividing tumor cells. The predominant local adverse events seen with TTFs are dermatologic, due to continuous contact between the arrays and the shaved scalp. The AEs associated with the Optune device have been previously described [14–16].

To date, there is no standard treatment for recurrent GBM. Prior to the introduction of tumor treating fields which was first approved by Food and Drug Administration in 2011, clinical trials, chemotherapy, re-operation, radiation, and immunotherapy were the only potential treatment options. Increasing evidence suggests chemotherapy-free treatment is needed as it has less toxicity and improved quality of life. NAT-101, is prospective, open-label, multi-center trial conducted in the US and Australia to assess if the Voyager *ulRFE* therapy either alone or when combined with chemotherapy is a safe and feasible treatment for recurrent GBM. This report reflects the data from the first and second cohorts of the NAT-101 study in patients with recurrent GBM.

Methods

Patient selection & study design

This study (NAT-101) is registered as NCT02296580 on www.clinicaltrials.gov. The protocol and informed consent documents were reviewed and approved by Western Institutional Review Board. Patients were enrolled to participate in the study if they were at least 18 years of age, had a histologically-confirmed diagnosis of GBM, had failed or were intolerant to radiotherapy, failed or were intolerant to temozolomide, had progressive disease with at least one measurable lesion on MRI, had a KPS score $\geq$60, had adequate organ and marrow function, and provided signed, informed consent as described in Cobbs *et al.* [11]. Patient enrollment, allocation, follow-up and analysis are as diagrammed in Figure 1.

There are 3 major versions of the study protocol that enrolled 3 cohorts of patients with recurrent GBM. In the first cohort [12], 4 patients were treated with the Voyager and 7 patients treated with the Voyager + the Investigator's choice of chemotherapy (i.e., local standard-of-care, SoC) with no restriction on number of recurrences (original approval 5/3/14). An amendment approved by the institutional review board (IRB) allowed for an increase in the sample size from 11 to 64 with planned 32 patients in Voyager alone and 32 patients in Voyager + SoC (Lomustine, bevacicumab, etc) arms and did not exclude prior bevacicumab usage (amendment date 8/17/15). Therefore, 17 additional patients were treated with the Voyager alone and 31 additional patients were treated with

