Instructions for Use

OPTUNE™

(NovoTTF™-100A System)

This manual is intended for physicians prescribing the use of Optune.

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

novocure

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Indications for Use

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

Optune™ 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™ is indicated following histologically-or radiologically-confirmed recurrence in the supra-tentorial 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 and Precautions

Contraindications

Do not use Optune 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 together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune 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 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 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 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 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 if you are 21years 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 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 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 break down, 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 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 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 round disks 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 round disks 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 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 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 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 treatment.

Notices

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

Notice! Do not use Optune 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 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 for at least 18 hours a day to get the best response to treatment. Using Optune for less than 18 hours a day lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune 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 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 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 sides of the Optune 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 front of the battery chargers. 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, for the treatment of newly diagnosed and/or recurrent GBM, is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment 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 is comprised of two main components: (1) an Electric Field Generator (the Optune device); and (2) INE Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included in the Optune Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

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 once to twice a week 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 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 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).

NEWLY DIAGNOSED GLIOBLASTOMA (see page 18 for recurrent GBM)

Pilot Clinical Study in Newly Diagnosed GBM

Optune 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 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 and TMZ to those treated with TMZ alone.

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

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 was given together with maintenance TMZ. At treatment initiation patients were seen at an outpatient clinic. During this visit baseline examinations were performed and Optune treatment initiated. The patients were instructed on the operation of Optune 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 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, when treatment on both arms of the study was terminated). 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 analysis on the full study cohort of 695 patients.

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 treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

In the final 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 treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

Analysis Populations: Progression free survival was analyzed in the intent to treat (ITT) population which included all randomized subjects (210 Optune / TMZ and 105 TMZ alone at the interim analysis; 466 Optune / TMZ and 229 TMZ alone at the final analysis). Overall survival 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 / TMZ and 84 TMZ alone at the interim analysis; 429 Optune / TMZ and 180 TMZ alone at the final analysis). Major protocol deviations included patients who received other experimental therapies on protocol or crossed over from the TMZ alone arm to Optune / TMZ.

Subject Characteristics: 315 subjects (210 Optune/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 Characteristic	Treatment Group	
	Optune/TMZ (N=210) n (%)	TMZ Alone (N=105) 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 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 (27.94%) did not have tissue available for analysis.

695 subjects (466 Optune / TMZ; 229 TMZ alone) with newly diagnosed GBM were enrolled in the study and had CRF information available at the time of the **final analysis**. Baseline characteristics in the ITT population were as follows:

Baseline Characteristic	**Treatment Group**	
	Optune/TMZ (N=466) n (%)	**TMZ Alone (N=229) n (%)**
Gender		
Male	316 (67.81)	157 (68.56)
Female	150 (32.19)	72 (31.44)
Central MGMT Assessment		
Invalid	46 (9.87)	18 (7.86)
Unknown	106 (22.75)	57 (24.89)
Methylated	127 (27.25)	67 (29.26)
Unmethylated	187 (40.13)	87 (37.99)
Extent of Resection		
Biopsy	61 (13.09)	30 (13.1)
Gross Total Resection	253 (54.29)	124 (54.15)
Partial Resection	152 (32.62)	75 (32.75)
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	5	4
	Min, Max	1, 26	1, 24
No. of Cycles of Optune Received	Median	6	0
	Min, Max	1, 58	0, 0
Time from GBM Diagnosis to Randomization (Days)	Median	113	111
	Min, Max	59, 498	43, 500

