

Washington State
Health Care Authority
Health Technology Assessment

Program Updates

Josh Morse, MPH
HTA Program Director

March 18, 2016

Today's Agenda

- **Extracorporeal Membrane Oxygenation (ECMO)**
- **Spinal Injections – Re-review**

Background

- **Extracorporeal Membrane Oxygenation (ECMO)**
 - New topic
 - Selected by the HCA Director for review in 2015
- **Spinal Injections – Re-review**
 - Originally subject to HTCC review in 2011
 - Selected for re-review in 2015 based on:
 - New literature
 - Changing standards of practice

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Other Topics Scheduled for 2016

May 20:

- Bronchial Thermoplasty for Asthma
- Autologous Blood or Platelet-rich Plasma Injections

November 18:

- Fecal Microbiota Instillation
- Negative-Pressure Wound Therapy

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To Participate...

- Visit the HTA Web site: <http://www.hca.wa.gov/hta>
- Join the HTA stakeholder distribution list: shtap@hca.wa.gov
Stakeholders notified of all program publications and meetings.
- Comment on:
 - Proposed topics
 - Key questions
 - Draft & final reports
 - Draft decisions
- Attend HTCC public meetings.
All meeting materials posted on the web.
- Present comments at Clinical Committee meetings.
- Nominate health technologies for review.

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Health Technology Clinical Committee

Date: January 15, 2016

Time: 8:00 am – 5:00 pm

Location: SeaTac Conference Center, SeaTac, WA

Adopted:

Meeting materials and transcript are available on the HTA website at:

www.hca.wa.gov/hta/meetingmaterials/Forms/ExtMeetingMaterials.aspx

HTCC MINUTES

Members Present: Gregory Brown, MD, PhD; Joann Elmore, MD MPH; Louise Kaplan, PhD, ARNP; David K. McCulloch, MD, FRCP; Carson Odegard DC, MPH; Seth Schwartz, MD, MPH; Michelle Simon, PhD, ND; Michael Souter, MB, Ch-B, DA, Christopher Standaert, MD; Kevin Walsh, MD; Tony Yen, MD

HTCC FORMAL ACTION

- 1. Call to Order:** Dr. Standaert, chair called the meeting to order. Sufficient members were present to constitute a quorum.
- 2. November 20, 2015 Meeting Minutes:** Chair referred members to the draft minutes; motion to approve was seconded. Minutes adopted by the committee with corrections noted.

Action: Ten committee members approved the November 20, 2015 meeting minutes. One member abstained.

- 3. Lumbar Fusion for Degenerative Disc Disease – Re-review Draft Findings & Decision:** Chair referred members to the draft findings and decision and called for further discussion. Four comments were received on the draft decision. The committee reviewed and discussed the comments. No changes were made to the draft based on the comments. A typographical error was noted in the draft and staff were directed to correct this.

Action: Ten committee members voted to approve the Lumbar Fusion – Re-review Findings and Decision document with correction to footer; One member abstained.

- 4. Tympanostomy Tubes in Children Draft Findings & Decision:** Chair referred members to the draft findings and decision and called for further discussion. One comment was received on the draft decision. Committee members reviewed the comment and modified the draft. Staff were directed to modify the final determination per the committee's changes.

Action: Ten members voted to approve the Tympanostomy Tubes in Children Draft Findings and Decision document; One member abstained.

DRAFT

5. Novocure (Tumor Treating Fields):

Agency Utilization and Outcomes:

Daniel Lessler, MD, MHA, Chief Medical Director, Washington Health Care Authority presented the state agency perspective for Novocure to the committee. The full presentation is published with [January 15, meeting materials](#).

Scheduled and Open Public Comments:

The chair called for public comments. No comments were provided.

Vendor Report and HTCC Q & A:

The chair introduced the clinical expert for Novocure, Lynne P. Taylor, MD, FAAN, FANA, neuro-oncologist, Virginia Mason Medical Center, Seattle, WA.

Natalie Slezack, PhD, Hayes, Inc. presented the evidence review of **Novocure (Tumor Treating Fields)**. The full presentation is published with [January 15, meeting materials](#).

HTCC Coverage Vote and Formal Action

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee concluded that the current evidence on Novocure is sufficient to make a determination on this topic. The committee discussed and voted on the evidence for use of Novocure compared to current alternative chemotherapeutic strategies for 1) newly diagnosed and untreated glioblastoma multiforme, recurrent and previously treated glioblastoma multiforme (GBM), and 3) tumors other than glioblastoma. The committee considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to not cover Novocure (Tumor Treating Fields) for GBM, recurrent GBM or other tumors.

	Not Covered	Covered Under Certain Conditions	Covered Unconditionally
Novocure for newly diagnosed and untreated glioblastoma multiforme (GBM)	9	2	0
Novocure for recurrent and previously treated GBM	9	2	0
Novocure for other tumors (Non-GBM)	11	0	0

Discussion

The committee discussed the meaning quality of and methodology of the available studies of Novocure. In considering the evidence the committee cited concerns related to the limited number of trials, limited reporting of quality of life outcomes, and potential biases present in the available literature.

Limitations

N/A

Action

The committee checked for availability of a Medicare national coverage decision (NCD). There is no NCD for Novocure or tumor treating fields.

The committee discussed clinical guidelines identified for treatment of GBM and non-small cell lung cancer from the following organizations:

American Association of Neuroscience Nurses (AANN),
American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS),
European Association of Neuro-Oncology (EANO),
European Society for Medical Oncology (ESMO),
National Comprehensive Cancer Network (NCCN)

The Chair noted consistency with existing guidelines that include mention of tumor treating fields as some consider this an investigational treatment. Also noted is the fact that the most recent trial published was not considered in existing guidelines due as it was published 30 days prior to this committee's review?

The committee Chair directed HTA staff to prepare a Findings and Decision document on Novocure (Tumor Treating Fields) reflective of the majority vote for final approval at the next public meeting.

6. Charissa Fotinos MD, MSc, presented the state agency utilization rates for cardiac stents to the committee. The full presentation is published with [January 15, meeting materials](#).