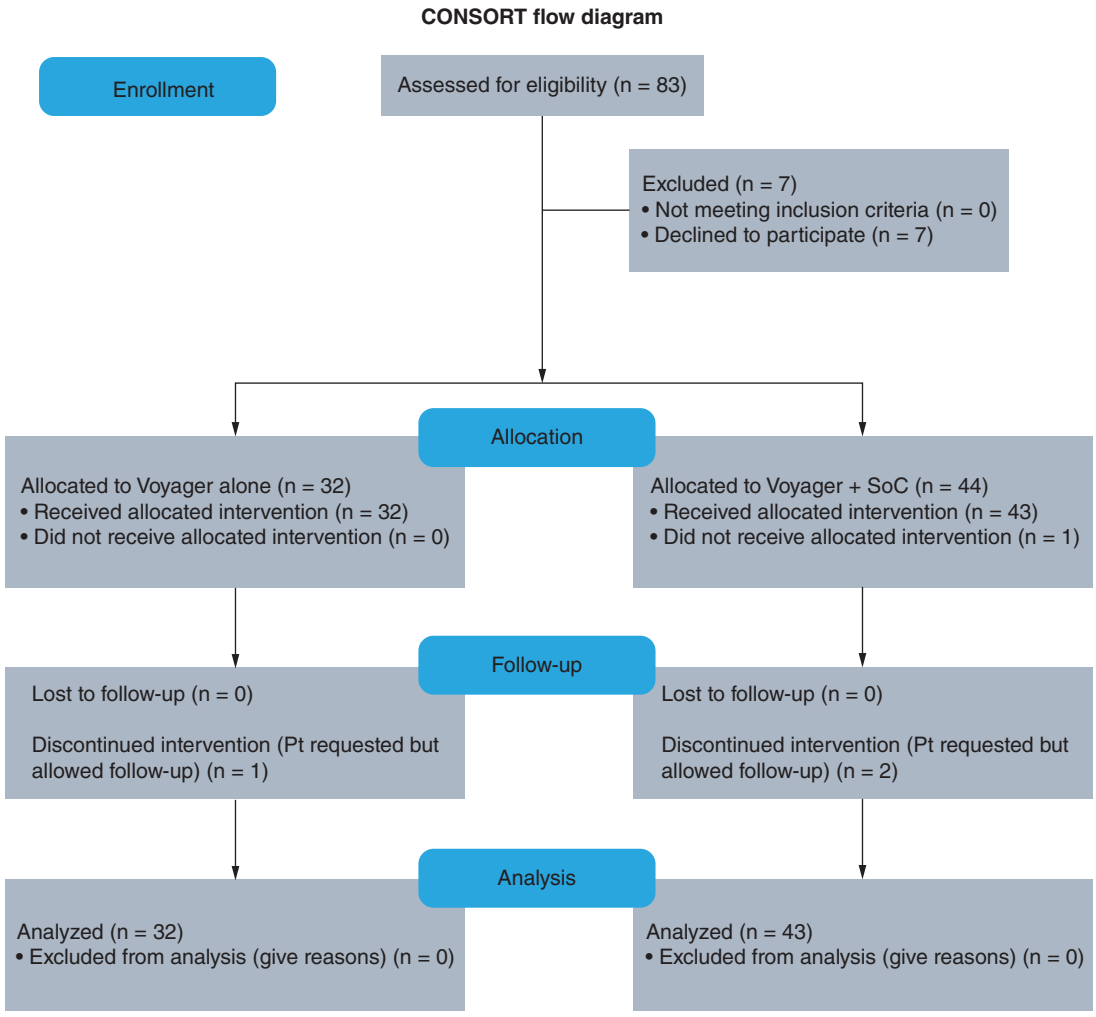

Figure 1. CONSORT flow diagram.
Pt: Patient; SoC: Standard of care.

the Voyager + SoC. A later amendment approved by the IRB allowed (amendment date 5/1/2018) narrowed the criteria to allow for an enrollment of patients with only first and second recurrence GBM treated with Voyager in combination with the standard chemotherapy Lomustine and excluded prior bevacicumab failures and a further 7 additional patients were treated with the Voyager alone and 4 additional patients were treated with the Voyager + SoC for total 32 patients on Voyager alone arm and 43 patients on the Voyager + SoC arm (Table 1). Once enrolled, patients were treated with Voyager alone or with Voyager + SoC, at the Investigator's discretion. Treatment with the investigational device was administered continuously (i.e., 24/7) until unequivocal disease progression, occurrence of a device-related clinically significant adverse event, unacceptable adverse reactions, or removal from the study as described in Cobbs *et al.* [11]. At the discretion of the Investigator, patients could remain on voyager treatment post-progression with the option to add concurrent bevacizumab with any other chemotherapies. Patient visits occurred at least every 42 days during the first 6 months and follow-up every 4 months (±2 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 [11]. Subjects who drop out of study prior to completing six months (6 cycles) of therapy for reasons other than toxicity related to the investigational treatment or disease progression may be replaced with another subject. All subjects who have received treatment will be included in the safety end point analysis.

Table 1. Demographics and baseline characteristics.

