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About Optune

- Optune is the Tumor Treating Fields (TTFields) delivery system that is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with glioblastoma.[1]
  It is indicated:
  - For the treatment of newly diagnosed GBM, Optune is used together with the chemotherapy temozolomide (TMZ) following surgery and radiation together with chemotherapy[1]
  - For the treatment of recurrent GBM, Optune is indicated following histologically-or radiologically-confirmed tumor recurrence after receiving chemotherapy. The device is intended to be used as monotherapy as an alternative to standard medical therapy after surgical and radiation options have been exhausted[1]
- TTFields are frequency-specific, low-intensity alternating electric fields that interrupt cancer cell structures during division and may cause cancer cells to die[1]
- Optune is a portable, noninvasive medical device designed for continuous use (at least 18 hours per day) by patients[1]
- Treatment with Optune generally spares and does not harm healthy, normal, nondividing brain cells[1]
- In newly diagnosed GBM, Optune plus the standard-of-care chemotherapy TMZ significantly increased median progression-free survival (PFS), median overall survival (OS), and 2-year survival rates with no statistically significant increase in serious adverse events (AEs) compared with TMZ alone[1,2]
  - The most common (≥10%) adverse events involving Optune in combination with TMZ were low blood platelet count, nausea, constipation, vomiting, fatigue, scalp irritation from device use, headache, convulsions, and depression[2]
- In recurrent GBM, Optune has shown clinical efficacy comparable to that of physician's choice of chemotherapy (including bevacizumab) with better quality of life and without many of the side effects of chemotherapy[1]
  - Mild to moderate skin irritation, the most common device-related side effect with Optune, was easily manageable, reversible, and did not result in treatment discontinuation[3]
- Physicians at more than 360 cancer treatment centers in the United States have been certified to prescribe Optune to newly diagnosed and recurrent GBM patients. Physicians at an additional 140 medical institutions throughout the world are also certified to prescribe Optune to GBM patients
- Over 3100 clinical and commercial patients have been treated with Optune to date[4]

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Second Generation Optune System

- Smaller, lighter, and designed for everyday life
  - Half the weight of the original Optune system (from 6 lbs to 2.7 lbs)
- New design features for greater comfort and ease
  - Easy-grip texture allows for better handling
  - Battery indicator displays power and alerts user when it's time to change the battery
  - Light-detecting sensor auto-dims the device and charger in the dark
- "No-Stop Swap" enables patients to swap batteries or power source without disrupting delivery of TTFields
  - By connecting to wall power, patients can quickly swap batteries or power source without powering down the device
- Easy-access sleeve bag–openings at the top and bottom make it easy to reach device controls

Clinical Data Overview

Optune is FDA-approved for the treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM) based on the results of 2 pivotal phase 3 studies, EF-14 and EF-11.[1]

EF-14 Dataset

- Optune was studied in the EF-14 trial, a prospective, international, multicenter, open-label, controlled, phase 3 trial in newly diagnosed GBM patients comparing Optune + TMZ with TMZ alone (N=700)[1]
- The prespecified interim analysis occurred when the first 315 patients completed 18 months of follow-up. The primary endpoint was PFS (intent-to-treat, ITT); OS (per protocol) was a powered secondary endpoint; 1- and 2-year survival rates, PFS6, quality of life, and radiological response rates, along with safety, were also secondary endpoints[1]
- The final analysis included all patients randomized to EF-14 who had case report form information available at the database cutoff of December 3, 2014. This included 695 of the 700 patients randomized at that time: 466 patients in the Optune + TMZ arm and 229 patients in the TMZ-alone arm[1,2]
- Optune + TMZ significantly improved survival outcomes in patients with newly diagnosed GBM compared with TMZ alone[1]