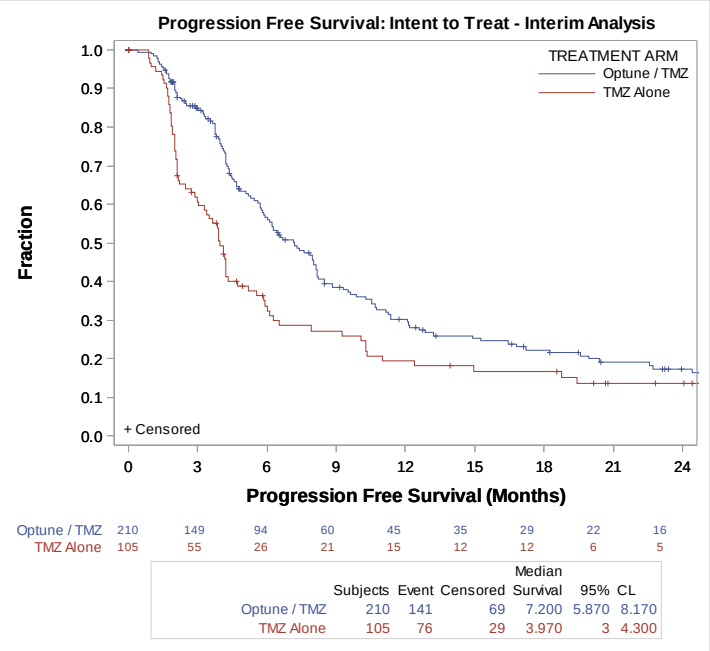
As seen above, all baseline characteristics are well balanced between arms in the ITT population at the final analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 64 patients (9.21%) had tissue that was not evaluable, and 163 patients (23.45%) did not have tissue available for analysis.

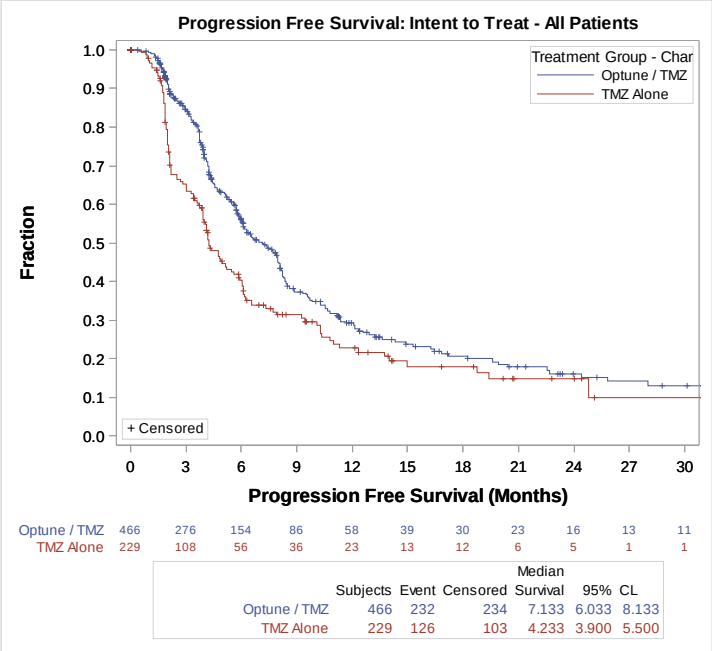
Effectiveness Results:

Primary Effectiveness Endpoint: Progression Free Survival at the Interim Analysis

The threshold for statistical significance based on the Lan-DeMets O'Brien-Fleming method at the interim analysis was pre-defined 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/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/TMZ compared to TMZ alone. At the final analysis, which included 695 patients (Optune/TMZ=466, TMZ alone=229), PFS was also highly significant with a hazard ratio of 0.694.

Primary Efficacy Endpoint - Progression Free Survival (ITT)





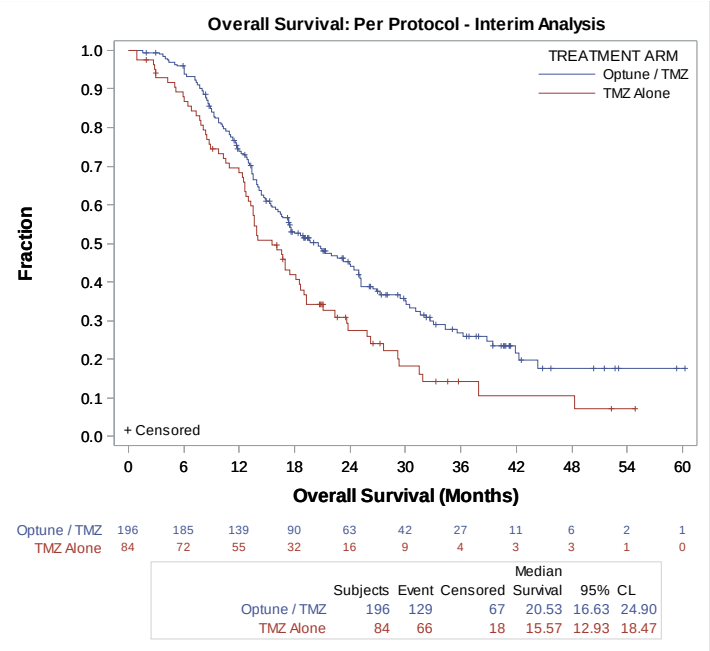
	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	7.2 (5.9, 8.2)	4.0 (3.0, 4.3)	7.1 (6.0, 8.1)	4.2 (3.9, 5.5)
Log-rank test	p=0.0013		p=0.0010	
Hazard Ratio (95% CI)	0.621 (0.468, 0.823)		0.694 (0.558, 0.863)	