Scheduled and Open Public Comments:

The chair called for public comments. Comments were provided by:

Gary Weeks MD speaking for Wayne Powell and representing the Society for Cardiovascular Angiography and Intervention, University of Washington, Seattle, WA.

Vendor Report and HTCC Q & A:

The chair introduced the clinical expert for cardiac stents, Mike Ring MD, Providence Spokane Cardiology.

Andrea Skelly, PhD, Spectrum Research Incorporated, presented the evidence review addressing cardiac stents. The full presentation is published with [January 15, meeting materials](#).

HTCC Coverage Vote and Formal Action:

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee concluded that the current evidence for newer generation cardiac stents is sufficient to make a determination on this topic. The committee discussed and voted on the evidence for use of cardiac stents compared to current medical management strategies for stable angina. The committee then considered the evidence of newer generation drug eluting stents versus bare metal stents for stable or unstable angina. The committee considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover with conditions cardiac stents for unstable angina. The committee voted separately to cover with no conditions the use of drug eluting stents or bare metal stents when appropriate for stable or unstable angina.

	Not Covered	Covered Under Certain Conditions	Covered Unconditionally
Cardiac stents for stable angina	0	10	1
Cardiac stents, drug eluting vs bare metal	1	0	10

Discussion

The committee reviewed and discussed the evidence for use of cardiac stents compared to medical management for stable angina and discussed the meaning, quality and methodology of the available studies for stents vs medical management. The committee determined that coverage with conditions for the question of stable angina when compared to medical management. Limitations are for this condition and question only. For the question of drug eluting stents versus bare metal stents when stents are indicated the committee determined to cover without conditions. Therefore there are no limitations on the use of drug eluting or bare metal stents when intervention with cardiac stents is appropriate.

Limitations

For patients with **stable angina** cardiac stents are covered for the following:

1. Angina refractory to optimal medical therapy, and
2. Objective evidence of myocardial ischemia.

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). There is a NCD (National Coverage Determination Manual: 20.7 (2014)) for percutaneous transluminal angioplasty with and without stent. The HTCC coverage determination is similar to the CMS decision.

The committee discussed and reviewed treatment criteria from clinical guidelines identified for treatment of stable angina and revascularization from the following organizations:

American College of Cardiology and American Heart Association;
American Association for Thoracic Surgery;
American College of Cardiology Foundation;
American College of Physicians;
American Diabetes Association;
Council on Clinical Cardiology;
Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure;
National Cholesterol Education Program (NCEP);
Preventive Cardiovascular Nurses Association;
Society for Cardiovascular Angiography and Interventions;
Society of Thoracic Surgeons

The chair noted consistency with existing guidelines that include risk identification, risk reduction, medical and revascularization treatment criteria.

The committee chair directed HTA staff to prepare a findings and decision document on Cardiac Stents reflective of the majority vote for final approval at the next public meeting.

7. Josh Morse, HTA program director presented a status update on HTA technology assessments now in process and those scheduled for 2016.
8. **Meeting adjourned.**

**Health Technology Clinical Committee
Findings and Decision**

Topic: Novocure (Tumor Treating Fields)
Meeting Date: January 15, 2016
Final Adoption:

Meeting materials and transcript are available on the HTA website:
www.hca.wa.gov/hta/meetingmaterials/Forms/ExtMeetingMaterials.aspx

Number and Coverage Topic:

20160115A – Novocure (Tumor Treating Fields)

HTCC Coverage Determination:

Novocure (Tumor Treating Fields) is **not a covered benefit**.

HTCC Reimbursement Determination:

Limitations of Coverage: N/A

Non-Covered Indicators: N/A

Agency Contact Information:

Agency	Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

Draft

HTCC Coverage Vote and Formal Action

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments and state agency utilization information. The committee concluded that the current evidence on Novocure is sufficient to make a determination on this topic. The committee discussed and voted on the evidence for use of Novocure compared to current alternative chemotherapeutic strategies for 1) newly diagnosed and untreated glioblastoma multiforme; 2) recurrent and previously treated glioblastoma multiforme; and 3) tumors other than glioblastoma. The committee considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to not cover Novocure (Tumor Treating Fields) for GBM, recurrent GBM or other tumors.

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Discussion

The committee discussed the meaning, quality, and methodology of the available Novocure studies. In considering the evidence, the committee cited concerns related to the limited number of trials, limited reporting for quality of life outcomes and potential biases present in the available literature.

Limitations

N/A

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). There is no NCD for Novocure or tumor treating fields.

The committee discussed clinical guidelines identified for treatment of GBM and non-small cell lung cancer from the following organizations:

- American Association of Neuroscience Nurses (AANN);
- American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS);
- European Association of Neuro-Oncology (EANO);
- European Society for Medical Oncology (ESMO);
- National Comprehensive Cancer Network (NCCN)

Draft

The chair noted consistency with existing guidelines that include mention of tumor treating fields as some consider this an investigational treatment. Also noted is the fact that the most recent trial published was not considered in existing guidelines as it was published 30 days prior to this committee's review

The committee chair directed HTA staff to prepare a findings and decision document on Novocure (Tumor Treating Fields) reflective of the majority vote for final approval at the next public meeting.

Health Technology Clinical Committee Authority:

Washington State's legislature believes it is important to use a science-based, clinician-centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority (HCA), through its Health Technology Assessment (HTA) program, to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and that takes public input at all stages.

Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State HTCC determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.

