**SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)**

## I. GENERAL INFORMATION

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|---|---|
| Device General Name: | Tumor Treatment Fields |
| Device Trade Name: | Optune™ (formerly NovoTTF-100A™ System) |
| Device Product Code: | NKZ |
| Applicant's Name and Address: | Novocure, Inc.<br>195 Commerce Way<br>Portsmouth, NH 03801 |
| Date of Panel Recommendation: | Not Applicable (for newly diagnosed GBM) |
| PMA Number: | P100034/S013 |
| Date of FDA Notice of Approval: | October 5, 2015 |
| Priority Review: | Granted priority review status on May 8, 2015, because the condition the device is intended to address is the treatment of newly diagnosed Glioblastoma Multiforme, which represents a life-threatening condition and no legally marketed alternative device is currently available. |

*The original PMA (P100034) was approved on April 8, 2011 and Optune is indicated as follows:*

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

*The SSED to support the above indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indications for use:*

***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.***

## II. 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 (TMZ) 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.

## III. CONTRAINDICATIONS

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

- Do not use the 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 electrode gel used with the Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

## IV. WARNINGS AND PRECAUTIONS

The Warnings and Precautions can be found in the Optune Instructions for Use and Patient Information and Operation Manual.

## V. DEVICE DESCRIPTION

Optune for the expanded indication of newly diagnosed GBM is identical to the previously approved device for the treatment of recurrent GBM.

Optune is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields (TTFields) within the human body. The TTFields are applied to the patient's shaved head by means of electrically insulated surface transducer arrays, such that resistively coupled electric currents are not delivered to the patient. The TTFields disrupt the rapid cell division exhibited by cancer cells.

Treatment parameters are preset by Novocure such that there are no electrical output adjustments available to the patient. The patient must simply learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays must be replaced every few days and the scalp re-shaved in order to maintain optimal capacitive coupling between the transducer arrays and the head. Patients carry the device in a specialized over-the-shoulder bag and receive continuous treatment without changing their daily routine.

## A. Technological Characteristics

Optune is comprised of two main components: (1) an Electric Field Generator; and (2) INE Insulated Transducer Arrays.

1. Electric Field Generator

The Optune Electric Field Generator is a portable, battery or power supply operated device. The outputs are connected to two pairs of insulated transducer array sets operated sequentially. The intensity of the field, the frequency of the waves, and the temperature of the transducer arrays are pre-set, and are controlled by two micro-controllers which run Novocure's software.

The output parameters of the Electric Field Generator are either pre-programmed or set by the service technician through a "service only" USB-type connector. The device status and monitored parameters are continuously stored in an internal log

memory and can be transferred by an isolated serial connection to a PC. In addition, the front panel includes visual indicators for power ON, Treatment ON, alarms and low battery.

INE Insulated Transducer Arrays

Two sets of INE Insulated Transducer Arrays are connected to the Electric Field Generator. Each set includes a pair of arrays, with 9 serially interconnected single transducers in each array. Each transducer array includes 8 thermistors. A single, sterile, 'ready to use' INE Insulated Transducer Array unit incorporates the following: one INE transducer array; conductive gel layer; mid-pads; medical tape; and overlapping liner.

The transducer arrays are made from high dielectric constant insulated ceramic discs soldered to a flexible circuit board. The flexible printed circuit incorporates the components required for delivering the current for each ceramic plate and for measuring the temperature of the thermistors. At the set parameters, the electrodes do not cause significant heating due to dielectric losses of the insulation or induced fields in the target tissue. As an additional safety feature, the temperature of the transducer arrays is monitored by a temperature sensor. If temperature rises beyond 41°C, the device automatically shuts off.

2. Additional Components

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

Optune can be powered by a mains-connected power supply of 24V± 2 V. The power supply connects to the power connector on the front panel of the device.

Alternatively, Optune can also be powered by battery using a portable, external 33 V ± 2 V (when fully charged) rechargeable battery. Several batteries placed in a battery rack can be recharged at the same time using a dedicated battery charger, when not connected to the device. The connection between the battery and the device is through a dedicated connector on the device's front panel.

The transducer arrays are connected to the device by a spiral extension cable. Patients carry the device and the battery in a specialized over-the-shoulder bag, which allows them to receive continuous treatment without changing their daily routine.

## B. 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 through the surface of 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, geometrical shape, and rate of dividing cancer 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., 200 kHz for GBM). TTFields have been shown to disrupt mitotic spindle microtubule assembly and to lead to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis. These processes lead to physical disruption of the cell membrane and to programmed cell death (apoptosis).

The TTFields have not been shown to affect cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are minimally 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. Since TTFields are only applied to the brain, they are unlikely to have an 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 clinically meaningful increase in tissue temperature.

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.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of newly diagnosed GBM, described below. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

In addition to Surgical Resection, there are currently three approved treatment options for GBM:

- Radiation therapy
- TMZchemotherapy
- GLIADEL® Wafer in combination with surgical resection
- Stereotactic radiosurgery
- Re-operate for additional tumor resection

## VII. MARKETING HISTORY

Optune has been FDA approved for the treatment of recurrent GBM and has received CE mark for the treatment of both recurrent and newly diagnosed GBM. The device has been available commercially in the European Union (EU) 42009 and in the US since October 2011. Optune was approved in Japan for the treatment of recurrent GBM in March 2015. The device has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device in any country.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Treatment with the Optune is not expected to cause any serious side effects. However, it is possible that treatment may cause any of the following:

- Allergic reaction to the plaster or to the gel
- Electrode overheating leading to pain and/or local skin burns
- Falls
- Fatigue / malaise
- Headache
- Infection at the sites of electrode contact with the skin
- Local warmth and tingling sensation beneath the electrodes
- Medical device site reaction
- Muscle twitching
- Skin breakdown / skin ulcer

A detailed table of adverse events observed in the pivotal clinical study of the Optune for newly diagnosed GBM can be found in **Section X** below.

## IX. SUMMARY OF PRECLINICAL STUDIES

TTFields have been shown both *in vitro* and *in vivo* to effectively inhibit cancer cell replication during mitosis without 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.

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 or for different periods of time.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for the device was determined to be approximately 4 weeks to reach tumor stabilization. This finding was later validated in independent animal studies and human pilot clinical studies. Stopping treatment prior to completion of a 4 week treatment course may lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

The preclinical data to support this PMA Supplement are the same as the preclinical data submitted in support of the original PMA (P100034). Please refer to the SSED to support the original PMA, which is available on the CDRH website and is incorporated by reference here, for a detailed summary of the preclinical data.

## X. SUMMARY OF PRIMARY CLINICAL STUDIES

A summary table of the clinical studies of the Optune in the treatment of GBM is presented below. These studies are discussed in detail in the following sections.

**Table 1. Summary of Optune GBM Clinical Studies**

| Study Type | Study Design | Type of GBM | Objective | Number of Sites | Number of Subjects | Accountability |
|---|---|---|---|---|---|---|
| Pilot | Prospective single arm study | Recurrent | To assess the safety and effectiveness of Optune treatment compared to recurrent GBM historical controls | 1 | 10 | All subjects were followed until death. Two subjects were still alive 6.5 years after |
| Pilot | Prospective single arm study | Newly Diagnosed | To assess the safety and effectiveness of Optune treatment compared to newly diagnosed historical controls | 1 | 10 | All subjects were followed until death. 8 patients were alive 2 years after starting the study. |

| Study Type | Study Design | Type of GBM | Objective | Number of Sites | Number of Subjects | Accountability |
|---|---|---|---|---|---|---|
| Pivotal | Prospective, open label, best standard of care randomized control trial | Recurrent | To compare the overall survival (OS)of subjects treated with the Optune alone to subjects treated with the best standard of care chemotherapy available for recurrent GBM | 28 | 237 | Vital status is known for 221 (93%) of subjects. 207 subjects received treatment. Last follow up date - June 29, 2010. |
| Pivotal | Prospective, open label, best standard of care randomized control trial | Newly Diagnosed | To compare the efficacy and safety outcome of newly diagnosed GBM patients treated with Optune concomitant to maintenance TMZ to those treated with Temozolomide alone | 83 | 700 | 695 patients received treatment. Vital status is known for >94% of subjects. |

### A. Effect of Optune on Recurrent GBM Subjects - A Pilot Study

Novocure conducted a pilot study in Europe of ten recurrent GBM patients treated with the Optune device. All patients underwent surgery and radiotherapy for the primary tumor, and were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. Patients completed between 1 and 18 treatment courses leading to maximal treatment duration of 18 months. Overall, more than 70 four-week treatment courses were completed (> 7 courses per patient on average).