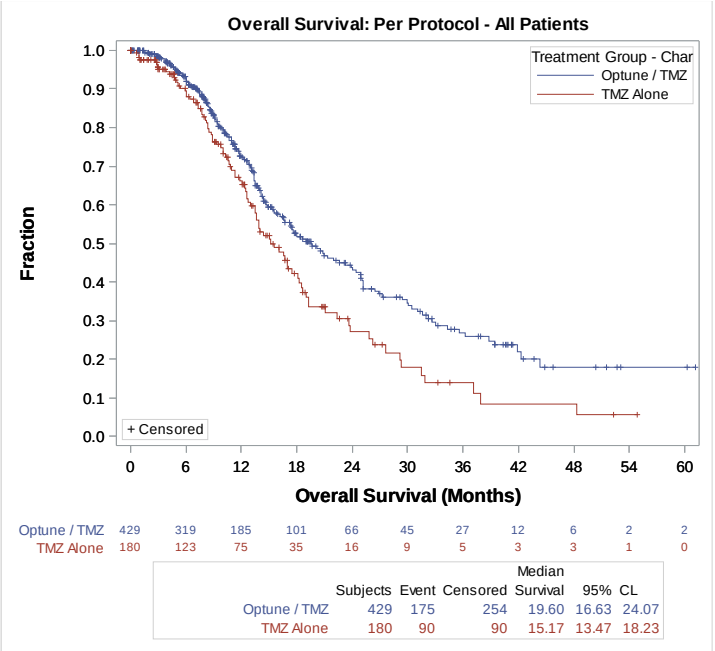
Although not a pre-specified endpoint, PFS was also analyzed in the PP population at the interim and final analyses. Median PFS in the PP population was identical to the ITT population at the interim analysis and slightly longer than the ITT population at the final analysis. Notably, median PFS remained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

Powered Secondary Effectiveness Endpoint: Overall Survival at the Interim Analysis

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/TMZ=196, TMZ=84), OS was also significantly longer in the Optune/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/TMZ compared to TMZ alone. At the final analysis, which included 609 patients (Optune/TMZ=429, TMZ alone=180), OS was also highly significant with a hazard ratio of 0.683.

Overall Survival (PP)





	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	20.5 (16.6, 24.9)	15.6 (12.9, 18.5)	19.6 (16.6, 24.1)	15.2 (13.5, 18.2)
Log-rank test	p=0.0042		p=0.0030	
Hazard Ratio (95% CI)	0.666 (0.495, 0.898)		0.683 (0.529, 0.882)	

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/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/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/TMZ compared to TMZ alone.

Furthermore, at the final analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by 17%. The median OS was 19.4 months (95% CI 16.5-23.8) in the Optune/TMZ group and 16.6 months in the TMZ alone group (95% CI 13.7-18.5). An increase of almost 3 months as seen here is highly significant statistically and clinically (log-rank p=0.0229). The hazard ratio for OS was 0.754 using a Cox regression analysis. This translates into a 24.6% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Secondary Endpoints: Secondary endpoints also showed an advantage for Optune/TMZ compared to TMZ alone. The results below are from the interim analysis which included 315 patients (210 Optune/TMZ and 105 TMZ alone):

Endpoint	Optune/TMZ	TMZ Alone	P-Value
Progression Free Survival at 6 months (ITT)	56.7%	33.7%	0.0004
1-year survival (PP)	75%	69%	0.151
2-year survival (PP)	48%	32%	0.0058
Complete response rate (ITT)	9%	3.5%	NA