Draft

Novocure (Tumor Treating Fields)

Draft Findings & Decision
 Timeline and Overview of Comments

The Health Technology Assessment (HTA) program received no comments in response to the posted Health Technology Clinical Committee (HTCC) draft findings and decision on **Novocure (Tumor Treating Fields)**

Timeline

Phase	Date	Public Comment Days
Technology recommendations published	January 5, 2015	
Public comments	January 5 to January 20, 2015	16
Selected technologies published	February 4, 2015	
Public comments	February 4 to March 5, 2015	30
Draft key questions published	July 10, 2015	
Public comments	July 10 to 24, 2015	15
Final key questions published	August 7, 2015	
Draft report published	October 20, 2015	
Public comments	October 20 to November 18, 2015	30
Final report published	December 14, 2015	
Public meeting	January 15, 2016	
Draft findings & decision published	February 4, 2016	
Public comments	February 4, to 18, 2016	15

Attachments: Justin Kelly, RN, BSN, Senior Director, Health Policy Novocure

Overview

Category	Comment Period	
	<i>February 4 – 18, 2016</i>	Cited Evidence
Patient, relative, and citizen	0	0
Legislator and public official	0	0
Health care professional	0	0
Industry & manufacturer	1	1
Professional society & advocacy organization	0	0
Total	1	1

From: Justin Kelly <JKelly@novocure.com>
Sent: Monday, February 15, 2016 3:55 PM
To: HCA ST Health Tech Assessment Prog
Cc: Justin Kelly
Subject: NOVOCURE (TUMOR TREATING FIELDS)
Attachments: JAMA Stupp 2015.pdf; Optune_IFU_8.5x11.pdf

Follow Up Flag: Follow up
Flag Status: Completed

This message was sent securely using ZixCorp.

Dear HTA Program:

Thank you for the opportunity to offer updated information on Optune™, an FDA-approved treatment option for patients with newly diagnosed and recurrent glioblastoma multiforme (GBM). We respectfully ask that you consider the attached information for inclusion in your recently released Technology Assessment.

Device Name: TTFields are delivered by Optune™ (formerly known as the NovoTTF-100A System). The therapy is manufactured and distributed by Novocure.

Indications for Use:

The current indication in your technology assessment does not include the recently approved indication in newly diagnosed glioblastoma in combination with temozolomide. I have included an updated Instructions for Use (IFU) for Optune as well. The updated indication is copied below.

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.

The most recent FDA approval was based on the results of a large randomized controlled trial which was recently published in the Journal of the American Medical Association (JAMA). I have attached the publication for your review as your current assessment states the publication is pending. Thank you for your time and consideration. Please don't hesitate to contact me if you should have any questions, or if I can provide any additional information.

Kind regards,

Justin M. Kelly, RN, BSN

Senior Director, Health Policy

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Reprint Article

Preliminary Communication

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew A. Kanner, MD; Santosh Kesari, MD, PhD; David M. Steinberg, PhD; Steven A. Toms, MD, FACS, MPH; Lynne P. Taylor, MD, FAAN; Frank Lieberman, MD; Antonio Silvani, MD; Karen L. Fink, MD, PhD; Gene H. Barnett, MD, MBA; Jay-Jiguang Zhu, MD, PhD; John W. Henson, MD, MBA, FAAN; Herbert H. Engelhard, MD, PhD; Thomas C. Chen, MD, PhD; David D. Tran, MD, PhD; Jan Sroubek, MD; Nam D. Tran, MD, PhD; Andreas F. Hottinger, MD, PhD; Joseph Landolfi, DO; Rajiv Desai, MD; Manuela Caroli, MD; Yvonne Kew, MD, PhD; Jerome Honnorat, MD, PhD; Ahmed Idbaih, MD, PhD; Eilon D. Kirson, MD, PhD; Uri Weinberg, MD, PhD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

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Preliminary Communication

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma

A Randomized Clinical Trial

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IMPORTANCE Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Most patients die within 1 to 2 years of diagnosis. Tumor-treating fields (TTFields) are a locoregionally delivered antimetabolic treatment that interferes with cell division and organelle assembly.

OBJECTIVE To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

INTERVENTIONS Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m²/d) was given for 5 days of each 28-day cycle.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival in the intent-to-treat population (significance threshold of .01) with overall survival in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). This prespecified interim analysis was to be conducted on the first 315 patients after at least 18 months of follow-up.

RESULTS The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004).

CONCLUSIONS AND RELEVANCE In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

JAMA. 2015;314(23):2535-2543. doi:10.1001/jama.2015.16669

← Editorial page 2511

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Roger Stupp, MD, Department of Oncology and Cancer Center, University Hospital Zurich, CH-8091 Zurich, Switzerland (roger.stupp@usz.ch).

Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gy) with concomitant daily temozolomide chemotherapy, and then maintenance treatment with temozolomide for 6 to 12 months.¹ However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials.¹⁻⁴ The reported 2- and 5-year survival rates⁵ are 27% and 10%, respectively. During the last decade, all attempts to improve the outcome for patients with glioblastoma have failed when evaluated in large randomized trials.^{2-4,6,7}

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively disrupts the division of cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp.⁸⁻¹⁰ In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis.^{8,10-12} In a randomized phase 3 trial in which TTFields were compared with chemotherapy in 237 patients with recurrent glioblastoma, the use of TTFields did not prolong progression-free survival or overall survival, but the therapy was associated with better quality of life without the typical chemotherapy-associated toxic effects.¹³

Based on preclinical data demonstrating a synergistic antitumor effect with chemotherapy and TTFields, and pilot clinical feasibility data in combination with temozolomide,⁹ we initiated this phase 3 trial. The objective was to evaluate the efficacy and safety of TTFields used in combination with maintenance temozolomide in patients with glioblastoma after initial treatment with temozolomide and radiotherapy.

Methods

Study Population

Patients eligible for this study (1) had histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma¹⁴), (2) were progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and (3) had completed standard concomitant chemoradiotherapy with temozolomide. Other eligibility criteria were (1) age of 18 years or older, (2) Karnofsky Performance Status (KPS) score of 70% or higher (the KPS score describes the general condition of a patient; a KPS score $\geq 70\%$ ensures some independence in activities of daily living), and (3) adequate bone marrow, liver, and renal function.

Prior use of implanted carmustine wafers was allowed. Patients with infratentorial tumor location and severe comorbidities were excluded. All patients provided written informed consent before entering the study; the study was approved by the institutional review boards or ethics committees of all 83 participating centers. The trial protocol appears in Supplement 1.

