INSTRUCTIONS FOR USE

novocure®

This manual is intended for physicians prescribing the use of Optune Gio.
Additional information is found in the following materials:

- Patient Information and Operation Manual

Caution: Federal law restricts this device to sale by or on the order of a physician

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Indications for Use

Optune Gio is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune Gio with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune Gio is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Contraindications, Warnings, Precautions and Notices

Contraindications

Do not use Optune Gio if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators and programmable shunts. Use of Optune Gio together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune Gio together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune Gio ineffective.

Do not use Optune Gio if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Gio may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

Warning – Use Optune Gio only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). Ask to see a certificate signed by Novocure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune Gio without receiving this training can result in breaks in treatment and may rarely cause increased scalp rash, open sores on your head, allergic reactions or even an electric shock.

Warning – Optune Gio is not intended to be used as a substitute for chemotherapy but rather as an adjunct to treatment with TMZ for newly diagnosed GBM.

Warning – Do not use Optune Gio if you are 21 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Warning – Do not use Optune Gio if you are pregnant, you think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune Gio was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant or if it will be effective.

Warning – In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), use high potency topical steroids (hydrocortisone cream) when replacing transducer arrays. This will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin breakdown, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals. Taking a break from treatment may lower your chance to respond to treatment.

Warning – All servicing procedures must be performed by qualified and trained personnel. If you attempt to open and service the system alone you may cause damage to the system. You could also get an electric shock by touching the inner parts of the device.

Precautions

Caution – Keep Optune Gio out of the reach of children. If children touch the device, they could damage the device. This could cause a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution – Do not use any parts that do not come with the Optune Gio Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution – If your doctor used plates or screws to close your skull bone during your surgery, be careful when placing the transducer arrays. Make sure the segments that make up the transducer arrays are not on top of the areas where you can feel the screws or plates under your skin. In other words, make sure the screws or plates under your skin are in between the segments that make up the transducer arrays. If you do not do this, you may have increased skin damage which may lead to a break in treatment. Breaks in treatment may lower the chance of the device being effective.

Caution – Tell your doctor before using the device if you have an inactive implanted medical device in the brain (for example, stents, plastic drug delivery reservoirs, aneurysm clips or coils, device leads). Use of Optune Gio in subjects with inactive implanted medical devices in their brain was not tested and could lead to tissue damage or lower the chance of the device being effective.

Caution – Do not use Optune Gio if any parts look damaged (torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment. Breaks from treatment may lower your chance to respond to treatment.

Caution – Do not wet the device or transducer arrays. Getting the device wet may damage it, preventing you from receiving treatment for the right amount of time. Getting the transducer arrays very wet is likely to cause the transducer arrays to come loose from your head. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution – Before connecting or disconnecting the transducer arrays, make sure that the Optune Gio power switch is in the OFF position. Disconnecting transducer arrays with the device power switch in the ON position may cause a device alarm to go off, and could damage the device.

Caution – If you have an underlying serious skin condition on the scalp, discuss with your doctor whether this may prevent or temporarily interfere with Optune Gio treatment.

Notices

Notice! The Optune Gio device and transducer arrays will activate metal detectors.

Notice! Do not use Optune Gio if your tumor is located in the lower parts of the brain close to the spinal cord. Ask your doctor if your tumor is located in this part of your brain. Optune Gio has not been tested in patients with tumors in these locations. It is unknown whether these tumors will respond to treatment.

Notice! You should use Optune Gio for at least 18 hours a day to get the best response to treatment. Using Optune Gio for less than 18 hours a day lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune Gio before you finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune Gio even if you have used it less than the recommended 18 hours per day. You should stop using the device only if your doctor tells you to. Stopping treatment could lower the chances that you will respond to treatment.

Notice! If you plan to be away from home for more than 2 hours, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Make sure you have at least 12 extra transducer arrays at all times. This will last you until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays in time you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1.5 hours from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! You should carry the Troubleshooting Guide (Section 26) at all times. This guide is necessary to ensure Optune Gio works properly. If you do not work the system correctly you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Do not block the device vents located on the front and back of the Optune Gio device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device.

Notice! Do not block the battery charger vents located on the sides of the battery charger. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging.

Notice! Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

Notice! The transducer arrays are for single use and should not be taken off your head and put back on again. If you put a used transducer array back on your head again, it may not stick well to your skin and the device could turn off.

Description

Optune Gio, for the treatment of newly diagnosed and/or recurrent GBM, is a battery or power supply operated device which produces alternating electrical fields, called tumor treating fields ("TTFields") within the human body.
TTFields are applied to the patient by electrically- insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells.[1]

Optune Gio is comprised of two main components: (1) an Electric Field Generator (the Optune Gio device); and (2) Optune HFE transducer arrays (the transducer arrays). In addition, the following components are also included in the Optune Gio Treatment Kit: power supply, battery, battery charger, connection cable and carrying bag.

Treatment parameters are preset by Novocure such that there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced at least two times per week (every 4 days at most) and the scalp re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack and receive continuous treatment without changing their daily routine.

[1]Kirson, E. D., V. Dbaly, et al. (2007). "Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors." Proc Natl Acad Sci U S A 104(24): 10152-7.

Principles of Operation

Optune Gio produces alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp.

TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTField technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g.,200kHz for GBM).

In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells, nor do they stimulate nerves and muscles. It is noted that, because TTFields are only applied to the brain, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature. Thus, TTField application has the advantage of being highly selective and is not expected to be associated with significant toxicity.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

Preclinical Data

TTFields have been shown both in vitro and in vivo to effectively inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase.[2]

Specifically, TTFields have been shown to inhibit glioblastoma cells in vitro and in vivo at a frequency of 200 kHz and an intensity of 0.7 V/cm. Based on realistic finite element mesh simulations and direct measurements of TTFields intensity in experimental animals, and in the human brain, Novocure has concluded that effective TTField intensities can be generated in the brains of large animals and humans. Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TTFields are not associated with significant systemic toxicities. Neither acute, nor chronic systemic toxicities were seen when TTFields were applied to the torso or head, at different frequencies (100-200 kHz), different intensities and for different periods of time.[3]

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for Optune Gio has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

[2]Kirson, E. D., Z. Gurvich, et al. (2004). "Disruption of cancer cell replication by alternating electric fields." Cancer Res 64(9): 3288-95.

[3]Kirson, E. D., V. Dbaly, et al. (2007)

Clinical Data

NEWLY DIAGNOSED GLIOBLASTOMA (see page 23 for recurrent GBM)

Pilot Clinical Study in Newly Diagnosed GBM

Optune Gio together with temozolomide (TMZ) has been tested in ten newly diagnosed GBM subjects in a single center, pilot study in Europe. Median progression free survival (PFS) of the patients in this study exceeded historical controls (14.4 months versus 7.1 months, respectively). At the end of the study (4 years from initiation) 5 of the 10 patients died; of the remaining 5 patients 2 were lost to follow-up and 3 were reported alive and progression free. Median OS from diagnosis was greater than 40 months (compared to 14.7 months in historical controls). The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Pivotal Clinical Study in Newly Diagnosed GBM

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM subjects treated with Optune Gio and temozolomide (TMZ) to those treated with TMZ alone.

The following were the objectives of the study:

To prospectively compare the progression free survival and overall survival of newly diagnosed GBM subjects treated with Optune Gio and TMZ to those treated TMZ alone.

To collect evidence of the safety of TTFields applied to subjects with newly diagnosed GBM using Optune Gio.