The treatment was well tolerated with no treatment- related serious adverse events seen in any of the patients. Patients received treatment on average about three quarters of the scheduled time, indicating that compliance with treatment was very high. Mild to moderate contact dermatitis appeared beneath the transducer arrays in 8 of the 10 patients during treatment following the first treatment course. The skin irritation improved with use of topical corticosteroids. Regular relocation of the transducer array was necessary in order to allow for continuous treatment.

The median progression free survival (PFS) of the patients in this study exceeded historical controls[1] (26.1 weeks versus 9 weeks, respectively). The PFS at 6 months (PFS6) was 50% compared to 15% in historical controls[1]. At the end of the

study, 8 of the 10 patients had died (at 4 years from study initiation); the remaining 2 patients we reported are alive at 5 years follow up and are progression free. Median OS from diagnosis was 14.7 months (compared to 6 months in the historical control[1]).

**B. Effect of Optune on Newly Diagnosed GBM Subjects - A Pilot Study**

Novocure conducted a pilot study in Europe of ten newly diagnosed GBM patients treated with the Optune device. All patients underwent surgery and radiotherapy for the primary tumor. Following radiotherapy all patients received maintenance TMZ in addition to Optune treatment, which was administered in the same manner as in the pilot recurrent GBM study. Patients completed between 1 and 17 treatment courses leading to maximal treatment duration of 16.5 months. Overall, more than 96, four-week treatment courses have been completed to date (> 9.6 courses per patient on average).

The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about 80% of the scheduled time, again, indicating that compliance with treatment was very high. Mild to moderate contact dermatitis was experienced by all patients during treatment, again, following the first treatment course. The skin irritation improved with use of topical corticosteroids. Regular relocation of the transducer arrays was necessary in order to allow for continuous treatment.

Median 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; these patients were progression free. Median OS from diagnosis was greater than 40 months (compared to 14.6 months in historical controls[2]).

**C. Pivotal Study for Recurrent GBM**

In a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with Optune (n=120) to those treated with an effective best standard of care chemotherapy (including bevacizumab; n=117), 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 were seen in all secondary endpoints (e.g., PFS6 = 21.4% for Optune vs. 15.2% for chemotherapy).

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

[1] Wong, E.T., et al., Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol, 1999. 17(8): p. 2572-8.

[2] Stupp, R., et al., *Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.* N Engl J Med, 2005. 352(10): p. 987-96.

adverse events seen were a mild to moderate skin irritation beneath the device electrodes, which was easily treated with topical ointments. Finally, quality of life measures were better in Optune subjects as a group when compared to subjects receiving effective best standard of care chemotherapy.

The clinical data from this pivotal clinical study was submitted in P100034 to support approval for the treatment of recurrent GBM. A detailed summary of these data can be found in the SSED to support the original PMA, which is available on the CDRH website and is incorporated by reference here, and in a peer reviewed publication by Stupp et al., in 2012[3].

## D. Pivotal Study for Newly Diagnosed GBM

1. Study Design

The clinical study that formed the basis for determining that the Optune System is safe and effective for its intended use was a multicenter, randomized, controlled clinical trial designed to evaluate the safety and effectiveness of Optune in the treatment of newly-diagnosed GBM. Subjects were randomized to receive either Optune together with maintenance TMZ or TMZ alone. The hypothesis of this study was that the addition of Optune treatment to maintenance TMZ would increase progression free survival of newly diagnosed GBM patients compared to patients treated with TMZ alone. The specific objectives of the study were:

- To prospectively compare the PFS time of newly diagnosed GBM patients treated with Optune together with TMZ to those treated with TMZ alone.
- To prospectively compare the overall survival time of newly diagnosed GBM patients treated with Optune together with TMZ to those treated with TMZ alone.
- To prospectively determine %6-month PFS ("PFS6"), %1and 2-year survival and quality of life of patients treated with Optune together with TMZ to those treated with TMZ alone.
- To collect evidence of the safety of the Optune device applied together with TMZ to patients with newly diagnosed GBM.

Subjects with newly diagnosed GBM were recruited into the study at thirty-eight (38) United States (US) and forty-five (45) outside US (OUS) clinical centers.

Immediately following screening, subjects were randomized at a 2:1 ratio to receive either Optune treatment together with maintenance TMZ or maintenance TMZ alone. The nature of the treatment precluded blinding of subjects and their treating clinicians to the actual treatment received by the subjects. However, a central MRI review was performed by an independent neuro-radiologist blinded to the treatment group assignment of each subject. In addition, an independent Data Monitoring Committee (DMC) monitored the safety data

[3] Stupp et al., NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer. 2012 Sep;48(14):2192-202.

from the study, and a Clinical Events Committee (CEC) was convened to evaluate and adjudicate, where necessary, regarding final safety and effectiveness results of the trial.

The protocol specified that an interim analysis was to be performed on the first 315 patients with a minimum follow up of 18 months. This interim analysis was conducted as planned and on October 9, 2014, the DMC recommended the study be closed early for success. On October 24, 2014, the DMC further recommended that the patients in the control arm be offered the option to crossover to receive Optune treatment prior to disease progression.

Patient follow-up for PFS and OS continued for 18 months from accrual of the last patient in each center. An interim analysis was provided on the first 315 patients as of the database cutoff, September 5, 2014. A final analysis was also provided limited to the PFS and OS endpoints using data from all 700 patients based on a database cutoff of December 29, 2014.

The study analysis as of the interim database cut-off date compared data between 210 Optune subjects and 105 control subjects. The final analysis compared results between 466 Optune subjects and 229 Optune/TMZ subjects.

**Eligibility Criteria**

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 (45-70 Grays (Gy)) :
    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 TMZ 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 – aspartate transaminase (AST) or alanine transaminase 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 > 5 mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
h. History of hypersensitivity reaction to TMZ or a history of hypersensitivity to DTIC.

**Treatment Arm**

At treatment initiation, patients were seen at an outpatient clinic. During this period, baseline examinations were performed and Optune treatment was initiated. The investigator also instructed the subjects on the operation of the Optune System and battery replacement. Once the subjects were trained in operating the device, they were released to continue treatment at home. The subjects receive multiple 1 month courses of continuous Optune treatment. Optune treatment was discontinued in the case of clinical disease progression, if a device-related serious adverse event occurred, or after 24 months or second progression whichever occurred first.

**Control Arm**

Patients in the control arm were treated with maintenance TMZ. Following radiological progression or unacceptable toxicity, TMZ was replaced with best standard of care second line therapy (re-operation, local radiation therapy, second line chemotherapy, or a combination).

**Follow-up**

During treatment, all patients were seen once every month at an outpatient clinic where they underwent medical follow up and routing laboratory exams. An MRI was performed every 2 months following the baseline MRI until second progression. 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. **Table 2** below provides the full schedule of evaluations in the study.

**Table 2. Schedule of Evaluations to be Performed for Each Subject**

| | T=-7 (baseline) | T=1 month (±7 days) | T=2 months (±7 days) | T=3 months (±7 days) | T=4 months (±7 days) | T=5 months (±7 days) | T=6 months (±14 days) | T=every month until treatment stop+ | T=Progression | T=1 month From treatment stop+ | T=2 months From treatment stop+ | Monthly thereafter+ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MRI of the head | X* | | X* | | X* | | X* | X* | X* | | | |
| Physical examination | X | X | X | X | X | X | X | X | X | X | X | |
| Neurological status | X | X | X | X | X | X | X | X | X | X | X | |
| Complete blood count (CBC) and differential | X | X | X | X | X | X | X | X | | X | X | |
| Chemistry panel (SMAC) | X | X | X | X | X | X | X | X | | X | X | |
| Coagulation study | X | X | X | X | X | X | X | X | | X | X | |
| Mini Mental State Exam (MMSE) | X | X | X | X | X | X | X | X | X | X | X | |
| Quality of life questionnaire | X | | | X | | | X | X^ | | | | |
| Telephone interview | | | | | | | | | | | | X |

* Screening MRI was performed within 2 weeks before study start. MRI of the head was performed routinely at baseline and again every 2 months until treatment termination or second progression, whichever was later. An MRI of the head was to be obtained in the event of clinical signs of progression.