Study Design and Treatment

This multicenter, open-label, randomized phase 3 trial was designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. After the completion of treatment with temozolomide and radiotherapy, patients were randomized at a ratio of 2 to 1 (Figure 1) to receive standard maintenance temozolomide chemotherapy (150-200 mg/m²/d for 5 days every 28 days for 6-12 cycles according to the protocol¹ from the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group) with or without the addition of TTFields. Treatment with TTFields was to be initiated within 4 to 7 weeks from the last dose of concomitant temozolomide and radiotherapy. Randomization was performed through a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by O⁶-methylguanine-DNA methyltransferase (*MGMT*) methylation status (methylated, unmethylated, or unknown).

For patients with available paraffin-embedded tumor tissue, evaluation of *MGMT* gene promoter methylation status was performed as described previously^{7,15,16} by a central laboratory blinded to treatment group (MDxHealth). If *MGMT* methylation status could not be determined centrally prior to randomization, local *MGMT* methylation status was used for stratification.

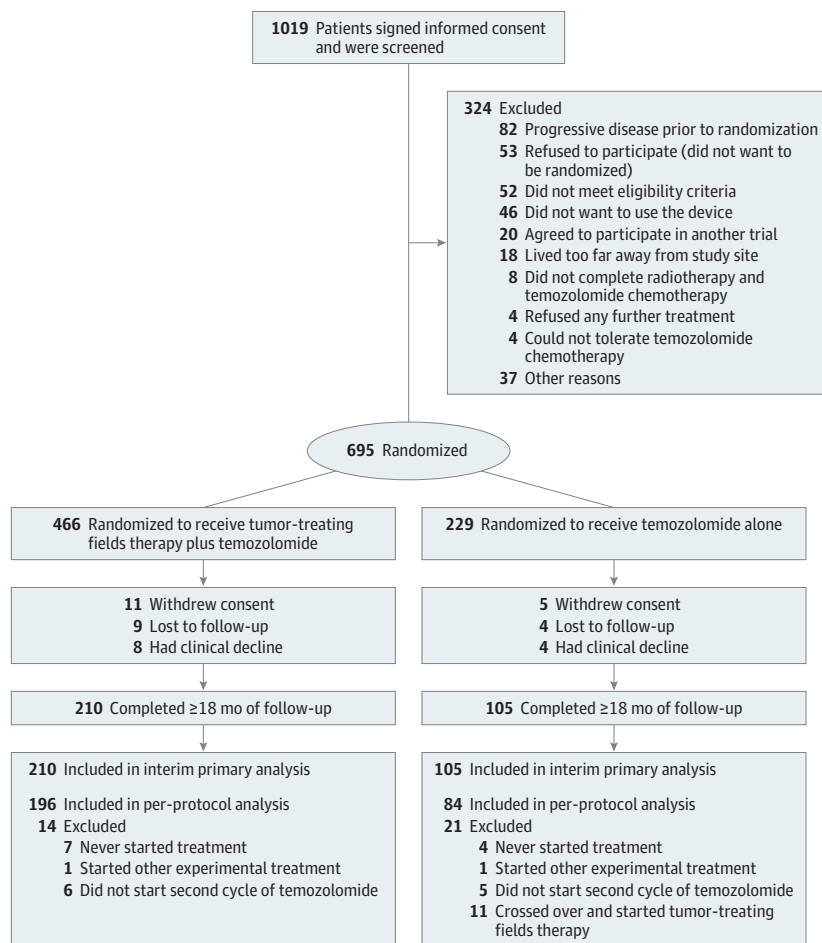
Patients in the TTFields plus temozolomide group received continuous TTFields combined with standard maintenance temozolomide. Patients receiving TTFields had 4 transducer arrays placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Ltd). Transducer array layouts were determined using a mapping software system for TTFields to optimize field intensity within the treated tumor (NovoTAL, Novocure Ltd). After being trained to operate the device, the patient continued treatment at home. The transducer arrays were supplied in sterile packaging and replaced by the patient, a caregiver, or a device technician twice per week. Although uninterrupted treatment was recommended, short treatment breaks for personal needs were allowed.

If a patient experienced tumor progression, second-line chemotherapy was offered per local practice. However, in the TTFields plus temozolomide group, TTFields could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

Patient Surveillance and Follow-up

Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance temozolomide with or without TTFields. A complete physical examination with collection of laboratory parameters was performed within 1 week of treatment initiation. The evaluation also included a quality-of-life questionnaire (QLQ-C30) that has a brain-specific module (BN-20), which was developed by the European Organisation

Figure 1. Recruitment and Inclusion of Patients in the Study



for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups.^{17,18} A Mini-Mental State Examination (a short bedside test used to evaluate cognition and memory) also was administered (a test result of 27-30 points is considered normal function).

Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months. Magnetic resonance imaging was to be performed every second month after the baseline MRI until second radiological progression in all patients. In the event of clinical progression, MRI was to be performed within 1 week after the study investigator became aware of it. All MRIs were reviewed centrally by 2 blinded independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression using the criteria developed by Macdonald et al.¹⁹ In cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was involved in 17% of the cases in the TTFields plus temozolomide group and in 18% of the cases in the temozolomide alone group.

The results of the central review were not communicated to the study investigator, and all treatment decisions were based on local imaging interpretation. Eight patients in the

TTFields plus temozolomide group (4%) compared with 6 patients in the temozolomide alone group (3%) were considered stable by blinded central review; however, treatment had been changed by the study investigator due to local interpretation of tumor progression. Patients were removed from the progression-free survival analysis at the date of treatment change when this occurred before evidence of tumor progression or when patients reached the cutoff date without tumor progression.

Adverse events were recorded prospectively according to the National Cancer Institute's Common Terminology Criteria (version 3.0) until 2 months after treatment discontinuation. Adverse events are presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the interim analysis. Treatment adherence with TTFields was recorded electronically by the device as average daily use in hours per day and information was reviewed and transferred at the monthly follow-up visit.