Characteristic	Treatment arms			
	Voyager only (N = 32)	Voyager + SoC		
		Total (N = 43)	Voyager + SoC 1st and 2nd (N = 32)	Voyager + SoC 3rd and 4th (N = 11)
Age (years), n				
Mean (SD)	55.97 (14.24)	53.09 (14.47)	51.91 (13.79)	56.55 (16.49)
Median (min, max)	59.5 (26, 82)	56 (17, 79)	55 (17, 79)	61 (22, 77)
Gender, n (%)				
Female	13 (41)	17 (40)	13 (41)	4 (36)
Male	19 (59)	26 (60)	19 (59)	7 (64)
Race, n (%)				
Black or African–American	1 (3)	1 (2)	1 (3)	0 (0)
Asian	2 (6)	1 (2)	1 (3)	0 (0)
White	28 (88)	40 (94)	29 (91)	11 (100)
Unknown	1 (3)	1 (2)	1 (3)	0 (0)
Ethnicity, n (%)				
Hispanic or Latino	3 (10)	5 (12)	4 (13)	1 (9)
Not Hispanic or Latino	26 (81)	35 (82)	26 (81)	9 (82)
Unknown	1 (3)	2 (4)	1 (3)	1 (9)
Not reported	2 (6)	1 (2)	1 (3)	0 (0)
Karnofsky performance score, n (%)				
100%	6 (19)	3 (7)	2 (6)	1 (9)
90%	8 (25)	14 (32)	13 (41)	1 (9)
80%	11 (34)	9 (21)	5 (16)	4 (36)
70%	3 (9)	11 (26)	9 (28)	2 (18)
60%	4 (13)	6 (14)	3 (9)	3 (28)
<60%	0 (0)	0 (0)	0 (0)	0 (0)
Number of recurrences, n (%)				
1	19 (60)	22 (51)	22 (69)	0 (0)
2	9 (28)	10 (23)	10 (31)	0 (0)
3 or more	4 (12)	11 (26)	0 (0)	11 (100)
Days from GBM diagnosis to enrollment				
Median	415	279	221	584
Days from last radiotherapy to enrollment				
Median	323	205	159	534
Days from last temozolomide dose to enrollment				
Median	209	133	83	169
Prior use of bevacizumab, n (%)				
Yes	11 (34)	7 (16)	4 (12)	3 (27)
No	21 (66)	36 (84)	28 (88)	8 (73)
MGMT methylation, n (%)				
Yes	9 (28)	10 (23)	6 (18)	4 (36)
No	7 (22)	19 (44)	12 (38)	7 (64)
Unknown	16 (50)	14 (33)	14 (44)	0 (0)

GBM: Glioblastoma; SD: Standard deviation; SoC: Standard of care.

Safety & clinical utility measurements

Safety was assessed by incidence and evaluation of any adverse events (AEs) associated with the investigational therapy, abnormal laboratory findings, vital signs and findings on physical and neurological exam [11]. Adverse events were coded with MedDRA Coding Dictionary Version 19.1.

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 studies according to RANO criteria. 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 [11]. Patients whose MRI response was suspected to be pseudoprogression, had a repeat MRI confirmatory scan after 4 weeks.

Data analysis

The Voyager alone and Voyager + SoC arms were evaluated separately, and 2 patient populations were defined: safety population: the safety population included all patients that received at least one day of treatment with the Voyager; treated population: the treated population included all patients who received at least one month of treatment with the Voyager.

The primary objectives were to assess the safety and feasibility of the Voyager alone and combined with SoC for treatment of recurrent glioblastoma (rGBM). The secondary objectives were to measure clinical utility with PFS and OS. 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 non-missing responses. Categorical variables (gender, race, ethnicity, and KPS) were summarized via counts and percentages [11].

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 [11].

For the median survival end points – i.e., 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 [11]. PFS was assessed by the Investigators, using RANO criteria [17,18]. A modified waterfall plot of survival per treatment arm was plotted: survival time and best overall tumor response is displayed for each patient.

Results

Eighty-three patients were screened, and 75 were enrolled and received at least one day of treatment with the device. 32 patients enrolled on Voyager only arm and 43 on Voyager + SoC arm. The most common concurrent treatments either before or after progressive disease were the voyager alone or in combination with bevacizumab (n = 18), temozolomide (n = 12), and lomustine (n = 5). Demographics and other baseline characteristics are presented in Table 1.

Summary of safety

No clinically significant changes on physical exams (including changes in vital signs and neurological exams) or in laboratory findings (data not shown) were attributed to Voyager. A summary of adverse events for the study is presented in Table 2. Overall, 61 (81%) patients in the safety population reported at least one AE, and 24 (32%) patients reported at least one serious adverse event (SAE). In the Voyager + SoC treatment arm 86% of patients reported at least one AE, and 35% reported at least one SAE. In the Voyager only treatment arm 75% of patients reported at least one AE, and 28% reported at least one SAE. The higher incidence of AEs in the Voyager + SoC was an expected outcome, likely related to chemotherapy treatment. No SAEs were related to the Voyager, and no AEs resulted in withdrawal from treatment.

The grade 4–5 AEs reported included sepsis, encephalopathy, shortness of breath, weakness, fatigue, nausea, vomiting and failure to thrive. The AEs that were reported most frequently by MedDRA preferred term (≥5% frequency) are summarized in Table 3.