In addition, although not a pre-specified endpoint, 1- and 2-year survival were also analyzed in the ITT population at the interim analysis. In the ITT population, 1-year survival was 75% in the Optune/TMZ group and 70% in the TMZ alone group (p-value=0.162) at the interim analysis. 2-year survival in the ITT population at the interim analysis was 48% in the Optune/TMZ group and 34% in the TMZ alone group (p-value=0.0122). Furthermore, the 1-year survival rates at the final analysis are shown in the table below:

Endpoint	Optune/TMZ	TMZ Alone	P-Value
1-year Survival (PP)	69%	63%	0.131
1-year Survival (ITT)	69%	66%	0.265

Quality of Life: Quality of Life assessments were based on the interim analysis cohort of 315 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 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 analysis who received any treatment at the time of the analysis (Optune/TMZ=437, TMZ alone=207). A slightly higher incidence of grade 1-2 adverse events was seen in some of the systems in the Optune/TMZ arm of the study. This is most likely a reflection of the longer duration of TMZ treatment in these patients (median of 6 cycles versus 4 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 by any of the investigators except for 1% grade 3 skin irritation.

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

	Optune/TMZ			TMZ Alone		
	(N=437)			(N=207)		
System Organ Class	Low-Medium	Severe	Fatal	Low-Medium	Severe	Fatal
Number of Patients with ≥1 AE	214 (49%)	169 (39%)	15 (3%)	91 (44%)	82 (40%)	7 (3%)
Blood and Lymphatic System Disorders	86 (20%)	47 (11%)	0	49 (24%)	21 (10%)	0
Cardiac Disorders	12 (3%)	4 (1%)	3 (1%)	6 (3%)	4 (2%)	0
Ear and Labyrinth Disorders	25 (6%)	0	0	8 (4%)	0	0
Endocrine Disorders	11 (3%)	0	0	4 (2%)	0	0
Eye Disorders	36 (8%)	3 (1%)	0	15 (7%)	2 (1%)	0
Gastrointestinal Disorders	202 (46%)	18 (4%)	0	76 (37%)	4 (2%)	0
General Disorders and Administration Site Conditions	175 (40%)	27 (6%)	1 (<1%)	76 (37%)	10 (5%)	1 (<1%)
Hepatobiliary Disorders	1 (<1%)	1 (<1%)	0	5 (2%)	0	0
Liver Disorder	1 (<1%)	0	0	3 (1%)	0	0
Immune System Disorders	10 (2%)	0	0	7 (3%)	0	0
Infections and Infestations	117 (27%)	19 (4%)	3 (1%)	50 (24%)	6 (3%)	1 (<1%)
Injury, Poisoning and Procedural Complications	216 (49%)	20 (5%)	0	13 (6%)	4 (2%)	0
Abnormal Laboratory Tests	58 (13%)	19 (4%)	0	26 (13%)	7 (3%)	1 (<1%)
Metabolism and Nutrition Disorders	89 (20%)	12 (3%)	0	44 (21%)	6 (3%)	0
Musculoskeletal and Connective Tissue Disorders	98 (22%)	16 (4%)	0	44 (21%)	8 (4%)	0
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts And Polyps)	5 (1%)	1 (<1%)	2 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
Nervous System Disorders	190 (43%)	83 (19%)	3 (1%)	75 (36%)	42 (20%)	0
Psychiatric Disorders	108 (25%)	16 (4%)	0	38 (18%)	6 (3%)	0
Renal and Urinary Disorders	42 (10%)	0	0	8 (4%)	2 (1%)	0
Reproductive System and Breast Disorders	8 (2%)	0	0	3 (1%)	0	0
Respiratory, Thoracic and Mediastinal Disorders	65 (15%)	9 (2%)	2 (<1%)	17 (8%)	4 (2%)	0
Skin and Subcutaneous Tissue Disorders	104 (24%)	0	0	32 (15%)	1 (<1%)	0
Surgical and Medical Procedures	2 (<1%)	0	0	2 (1%)	0	0
Vascular Disorders	48 (11%)	16 (4%)	1 (<1%)	19 (9%)	10 (5%)	3 (1%)

Patients treated with Optune/TMZ experienced a small increase in TMZ-related AEs and SAEs due to the longer TMZ exposure afforded to these patient by their longer PFS. The only AEs which may have been caused by Optune therapy are the known skin irritation seen in 45% of patients in this study (1% 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 is very well tolerated with mild to moderate toxicity mainly related to array contact with the scalp.