Statistical Considerations

The primary end point was progression-free survival in the intent-to-treat (ITT) population assessed by an independent review panel (80% power; hazard ratio [HR], 0.78; 2-sided α level

of .05). The study was also designed to have 80% power (HR, 0.76; 2-sided a level of .05) to examine overall survival as a secondary end point. To avoid an increase in the risk of a false-positive result, overall survival was to be tested statistically only if the primary end point was met.

This prespecified interim analysis was to be performed after the first 315 randomized patients reached a minimum 18-month follow-up. The final type I error rate of 0.05 was split between the interim and final analyses based on a standard a spending function.²⁰⁻²² The protocol prespecified that overall survival would be analyzed in an as-treated population, excluding all patients in both treatment groups who (1) never started maintenance temozolomide, (2) had major protocol violations, (3) crossed over to the other treatment group, or (4) received TTFields outside the protocol setting.

The primary end point would be achieved in the interim analysis if progression-free survival in the ITT population was significantly longer in the intervention group compared with the control group using a stratified log-rank test with an a level of .01. The secondary end point would be achieved in the interim analysis if overall survival in the as-treated population (per-protocol population) was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an a level of .006. The confidence intervals that go with the HRs are presented as 1 minus the prespecified a level for each analysis. For example, the a level in the per-protocol interim analysis for overall survival was .006. Therefore, the corresponding confidence interval used for presenting the HRs was 1.000 – 0.006 (99.4% confidence interval). An upper confidence limit of less than 1 indicates the prespecified statistical threshold was met. An independent data and safety monitoring committee was chartered to stop the trial if the interim analysis of progression-free survival (ITT population) and overall survival (per-protocol population) surpassed these predetermined thresholds, as well as for futility or safety concerns.

In addition to these prespecified analyses, an analysis of overall survival in the ITT population was performed. Furthermore, a robustness analysis including all 695 patients enrolled in the trial served to validate the findings of the interim analysis (database lock: December 29, 2014; eAppendix 1 in Supplement 2).

Multiple imputation analyses also were performed for the trial's primary end point of progression-free survival in the ITT population to test the sensitivity of the results to possible bias using informative and interval censoring. These analyses included (1) treating all patients with informative censoring as treatment failures in the TTFields plus temozolomide group, (2) censoring all patients with informative censoring in the temozolomide alone group (worst case scenario), and (3) treating all events in the TTFields plus temozolomide group and in the temozolomide alone group as occurring differentially at different periods during the inter-MRI interval before the date of tumor progression.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.1.1.²³ The final analysis will be performed when all 695 patients enrolled in the study have at least 18 months of follow-up and will include prespeci-

fied subgroup analyses and additional secondary end points, including quality of life.

Results

Study Participants

Between July 2009 and November 2014, there were 695 patients with newly diagnosed glioblastoma randomized to receive either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229). Data for the interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 to temozolomide alone (Figure 1; database lock: September 5, 2014). The independent data and safety monitoring committee met in October 2014 to review the interim analysis; the trial met the predefined boundaries for success (improvement of both progression-free and overall survival) and the committee recommended study termination, thus allowing patients in the control group to crossover and receive TTFields.

After approval of study termination by the US Food and Drug Administration, the trial was closed to recruitment on November 29, 2014, after 695 patients of the planned 700 patients had already been randomized. All patients in the control group with ongoing maintenance therapy were offered to receive TTFields. At the time of this report, 35 patients in the control group crossed over to receive TTFields. Follow-up for all patients continues according to the protocol.

Patient baseline characteristics were well balanced between the 2 groups (Table 1). The median age was 57 years and 66% were male. The median KPS score was 90%. Sixty-four percent of patients had a gross total resection and 11% had only a diagnostic biopsy. Tumor tissue for central *MGMT* testing was available for 72% of the patients; the *MGMT* methylation frequency was 39% (75/191 valid tests; 39% for the TTFields plus temozolomide group and 41% for the temozolomide alone group). Tumor location in the brain was also comparable.

Carmustine wafers (Gliadel) were used at initial surgery in 2.4% of patients in the TTFields plus temozolomide group vs 2.9% of patients in the temozolomide alone group. Ninety-five percent of the patients were white and 61% were treated in the United States. The rest of the patients were treated at centers in Canada, Europe, Israel, and South Korea. The median time from diagnosis to randomization was 3.8 months (range, 2.0-5.7 months) for patients in the TTFields plus temozolomide group and 3.8 months (range, 1.4-5.7 months) for those in the temozolomide alone group. The median time from the end of treatment with temozolomide and radiotherapy to randomization was 36 days in the TTFields plus temozolomide group and 38 days in the temozolomide alone group; 53% of patients were randomized after having started the first cycle of maintenance temozolomide. The median time from randomization to initiation of TTFields was 5 days.