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria

a. Pathological evidence of GBM using WHO classification criteria
b. ≥ 18 years of age
c. Received maximal debulking surgery and radiotherapy concomitant with temozolomide (45-70Gy):
    1) Patients may enroll in the study if received Gliadel wafers before entering the trial
    2) Any additional treatments received prior to enrollment will be considered an exclusion
    3) Minimal dose for concomitant radiotherapy is 45 Gy
d. Karnofsky scale ≥ 70
e. Life expectancy at least 3 months
f. Participants of childbearing age must use effective contraception
g. All patients must sign written informed consent
h. Treatment start date at least 4 weeks out from surgery
i. Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant temozolomide or radiotherapy

Exclusion Criteria

a. Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression
b. Actively participating in another clinical treatment trial
c. Pregnant
d. Significant co-morbidities at baseline which would prevent maintenance temozolomide treatment:
    1) Thrombocytopenia (platelet count < 100 x 103/µL)
    2) Neutropenia (absolute neutrophil count < 1.5 x 103/µL)
    3) CTC grade 4 non-hematological toxicity (except for alopecia, nausea, vomiting)
    4) Significant liver function impairment (AST or ALT > 3 times the upper limit of normal)
    5) Total bilirubin > upper limit of normal
    6) Significant renal impairment (serum creatinine > 1.7 mg/dL)
e. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias
f. Infra-tentorial tumor
g. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
h. History of hypersensitivity reaction to temozolomide or a history of hypersensitivity to DTIC

Study Procedures:

Treatment Arm

Optune Gio was given together with and after maintenance TMZ. TMZ was stopped after a median of 6 months. At treatment initiation patients were seen at an outpatient clinic. During this visit baseline examinations were performed and Optune Gio treatment initiated. The patients were instructed on the operation of Optune Gio and battery replacement. Once the patients were trained in operating the device they were released to continue treatment at home. The patients received multiple 1 month courses of continuous Optune Gio treatment. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Follow-up

During treatment all patients were seen once every month at an outpatient clinic where they underwent medical follow- up and routine laboratory exams. An MRI was performed every second month following the baseline MRI until second progression or 24 months (whichever came first). In the case of clinical progression an unscheduled MRI was obtained within 1 week of the investigator becoming aware of the clinical progression. No additional MRIs were required after second progression.

Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality was assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Analyses: Two analyses were performed in the study: An interim analysis on the first 315 patients with a minimum of 18 months follow-up and a final long term analysis on the full study cohort of 695 patients with a minimum follow-up of 24 months.

Protocol Deviations: Major protocol deviations were defined as deviations that have the potential to influence the primary and secondary efficacy endpoints of the study. There were a total of 13 major protocol deviations in the interim analysis and a total of 24 major protocol violations at the final analysis.

In the interim analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 11 patients in the TMZ alone arm received Optune Gio treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune Gio therapy was given without sponsor or investigator consent.

In the final long term analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 22 patients in the TMZ alone arm received Optune Gio treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune Gio therapy was given without sponsor or investigator consent. After the interim analysis, the protocol was modified to allow crossover. Twenty six patients in the control arm chose to crossover to receive Optune Gio.

Analysis Populations: Progression free survival was analyzed in the intent to treat (ITT) population which included all randomized subjects (210 Optune Gio/TMZ and 105 TMZ alone at the interim analysis; 466 Optune Gio/TMZ and 229 TMZ alone at the final long term analysis). Overall survival at the interim analysis was analyzed in the per protocol (PP) population which included all patients receiving at least the first course of TMZ and had no major protocol deviations (196 Optune Gio/ TMZ and 84 TMZ alone). Major protocol deviations included patients who received other experimental therapies on protocol or crossed over from the TMZ alone arm to Optune Gio/TMZ before the agency approved the crossover.

At the final long term analysis, overall survival and other secondary endpoints were analyzed in the intent to treat (ITT) population to avoid bias due to the approved crossover of 26 patients to Optune Gio (466 Optune Gio/TMZ and 229 TMZ alone), whose Optune Gio use may have affected their results compared to other control patients. Therefore, the ITT population is a conservative population for all endpoints in the final long term analysis.

Subject Characteristics: 315 subjects (210 Optune Gio/TMZ; 105 TMZ) with newly diagnosed GBM were enrolled in the interim analysis of the study. Baseline characteristics in the ITT population were as follows:

Baseline Characteristics	Treatment Group	
	Optune Gio/TMZ	TMZ Alone
	(N=210)	(N=105)
	n(%)	n(%)
Gender		
Male	140 (66.67)	67 (63.81)
Female	70 (33.33)	38 (36.19)
Central MGMT Assessment		
Invalid	24 (11.43)	11 (10.48)
Unknown	58 (27.62)	30 (28.57)
Methylated	49 (23.33)	26 (24.76)
Unmethylated	79 (37.62)	38 (36.19)
Extent of Resection		
Biopsy	23 (10.95)	11 (10.48)
Gross Total Resection	135 (64.29)	67 (63.81)
Partial Resection	52 (24.76)	27 (25.71)
Area		
ROW	83 (39.52)	41 (39.05)
USA	127 (60.48)	64 (60.95)
Tumor Position		
Missing	0 (0)	3 (2.86)
Corpus Callosum	12 (5.71)	3 (2.86)
Frontal Lobe	64 (30.48)	32 (30.48)
Occipital Lobe	7 (3.33)	4 (3.81)
Parietal Lobe	35 (16.67)	27 (25.71)
Temporal Lobe	92 (43.81)	36 (34.29)

Tumor Location			
Missing		0 (0)	1 (0.95)
Both		2 (0.95)	1 (0.95)
Corpus Callosum		8 (3.81)	3 (2.86)
Left		93 (44.29)	41 (39.05)
Right		107 (50.95)	59 (56.19)
Karnofsky Performance Score	Median	90	90
	Min, Max	60, 100	70, 100
Age in Years	Median	57	58
	Min, Max	20, 83	21, 80
No. of Cycles of TMZ Received	Median	6	4
	Min, Max	1, 26	1,24
No. of Cycles of Optune Gio Received	Median	9	0
	Min, Max	1, 58	0, 0
Time from GBM Diagnosis to Randomization (Days)	Median	115	113
	Min, Max	59, 171	43, 170

As seen above, all baseline characteristics are well balanced between arms in the ITT population at the interim analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 35 patients (11.11%) had tissue that was not evaluable, and 88 patients (27.9%) did not have tissue available for analysis.

695 subjects (466 Optune Gio / TMZ; 229 TMZ alone) with newly diagnosed GBM were enrolled in the study and were analyzed in the final long term analysis. Baseline characteristics in the ITT population were as follows:

Baseline Characteristics	Treatment Group	
	Optune Gio/TMZ	TMZ Alone
	(N=466)	(N=229)
	n(%)	n(%)
Gender		
Male	316 (67.8)	157 (68.6)
Female	150 (32.2)	72 (31.4)
Central MGMT Assessment		
Invalid	40 (10.4)	13 (7.0)
Unknown	82 (17.6)	44 (19.2)
Methylated	136 (35.4)	77 (41.6)
Unmethylated	208 (54.2)	95 (51.4)
Extent of Resection		
Biopsy	60 (12.9)	29 (12.7)
Gross Total Resection	249 (53.4)	123 (53.7)
Partial Resection	157 (33.7)	77 (33.6)
Area		
ROW	245 (52.58)	111 (48.47)
USA	221 (47.42)	118 (51.53)
Tumor Position		
Missing	31 (6.65)	15 (6.55)
Corpus Callosum	21 (4.51)	9 (3.93)
Frontal Lobe	142 (30.47)	67 (29.26)
Occipital Lobe	14 (3)	4 (1.75)
Parietal Lobe	77 (16.52)	50 (21.83)
Temporal Lobe	181 (38.84)	84 (36.68)

Tumor Location			
Missing		30 (6.44)	12 (5.24)
Both		12 (2.58)	3 (1.31)
Corpus Callosum		12 (2.58)	7 (3.06)
Left		193 (41.42)	93 (40.61)
Right		219 (47)	114 (49.78)
Karnofsky Performance Score	Median	90	90
	Min, Max	60, 100	70, 100
Age in Years	Median	56	57
	Min, Max	19, 83	19, 80
No. of Cycles of TMZ Received	Median	6	6
	Min, Max	1, 28	1, 24
No. of Cycles of Optune Gio Received	Median	8	10
	Min, Max	1, 80	1, 17
Time from GBM Diagnosis to Randomization (Days)	Median	113	111
	Min, Max	50, 498	43, 500