In the Voyager only treatment arm, the most frequently reported AE was fatigue, which occurred in 7 (22%) patients. The next most reported AEs were headache (6 patients; 19%) and aphasia (5 patients; 16%). Investigators determined that 6 AEs were at least possibly related to the device: 5 reports of headache (1 of which was reported as definitely related) and 1 report of confusion.

In the Voyager + SoC treatment arm, the most frequently reported AE was headache, which occurred in 13 (30%) patients. The next most reported AE was fatigue, which occurred in 12 (28%) patients. Seizure was reported

Table 2. Adverse event summary (safety population).

	Voyager only (N = 32)	Voyager + SoC (N = 43)	Voyager + SoC 1st and 2nd (N = 32)	Voyager + SoC 3rd and 4th (N = 11)	Combined (N = 75)
Patients with at least one adverse event, n (%)	24 (75)	37 (86)	27 (84)	10 (91)	61 (81)
Highest AE severity grade, n (%)					
Grade 1 mild	7 (22)	9 (21)	9 (28)	0 (0)	16 (21)
Grade 2 moderate	7 (22)	10 (23)	7 (22)	3 (27)	17 (23%)
Grade 3 severe or medically significant	7 (22)	9 (21)	7 (22)	2 (18)	16 (21)
Grade 4 life-threatening or disabling	1 (3)	5 (12)	2 (6)	3 (27)	6 (8)
Grade 5 death	1 (3)	1 (2)	1 (3)	0 (0)	2 (3)
Strongest relationship of AE to study device, n (%)					
Not related	15 (47)	25 (58)	19 (59)	6 (55)	40 (53)
Unlikely	4 (12)	5 (12)	2 (6)	3 (27)	9 (12)
Possibly	4 (12)	7 (16)	6 (19)	1 (9)	11 (15)
Probably	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Definitely	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
Patients experiencing at least one serious adverse event, n (%)	9 (28)	15 (35)	9 (28)	6 (55)	24 (32)

SoC: Standard of care.

Table 3. Number and percentage of patients with adverse events for most frequently reported preferred terms (safety population).

	Voyager only (N = 32)	Voyager + SoC (N = 43)	Voyager + SoC 1st and 2nd (N = 32)	Voyager + SoC 3rd and 4th (N = 11)	Combined (N = 75)
Total number of adverse events	116	264	195	69	380
Patients with at least one adverse event, n (%)	24 (75)	37 (86)	27 (84)	10 (91)	61 (81)
Fatigue	7 (22)	12 (28)	11 (34)	1 (9)	19 (25)
Headache	6 (19)	13 (30)	10 (31)	3 (27)	19 (25)
Seizure	4 (12)	9 (21)	6 (19)	3 (27)	13 (17)
Asthenia	4 (12)	6 (14)	5 (16)	1 (9)	10 (13)
Aphasia	5 (16)	3 (7)	3 (9)	0 (0)	8 (11)
Nausea	4 (12)	4 (9)	3 (9)	1 (9)	8 (11)
Fall	3 (9)	5 (12)	5 (16)	0 (0)	8 (11)
Urinary incontinence	3 (9)	5 (12)	3 (9)	2 (18)	8 (11)
Vomiting	3 (9)	4 (9)	4 (12)	0 (0)	7 (9)
Confusional state	2 (6)	4 (9)	3 (9)	1 (9)	6 (8)
Edema peripheral	2 (6)	4 (9)	4 (12)	0 (0)	6 (8)
Hemiparesis	2 (6)	4 (9)	2 (6)	2 (18)	6 (8)
Cognitive disorder	2 (6)	3 (7)	2 (6)	1 (9)	5 (7)
Diarrhea	1 (3)	4 (9)	3 (9)	1 (9)	5 (7)
Ataxia	1 (3)	3 (7)	3 (9)	0 (0)	4 (5)
Dizziness	3 (9)	1 (2)	1 (3)	0 (0)	4 (5)
Dysphagia	1 (3)	3 (7)	3 (9)	0 (0)	4 (5)
Gait disturbance	3 (9)	1 (2)	1 (3)	0 (0)	4 (5)
Thrombocytopenia	1 (3)	3 (7)	3 (9)	0 (0)	4 (5)
Upper respiratory tract infection	0 (0)	4 (9)	3 (9)	1 (9)	4 (5)

SoC: Standard of care.