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the TTFields

Table 1. Patient Baseline Characteristics and Treatment Details

	All Patients (N = 315)	TTFIELDS Plus Temozolomide (n = 210)	Temozolomide Alone (n = 105)
Age, y			
Mean (SD)	55.8 (11.1)	55.3 (11.3)	56.8 (10.5)
Median (range)	57 (20-83)	57 (20-83)	58 (21-80)
Karnofsky Performance Status score, median (range), % ^a	90 (60-100)	90 (60-100)	90 (70-100)
Sex, No. (%)			
Male	207 (66)	140 (67)	67 (64)
Female	108 (34)	70 (33)	38 (36)
Use at baseline, No. (%)			
Antiepileptic medication	126 (40)	88 (42)	38 (36)
Corticosteroid therapy	77 (24)	51 (24)	26 (25)
Mini-Mental State Examination score, No. (%) ^b			
≤26	45 (15)	31 (15)	14 (13)
27-30	247 (78)	174 (83)	73 (70)
Unknown	23 (7)	5 (2)	18 (17)
Extent of resection, No. (%)			
Biopsy	34 (11)	23 (11)	11 (10)
Partial resection	79 (25)	52 (25)	27 (26)
Gross total resection	202 (64)	135 (64)	67 (64)
Tissue available and tested, No. (%)			
MGMT methylation	75 (33)	49 (32)	26 (35)
No methylation	116 (51)	79 (52)	38 (51)
Invalid test result	36 (16)	24 (16)	11 (15)
Region, No. (%)			
United States	191 (61)	127 (60)	64 (61)
Rest of world	124 (39)	83 (40)	41 (39)
Completed radiation therapy, No. (%)			
<57 Gy	18 (6)	13 (6)	5 (5)
60 Gy (standard; ±5%)	291 (92)	191 (91)	100 (95)
>63 Gy	6 (2)	6 (3)	0 (0)
Concomitant temozolomide use, No. (%)			
Yes	308 (98)	207 (99)	101 (96)
Unknown	7 (2)	3 (1)	4 (4)
Time from event to randomization, median (range), d			
Last day of radiotherapy	37 (13-68)	36 (13-53)	38 (13-68)
Initial diagnosis	114 (43-171)	115 (59-171)	113 (43-170)
No. of maintenance temozolomide cycles until first tumor progression, median (range)	6 (1-26)	6 (1-26)	4 (1-24)
Duration of treatment with TTFIELDS, median (range), mo	9 (1-58)	9 (1-58)	
Adherence to TTFIELDS therapy ≥75% during first 3 mo of treatment		157 (75)	

Abbreviations: MGMT, O⁶-methylguanine-DNA methyltransferase; TTFIELDS, tumor-treating fields.

^a A higher score indicates better functional status.

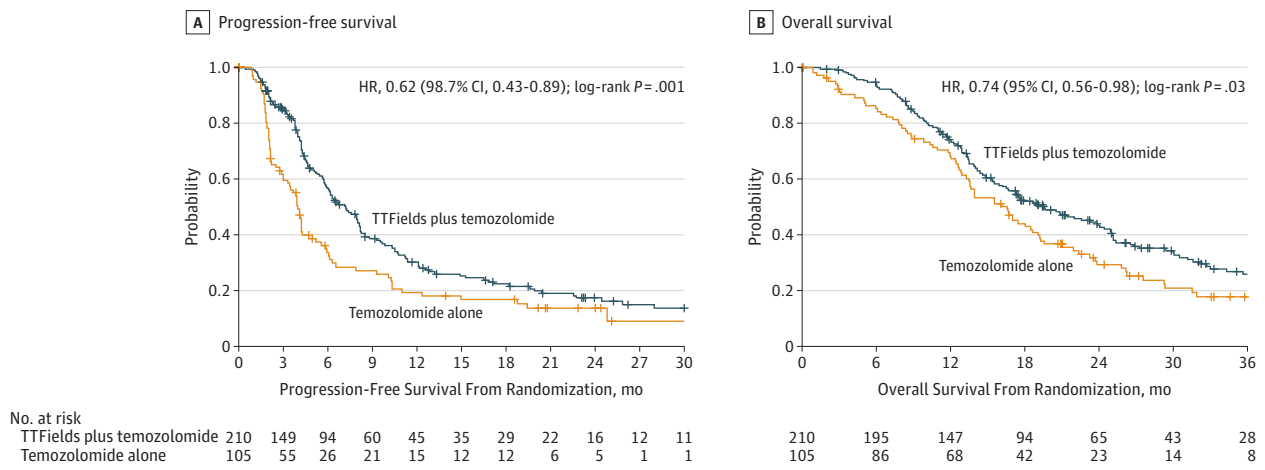
^b A higher score indicates better cognitive capability.

plus temozolomide group and 4.0 cycles (range, 1-24 cycles) for patients in the temozolomide alone group; the median duration of treatment with TTFIELDS was 9 months (range, 1-58 months). Two-thirds (n = 141) of patients in the TTFIELDS plus temozolomide group continued treatment with TTFIELDS after first tumor progression. Three-quarters (n = 157) of patients receiving treatment with TTFIELDS were adherent to therapy (ie, wearing the device >18 hours per day on average during the first 3 treatment months).

Efficacy End Points

As prespecified, the primary end point for the efficacy results was based on progression-free survival in the ITT population of the interim analysis data set. After a median follow-up of 38 months (range, 18-60 months), the median progression-free survival from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the TTFIELDS plus temozolomide group compared with 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (HR, 0.62 [98.7% CI, 0.43-0.89];

Figure 2. Survival Curves for Patients Included in the Interim Analysis in the Intent-to-Treat Population



Survival analyses on time from date of randomization until tumor progression, death, or last follow-up (censored patients) according to the Kaplan-Meier

method. The small vertical ticks on the curves indicate censored patients. HR indicates hazard ratio; TTFIELDS, tumor-treating fields.

stratified log-rank $P = .001$; **Figure 2A**). Thus, adding TTFIELDS to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

As per the statistical analysis plan, overall survival was to be tested in a prespecified per-protocol population only after the primary end point was found to surpass the threshold for significance in the interim analysis. Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFIELDS plus temozolomide group ($n = 196$) compared with 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group ($n = 84$) (HR, 0.64 [99.4% CI, 0.42-0.98]; stratified log-rank $P = .004$). The details on the per-protocol population and analyses are summarized in eAppendix 2 in Supplement 2.

In additional analyses in the ITT population, the median overall survival was 19.6 months (95% CI, 16.6-24.4 months) in the TTFIELDS plus temozolomide group compared with 16.6 months (95% CI, 13.6-19.2 months) in the temozolomide alone group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank $P = .03$; **Figure 2B**). The percentage of patients alive at 2 years following enrollment was 43% in the TTFIELDS plus temozolomide group and 29% in the temozolomide alone group ($P = .006$).

To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Patient characteristics of all patients randomized did not differ significantly from the interim data set, and the results for the main end points were similar in these analyses compared with the interim analysis (eAppendix 1 in Supplement 2).

Second-line treatments, such as nitrosoureas, temozolomide rechallenge, and bevacizumab, were received by 67% of the patients in the TTFIELDS plus temozolomide group compared with 57% in the temozolomide alone group; about 40% of second-line therapies included bevacizumab and about 40% included nitrosoureas. The type of chemotherapy used at recurrence was balanced between treatment groups.