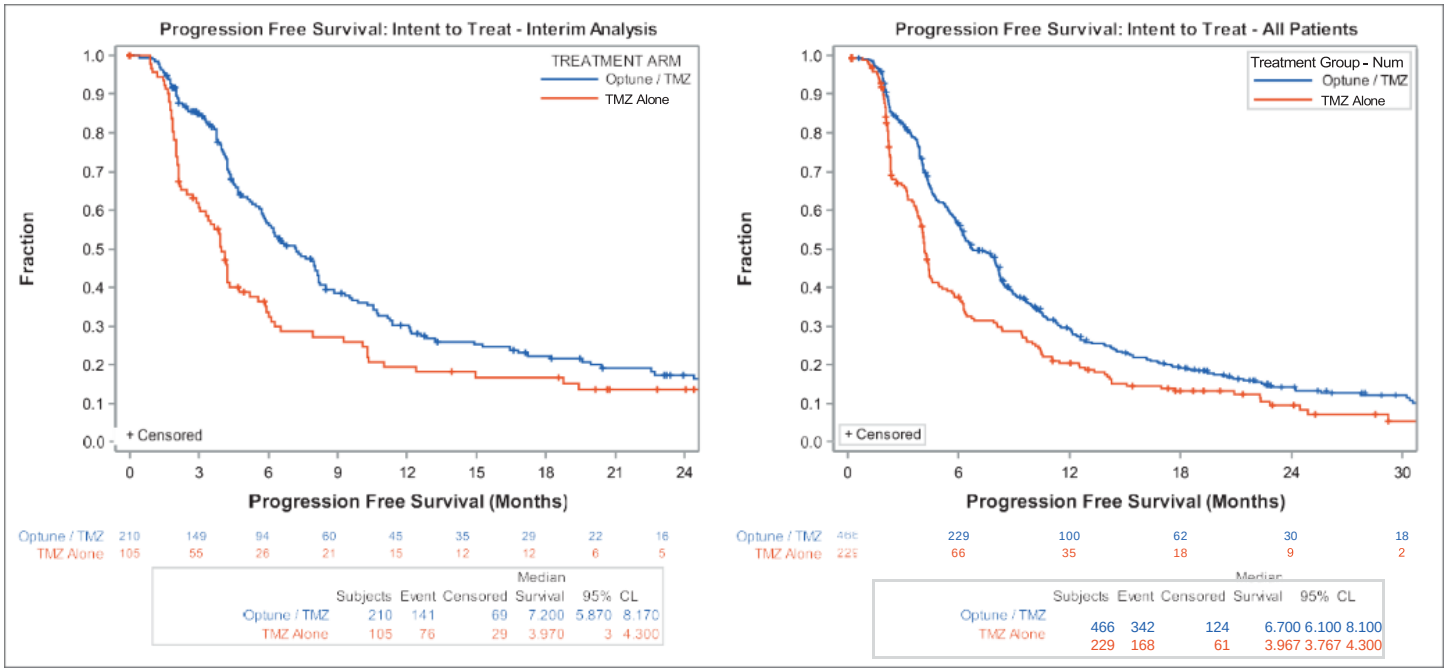
As seen above, all baseline characteristics are well balanced between arms in the ITT population at the final long term analysis. As noted in the table above, 53 patients (7.6%) had tissue that was not evaluable, and 126 patients (18.1%) did not have tissue available for analysis.

Effectiveness Results:

Primary Effectiveness Endpoint: Progression Free Survival

The threshold for statistical significance based on the Lan-DeMets O'Brien-Fleming method at the interim analysis was predefined as p=0.01394, and the test was to be performed in the ITT population according to the protocol. In the ITT population, which included all randomized subjects (Optune Gio/TMZ=210, TMZ alone=105), PFS at the interim analysis met this threshold. The difference of more than 3 months in median PFS is highly clinically significant. The hazard ratio for PFS was 0.621, which translates into a 37.9% decrease in the risk of progression when using Optune Gio/TMZ compared to TMZ alone. At the final long term analysis, which included 695 patients with a minimum follow-up of 24 months (Optune Gio/TMZ=466, TMZ alone=229), PFS was also highly significant with a hazard ratio of 0.63 and a p-value of 0.00004.

Primary Efficacy Endpoint – Progression Free Survival (ITT)



	Interim Analysis		Final Long Term Analysis	
	Optune Gio/TMZ	TMZ Alone	Optune Gio/TMZ	TMZ Alone
Median (95 CI %)	7.2 (5.9, 8.2)	4.0 (3.0, 4.3)	6.7 (6.1, 8.1)	4.0 (3.8, 4.3)
Log-rank test	p=0.0013		p=0.00004	
Hazard Ratio (95% CI)	0.62 (0.47, 0.82)		0.63 (0.52, 0.76)	

Although not a pre-specified endpoint, PFS was also analyzed in the PP population at the interim and final long term analyses. Median PFS in the PP population was identical to the ITT population at both analyses. Notably, median PFS remained significantly higher in the Optune Gio/TMZ group than in the TMZ alone group in the PP population at both analyses.

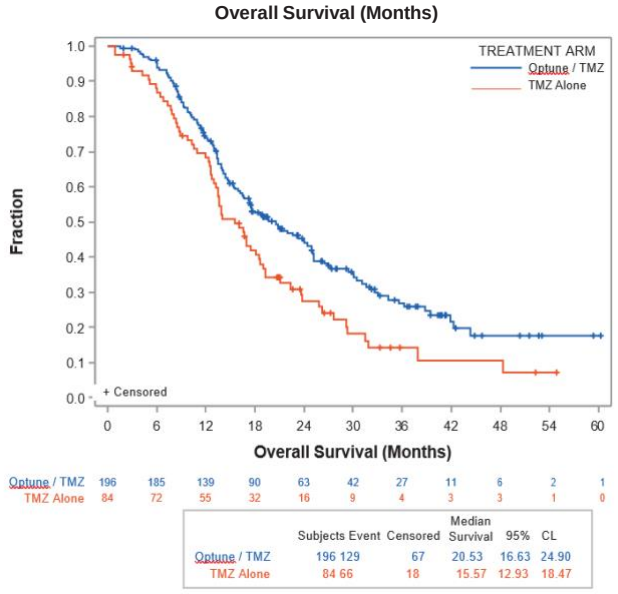
Powered Secondary Effectiveness Endpoint: Overall Survival

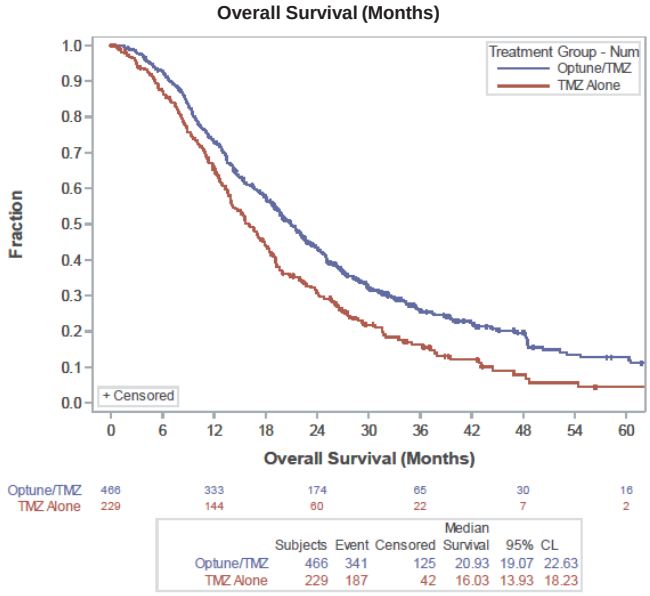
Overall survival (OS) was a powered secondary analysis in the trial. The threshold for superior OS at the interim analysis was predefined in the protocol at 0.00598 according to the Lan-DeMets O'Brien-Fleming alpha spending function, and was to be

tested in the PP population. In the PP population, which analyzed patients according to the treatment they actually received (as treated: Optune Gio/TMZ=196, TMZ=84), OS was also significantly longer in the Optune Gio/TMZ arm compared to the TMZ alone arm. An increase of almost 5 months as seen here is highly significant clinically. The hazard ratio for OS was 0.666. This translates into a 33.4% decrease in the risk of death when using Optune Gio/TMZ compared to TMZ alone. At the final long term analysis, which included 695 patients with at least 24 months follow-up (Optune Gio/ TMZ=466, TMZ alone=229), OS was analyzed in the intent to treat (ITT) population, as described above.