^ Every third month until treatment termination.

+ Visit window of ± 7 days if visit occurred prior to the 6 month follow-up window, ± 14 days if visit occurred on or after the 6 month follow-up window, ± 1 month if visit occurred on or after the 12 month follow-up window.

**Endpoints**

*Primary Effectiveness Endpoint*

The primary outcome of the study was progression free survival

*Secondary Effectiveness Endpoints*

The secondary outcome measures of the study were:
- Overall survival– powered secondary endpoint
- Progression free survival at 6 months
- One and two year survival rate (% 1 and 2 year survival)
- Quality of life (EORTC Quality of Life- C30 questionnaire)
- Radiological response rate

*Safety*

The safety endpoint was the safety and tolerability of Optune treatment based on the incidence and severity of adverse events and toxicities.

2. Statistical Analysis Plan and Analysis Populations

**Sample Size**

The sample size of 700 subjects was designed to test the superiority hypothesis that Optune with maintenance TMZ would significantly increase the PFS of newly-diagnosed GBM patients compared to patients who used maintenance TMZ alone.

**Statistical Analysis**

The statistical hypothesis that was to be tested for the primary endpoint of progression free survival (PFS) was:

$H_0 : PFS_t = PFS_c$ versus $H_A : PFS_t \neq PFS_c$

where,

$PFS_t$= K-M progression free survival curve in the Optune/TMZ arm; and

$PFS_c$ = K-M progression free survival curve in the TMZ alone arm.

A hierarchical approach was used to first test the primary endpoint of PFS (in the ITT population) and then the secondary endpoint of overall survival (in the Per Protocol population) to avoid problems with statistical multiplicity.

The statistical hypothesis that was to be tested for the powered secondary endpoint of overall survival (OS) was:

$H_0 : OS_t = OS_c$ versus $H_A : OS_t \neq OS_c$

where,

$OS_t$ = K-M overall survival curve for the Optune/TMZ arm; and
$OS_c$ = K-M overall survival curve for the TMZ alone arm.

The following were non-powered secondary endpoints:

- Progression free survival at 6 months (PFS6) – This endpoint was tested with a one-sided chi-square test, assuming the Optune/TMZ arm would have a higher PFS6 than the TMZ alone arm of the study. No analysis of this endpoint was performed at the interim analysis.

- 1- and 2- year overall survival rates – For 1- and 2- year survival, the analyses were performed based on the Kaplan- Meier estimated proportions of patients alive at 12 and 24 months, respectively, in both arms of the study. These secondary endpoints were tested with a one-sided chi-square test, assuming the Optune/TMZ arm would have higher 1- and 2-year survival rates than the TMZ alone arm of the study. No analysis of this endpoint was performed at the interim analysis.

- Quality of life (EORTC QLQ-C30 questionnaire) – Change from baseline (CFB) to 3, 6, 9 and 12 months was calculated for each subscale domain and symptom scale in the questionnaire. Results were presented descriptively as a ratio in CFB at each of the above time points in the treatment Optune/TMZ arm compared to the control TMZ alone arm of the study.

- Radiological response rate – This endpoint was compared between groups using a one-sided chi-square test assuming the Optune/TMZ arm would have a higher response rate than the TMZ alone arm of the study. No analysis of this endpoint was performed at the interim analysis.

**Analysis Datasets and Populations**

Two analyses were performed to support the approval of the Optune for the treatment of newly diagnosed GBM:

1. The pre-specified interim analysis was performed on the first 315 patients enrolled after the 315$^{th}$ patient had 18 months of follow up (database cutoff September 5, 2014).
2. A final analysis was performed on the entire 700 patient trial cohort (data available for 695 patients as of the database cutoff December 29, 2014).

In both of these analyses the following pre-specified analysis populations were used to evaluate the study results:

*Intent-to-Treat*

The Intent to Treat (ITT) population includes all subjects who were randomized to the trial. The analysis was performed by the treatment group to which the patient was randomized.

*Per Protocol*

The Per Protocol (PP) population excludes:

- Patients who never started any treatment (on either arm)
- Patients who did not receive adequate therapy defined as:
  - Optune/TMZ patients who did not receive a full treatment course (4 weeks) from the ITT population.
  - TMZ patients who did not receive the first day of the second course of TMZ.
- Patients in the TMZ arm who received Optune therapy off protocol
- Patients in either arm with major protocol violations (received another experimental treatment while on the protocol).

*Safety Population*

This population includes all patients who received at least one dose of TMZ or one day of Optune treatment.

**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.

See **Figure 1** below showing the interim analysis populations for the trial and **Figure 2** below showing the final analysis populations for the trial.

**Figure 1. Interim Analysis – Analysis Populations**

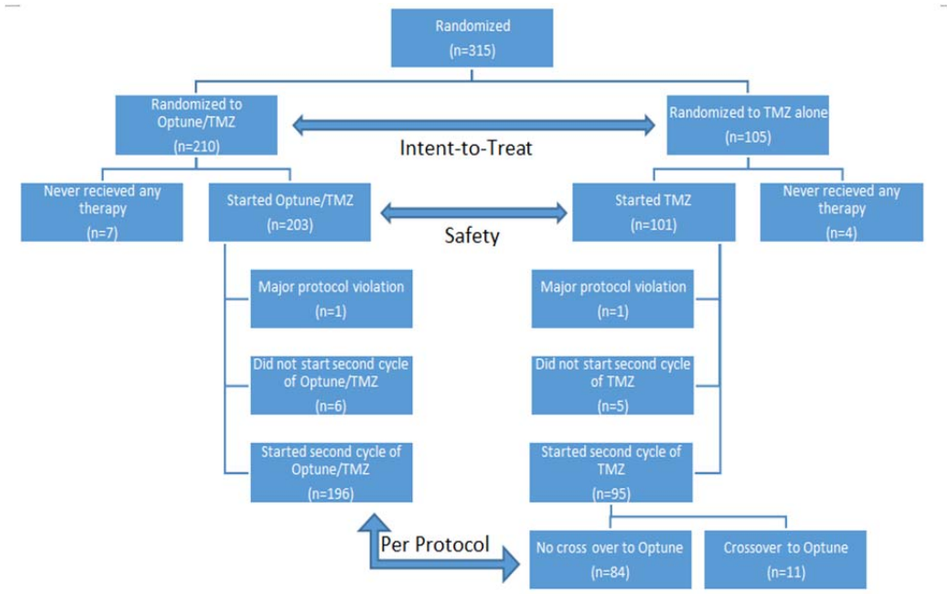
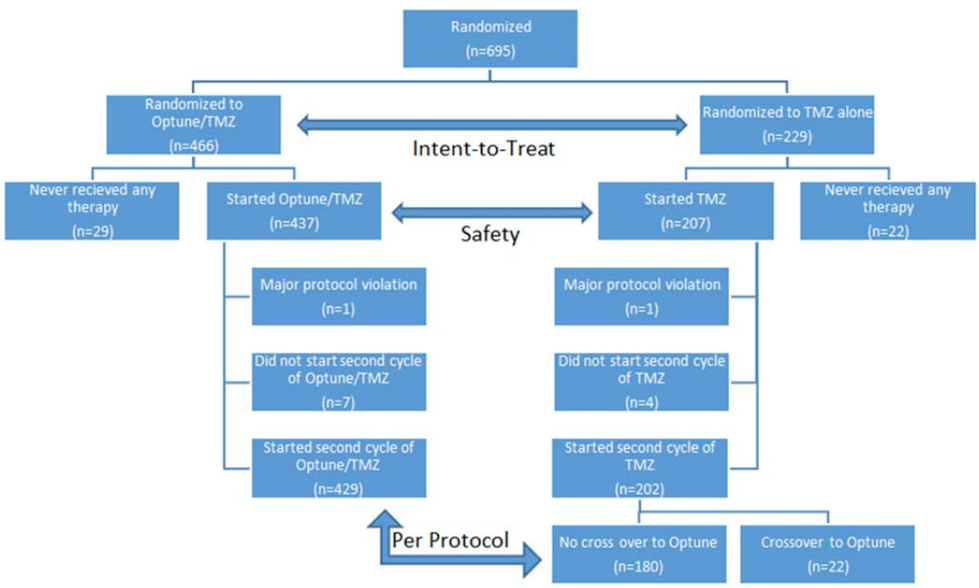



**Figure 2. Final Analysis – Analysis Populations**



3. Subject Accountability

700 subjects (466 Optune/TMZ; 229 TMZ alone) with newly diagnosed GBM were enrolled in the study. 5 patients did not yet have baseline characteristics entered nor any follow-up performed at the time of this submission. The first 315 subjects (210 Optune/TMZ; 105 TMZ alone) who had 18 months of follow-up were used in the interim analysis. All 695 patients with data were used for the final analysis.