Table 4. Summary of clinical utility (treated population).

End point	Treatment arms			
	Voyager only (N = 24)	Voyager + SoC (N = 36)	Voyager + SoC, 1st and 2nd (N = 26)	Voyager + SoC, 3rd and 4th (N = 10)
Days in treatment				
Median (range)	60 (1–1095)	73 (7–1335)	138 (7–1335)	54 (10–217)
Progression-free survival (weeks)				
Median (95% CI)	17 (7.6–29.1)	21 (9.1–26.7)	24 (13.9–33.9)	8 (3.3–14.6)
Progression-free survival at 6 months				
n (%)	8 (33)	14 (38)	13 (48)	1 (10)
Overall survival (months)				
Median (95% CI)	7 (4.4–14.3)	9 (6.2–11.1)	10 (6.7–11.5)	6 (3.4–11.1)
Overall survival at 6 months				
n (%)	14 (58)	25 (68)	19 (70)	6 (60)
Overall survival at 12 months				
n (%)	7 (29)	7 (19)	5 (18%)	2 (20)
Overall survival at 18 months				
n (%)	2 (8)	5 (14)	4 (15)	1 (10)
Overall survival at 24 months				
n (%)	2 (8)	4 (11%)	3 (11)	1 (10)
Overall survival at 36 months				
n (%)	0 (0)	1 (3)	1 (11)	0 (0)
Best overall response (by investigator), n				
Disease controlled	16	25	20	5
Complete response (CR)	1	0	0	0
Partial response (PR)	4	7	6	1
Stable disease (SD)	11	18	14	4
Progressive disease (PD)	5	5	2	3

SoC: Standard of care.

in 9 (21%) of the patients. Investigators determined that 7 AEs were at least possibly related to the device: 6 reports of headache and 1 report of insomnia.

Summary of clinical utility

Sixty patients were treated for at least one month (treated population); 24 were treated with Voyager only, and 36 were treated with Voyager + SoC. A summary of clinical utility end points is provided in Table 4. PFS-6 was achieved in 8 (33%) patients treated with Voyager only and in 14 (38%) patients treated with Voyager + SoC. Of the 14 Voyager + SoC patients with PFS-6, 13 were enrolled with their 1st or 2nd recurrence.

OS-6 was achieved in 14 (58%) patients treated with Voyager alone and in 25 (68%) patients treated with Voyager + SoC. Of the 25 Voyager + SoC patients reaching OS-6, 19 were enrolled with their 1st or 2nd recurrence and 6 with their 3rd or 4th recurrence.

OS rates were summarized up to 36 months, with 2 (8%) Voyager only patients and 4 (11%) Voyager + SoC patients achieving the OS-24 milestone and 1 Voyager + SoC patient the achieving OS-36 milestone. Four patients are still on study as of the database cut-off of 15 Mar 2019 for this interim analysis: 2 in the Voyager alone treatment arm and 2 in the Voyager + SoC treatment arm.

The PFS was 17 weeks (4.3 months) in the Voyager only treatment arm and 21 weeks in the Voyager + SoC treatment arm. The median time to death was 7 months in the Voyager only treatment arm and 9 months in the Voyager + SoC treatment arm. Correlation of MGMT methylation and IDH status of tumors with survival is inconclusive, given that both IDH and MGMT status was not able be retrieved for all patients since the clinical trial was from 2014–2018 and testing at sites was not consistently done.

In a sub-group analysis of the patients treated in the Voyager + SoC treatment arm, median PFS and OS were longer in patients who were enrolled with their first or second recurrence than in patients who were enrolled with