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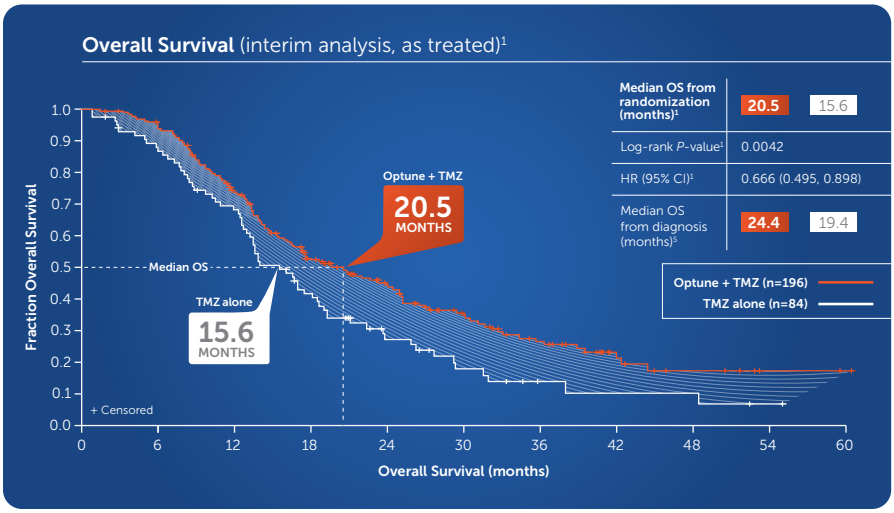
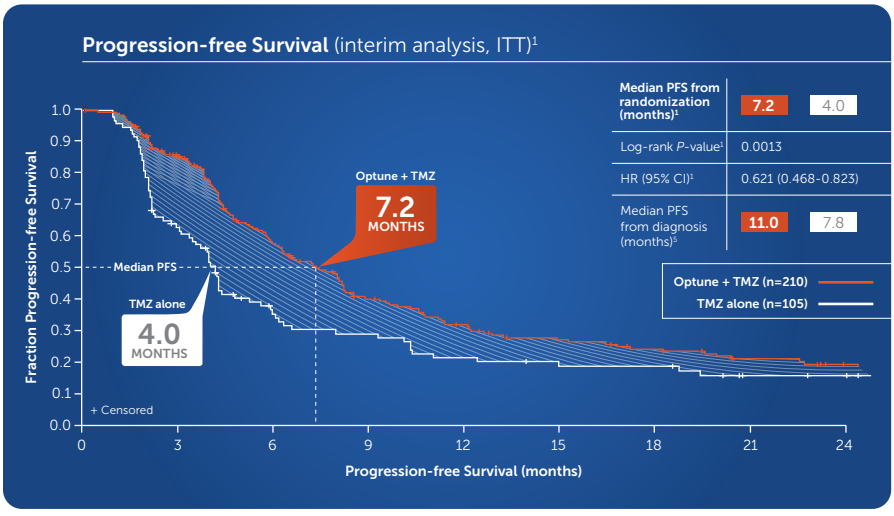
- Significantly extended median OS by 4.9 months: 20.5 months with Optune + TMZ compared with 15.6 months with TMZ alone (*P*=0.0042)[1,5]



- In the final analysis (n=695), Optune + TMZ extended median OS by 4.4 months, and this was consistent with the interim analysis (n=315)[1]
- 2-year survival was significantly higher at 48% in patients on Optune + TMZ vs 32% in patients on TMZ alone[1]
- Median PFS was significantly improved by more than 3 months: 7.2 months with Optune + TMZ compared with 4.0 months with TMZ alone (*P*=0.0013)[1,5]



- In the final analysis (n=695), Optune + TMZ extended median PFS by 2.9 months, and this was consistent with the interim analysis (n=315). Quality of life was maintained with Optune + TMZ[1]

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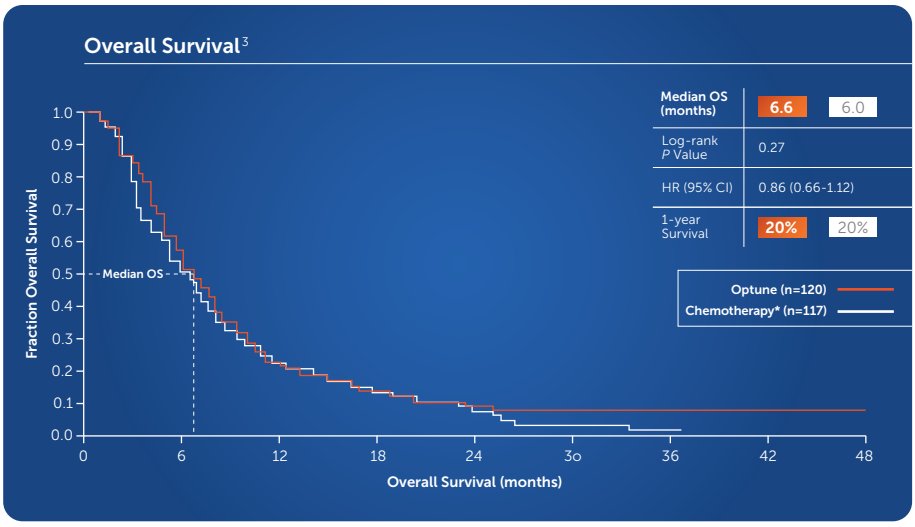
- The final analysis showed Optune can be safely combined with TMZ. There was no statistically significant increase in serious adverse events (AEs) compared with TMZ alone. The most common (≥10%) AEs in the Optune + TMZ arm included medical device site reaction, fatigue, nausea, headache, constipation, thrombocytopenia, vomiting, convulsions, and depression.[1,2]