Subject disposition and follow-up is shown in **Tables 3** and **4** below.

**Table 3. Subject Accountability - Interim Analysis - ITT**

| **Visit** | **Baseline** | | **6 Months** | | **12 Months** | | **18 Months** | | **24 Months** | |
|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Arm | Optune /TMZ | TMZ Alone | Optune /TMZ | TMZ Alone | Optune /TMZ | TMZ Alone | Optune /TMZ | TMZ Alone | Optune /TMZ | TMZ Alone |
| Expected | 210 | 105 | 199 | 90 | 157 | 73 | 114 | 49 | 100 | 36 |
| Total Censored | 0 | 0 | 4 | 4 | 10 | 5 | 20 | 7 | 35 | 13 |
| Disease Progression or AE | 0 | 0 | 1 | 1 | 5 | 1 | 7 | 1 | 9 | 4 |
| Withdrawn | 0 | 0 | 2 | 2 | 4 | 2 | 10 | 3 | 14 | 5 |
| Lost to Follow-up | 0 | 0 | 1 | 1 | 1 | 2 | 3 | 3 | 12 | 4 |
| Deaths | 0 | 0 | 11 | 15 | 53 | 32 | 96 | 56 | 110 | 69 |
| Available | 210 | 105 | 195 | 86 | 147 | 68 | 94 | 42 | 65 | 23 |
| % Follow-up | 100% | 100% | 98% | 96% | 94% | 93% | 82% | 86% | 65% | 64% |

**Table 4. Subject Accountability - Final Analysis - ITT**

| **Visit** | **Baseline** | | **6 Months** | | **12 Months** | | **18 Months** | | **24 Months** | |
|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Arm | Optune /TMZ | TMZ Alone | Optune /TMZ | TMZ Alone | Optune /TMZ | TMZ Alone | Optune /TMZ | TMZ Alone | Optune /TMZ | TMZ Alone |
| Expected | 466 | 229 | 336 | 154 | 206 | 101 | 125 | 56 | 96 | 37 |
| Total Censored | 2 | 1 | 107 | 59 | 181 | 82 | 219 | 99 | 241 | 110 |
| Active Follow- up | 2 | 1 | 103 | 55 | 171 | 77 | 201 | 92 | 215 | 97 |
| Disease Progression or AE | 0 | 0 | 1 | 1 | 5 | 1 | 7 | 1 | 10 | 5 |
| Withdrawn | 0 | 0 | 2 | 2 | 4 | 2 | 9 | 3 | 13 | 5 |
| Lost to Follow-up | 0 | 0 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 3 |
| Deaths | 0 | 0 | 29 | 21 | 91 | 52 | 142 | 82 | 157 | 96 |
| Available | 464 | 228 | 330 | 149 | 194 | 95 | 105 | 48 | 68 | 23 |
| % Follow-up | 100% | 100% | 98% | 97% | 94% | 94% | 84% | 86% | 71% | 62% |

4. Demographics and Baseline Characteristics

Baseline characteristics were well balanced between treatment groups in both the interim and final analyses. In the interim analysis, median age was 57 and 58 years in the Optune/TMZ group and TMZ alone group, respectively. Median KPS in both groups was 90. In patients who had evaluable tissue available, MGMT methylation was seen in 38% and 41% of patients in the Optune/TMZ group and TMZ alone group, respectively. "Invalid" refers to tissue that was not evaluable, while "Unknown" refers to patients who did not have tissue available for analysis. 35 patients (11.11%) had tissue that was not evaluable, and 88 patients (27.94%) did not have tissue available for analysis. Eleven percent of patients in both groups had biopsy only performed at diagnosis. Median time from diagnosis to randomization was 3.8 months in both groups. Tumor location and position were also well balanced between groups. Finally, the median number of TMZ courses in the Optune/TMZ arm was 6 and in the TMZ alone arm was 4 due to the longer PFS seen with the combined treatment. The median number of Optune cycles was 9 because some patients were treated beyond progression as defined in the protocol.

Baseline characteristics of the interim analysis ITT study population are shown in the table below.

**Table 5. Baseline Characteristics – Interim Analysis – ITT**

| **Baseline Characteristic** | **Treatment Group** | | | | **All Patients (N=315)** | |
|---|---|---|---|---|---|---|
| | **Optune/TMZ (N=210)** | | **TMZ Alone (N=105)** | | | |
| | **n** | **%** | **n** | **%** | **n** | **%** |
| Gender | | | | | | |
| Male | 140 | 66.67 | 67 | 63.81 | 207 | 65.71 |
| Female | 70 | 33.33 | 38 | 36.19 | 108 | 34.29 |
| Central MGMT Assessment | | | | | | |
| Invalid | 24 | 11.43 | 11 | 10.48 | 35 | 11.11 |
| Methylated | 49 | 23.33 | 26 | 24.76 | 75 | 23.81 |
| Unknown | 58 | 27.62 | 30 | 28.57 | 88 | 27.94 |
| Unmethylated | 79 | 37.62 | 38 | 36.19 | 117 | 37.14 |
| Extent of Resection | | | | | | |
| Biopsy | 23 | 10.95 | 11 | 10.48 | 34 | 10.79 |
| Gross Total Resection | 135 | 64.29 | 67 | 63.81 | 202 | 64.13 |
| Partial Resection | 52 | 24.76 | 27 | 25.71 | 79 | 25.08 |
| Area | | | | | | |
| ROW | 83 | 39.52 | 41 | 39.05 | 124 | 39.37 |

| Baseline Characteristic | Treatment Group | | | | All Patients (N=315) | |
|---|---|---|---|---|---|---|
| | Optune/TMZ (N=210) | | TMZ Alone (N=105) | | | |
| | n | % | n | % | n | % |
| USA | 127 | 60.48 | 64 | 60.95 | 191 | 60.63 |
| Tumor Position | | | | | | |
| Missing | 0 | 0 | 3 | 2.86 | 3 | 0.95 |
| Corpus Callosum | 12 | 5.71 | 3 | 2.86 | 15 | 4.76 |
| Frontal Lobe | 64 | 30.48 | 32 | 30.48 | 96 | 30.48 |
| Occipital Lobe | 7 | 3.33 | 4 | 3.81 | 11 | 3.49 |
| Parietal Lobe | 35 | 16.67 | 27 | 25.71 | 62 | 19.68 |
| Temporal Lobe | 92 | 43.81 | 36 | 34.29 | 128 | 40.63 |
| Tumor Location | | | | | | |
| Missing | 0 | 0 | 1 | 0.95 | 1 | 0.32 |
| Both | 2 | 0.95 | 1 | 0.95 | 3 | 0.95 |
| Corpus Callosum | 8 | 3.81 | 3 | 2.86 | 11 | 3.49 |
| Left | 93 | 44.29 | 41 | 39.05 | 134 | 42.54 |
| Right | 107 | 50.95 | 59 | 56.19 | 166 | 52.70 |

| Baseline Characteristic | | Treatment Group | | All Patients (N=315) |
|---|---|---|---|---|
| | | Optune/TMZ (N=210) | TMZ Alone (N=105) | |
| Karnofsky Performance Score | Median | 90 | 90 | 90 |
| | Min | 60 | 70 | 60 |
| | Max | 100 | 100 | 100 |
| | Mean | 88.65 | 87.65 | 88.32 |
| | Std. | 10.75 | 10.55 | 10.68 |
| Age in Years | Median | 57 | 58 | 57 |
| | Min | 20 | 21 | 20 |
| | Max | 83 | 80 | 83 |
| | Mean | 55.28 | 56.76 | 55.77 |
| | Std. | 11.31 | 10.54 | 11.06 |