Secondary imputation analyses of progression-free survival with relation to the effects of interval and informational censoring did not change the conclusions of the primary progression-free survival analysis (eAppendix 3 in Supplement 2).

Safety and Tolerability

The addition of TTFIELDS to temozolomide therapy in patients with newly diagnosed glioblastoma was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone (**Table 2**). The overall incidence, distribution, and severity of adverse events were similar in patients treated with TTFIELDS plus temozolomide and in those treated with temozolomide alone. The only notable exception was a higher incidence rate of localized skin toxicity (medical device site reaction beneath the transducer arrays) in patients treated with TTFIELDS plus temozolomide. Mild to moderate skin irritation was observed in 43% of patients treated with TTFIELDS plus temozolomide and severe skin reaction (grade 3) in 2%. Mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFIELDS plus temozolomide and occurred mainly at the time of therapy initiation. The incidence of seizures was almost identical in the 2 groups (15 [7%] in the TTFIELDS plus temozolomide group vs 8 [8%] in temozolomide alone group). A total of 12 patients died of causes considered unrelated to treatment while receiving adjuvant therapy (8 [3.9%] in the temozolomide plus TTFIELDS group and 4 [4.0%] in the temozolomide alone group; **Table 2**).

Discussion

Glioblastoma is a highly aggressive brain tumor affecting men and women, frequently at the peak of life. Prognosis remains poor with no major treatment advance in more than a decade. In the interim analysis of this randomized clinical trial,

the addition of TTFields to standard maintenance temozolomide significantly improved progression-free and overall survival. The prespecified analyses revealed that patients randomized to receive TTFields plus temozolomide compared with patients randomized to receive temozolomide alone had a median progression-free survival of 7.1 months vs 4.0 months (ITT analyses). Patients who received TTFields plus temozolomide had a median overall survival of 20.5 months compared with 15.6 months in those who received temozolomide alone (as per the prespecified per-protocol analysis; the ITT analysis did not differ substantially).

Based on the results of this planned interim analysis, the trial's independent data and safety monitoring committee recommended termination of the trial. Because almost all patients had been enrolled (695/700) in the study by the time the recommendation was implemented, the full trial population will be followed up for both progression-free and overall survival. Subsequent analyses of all secondary end points and subgroups will be performed when the follow-up data are available.

The trial population and the results in the control group in this study were comparable with other glioblastoma clinical trials. Nevertheless, patients in this trial were randomized only after the end of radiochemotherapy, and for most, the first cycle of maintenance temozolomide had been started at the time of randomization; thus, patients with early tumor progression during radiochemotherapy were excluded. Most glioblastoma trials have reported survival from the date of initial diagnosis or study enrollment before starting radiochemotherapy, thus 3 to 4 months before randomization of the current study.

When the interval from diagnosis to randomization is added to the outcome results in this study, the progression-free survival of 7.8 months in the control group is comparable with most other reported studies, and supports the generalizability of these results. The Radiation Therapy Oncology Group (RTOG) 0525 protocol randomized patients only after the end of treatment with temozolomide and radiotherapy, similar to our study.³ The control groups with standard dose temozolomide only in these 2 trials were comparable: progression-free survival from randomization of 4.0 months in the present study and 5.5 months in the RTOG 0525 trial and overall survival of 16.6 months in both trials. Thus, the benefit observed with TTFields cannot be simply attributed to patient selection. In the present trial, the gain of 3 months in both median progression-free survival (from 4.0 months to 7.2 months; HR, 0.62) and median overall survival (from 16.6 months to 19.6 months; HR, 0.74), translating into a survival gain at 2 years of 14% (from 29% to 43%) in the ITT population is in the range of benefit that is considered clinically meaningful for therapeutic agents in oncology.

The prespecified analysis for overall survival in the interim analysis was to be based on the per-protocol population (n = 280); ie, removal in both study groups of the patients who did not start their second course of maintenance temozolomide or had major protocol violations. This analysis met the prespecified threshold for efficacy in the interim analysis for the per-protocol population. In a more conserva-

Table 2. Grade 3 to 4 Treatment-Emergent Adverse Events

	No. (%) of Patients With Adverse Events ^a	
	TTFields Plus Temozolomide (n = 203) ^b	Temozolomide Alone (n = 101) ^c
Hematological disorders ^d	25 (12)	9 (9)
Anemia	1 (<1)	2 (2)
Leukopenia or lymphopenia	11 (5)	5 (5)
Neutropenia	6 (3)	1 (1)
Thrombocytopenia	19 (9)	3 (3)
Cardiac disorders	2 (1)	3 (3)
Eye disorders	2 (1)	1 (1)
Gastrointestinal disorders ^d	11 (5)	2 (2)
Abdominal pain	2 (1)	0
Constipation	2 (1)	0
Diarrhea	1 (<1)	2 (2)
Vomiting	3 (1)	1 (1)
General disorders	17 (8)	5 (5)
Fatigue	8 (4)	4 (4)
Infections	10 (5)	5 (5)
Injury and procedural complications ^d	14 (7)	5 (5)
Fall	6 (3)	2 (2)
Medical device site reaction	4 (2)	0
Metabolism and nutrition disorders	7 (3)	3 (3)
Musculoskeletal disorders	8 (4)	3 (3)
Nervous system disorders ^d	45 (22)	25 (25)
Seizure	15 (7)	8 (8)
Headache	4 (2)	2 (2)
Psychiatric disorders ^d	9 (4)	3 (3)
Anxiety	2 (1)	0
Bradyphrenia	0	1 (1)
Confusional state	2 (1)	1 (1)
Mental status changes	4 (2)	1 (1)
Psychotic disorder	2 (1)	0
Respiratory disorders	4 (2)	1 (1)
Skin disorders	0	1 (1)
Vascular disorders ^d	8 (4)	8 (8)
Deep vein thrombosis	1 (<1)	3 (3)
Pulmonary embolism	4 (2)	6 (6)

Abbreviation: TTFields, tumor-treating fields.