OS in the ITT population at the final long term analysis was also highly significant with a hazard ratio of 0.63 and a p-value of 0.00004.

Overall Survival





	Interim Analysis		Final Long Term Analysis	
	Optune Gio/TMZ	TMZ Alone	Optune Gio/TMZ	TMZ Alone
Median (95 CI %)	20.5 (16.6, 24.9)	15.6 (12.9, 18.5)	20.9 (19.1, 22.6)	16.0 (13.9, 18.2)
Log-rank test	p=0.0042		p=0.00004	
Hazard Ratio (95% CI)	0.666 (0.495, 0.898)		0.63 (0.53, 0.76)	

Although not a pre-specified secondary endpoint, OS was also analyzed in the ITT population. At the interim analysis, OS in the ITT population was also significantly longer in the Optune Gio/TMZ arm compared to TMZ alone by almost 20%. The median OS was 19.6 months (95% CI 16.5-24.1) in the Optune Gio/TMZ group and 16.6 months in the TMZ alone group (95% CI 13.5-19.1). An increase of 3 months as seen here is highly significant both statistically (log-rank p=0.0338) and clinically. The hazard ratio for OS was 0.744 using a Cox regression analysis. This translates into a 25.6% decrease in the risk of death when using Optune Gio/TMZ compared to TMZ alone.

Secondary Endpoints: Secondary endpoints also showed an advantage for Optune Gio/TMZ compared to TMZ alone. The results below are from the final long term analysis which included 695 patients with a minimum follow-up of 24 months (466 Optune Gio/TMZ and 229 TMZ alone):

Endpoint	Optune Gio/TMZ	TMZ Alone
Progression Free Survival at 6 months (ITT)	55.6%	36.5%
1-year survival (ITT)	72.8%	65.3%
2-year survival (ITT)	43.1%	30.7%
3-year survival (ITT)	25.9%	16.3%
4-year survival (ITT)	19.6%	7.9%
5-year survival (ITT)	12.7%	4.5%
Radiological clinical benefit rate (ITT) (Partial response + Complete response + Stable disease)	82.1%	71.8%

Quality of Life: Quality of Life assessments were based on the final long term analysis cohort which included all 695 subjects. Quality of life, cognitive function and functional status were all maintained throughout treatment with the device, leading to the clear conclusion that use of Optune Gio does not harm patients' quality of life, cognitive function or ability to perform activities of daily living.

Safety Results: Safety was assessed on all patients at the final long term analysis who received any treatment (Optune Gio/ TMZ=456, TMZ alone=216). A slightly higher incidence of grade 1-2 adverse events was seen in some of the systems in the Optune Gio/ TMZ arm of the study. This is most likely a reflection of the longer duration of TMZ treatment in these patients (average of 6.4 cycles versus 6 cycles in the control arm) due to the increase in PFS seen in the treatment group. Grade 3-5 adverse events were well balanced between arms. None of the grade 3-5 adverse events in these body systems were considered related to Optune Gio by any of the investigators except for 2% grade 3 skin irritation.

All Adverse Events by Body System and Severity (Safety Population)

	Optune Gio/TMZ (N-456)			TMZ (N=216)		
	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
Number of Patients with >=1 AE	203 (45%)	218 (48%)	15 (3%)	96 (44%)	94 (44%)	7 (3%)
Blood and lymphatic system disorders	97 (21%)	59 (13%)	0	50 (23%)	23 (11%)	0
Cardiac disorders	17 (4%)	5 (1%)	2 (<1%)	8 (4%)	(1%)	0
Ear and labyrinth disorders	32 (7%)	0	0	11 (5%)	0	0
Endocrine disorders	13 (3%)	2 (<1%)	0	6 (3%)	0	0
Eye disorders	47 (10%)	3 (1%)	0	20 (9%)	2 (1%)	0
Gastrointestinal disorders	237 (52%)	23 (5%)	1 (<1%)	93 (43%)	8 (4%)	0
General disorders	213 (47%)	42 (9%)	2 (<1%)	88 (41%)	13 (6%)	2 (1%)
Hepatobiliary disorders	2 (<1%)	3 (1%)	0	3 (1%)	1 (<1%)	0
Immune system disorders	7 (2%)	0	0	4 (2%)	0	0
Infections	151 (33%)	32 (7%)	4 (1%)	66 (31%)	10 (5%)	1 (<1%)
Injury and procedural complications	255 (56%)	24 (5%)	0	37 (17%)	7 (3%)	0
Metabolism and nutrition disorders	114 (25%)	16 (4%)	0	55 (25%)	10 (5%)	0
Musculoskeletal and connective tissue disorders	127 (28%)	21 (5%)	0	57 (26%)	9 (4%)	0
Nervous system disorders	217 (48%)	109 (24%)	4 (1%)	97 (45%)	43 (20%)	1 (<1%)
Psychiatric disorders	148 (32%)	17 (4%)	0	51 (24%)	6 (3%)	0
Renal and urinary disorders	56 (12%)	3 (1%)	0	14 (6%)	4 (2%)	0
Reproductive system	15 (3%)	0	0	6 (3%)	0	0
Respiratory, thoracic and mediastinal disorders	81 (18%)	24 (5%)	2 (<1%)	24 (11%)	11 (5%)	2 (1%)
Skin and subcutaneous tissue disorders	118 (26%)	2 (<1%)	0	46 (21%)	1 (<1%)	0
Surgical and medical procedures	0	0	0	1 (<1%)	0	0
Vascular disorders	63 (14%)	19 (4%)	0	25 (12%)	5 (2%)	1 (<1%)

Patients treated with Optune Gio/TMZ experienced a small increase in TMZ-related AEs and SAEs due to the longer TMZ exposure afforded to these patients by their longer PFS. The only AEs which may have been caused by Optune Gio therapy are the known skin irritation seen in 53% of patients in this study (2% severe), falls which were seen at a slightly higher incidence in patients carrying the device, headaches related to wearing the arrays 24 hours a day and mild psychiatric symptoms (anxiety, insomnia, confusion) which could be caused by the need to incorporate the device and arrays into daily life. No SAEs were considered related to device use. The remainder of AEs and SAEs seen in the trial were well balanced between treatment arms. In conclusion, Optune Gio is very well tolerated with mild to moderate toxicity mainly related to array contact with the scalp.

Conclusions: Optune Gio is a portable, battery operated device which delivers TTFields to patients with newly diagnosed GBM. The results of the pivotal trial in newly diagnosed GBM showed that Optune Gio/TMZ extends progression free and overall survival significantly compared to patients receiving TMZ alone. No significant increase in adverse events was seen when Optune Gio treatment was added to TMZ. The only common device-related AE was a skin irritation seen beneath the transducer arrays in 53% percent of patients. The majority (52% of 53%) of these events were mild to moderate. Based on an assessment of the quality of life of the final long term analysis cohort of 695 patients, quality of life, cognitive function and functional status did not decline due to the use of Optune Gio/TMZ.

RECURRENT DIAGNOSED GLIOBLASTOMA

Pilot Clinical Study in Recurrent GBM

Optune Gio has been tested in 10 recurrent GBM subjects in a single center, pilot study in Europe. In this study, Optune Gio monotherapy led to a significant increase in time to progression (from 13 to 26 weeks; p=0.013), progression free survival at 6 months (PFS6) (from 15% to 50%) and overall survival (OS) (from 6.0 to 14.7 months; p=0.002) compared to matched concomitant and historical comparator groups. The only device related adverse event (AE) seen in this trial was a mild to moderate skin reaction beneath the device transducer arrays.