EF-11 Dataset

- EF-11 was a large, randomized, controlled, pivotal phase 3 study that compared Optune versus physician's choice of chemotherapy for patients with recurrent GBM[3]
- OS and PFS for patients treated with Optune monotherapy were comparable to patients treated with physician's choice of chemotherapy, including bevacizumab[1,*]



*Therapy options were the physican's best choice for chemotherapy, including bevacizumab, which were defined given historical assessment of effective recurrent GBM therapies. The best available therapy was prescribed according to local practice and depending on prior treatment exposure.

- Twice as many patients experienced a radiographic response to Optune versus physician's choice of chemotherapy (14 out of 120 for Optune vs 7 out of 117 for chemotherapy)[6]
- OS was significantly higher in patients who were on Optune therapy for ≥18 hours per day compared with those who received therapy <18 hours per day (7.7 months vs 4.5 months, respectively, $P=0.042$)[7]
- Patients treated with Optune monotherapy experienced significantly fewer systemic side effects commonly associated with chemotherapy[1,3]
- Mild to moderate skin irritation, the most common side effect related to treatment with Optune, was easily manageable, reversible, and did not result in treatment discontinuation[1,3]
- Patients treated with Optune reported higher quality of life scores with an improvement in cognitive and emotional functioning[1,3]

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About Glioblastoma (GBM)

- GBM is the most common and aggressive form of primary malignant brain tumors in the United States and continues to be an area of high unmet medical need[8,9]
- The disease affects approximately 12,500 Americans each year[9]
- Historically, the median OS time from initial diagnosis is 15 months with optimal treatment, and median OS from the time of tumor recurrence is only 3 to 5 months without additional effective treatment[3]
- Standard treatment for GBM is surgery, followed by radiation therapy or combined radiation therapy and chemotherapy with TMZ. If inoperable, then radiation or radiation + TMZ is utilized[10]
- The disease is one of the deadliest forms of cancer[3]

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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 supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Important Safety Information

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. 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. 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 and Precautions

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 Novocure (the device manufacturer).

Do not use Optune if you are pregnant, you think you might be pregnant or are trying to get pregnant. It is not known if Optune is safe or effective in these populations.

The most common (≥10%) adverse events involving Optune in combination with temozolomide were low blood platelet count, nausea, constipation, vomiting, fatigue, scalp irritation from device use, headache, convulsions, and depression.

The most common (≥10%) adverse events seen when using Optune alone were scalp irritation from device use and headache.

The following adverse reactions were considered related to Optune when using the device alone: scalp irritation from device use, headache, malaise, muscle twitching, fall and skin ulcer.

All servicing procedures must be performed by qualified and trained personnel.

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.

Do not wet the device or transducer arrays.

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.

Please visit Optune.com/safety for Optune Instructions For Use (IFU) for complete information regarding the device's indications, contraindications, warnings and precautions.

References: 1. Optune Instructions For Use. Novocure 2015. **2.** Novocure Data on File. OPT-103. Novocure 2015. **3.** Stupp R, Wong ET, Kanner AA, 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;48(14):2192-2202. **4.** Novocure Data on File. OPT-116. **5.** Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA*. 2015;314(23):2535-2543. **6.** Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. *Cancer Med*. 2014;3(3):592-602. **7.** Kanner AA, Wong ET, Villano JL, Ram Z; EF-11 Investigators. Post hoc analyses of intention-to-treat population in phase III comparison of NovoTTF-100A™ system versus best physician's choice chemotherapy. *Semin Oncol*. 2014;41(5)(suppl 6):S25-S34. **8.** National Brain Tumor Society. Grade IV - Glioblastoma (GBM). http://braintumor.org/brain-tumor-information/understanding-brain-tumors/tumor-types/#glioblastoma-multiforme. Accessed August 25, 2015. **9.** Ostrom QT, Gittleman, Jordonna F et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro Oncol*. 2015;17(suppl 4):iv1–iv62. **10.** National Comprehensive Cancer Network. Clinical practice guidelines in oncology: central nervous system cancers, version 1.2015. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed June 16, 2016.

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