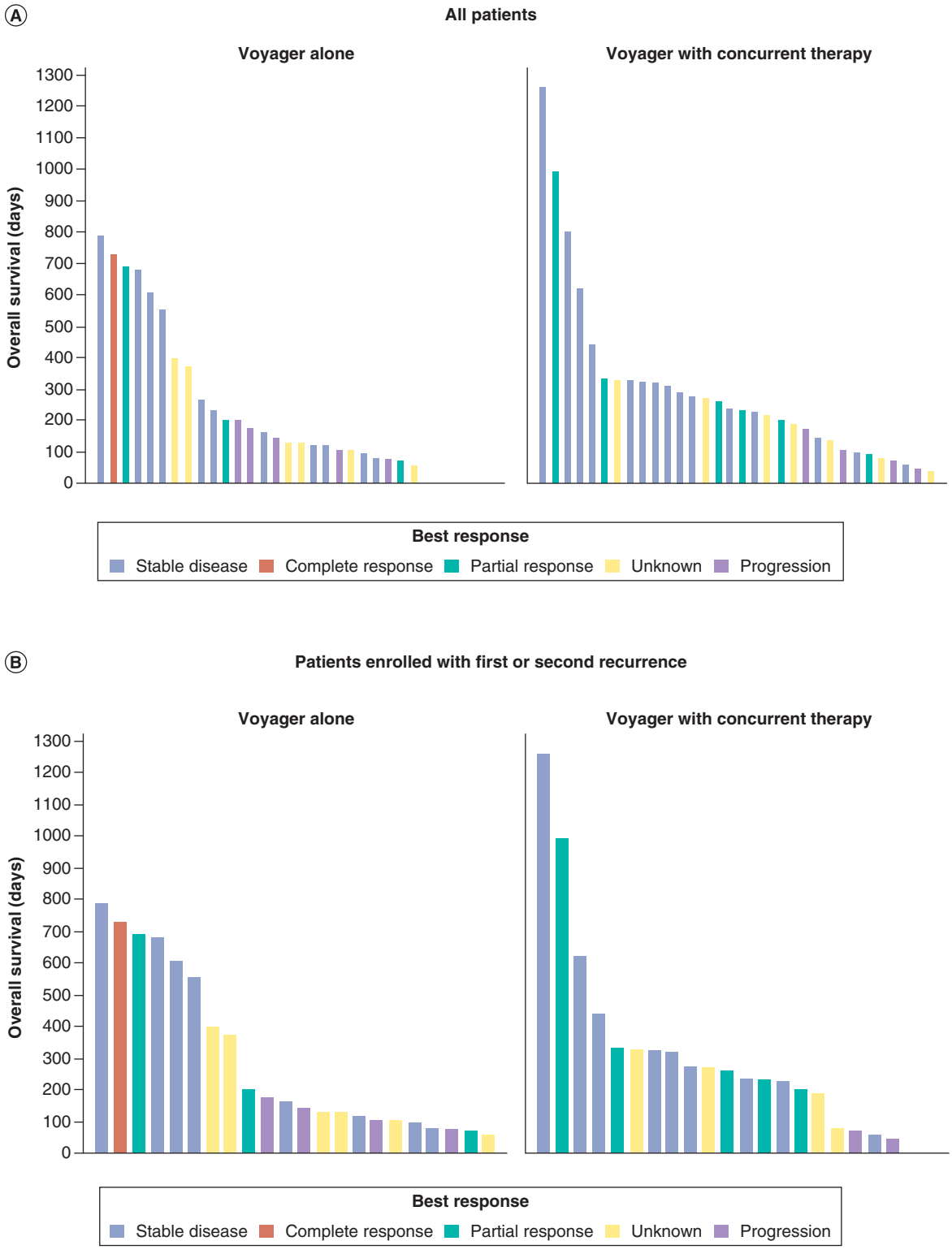

Figure 2. Relationship of survival and tumor response (treated population). Patients received continuous Voyager therapy. The protocol allowed for investigators to treat patients with Voyager alone or to treat with Voyager plus anticancer agents of their choice. Tumor response was assessed via MRI every 42 days. This modified waterfall plot illustrates the relationship between overall survival (in months) and the best overall tumor response. **(A)** All treated patients (n = 75). **(B)** Patients who entered the study with their first or second recurrence (n = 32).

their third or fourth recurrence (PFS 24 vs 8 wks; OS 10 vs 6 mths). Bevacizumab and repeat temozolomide were the most administered agents after progression with lomustine; 18 received bevacizumab, and 12 received temozolomide. The specific anti-cancer agent administered did not correlate with survival ($p > 0.2$), however those patients who achieved PFS-6 did live longer than those who did not (median OS 19 months vs 6 months, $p < 0.001$).