Other Clinical Experience in Recurrent GBM

The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received Optune Gio in a real-world, clinical practice setting in the US between 2011 and 2013. The registry included 457 recurrent GBM patients who received Optune Gio in 91 US cancer centers. More patients in PRiDe than the pivotal clinical trial in recurrent GBM (EF-11) received Optune Gio for first recurrence (33% vs. 9%) and had received prior bevacizumab therapy (55.1% vs. 19%).
Median OS was significantly longer with Optune Gio in clinical practice (PRiDe data set) than in the EF-11 pivotal trial in recurrent GBM (9.6 vs. 6.6 months). One- and 2-year OS rates were more than double for Optune Gio patients in PRiDe than in the EF-11 trial (1-year: 44% vs. 20%; 2-year: 30% vs. 9%). Favorable prognostic factors included first and second vs. third and subsequent recurrences, high Karnofsky Performance Score (KPS) and no prior bevacizumab use. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Optune Gio transducer arrays.

Pivotal Clinical Study in Recurrent GBM[4]

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with Optune Gio to those treated with an effective best standard of care (BSC) chemotherapy (including bevacizumab).

The following were the objectives of the study:

- To prospectively compare the median overall survival of recurrent GBM subjects treated with Optune Gio to those treated with best standard of care (BSC) active chemotherapy
- To prospectively determine PFS6, TTP, 1%-year survival and quality of life of subjects treated with Optune Gio compared to BSC
- To collect evidence of the safety of TTFields applied to subjects with recurrent GBM using Optune Gio

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria

a. Pathological evidence of GBM using WHO classification criteria
b. ≥ 18 years of age
c. Not a candidate for further radiotherapy or additional resection of residual tumor
d. Subjects with disease progression (by Macdonald criteria [i.e., > 25% or new lesion]) documented by CT or MRI within 4 weeks prior to enrollment
e. Karnofsky scale ≥ 70
f. Life expectancy at least 3 months
g. Participants of childbearing age must use effective contraception
h. All subjects must sign written informed consent

[4]Stupp, R., et al., (2012). "NovoTTF-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.

Exclusion Criteria

a. Actively participating in another clinical treatment trial
b. Within 4 weeks from surgery for recurrence
c. Within 4 weeks from any prior chemotherapy
d. Within 4 weeks from radiation therapy
e. Pregnant
f. Significant co-morbidities within 4 weeks prior to enrollment:
    1) Significant liver function impairment (AST or ALT > 3 times the upper limit of normal)
    2) Total bilirubin > upper limit of normal
    3) Significant renal impairment (serum creatinine > 1.7 mg/dL)
    4) Coagulopathy (as evidenced by PT or APTT > 1.5 times control in subjects not undergoing anticoagulation)
    5) Thrombocytopenia (platelet count < 100 x 103/µL)
    6) Neutropenia (absolute neutrophil count < 1 x 103/µL)
    7) Anemia (Hb < 10 g/L)
    8) Severe acute infection
g. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias
h. Infra-tentorial tumor
i. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

Study Procedures:

Treatment Arm

At treatment initiation subjects were hospitalized for 24 hours. During this period baseline examinations were performed and Optune Gio treatment was initiated by the investigator under continuous medical supervision. The subjects were also instructed by the investigator on the operation of Optune Gio and battery replacement. Once the subjects were trained in operating the device they were released to continue treatment at home. The subjects received continuous Optune Gio treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Subjects received the best effective standard of care chemotherapy practiced at each of the participating centers. The effective BSC treatments used in the study were comprised mainly of the following chemotherapies: Platinum based chemotherapy (carboplatin), nitrosureas (BCNU), procarbazine, lomustine and vincristine (PCV), TMZ, bevacizumab, and imatinib, erlotinib, irinotecan (mainly in Europe). Because these therapies were included in the trial as a group, no comparisons can be made to each individual chemotherapy regimen. Chemotherapeutic treatment protocol was according to standard procedures at each of the participating centers.

Follow-up

During treatment, and until progression for subjects who stopped treatment before progression, all subjects were seen once a month at an outpatient clinic where they underwent medical follow-up and routine laboratory exams. An MRI was performed every 2 months until disease progression. Central MRI review was performed by a neuro-
radiologist blinded to the treatment group of each subject. Medical follow-up continued for 2 months following disease progression. Subject survival was assessed based on monthly telephone interviews with the subjects' caregivers.

Subject Characteristics: 237 subjects (120 Optune Gio; 117 BSC) with progressive or recurrent GBM were enrolled in the study. Baseline characteristics were as follows: mean age: 53.6 years; mean Karnofsky score: 81.6±10.9%; tumor size (cm2): 16.2±12.4; progression number: 1.4±0.9; re-operated: 26%; male: 70%; previous low grade: 10%; prior bevacizumab failure: 19%. Baseline characteristics were similar between treatment groups with slightly more men in the Optune Gio group than in the BSC group (77% vs. 62%), a lower incidence of frontal lobe tumors in the Optune Gio group than in the BSC group (32% vs. 50%), and a slightly higher mean KPS in the Optune Gio group than in the BSC group (83% vs. 80%), though the median KPS was 80 in both groups. Adjusted analyses for all pre-specified or all statistically significant baseline covariates for overall survival did not change the outcome of the trial.

Demographics and Baseline Characteristics (ITT)		
	Optune Gio	BSC
Characteristics	(N=120)	(N=117)
	n (%)	n (%)
Caucasian	111 (93)	106 (91)
African American	2 (2)	5 (4)
Asian	0	3 (3)
Hispanic	7 (6)	2 (2)
Other	0	1 (1)
Female Gender	28 (23)	44 (38)
Frontal Tumor Position	38 (32)	58 (50)
Bilateral or Midine Tumor Location	23 (19)	17 (15)
Prior Avastin Use	24 (20)	21 (18)
Re-operation for Recurrence	33 (28)	29 (25)
Prior Low-grade Glioma	12 (10)	11 (9)
Median Age (years) (min, max)	54 (24, 80)	54 (29, 74)
Median Weight (kg)	80	80
Mean Number of Prior GBM Recurrences	1.5	1.3
Median Karnofsky Performance Score (min, max)	88 (50, 100)	80 (50, 100)
Median Tumor Area (mm2)	1440	1391
Median Time from GBM Diagnosis to Randomization (days)	334	340
Mean Time from Last Radiotherapy Dose to Randomization (Months)	13.71	13.93

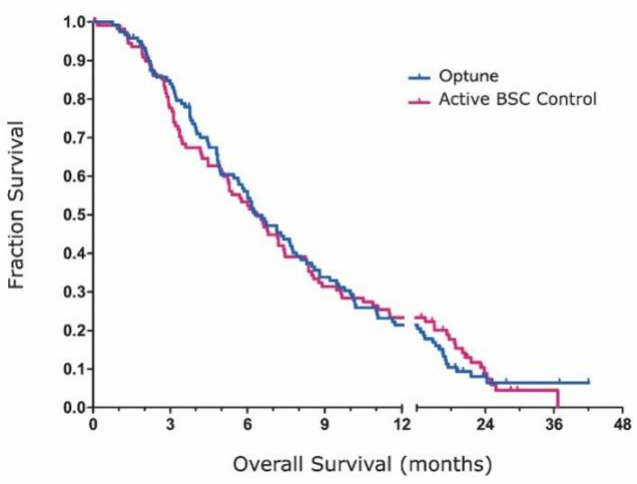
Effectiveness Results:

Primary Effectiveness Endpoint: Overall Survival (ITT)

In the ITT population which included all randomized subjects (Optune Gio=120, BSC=117), overall survival in subjects treated with Optune Gio was comparable to that observed in subjects treated with BSC (median OS=6.3 vs. 6.4 months; p=0.98). In the US, the median overall survival was 6.1 vs. 5.3 months in the ITT population. The pivotal study data established that Optune Gio treatment was comparable to BSC therapy in extending OS.