| Baseline Characteristic | | Treatment Group | | All Patients (N=315) |
|---|---|---|---|---|
| | | Optune/TMZ (N=210) | TMZ Alone (N=105) | |
| No. of Cycles of TMZ Received | Median | 6 | 4 | 6 |
| | Min | 1 | 1 | 1 |
| | Max | 26 | 24 | 26 |
| | Mean | 6.67 | 5.66 | 6.34 |
| | Std. | 5.01 | 4.67 | 4.92 |
| No. of Cycles of Optune Received | Median | 9 | 0 | 9 |
| | Min | 1 | 0 | 1 |
| | Max | 58 | 0 | 58 |
| | Mean | 12.65 | 0 | 12.65 |
| | Std. | 10.96 | 0 | 10.96 |
| Time from GBM Diagnosis to Randomization (Days) | Median | 115 | 113 | 114 |
| | Min | 59 | 43 | 43 |
| | Max | 171 | 170 | 171 |
| | Mean | 115.40 | 114.70 | 115.20 |
| | Std. | 17.25 | 16.50 | 16.98 |

In the final analysis, baseline characteristics were balanced between treatment groups. Median age was 56 and 57 years in the Optune/TMZ group and TMZ alone group, respectively. Median KPS in both groups was 90. In patients who had evaluable tissue available, MGMT methylation was seen in 41% and 44% of patients in the Optune/TMZ group and TMZ alone group, respectively. 64 patients (9.21%) had tissue that was not evaluable, and 163 patients (23.45%) did not have tissue available for analysis. Thirteen percent of patients in both groups had biopsy only performed at diagnosis. Median time from diagnosis to randomization was 3.8 months in both groups. Tumor location and position were also well balanced between groups. Finally, the median number of TMZ courses in the Optune/TMZ arm was 5 and in the TMZ alone arm was 4 due to the longer PFS seen with the combined treatment. The median number of Optune cycles was 6 because some patients were treated beyond progression as defined in the protocol. It should be noted that the lower number of treatment cycles in the Optune/TMZ arm at the final analysis is likely an underestimation, since many patients were still on Optune/TMZ treatment at the time of database lock.

Baseline characteristics of the final analysis ITT study population are shown in the table below.

**Table 6. Baseline Characteristics – Final Analysis – ITT**

| Baseline Characteristic | Treatment Group | | | | All Patients (N=695) | |
|---|---|---|---|---|---|---|
| | Optune/TMZ (N=466) | | TMZ Alone (N=229) | | | |
| | n | % | n | % | n | % |
| Gender | | | | | | |
| Male | 316 | 67.81 | 157 | 68.56 | 473 | 68.06 |
| Female | 150 | 32.19 | 72 | 31.44 | 222 | 31.94 |
| Central MGMT Assessment | | | | | | |
| Invalid | 46 | 9.87 | 18 | 7.86 | 64 | 9.21 |
| Methylated | 127 | 27.25 | 67 | 29.26 | 194 | 27.91 |
| Unknown | 106 | 22.75 | 57 | 24.89 | 163 | 23.45 |
| Unmethylated | 187 | 40.13 | 87 | 37.99 | 274 | 39.42 |
| Extent of Resection | | | | | | |
| Biopsy | 61 | 13.09 | 30 | 13.10 | 91 | 13.09 |
| Gross Total Resection | 253 | 54.29 | 124 | 54.15 | 377 | 54.24 |
| Partial Resection | 152 | 32.62 | 75 | 32.75 | 227 | 32.66 |
| Area | | | | | | |
| ROW | 245 | 52.58 | 111 | 48.47 | 356 | 51.22 |
| USA | 221 | 47.42 | 118 | 51.53 | 339 | 48.78 |
| Tumor Position | | | | | | |
| Missing | 31 | 6.65 | 15 | 6.55 | 46 | 6.62 |
| Corpus Callosum | 21 | 4.51 | 9 | 3.93 | 30 | 4.32 |
| Frontal Lobe | 142 | 30.47 | 67 | 29.26 | 209 | 30.07 |
| Occipital Lobe | 14 | 3.00 | 4 | 1.75 | 18 | 2.59 |
| Parietal Lobe | 77 | 16.52 | 50 | 21.83 | 127 | 18.27 |
| Temporal Lobe | 181 | 38.84 | 84 | 36.68 | 265 | 38.13 |
| Tumor Location | | | | | | |
| Missing | 30 | 6.44 | 12 | 5.24 | 42 | 6.04 |
| Both | 12 | 2.58 | 3 | 1.31 | 15 | 2.16 |
| Corpus Callosum | 12 | 2.58 | 7 | 3.06 | 19 | 2.73 |
| Left | 193 | 41.42 | 93 | 40.61 | 286 | 41.15 |
| Right | 219 | 47.00 | 114 | 49.78 | 333 | 47.91 |

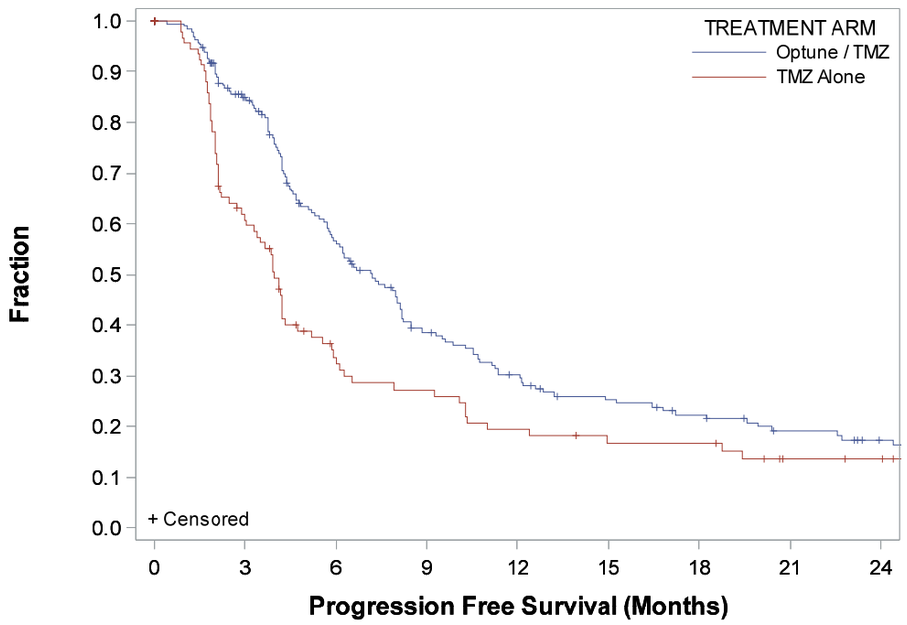
| Baseline Characteristic | | Treatment Group | | All Patients (N=695) |
|---|---|---|---|---|
| | | Optune/TMZ (N=466) | TMZ Alone (N=229) | |
| Karnofsky Performance Score | Median | 90 | 90 | 90 |
| | Min | 60 | 70 | 60 |
| | Max | 100 | 100 | 100 |
| | Mean | 87.72 | 88.14 | 87.86 |
| | Std. | 10.28 | 9.71 | 10.09 |
| Age in Years | Median | 56 | 57 | 56 |
| | Min | 19 | 19 | 19 |
| | Max | 83 | 80 | 83 |
| | Mean | 54.84 | 55.26 | 55.24 |
| | Std. | 11.58 | 11.42 | 16.46 |
| No. of Cycles of TMZ Received | Median | 5 | 4 | 5 |
| | Min | 1 | 1 | 1 |
| | Max | 26 | 24 | 26 |
| | Mean | 5.60 | 5.17 | 5.46 |
| | Std. | 4.19 | 3.95 | 4.11 |
| No. of Cycles of Optune Received | Median | 6 | 0 | 6 |
| | Min | 1 | 0 | 1 |
| | Max | 58 | 0 | 58 |
| | Mean | 9.12 | 0 | 9.12 |
| | Std. | 9.06 | 0 | 9.06 |
| Time from GBM Diagnosis to Randomization (Days) | Median | 113 | 111 | 112 |
| | Min | 59 | 43 | 43 |
| | Max | 498 | 500 | 500 |
| | Mean | 116.30 | 114.70 | 115.80 |
| | Std. | 30.01 | 30.30 | 30.09 |

5. Study Results

**Primary Efficacy Results**

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. As seen in **Figure 3**, PFS at the interim analysis in the ITT population met this threshold. The median PFS in the Optune/TMZ group was 7.2 months (95% CI 5.9-8.2) compared to 4 months (95% CI 3.0-4.3) in the TMZ alone group. The difference of more than 3 months in median PFS, in favor of Optune is highly clinically significant (log-rank p=0.0013) and represents an 80% increase in PFS when utilizing Optune/TMZ compared to TMZ alone. The hazard ratio for PFS was 0.621 using a Cox regression analysis (see **Table 7**). This translates into a 37.9% decrease in the risk of progression when using Optune/TMZ compared to TMZ alone. Therefore, the trial met its primary endpoint at the interim analysis.