Survival plots are provided in Figure 2 to illustrate the relationship between the best overall tumor response and the overall survival time (in days) per patient. Stable disease as the most frequent best overall response reported by Investigators. Overall survival was longer in patients who were enrolled with their first or second recurrence.

Discussion

The Voyager system manufactured by EMulate Therapeutics is a non-sterile, wearable, non-thermal, non-ionizing, battery-operated, portable medical device that uses localized *ul*RFE for the treatment of malignant solid tumors, such as GBM [11,12]. Overall, treatment with the Voyager was safe; no device-related serious adverse events were reported and there were no clinically relevant trends in findings of clinical laboratory tests or physical exams (including vital signs and neurological findings) in this study. Larger studies in future will be needed to further define the AE profile.

Interpretation of efficacy is limited due to non-randomized nature of study, protocol amendments and higher than expected rate of loss of follow of patients. Certainly, based tumor response, PFS, and OS adding Voyager did no worse than standard of care approaches based on historical controls [3–9]. The best overall response (as assessed by the investigator) in each treatment arm was disease control (i.e., stable disease or partial response). Patients who were enrolled and treated with a first or second recurrence of GBM were more likely to have a partial response and longer PFS and OS.

Novocure's Optune is the first medical device to be used to treat GBM [4,8]. The device weighs 1.2 kg and requires electrodes to be placed on the shaved head of patients. The electrodes must be replaced every few days. The batteries must be recharged every 2–3 hours and take 2–4 hours to fully recharge. Optune delivers electrical energy, which requires close contact with the skin and penetrates bone and other tissues poorly and must be worn >18 hrs/day. In comparison, the Voyager is a small, lightweight device that is easy to use. The controller weighs 88 grams, measures approximately 8 cm × 3cm × 3 cm, and can fit in a pocket or in a waist pack. The battery in the controller holds a charge for about 16 hours and can be fully recharged in 2 hours. The headband is available in 4 sizes, with a diameter range of 182–204 mm, and sits on the patient's head like a crown. There is no need to shave the patient's head. The Voyager delivers electromagnetic energy, which readily penetrates bone and other tissues to reach the entire brain.

Lomustine monotherapy was investigated in several clinical trials with relapsed GBM and the median overall survival ranged from 5.6 to 8.6 months. The median overall survival in the phase 2 BELOB trial of lomustine at 110 mg/m^2 was 8 months (95% CI, 6–11 months) [19]. In another trial, the phase 2 REGOMA study, the median overall survival was 5.6 months (95% CI, 4.7–7.3 months) [20]. The phase 3 EORTC trial, showed a median overall survival of 8.6 months (95% CI, 7.6–10.4 months) [19]. Results of lomustine combined with Voyager shows the median OS in patients enrolled with their first or second recurrence was OS 10 months. Given the safety profile of the Voyager, these outcomes show hope in the use of Voyager in a combination therapy. However, a larger clinical trial is needed to power the study appropriately so that a true understanding of the control/comparator group can be demonstrated.

Conclusion

The objective of this study is to assess whether the Voyager therapy is a safe and feasible treatment for recurrent GBM. Based on the favorable safety profile and suggestion of clinical benefit, further investigation of the Voyager in the treatment of GBM is warranted in a prospective, randomized, controlled clinical trial.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cns-2022-0016

Acknowledgments

The authors thank their patients and research staff for support of this study.

Financial & competing interests disclosure

This study was funded and supported by EMulate Therapeutics, Inc. (formerly known as Nativis, Inc.). S Kesari was previously an advisor for Emulate Therapeutics, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Data sharing

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms agreed upon their receipt.

Summary points

- Glioblastoma is still a deadly disease with less than 5% 5-year survival.
- More clinical trials with new approaches are needed to advance the field faster.
- Various electromagnetic technologies that affect tumor growth are being tested in the clinic.
- Voyager therapy has shown safety in this study as single agent and when combined with standard of care chemotherapy in recurrent glioblastoma and adds minimal toxicity.
- Further studies are needed to expand the role of Voyager therapy in brain cancers as single agent and combined with other approaches from radiation to chemotherapy.
- Future studies will test the combination of Voyager in newly diagnosed setting with chemoradiation.

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