	Treatment Group	
	Optune Gio	BSC
N	120	117
Median OS (months)	6.3	6.4
Log-rank p-Value	0.98	
Hazard Ratio (95% CI)	1.00 (0.76-1.32)	

The Kaplan-Meier survival curve for the two treatment groups appeared to be very similar during the first 12 months of follow-up, where 80% of the events occurred in both groups. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control group. However, after 12 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome.



	Optune Gio (N=120)	Active BSC Control (N=117)
Deaths	105	97
Censored	15	20
Lost to follow-up	6	10
Alive at end of follow-up	9	10
Median (months)	6.3	6.4
95% Confidence Interval	5.6, 7.8	5.2, 7.4

Correlation between Treatment Compliance and Overall Survival: Optune Gio has an internal log file which allows the calculation of patient compliance with treatment. Significantly higher overall survival (p=0.0447) was observed in patients who were treated 75% or more of the time on average (OS=7.7 months) compared to patients treated less than 75% of the time on average (OS=4.5 months).

Secondary Effectiveness Endpoints: Secondary endpoint results support the findings in the primary endpoint. The one-year survival is similar in the Optune Gio and BSC groups in the ITT population (21.9% vs. 22.1%). Progression free survival at 6 months (PFS6) is the same in the ITT population (21.4% vs. 15.2%). Radiological response rates from the subset of patients evaluated were reported as 14% for the Optune Gio group compared to 9.6% for the BSC group in the ITT population. Median time to progression (TTP) was 9.3 weeks for Optune Gio vs. 9.6 weeks for BSC.

	Treatment Group	
	Optune Gio	BSC
N	120	117
1-year survival	21.9% 25/114	22.1% 23/104
PFS6 (%)	21.4% 22/103	15.2% 14/92
Radiological Response Rate (%)	14.0% 14/100	9.6% 7/73
Median TTP (weeks)	9.3	9.6

Quality of Life: Quality of life in subjects using Optune Gio was better than those on BSC chemotherapy in most subscale domains, including vomiting, nausea, pain, diarrhea, constipation, cognitive and emotional functioning.

Safety Results: The characteristic adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control subjects than in Optune Gio subjects: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infectious (12% vs. 4%). Mild to moderate skin irritation beneath the device transducer arrays was observed in 16% of Optune Gio subjects; none of these cases were assessed as severe by the investigator, all resolved after discontinuing treatment, and all were treated with topical steroids and periodic shifting of transducer array positions.

Number of Patients with Adverse Events by Body System (>2%)

System Organ Class	Optune Gio	BSC Chemotherapy
	N=116 (%)	N=91 (%)
Blood and lymphatic disorders	5 (4.3%)	17 (18.7%)
Gastrointestinal disorders	9 (7.8%)	27 (29.7%)
General disorders and administration site conditions	15 (12.9%)	14 (15.4%)
Infections and infestations	5 (4.3%)	11 (12.1%)
Injury, poisoning and procedural complications	21 (18.1%)	1 (1.1%)
Metabolism and nutrition disorders	9 (7.8%)	12 (13.2%)
Nervous system disorders	50 (43.1%)	33 (36.3%)
Psychiatric disorders	12 (10.3%)	7 (7.7%)
Respiratory, thoracic and mediastinal disorders	7 (6.0%)	10 (11.0%)

Conclusions: Optune Gio is a portable, battery operated device which delivers TTFields to patients with recurrent GBM. The results of the pivotal trial showed that Optune Gio subjects had comparable overall survival to subjects receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of Optune Gio to BSC chemotherapy in the ITT population were seen in all secondary endpoints.

Optune Gio subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse event seen was a mild to moderate skin irritation beneath the device transducer arrays, which was easily treated with topical ointments. Finally, certain quality of life measures were better in Optune Gio subjects as a group when compared to subjects receiving effective BSC chemotherapy.

Post Approval Clinical Study in Recurrent GBM

Study Design: The study was a prospective, non-randomized, open label, post-approval registry study of Optune Gio treatment compared to the best standard of care (BSC) arm of the pivotal clinical study in recurrent GBM (EF-11).

The following were the objectives of the study:

- To confirm that the efficacy of Optune Gio in patients with recurrent GBM treated in a real life setting following FDA approval is comparable to that of BSC chemotherapy treated patients in the pivotal study
- To collect additional data on the safety profile of Optune Gio in a real life setting
- To define Optune Gio overall survival (OS) (months) by MGMT methylation status (where available)
- To define Optune Gio overall survival (months) by baseline MMSE score (where available)
- To compare time to treatment failure (months) on Optune Gio to that of BSC chemotherapy treated patients
- To evaluate Optune Gio functional impairment using Karnofsky Performance Score (KPS)

Eligibility Criteria: The inclusion and exclusion criteria for the study were as follows:

Inclusion Criteria

a. Histological diagnosis of GBM (WHO grade IV)
b. ≥ 22 years of age
c. Tumor located in the supra-tentorial region of the brain
d. Received maximal, safe, surgical resection
e. Received maximal radiation therapy (45-70Gy)
f. Received concomitant Temozolomide (75mg/m^2/day for 6 weeks)
g. Received maintenance Temozolomide (150-200 mg/m^2 daily for 5 days followed by 23 days withouttreatment for 6 cycles or until disease progression)
h. Any recurrence (based on radiological or histological evidence of recurrence)
i. Karnofsky Performance Score 70 or above
j. Women of childbearing age must be on effective contraception
k. Signed informed consent

Exclusion Criteria

a. Implanted electronic medical device in the brain:
    1) Deep brain stimulator
    2) Vagus nerve stimulator
    3) Programmable shunt
b. Skull defect without replacement
c. Receiving concomitant chemotherapy
d. Unable to comply with treatment with Optune Gio
e. Pregnant
f. Actively participating in another therapeutic clinical trial
g. Radiological suspicion of pseudo-progression or radio-necrosis (a cold PET scan or negative biopsy are required in order to rule out these conditions if radiological suspicion exists)
h. Any serious co-morbidity which is expected to affect survival more adversely than GBM

Data Source: Post marketing data from the Optune Gio clinical PRiDE registry (over 300 Optune Gio certified sites in the US) and the BSC arm of the EF-11 study

Study Procedures:

Optune Gio Treatment Arm

Prior to treatment start with the device all patients underwent training by their treating medical professional or personnel who received complete device training from Novocure. Treatment was performed according to the Optune Gio Patient Information and Operation Manual.

At baseline after signing the informed consent all patients underwent clinical evaluation.

Control Arm

The historical control group used in this study was the BSC group from the pivotal clinical study in recurrent GBM.

Follow-up

Patients were followed at the treating clinic according to standard follow-up practiced at each center and by Novocure trained device support specialist (DSS) once per month. During the follow up visits all AEs were collected and reported to Novocure, vital status and KPS (where available) were also recorded.

Although progression was not an endpoint in this study, it served as a guide for when to stop Optune Gio treatment – a decision that was based on the investigators' assessment of the patient and imaging studies. Following progression all patients were followed for survival.

Median follow-up duration was 6.1 months.

Primary endpoint

- Overall survival (measured in months)

Key Secondary endpoints

- Overall survival in per protocol (PP) population
- Overall Survival in Optune Gio Patients with MGMT Methylated versus MGMT Unmethylated Tumors
- Time to Treatment Failure between Optune Gio and BSC Patients (ITT Population)
- Functional Impairment in Optune Gio Patients using KPS
- Overall Survival in Optune Gio Patients as a Function of Usage-Time (Compliance)

Strengths and weaknesses of the study design

This study is a prospective, registry study that involves a hypothesis testing comparing Optune Gio as a monotherapy for recurrent GBM to a historical BSC control arm. The study included patients from a high number of sites and provided real world data from patients treated with the study device for its intended use. The study also added important safety data collected from recurrent GBM patients treated with Optune Gio following its approval for this indication. At the same time, it should be noted that the study was non-randomized and used the EF-11 BSC arm as the control arm, therefore distribution of baseline characteristics between the study arms could not be controlled. In addition, the loss-to-follow up rate was higher than expected.