Conclusions: Optune 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/TMZ extends progression free and overall survival significantly compared to patients receiving TMZ alone. No significant increase in adverse events is seen when Optune treatment is added to TMZ. The only common device-related AE was a skin irritation seen beneath the transducer arrays in 45% percent of patients. The majority (44 of 45%) of these events were mild to moderate. Based on an assessment of the Quality of life of the interim analysis cohort of 315 patients, cognitive function and functional status did not decline due to the use of Optune/TMZ.

RECURRENT DIAGNOSED GLIOBLASTOMA

Pilot Clinical Study in Recurrent GBM

Optune has been tested in 10 recurrent GBM subjects in a single center, pilot study in Europe. In this study, Optune 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 irritation 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 in a real-world, clinical practice setting in the US between 2011 and 2013. The registry included 457 recurrent GBM patients who received Optune in 91 US cancer centers. More patients in PRiDe than the pivotal clinical trial in recurrent GBM (EF-11) received Optune for first recurrence (33% vs. 9%) and had received prior bevacizumab therapy (55.1% vs. 19%). Median OS was significantly longer with Optune 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 NovoTTF Therapy 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 transducer arrays.

Pivotal Clinical Study in Recurrent GBM[1]

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 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 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 compared to BSC.
- To collect evidence of the safety of TTFields applied to subjects with recurrent GBM using Optune.

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

Exclusion Criteria

a. Actively participating in another clinical treatment trial
b. Within 4 weeks from surgery for recurrence

[1] 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.

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 treatment was initiated by the investigator under continuous medical supervision. The subjects were also instructed by the investigator on the operation of Optune 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 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; 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 (cm^2): 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 group than in the BSC group (77% vs. 62%), a lower incidence of frontal lobe tumors in the Optune group than in the BSC group (32% vs. 50%), and a slightly higher mean KPS in the Optune 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	**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 Midline 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)	80 (50, 100)	80 (50,100)
Median Tumor Area (mm^2)	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

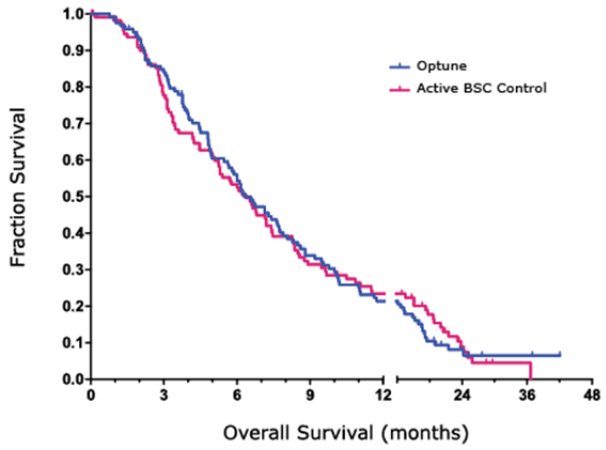
Effectiveness Results:

Primary Effectiveness Endpoint: Overall Survival (ITT)

In the ITT population which included all randomized subjects (Novo-TTF=120, BSC=117), overall survival in subjects treated with Optune 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 establish that Optune therapy is comparable to BSC therapy in extending OS.

	Treatment Group	
	Optune	**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.



Overall Survival (months)

	Optune (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 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 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 group compared to 9.6% for the BSC group in the ITT population. Median time to progression (TTP) was 9.3 weeks for Optune vs. 9.6 weeks for BSC.

	Treatment Group	
	Optune	**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 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 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 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	BSC Chemotherapy
	N=116(%)	N=91(%)
Blood and lymphatic system 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 is a portable, battery operated device which delivers TTFields to patients with recurrent GBM. The results of the pivotal trial showed that Optune 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 to BSC chemotherapy in the ITT population were seen in all secondary endpoints.

Optune 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 subjects as a group when compared to subjects receiving effective BSC chemotherapy.

Directions for Use

Detailed directions for use for Optune can be found in:
The Optune Patient Information and Operation Manual

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– A portable battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with 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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