**Figure 3. Progression Free Survival - Interim Analysis - ITT**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Optune / TMZ | 210 | 149 | 94 | 60 | 45 | 35 | 29 | 22 | 16 |
| TMZ Alone | 105 | 55 | 26 | 21 | 15 | 12 | 12 | 6 | 5 |

| | Subjects | Event | Censored | Median Survival | 95% CL | |
|---|---|---|---|---|---|---|
| Optune / TMZ | 210 | 141 | 69 | 7.200 | 5.870 | 8.170 |
| TMZ Alone | 105 | 76 | 29 | 3.970 | 3 | 4.300 |

**Table 7. Log-Rank Test for PFS - Interim Analysis – ITT**

| | **Optune/TMZ** | **TMZ Alone** |
|---|---|---|
| Median (95% CI) | 7.2 (5.9, 8.2) | 4.0 (3.0, 4.3) |
| Log-rank test | p=0.0013 | |
| Hazard Ratio | 0.621 (0.468, 0823) | |

The threshold for statistical significance based on the Lan-DeMets O'Brien-Fleming method at the final analysis was pre-defined as p=0.04574, and the test was to be performed in the ITT population according to the protocol. As seen in **Figure 4**, PFS at the final analysis in the ITT population met this threshold. The median PFS in the Optune/TMZ group was 7.1 months (95% CI 6.0-8.1) compared to 4.2 months (95% CI 3.9-5.5) in the TMZ alone group. The difference of 2.9 months in median PFS, in favor of Optune is highly clinically significant (log-rank p=0.0010) and represents a 69% increase in PFS when utilizing Optune/TMZ compared to TMZ alone. The hazard ratio for PFS was 0.694 using a Cox regression analysis. This translates into a 30.6% decrease in the risk of progression when using Optune/TMZ compared to TMZ alone. Therefore, the trial met its primary endpoint at the final analysis as well as at the interim analysis.

**Figure 4. Progression Free Survival - Final Analysis - ITT**

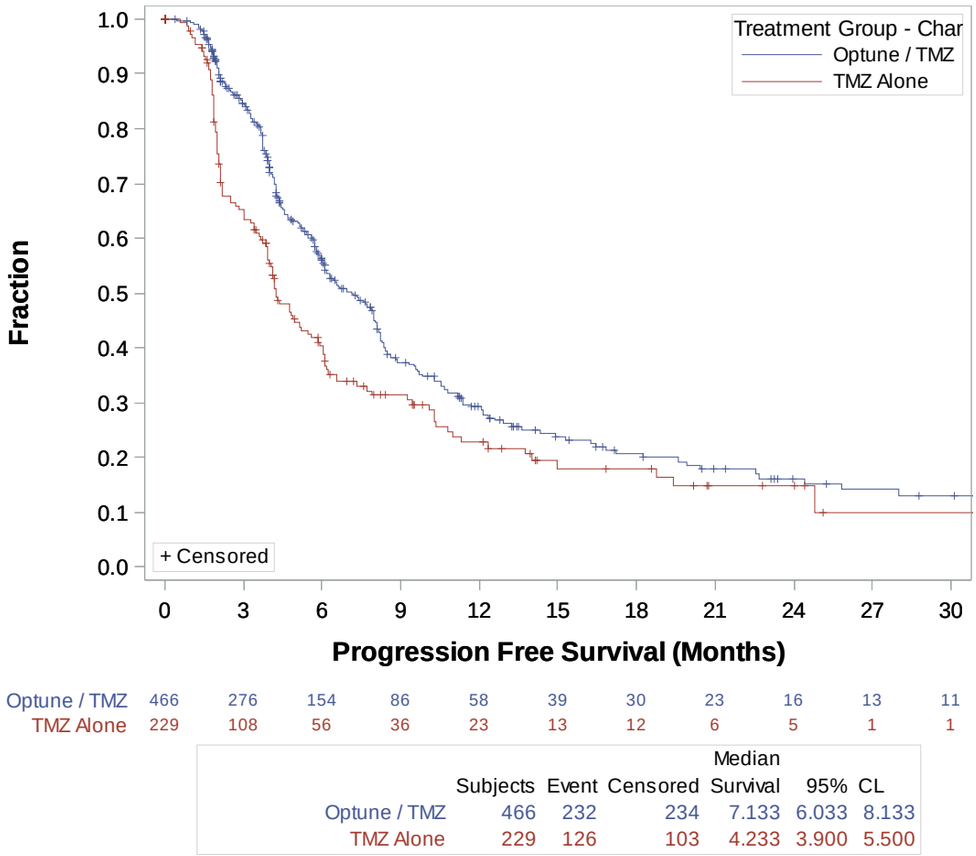



**Table 8. Log-Rank Test for PFS - Final Analysis – ITT**

| | **Optune/TMZ** | **TMZ Alone** |
|---|---|---|
| Median (95% CI) | 7.1 (6.0, 8.1) | 4.2 (3.9, 5.5) |
| Log-rank test | p=0.0010 | |
| Hazard Ratio | 0.694 (0.558, 0863) | |

**Secondary Efficacy Results**

Overall survival was the only powered secondary endpoint. 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 pre-specified to be tested in the PP population.

As seen in **Figure 5** and **Table 9**, at the interim analysis, OS was also significantly longer in the Optune/TMZ arm compared to TMZ alone by about 31%. The median OS was 20.5 months (95% CI 16.6-24.9) in the Optune/TMZ group and 15.6 months in the TMZ alone group (95% CI 12.9-18.5). An increase of almost 5 months as seen here is highly significant clinically (log-rank p = 0.0042). The hazard ratio for OS was 0.666 using a Cox regression analysis. This translates into a 33.4% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

**Figure 5. Overall Survival - Interim Analysis – PP**

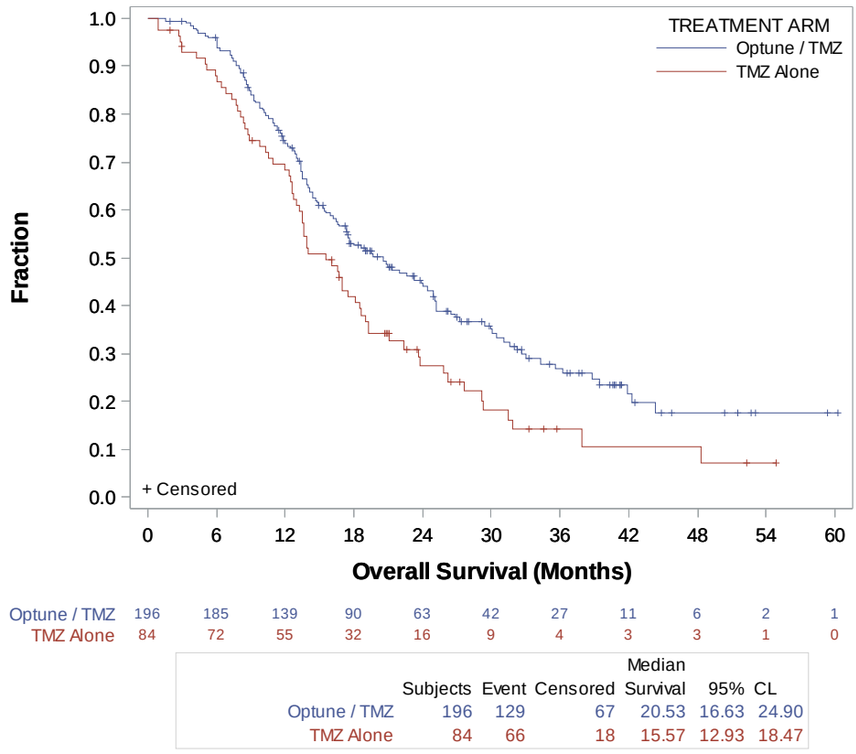



**Table 9. Log-Rank Test for OS - Interim Analysis – PP**

| | **Optune/TMZ** | **TMZ Alone** |
|---|---|---|
| Median (95% CI) | 20.5 (16.6, 24.9) | 15.6 (12.9, 18.5) |
| Log-rank test | p=0.0042 | |
| Hazard Ratio | 0.666 (0.495, 0898) | |