Subject Characteristics: All 1,082 recurrent GBM patients prescribed Optune Gio between February 2016 and December 2017 in the US were part of the registry and were therefore screened for this study. Only patients who met the eligibility criteria were included in this study. Per the protocol, the Intent-to-Treat (ITT) population includes all patients who met the eligibility criteria.

The final analysis included 192 patients from 151 certified prescribers. The ITT population included all 192 patients in the Optune Gio registry and the 117 patients from the BSC arm of the EF-11 pivotal study.

The table below summarizes the baseline characteristics in the Optune Gio registry and EF-11 BSC arm. The median age was 57 years and 54 years in the Optune Gio and BSC control arms, respectively, and median KPS was 80 in both arms.

Demographics and Baseline Characteristics		
Characteristics	Optune Gio Registry (N=192)	EF-11 BSC (N=117)
Age (Years)		
Mean (SD)	55.9 (12.20)	53.0 (10.77)
Median (min-max)	57.0 (23-80)	54.0 (29-74)
Karnofsky Performance Score		
Unknown	63 (33%)	3 (3%)
Mean (SD)	80 (9.83)	80 (11.01)
Median (min-max)	80 (70-100)	80 (50-100)
Gender		
Male	125 (65%)	73 (62%)
Female	67 (35%)	44 (38%)
Race		
Caucasian	141 (73%)	106 (91%)
African American	9 (5%)	5 (4%)
Asian	6 (3%)	3 (3%)
Hispanic	8 (4%)	2 (2%)
Other	0	1 (1%)
Unknown	28 (15%)	0
Extent of Resection for Newly Diagnosed GBM		
Unknown	3 (2%)	1 (1%)
None	0	0
Biopsy	15 (8%)	12 (10%)
Partial	44 (23%)	14 (12%)
Gross Total	130 (68%)	90 (77%)

Extent of Resection at Time of Recurrence		
Unknown	9 (5%)	0
None	106 (55%)	88 (75%)
Biopsy	4 (2%)	0
Partial	10 (5%)	3 (3%)
Gross Total	63 (33%)	26 (22%)
MGMT Methylation Status		
Unknown	108 (56%)	NA
Yes	35 (18%)	NA
No	49 (26%)	NA
IDH1 Expression		
Unknown	99 (52%)	NA
Yes	16 (8%)	NA
No	77 (40%)	NA
Number of Chemotherapy Lines Prior to Study Entry		
Mean (SD)	2.68 (0.97)	3.16 (0.93)
Median (Min-Max)	2 (0-7)	3 (1-6)
Unknown	2 (1%)	0
0	4 (2%)	0
1	96 (50%)	26 (22%)
2	60 (31%)	57 (49%)
3	20 (10%)	27 (23%)
4	8 (4%)	4 (3%)
5	1 (1%)	2 (2%)
6	0	1 (1%)
7	1 (1%)	0

Steroid Taken	85 (44%)	44 (38%)
Anticonvulsant Taken*	142 (74%)	50 (43%)
History of GBM		
Unknown	5 (3%)	
Histological Diagnosis of GBM	187 (97%)	117 (100%)
Received Maximal Radiation Therapy (45-70Gy)	187 (97%)	96 (82%)
Average compliance in the first 6 months (%), No. (%)		
Missing	8 (4%)	
≥75%	82 (43%)	
<75%	102 (53%)	

Cells with "NA" in the table above represent variables that were not collected in the original EF-11 study.

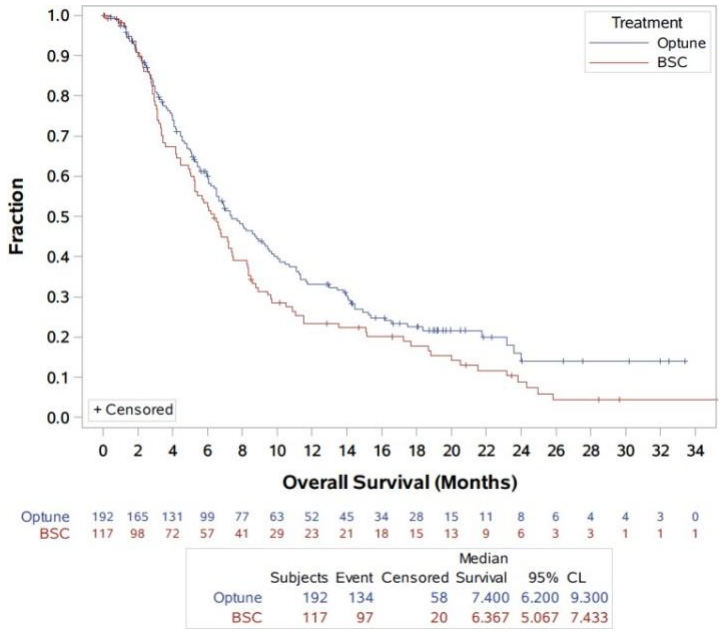
*Anticonvulsant use during the EF-11 study was recorded by study teams using clinical report forms. The recording of anticonvulsant use in the post approval registry study was done using patient charts. Any evidence of anticonvulsant use in the charts of each registry patient was recorded, as it was not possible to determine start and stop dates. Therefore, the number of patients noted under the Optune Gio registry does not reflect patients who used anticonvulsants at baseline, but rather the number of patients with any past or current use of anticonvulsants.

Effectiveness Results:

Primary Effectiveness Endpoint: Overall Survival (ITT)

In this post-approval study, patients in the Optune Gio registry arm had a median overall survival (OS) higher than that of patients assigned to the best standard of care effective chemotherapy (BSC) arm in the EF-11 study. The median OS was 7.4 months (95% CI 6.2, 9.3) in the Optune Gio group and 6.4 months (95% CI 5.1, 7.4) in the BSC group. The hazard ratio was 0.66 (95% CI 0.47, 0.92) (test for proportional hazards p=0.016), and indicated that the risk of death was reduced by 34% with Optune Gio compared to BSC treatment. Since the upper 95% confidence bound of the hazard ratio was less than the pre-defined threshold of 1.375, the null hypothesis was rejected and non-inferiority of Optune Gio treatment to BSC was demonstrated. Therefore, the primary endpoint of the post approval study was met. Per the protocol, superiority was to be tested if non-inferiority was achieved. The median OS in the Optune Gio registry arm was numerically higher than median OS in the BSC group and the data trended towards superiority, but did not meet statistical significance (log-rank p=0.053).

While comparison with the Optune Gio arm of the EF-11 study was not predefined in the protocol, notably, overall survival for Optune Gio in the EF-11 pivotal study (6.3 months) was comparable to that seen in the real-life clinical setting using the post approval EF-19 study.



	Treatment Group	
	Optune Gio Registry	EF-11 BSC
Median (95% CI) (Months)	7.4 (6.2, 9.3)	6.4 (5.1, 7.4)
Log-rank Test	p=0.053	
Hazard Ratio	0.66 (0.47, 0.92)	
Cox Test	P=0.016	

The Cox Proportional Hazards Model for overall survival included the following parameters: treatment group, race, gender, KPS, extent of resection for newly diagnosed GBM, extent of resection at time of recurrence, age and number of prior chemotherapy lines. Apart from Optune Gio treatment, only KPS was found to be a statistically significant covariate. This parameter is well balanced between the Optune Gio and BSC groups (median of 80 in both).

Parameter	Parameter Value	Hazard Ratio	95% CI	Two-sided p-value
Treatment Group	Optune Gio	0.66	0.47 – 0.92	0.016
Race	Caucasian or Unknown	1.39	0.82 – 2.37	0.219
Gender	Male	0.88	0.65 – 1.2	0.437
KPS	>80	0.66	0.47 – 0.92	0.014
Extent of Resection for Newly Diagnosed GBM	Biopsy	1.18	0.72 – 1.93	0.514
	Partial	0.79	0.53 – 1.18	0.127
Extent of Resection at Time of Recurrence	None or Biopsy	1.05	0.76 – 1.44	0.767
Age group	<65	0.78	0.54 – 1.13	0.196
Number of prior chemotherapy lines	>2	0.83	0.58 – 1.17	0.288
Reference values to above parameters: Treatment Group (BSC), Race (African American, Asian, Hispanic, Other), Gender (Female), KPS (≤80), Extent of Resection for Newly Diagnosed GBM (Gross Total), Extent of Resection at Time of Recurrence (Partial or Gross Total), Age (≥65), Number of prior chemotherapy lines (≤2)				

Key Secondary Effectiveness Endpoints:

There was no pre-specified hypothesis testing for the secondary endpoints.

Overall Survival (Per Protocol)

Overall survival in the Per Protocol (PP) population (patients who received at least one 28 day cycle of Optune Gio and at least one dose of systemic therapy in the BSC arm) was significantly longer in the Optune Gio registry arm (N=182) compared to BSC arm of the EF-11 study (N=117). The median OS was 8.1 months (95% CI 6.6, 9.8) in the Optune Gio PP arm and 6.4 months in the BSC group (95% CI 5.1, 7.4) (log-rank p=0.017). The hazard ratio was 0.6 (95% CI 0.42, 0.85) (test for proportional hazards p=0.004).

Overall Survival in Optune Gio Patients with MGMT Methylated versus MGMT Unmethylated Tumors

MGMT information was available for 84 patients in the Optune Gio arm. The median OS was 10.0 months (95% CI 6.0, 13.9) in the methylated group (N=35) and 6.5 months in the unmethylated group (N=49) (95% CI 4.5, 7.4) in the Optune Gio arm. The hazard ratio was 0.77 (95% CI 0.46, 1.30). This data is consistent with previous studies indicating that MGMT methylation is a prognostic factor for GBM patients.

Time to Treatment Failure between Optune Gio and BSC Patients (ITT Population)

Time to treatment failure was defined as the time from treatment start until treatment discontinuation. This analysis served as a surrogate measure for progression. The median time to treatment failure was longer in the Optune Gio arm (3.3 months (95% CI 2.6, 3.9)) compared to the BSC arm (1.6 months (95% CI 1.1, 1.9)). The hazard ratio was 0.53 (95% CI 0.41, 0.68).

Functional Impairment in Optune Gio Patients using KPS

Out of the 129 Optune Gio patients who had a baseline score recorded, only 12 patients had a KPS reported at follow-up. Although only a small amount of follow up data was available, no significant decrease in KPS over time was seen in patients with available data at follow up visits.

Overall Survival in Optune Gio Patients as a Function of Usage-Time (Compliance)

Usage-time (compliance) of Optune Gio treatment was collected from Optune Gio devices in the registry. Compliance with Optune Gio treatment showed a positive correlation between usage time and OS. Patients who used the device more than 75% of the time (18 hours a day or more) had longer median OS (N=82, 9.8 months (95% CI 6.5, 13.9)) than those who used it less than 75% of the time (N=102, 6.7 months (95% CI 4.8, 8.9)).

Safety Results

In an analysis of all AEs in the safety registry population, the following systems included AEs in more than 5% of patients: general disorders and administration site condition (23%), injury and procedural complications (11%) and nervous system disorders (27%). In addition 36% of Optune Gio patients experienced skin adverse events (mainly skin reaction underneath the transducer arrays). Skin reactions did not lead to treatment discontinuation in the study, nor were they considered serious in any of the cases. The skin irritation ranged from mild skin redness or rash in about a third of the device patients to moderate blistering or ulceration in individual cases. The skin reactions observed in the registry patients were expected and consistent with the pivotal study data.

Number of Patients with Adverse Events by Body System (>2%) and Term

System Organ Class \ Preferred Term	Optune Gio Registry (N=192)
Gastrointestinal Disorders	8 (4%)
Diarrhea	2 (1%)
Nausea	3 (2%)
Vomiting	4 (2%)
General Disorders And Administration Site Conditions	45 (23%)
Chest Pain	1 (1%)
Discomfort	1 (1%)
Electric Sensation	25 (13%)
Fatigue	6 (3%)
General Physical Health Deterioration	5 (3%)
Malaise	2 (1%)
Edema Peripheral	1 (1%)
Pain	11 (6%)
Pyrexia	1 (1%)

Infection And Infestations	6 (3%)
Herpes Zoster	2 (1%)
Nasopharyngitits	1 (1%)
Pneumonia	2 (1%)
Respiratory Syncytial Virus Infection	1 (1%)
Upper Respiratory Tract Infection	1 (1%)
Wound Infection	1 (1%)
Injury, Poisoning And Procedural Complications	22 (11%)
Ankle Fracture	1 (1%)
Clavicle Fracture	1 (1%)
Fall	19 (10%)
Hip Fracture	1 (1%)
Laceration	2 (1%)
Wound Complication	1 (1%)
Musculoskeletal And Connective Tissue Disorders	8 (4%)
Back Pain	1 (1%)
Muscle Spasms	1 (1%)
Muscular Weakness	4 (2%)
Musculoskeletal Pain	2 (1%)
Musculoskeletal Stiffness	1 (1%)
Pain In Extremity	1 (1%)

Nervous System Disorders	51 (27%)
Aphasia	1 (1%)
Balance Disorder	5 (3%)
Brain Edema	4 (2%)
Cerebral Hemorrhage	2 (1%)
Cerebrovascular Accident	1 (1%)
Cognitive Disorder	5 (3%)
Dizziness	1 (1%)
Gait Disturbance	2 (1%)
Headache	14 (7%)
Hemiparesis	3 (2%)
Hemiplegia	1 (1%)
Hydrocephalus	1 (1%)
Intracranial Pressure Increased	1 (1%)
Memory Impairment	3 (2%)
Mental Status Changes	1 (1%)
Seizure	19 (10%)
Syncope	1 (1%)
Tremor	1 (1%)
Psychiatric Disorders	7 (4%)
Agitation	2 (1%)
Anxiety	1 (1%)
Confusional State	1 (1%)
Depression	2 (1%)
Mental Status Changes	2 (1%)

Skin And Subcutaneous Tissue Disorders	70 (36%)
Heat Sensation	20 (10%)
Hyperhidrosis	5 (3%)
Night Sweats	1 (1%)
Rash	1 (1%)
Skin Reaction	59 (31%)
Skin Ulcer	1 (1%)

Conclusions: The post-marketing clinical study (EF-19) was a non-randomized, open label, post-marketing study of Optune Gio monotherapy (n=192) compared to the best standard of care (BSC) chemotherapy arm of the pivotal clinical study (EF-11) in recurrent GBM (n=117). Median OS was longer in the Optune Gio post-marketing study arm than in the chemotherapy arm for the EF-11 pivotal study in recurrent GBM (7.4 vs. 6.4 months). The main AE of skin irritation did not lead to treatment discontinuation and was consistent with the pivotal study data. The EF-19 post approval study confirmed the safety and efficacy conclusions from the EF-11 pivotal study with a longer median OS.

Directions for Use

Detailed information for patients on the use of Optune Gio can be found in the following documents:

- The Optune Gio Patient Information and Operation Manual (Optune HFE Transducer Arrays) - QSD-QR-812

Abbreviations

AE – Adverse event

BSC – Best standard of care (effective chemotherapies)

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor

ITT – Intent-to-Treat. This analysis population includes all randomized subjects

kHz – kilo hertz; number of cycles per second

Optune Gio – A battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with newly diagnosed and recurrent GBM

OS – Overall survival

PP – Per Protocol. This analysis population includes all patients who received at least the first course of TMZ and had no major protocol deviations

PFS – Progression free survival

PFS6 – Proportion of patients alive and progression free at 6 months from randomization Radiological Response Rate – sum of

complete and partial radiological response rates

TMZ – a type of cancer drug used to treat newly diagnosed GBM

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body inflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

TTP – Time to progression

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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