As seen in **Figure 6** and **Table 10**, at the final analysis, OS in the pre-specified per protocol population was significantly longer in the Optune/TMZ arm compared to TMZ alone by almost 30%. The median OS was 19.6 months (95% CI 16.6-24.1) in the Optune/TMZ group and 15.2 months in the TMZ alone group (95% CI 13.5-18.2). An increase of almost 4.5 months as seen here is highly significant clinically (log-rank p = 0.0030). The hazard ratio for OS was 0.683 using a Cox regression analysis. This translates into a 31.7% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

**Figure 6. Overall Survival - Final Analysis – PP**

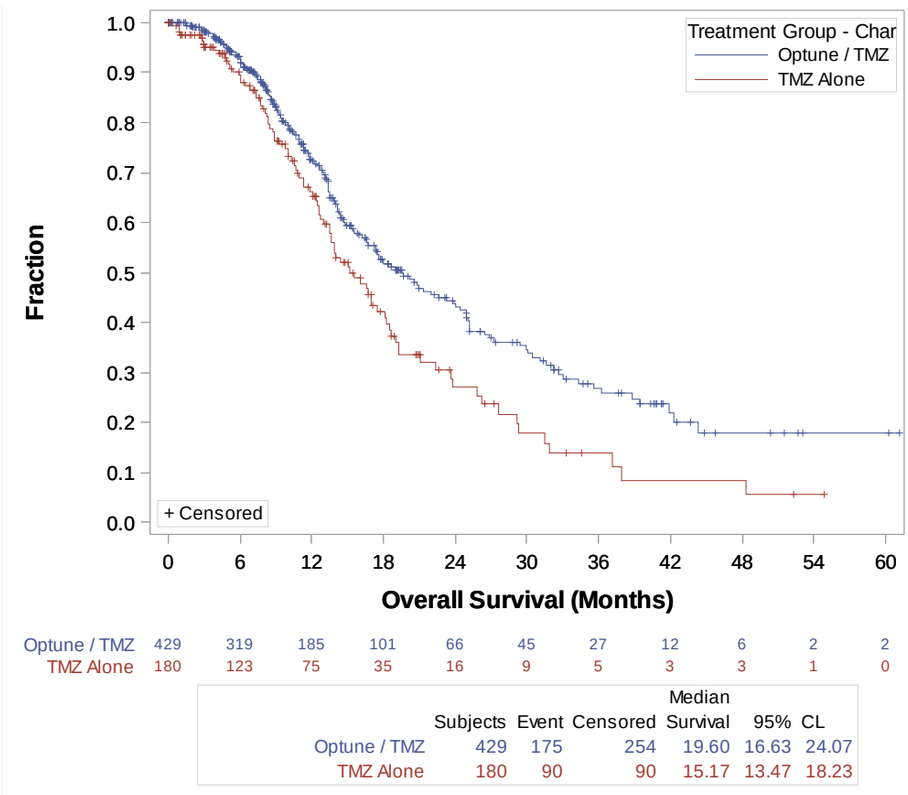



**Table 10. Log-Rank Test for OS - Final Analysis – PP**

| | **Optune/TMZ** | **TMZ Alone** |
|---|---|---|
| Median (95% CI) | 19.6 (16.6, 24.1) | 15.2 (13.5, 18.2) |
| Log-rank test | p=0.0030 | |
| Hazard Ratio | 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.

All other secondary efficacy endpoints (PFS6, 1- and 2-year survival and response rates) showed an advantage for Optune/TMZ over TMZ alone. PFS6 and 2-year survival were significantly higher in the Optune/TMZ group than the TMZ alone group in the interim analysis and final analysis, both in the PP and ITT analyses. Quality of life, cognitive function and functional status assessments, performed for the interim analysis cohort of 315 subjects, were all maintained throughout treatment with the Optune/TMZ.

**Table 11. Secondary Endpoints Summary (Except Quality of Life) – Interim Analysis**

| Endpoint | Optune/TMZ | TMZ Alone | p-value |
|---|---|---|---|
| 1-year Survival (PP) | 75% | 69% | 0.151 |
| 2-year Survival (PP) | 48% | 32% | 0.0058 |
| 1-year Survival (ITT) | 75% | 70% | 0.162 |
| 2-year Survival (ITT) | 48% | 34% | 0.0122 |
| PFS6 | 56.7% | 33.7% | 0.0004 |
| Complete Response Rate | 9% | 3.5% | N/A |

**Table 12. One and Two Year Survival Rate Summary – Final Analysis**

| Endpoint | Optune/TMZ | TMZ Alone | p-value |
|---|---|---|---|
| 1-year Survival (PP) | 69% | 63% | 0.131 |
| 2-year Survival (PP) | 37% | 24% | 0.0088 |
| 1-year Survival (ITT) | 69% | 66% | 0.265 |
| 2-year Survival (ITT) | 35% | 24% | 0.0211 |

**Safety Results**

A similar percentage of patients in both treatment groups experienced an AE during the trial (91 vs. 87% in the Optune/TMZ vs. TMZ alone groups, respectively). As seen in the table below, patients in the Optune/TMZ arm experienced gastrointestinal disorders (mainly nausea, constipation, diarrhea and vomiting) and injury/poisoning/procedural complications (mainly skin reactions under the device arrays and falls) at least 10% more than patients in the TMZ alone arm.

**Table 13. All AEs in the Final Safety Population**

| System Organ Class<br>Preferred Term | Optune/TMZ<br>(N=437)<br>Number (%) | TMZ Alone<br>(N=207)<br>Number (%) |
|---|---|---|
| Number of Patients with ≥1 AE | 398 (91%) | 180 (87%) |
| Blood and Lymphatic System Disorders | 133 (30%) | 70 (34%) |
| Cardiac Disorders | 19 (4%) | 10 (5%) |
| Ear and Labyrinth Disorders | 25 (6%) | 8 (4%) |
| Endocrine Disorders | 11 (3%) | 4 (2%) |
| Eye Disorders | 39 (9%) | 17 (8%) |
| Gastrointestinal Disorders | 220 (50%) | 80 (39%) |
| General Disorders and Administration Site Conditions | 203 (46%) | 87 (42%) |
| Hepatobiliary Disorders | 2 (<1%) | 5 (2%) |
| Immune System Disorders | 10 (2%) | 7 (3%) |
| Infections and Infestations | 139 (32%) | 57 (28%) |
| Injury, Poisoning and Procedural Complications | 236 (54%) | 17 (8%) |
| Abnormal Laboratory Tests | 77 (18%) | 34 (16%) |
| Metabolism and Nutrition Disorders | 101 (23%) | 50 (24%) |
| Musculoskeletal and Connective Tissue Disorders | 114 (26%) | 52 (25%) |
| Nervous System Disorders | 276 (63%) | 117 (57%) |
| Psychiatric Disorders | 124 (28%) | 44 (21%) |
| Renal and Urinary Disorders | 42 (10%) | 10 (5%) |
| Respiratory, Thoracic and Mediastinal Disorders | 76 (17%) | 21 (10%) |
| Skin and Subcutaneous Tissue Disorders | 104 (24%) | 33 (16%) |
| Vascular Disorders | 65 (15%) | 32 (15%) |

## E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 C.F.R. Part 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study for newly diagnosed GBM included 86 clinical investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

## XI. ANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

Not Applicable (for newly diagnosed GBM).

## XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

This pivotal study demonstrated the increased effectiveness of Optune/TMZ over TMZ alone. Both progression free survival and overall survival were extended significantly in the Optune/TMZ group compared to the TMZ alone group in patients with newly diagnosed GBM. The trial met its pre-specified thresholds for statistical significance at both the interim and final analyses.

At the interim analysis, median PFS was 7.2 months in the Optune/TMZ arm and only 4.0 months in the TMZ alone arm (HR 0.62; p=0.001), thus median PFS time was extended by 80% and the risk of progression was reduced by 38% in the Optune/TMZ arm compared to TMZ alone. Similarly, at the final analysis, median PFS was 7.1 months in the Optune/TMZ arm and only 4.2 months in the TMZ alone arm (HR 0.69; p=0.001), thus median PFS time was extended by 69% and the risk of progression was reduced by 31% in the Optune/ TMZ arm compared to TMZ alone.

At the interim analysis, median OS in the pre-specified PP analysis was 20.5 months in the Optune/TMZ arm and only 16.6 months in the TMZ alone arm (HR 0.67; p=0.004), thus median OS time was extended by 31% and the risk of death was reduced by 33% in the Optune/TMZ arm compared to TMZ alone. In an ITT analysis, which included patients who received Optune on the control arm, median OS was 19.6 months in the Optune/TMZ arm and only 16.6 months in the TMZ alone arm (HR 0.74; p=0.034), thus median OS time was extended by almost 20% and the risk of death was reduced by 26% in the Optune/TMZ arm compared to TMZ alone.

At the final analysis, median OS in the pre-specified PP analysis was 19.6 months in the Optune/TMZ arm and only 15.2 months in the TMZ alone arm (HR 0.68; p=0.003), thus median OS time was extended by 29% and the risk of death was reduced by 32% in the Optune/TMZ arm compared to TMZ alone. In an ITT analysis, which included patients who received Optune on the control arm, median OS was 19.4 months in the Optune/TMZ arm and only 16.6 months in the TMZ alone arm (HR 0.75; p=0.023), thus median OS time was extended by 17% and the risk of death was reduced by 25% in the Optune/TMZ arm compared to TMZ alone.

All of the secondary endpoints (PFS6, 1- and 2-year survival and response rates) showed a clear advantage for Optune/TMZ over TMZ alone at both the interim and final analyses.

PFS6 and 2-year survival were significantly higher in the Optune/TMZ group than the TMZ alone group in both the PP and ITT analyses.

Quality of life, cognitive function and functional status were all maintained throughout treatment with the device based on an assessment of the interim analysis cohort of 315 patients.

**B. Safety Conclusions**

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 balanced between treatment arms. The high incidence of neurological and psychiatric symptoms seen on both arms of the trial was expected as they are the known symptoms of patients with brain tumors in general and GBM specifically. These include headaches, seizures, focal signs and symptoms, cognitive changes, emotional disorders, and many more.

**C. Benefit-Risk Conclusions**

GBM is a fatal disease with a 4-year survival from initial diagnosis of only 12% and a median survival of 14.7 months. The benchmark for PFS and OS in newly diagnosed GBM has not changed in over a decade since the approval of TMZ. The current pivotal trial shows that Optune/TMZ extends both PFS and OS significantly compared to TMZ alone. This increase in PFS and OS is clinically significant in a patient population which has seen no improvement in outcomes for over a decade. The extension in PFS and OS is not accompanied by any decrease in quality of life, cognitive performance or ability to perform activities of daily living. The risks of using Optune/TMZ include primarily the risk of skin irritation on the scalp beneath the transducer arrays (which was seen in 45% of patients in the pivotal study). This risk is minor compared to the side effects of other oncology therapies, can be easily treated using topical ointments and resolves once treatment is discontinued. Other less common risks include headaches, insomnia and soft psychiatric symptoms.

The magnitude of the observed benefit and the statistical significance of the results was clinically meaningful in order to justify early stopping of the study based on interim results in only 315 of the 695 enrolled patients. At the interim analysis, median PFS was 7.2 months in the Optune/TMZ arm and only 4.0 months in the TMZ alone arm (HR 0.62; p=0.001), indicating that median PFS time was extended by 80% and the risk of progression was reduced by 38% in the Optune/TMZ arm compared to TMZ alone. Similarly, at interim analysis, median OS in the pre-specified PP analysis was 20.5

months in the Optune/TMZ arm and only 16.6 months in the TMZ alone arm (HR 0.67; p=0.004), thus median OS time was extended by 31% and the risk of death was reduced by 33% in the Optune/TMZ arm compared to TMZ alone. In an ITT analysis, which included patients who received Optune on the control arm, median OS was 19.6 months in the Optune/TMZ arm and only 16.6 months in the TMZ alone arm (HR 0.74; p=0.034), thus median OS time was extended by almost 20% and the risk of death was reduced by 26% in the Optune/TMZ arm compared to TMZ alone. These interim data support a clear benefit.

Importantly, similar results were confirmed in the final analysis which included available data at the time of database lock for all 695 enrolled subjects. Specifically, at the final analysis, median PFS was 7.1 months in the Optune/TMZ arm and only 4.2 months in the TMZ alone arm (HR 0.69; p=0.001), indicating that median PFS time was extended by 69% and the risk of progression was reduced by 31% in the Optune/TMZ arm compared to TMZ alone. Similarly, at the final analysis, median OS in the pre-specified PP analysis was 19.6 months in the Optune/TMZ arm and only 15.2 months in the TMZ alone arm (HR 0.68; p=0.003), thus median OS time was extended by 29% and the risk of death was reduced by 32% in the Optune/TMZ arm compared to TMZ alone. In an ITT analysis, which included patients who received Optune on the control arm, median OS was 19.4 months in the Optune/TMZ arm and only 16.6 months in the TMZ alone arm (HR 0.75; p=0.023), thus median OS time was extended by 17% and the risk of death was reduced by 25% in the Optune/TMZ arm compared to TMZ alone.

In summary, the final analysis results support the data from the interim analysis and confirm the observed benefit of Optune/TMZ over TMZ alone.

Moreover, various sensitivity analyses and subgroup analyses showed that the advantage of Optune/TMZ compared to TMZ alone is maintained regardless of the type of sensitivity analysis, missing MGMT methylation status data, or subgroup. Therefore, the conclusion of PFS and OS superiority in the Optune/TMZ group compared to TMZ alone group can be considered robust and not limited to a certain subgroup of patients.

In addition, all secondary efficacy endpoints (PFS6, 1-year survival, 2-year survival, response rates) support the primary endpoint results in that they show an advantage for Optune/TMZ over TMZ alone. In fact, PFS6 and 2-year survival were significantly higher in the Optune/TMZ group than the TMZ alone group. The fact that all secondary endpoints show a consistent improvement in patient outcomes when Optune/TMZ is used compared to TMZ alone strengthens the conclusions above regarding PFS and OS.

In conclusion, the benefits of Optune/TMZ for the treatment of newly diagnosed GBM, including clinically significant extensions of PFS and OS, outweigh the risks, particularly in this very sick population.

### D. Overall Conclusions

Newly diagnosed glioblastoma is a difficult to treat, deadly disease, where treatment of the disease has seen little progress in the past 20 years. Optune treatment exhibits negligible toxicity and superior outcome measures compared to the best available treatments today. The pivotal trial was a well-designed and conducted study (randomized control, active control group, multi-center, about half of the patients in the US, data poolable between countries, minimal loss to follow-up) that showed superiority of Optune/TMZ treatment over TMZ alone with respect to progression free survival and overall survival.

## XIII. CDRH DECISION

CDRH issued an approval order on October 5, 2015.

## XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XV. REFERENCES

1. Wong, E. T., K. **R.** Hess, et al. (1999). "Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials." J Clin Oncol 17(8): 2572-8.

2. Stupp, R., W. P. Mason, et al. (2005). "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma." N Engl J Med 352(10): 987-96.

3. Stupp, R., et al., (2012). "NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomized phase III trial of a novel treatment modality." Eur J Cancer 48(14): 2192-202.