^a Safety is reported on patients who have received any treatment. Randomized patients who never received any maintenance therapy were excluded from this safety analysis.

^b Eight patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and infection; and 4 patients with central nervous system disorders likely due to tumor progression).

^c Four patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and unknown).

^d Patients may have had more than 1 adverse event so subcategories do not total and not all events are subcategorized.

tive analysis using the ITT population, an overall survival benefit was also manifest. Furthermore, an analysis of robustness performed on all randomized patients enrolled at the time

of study termination (eAppendix 1 in Supplement 2) supports the conclusions of the interim analysis.

This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFIELDS plus temozolomide group, TTFIELDS were to be continued, and thus, more detailed treatment information has been tracked for this group.

This analysis reports a planned interim analysis on data from the first 315 patients with at least 18 months of follow-up; however, for detailed and meaningful subgroup analyses, the mature data of the full data set will be needed. Treatment failure patterns, effects of second-line therapies, and additional molecular analyses on baseline tumor biopsies will allow for better understanding of the clinical effects of this novel treatment modality. With the last patient randomized on November 29, 2014, however, these data are not expected before the end of 2016.

This was an open-labeled study. A sham or placebo treatment for the control group was considered neither practical (patients would be able to sense heat when they were receiving TTFIELDS) nor appropriate (due to the burden for patients and caregivers and the need to shave the scalp and have transducer arrays placed). In this respect, the trial resembles studies evaluating radiation therapy. This raises the question of a placebo effect leading to the improved outcome. Although some effect of placebo may be expected on subjective end points, such as cognitive function and quality of life, objective end points, such as overall and progression-free survival (assessed by a blinded review panel), are independent of pla-

cebo effects in cancer therapy.²⁴ The panel did not have information on treatment received and no stigmata of TTFIELDS array pads were evident on MRI.

Recent randomized studies of patients with glioblastoma, which did not use placebo controls, failed to show any increase in progression-free or overall survival^{3,7} despite intensive treatment regimens requiring twice weekly hospital visits.⁷ The magnitude of effect size seen in the present trial (HR of 0.62 for progression-free survival and 0.74 for overall survival) is beyond what could be attributed to a placebo effect. In addition, the support provided to patients in the TTFIELDS plus temozolomide group by device support specialists during the trial was largely technical in nature and did not include medical supportive care. Medical follow-up with monthly visits was the same for both treatment groups.

Because TTFIELDS were applied only to the head, an increase in systemic adverse events was neither seen nor expected. No increase in seizure rate or neurological adverse events was observed. Almost half of the patients treated with TTFIELDS did experience some grade 1 to 2 (mild to moderate) localized skin reaction related to the application of the transducer arrays used to deliver the TTFIELDS. This adverse effect could be managed using published skin care guidelines for patients receiving TTFIELDS.²⁵ Only 2% of patients receiving TTFIELDS had grade 3 to 4 (severe) skin reactions beneath the transducer arrays.

Conclusions

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFIELDS to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

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Author Contributions: Drs Stupp and Ram had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosure of Potential Conflicts of Interest. Dr Stupp reported receiving travel assistance from Novocure for data review and presentation of the results at medical meetings; and receiving personal fees for serving on advisory boards for Roche/Genentech, Merck KGaA, Merck & Co, and Novartis. Dr Taillibert reported receiving personal fees from Mundipharma EDO and Roche. Dr Kanner reported receiving institutional grant funding and personal fees for speaking and device training from Novocure. Dr Kesari reported receiving institutional grant funding and personal fees for consulting and attending advisory meetings from Novocure. Dr Steinberg reported receiving consulting fees from Novocure for performing the statistical analysis. Dr Toms reported receiving personal fees from Novocure for serving on an advisory board. Dr Lieberman reported receiving institutional grant funding from Novocure. Dr Fink reported receiving personal fees from Novocure for serving on an advisory board; and receiving personal fees from Genentech for serving in the speakers program. Dr Zhu reported receiving institutional grant funding and personal fees from Novocure. Dr Engelhard reported receiving institutional grant funding and personal fees from Novocure. Dr Chen reported receiving grant funding, personal fees, nonfinancial support, and being a stock holder and chief

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Role of the Funder/Sponsor: Novocure Ltd had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The study was designed by the first and last authors (R.S. and Z.R.), together with representatives from Novocure (mainly E.D.K.). The study oversight was supported and monitored by a clinical research organization (CRO), who also holds the database. Data were collected by the investigators and monitored by the CRO. Device use data were downloaded monthly and transferred to the study investigators or their research staff by device support specialists from Novocure Ltd. The data were analyzed separately by the statistician of the independent data monitoring committee and the study statistician (D.M.S.). Data interpretation was the responsibility of the first and last authors (R.S. and Z.R.), together with the study sponsor representative and project lead (E.D.K.). These 3 physicians also jointly developed the first draft. A subsequent mature draft and a prefinal version were circulated among all authors who gave additional input, contributed to, and approved the manuscript. The first and last authors (R.S. and Z.R.) and E.D.K. had full access to all data, and also reviewed all patient profiles for consistency (R.S. and E.D.K.). The decision to publish the data followed the independent data and safety monitoring committee recommendation for data release, and was supported by all coauthors.

The roles of employees of Novocure are described in the respective author contributions. Other employees' involvement was limited to technical support of the device.

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Indications For Use and Safety Information in the United States:

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

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.

Summary of Important Safety Information

Contraindications

Do not use Optune in patients with 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 in patients that 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

Optune can only be prescribed by a healthcare provider that has completed the required certification training provided by Novocure (the device manufacturer).

Do not prescribe Optune for patients that are pregnant, you think might be pregnant or are trying to get pregnant, as the safety and effectiveness of Optune in these populations have not been established.

The most common ($\geq 10\%$) adverse events involving Optune in combination with temozolomide were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression.

Use of Optune in patients with an inactive implanted medical device in the brain has not been studied for safety and effectiveness, and use of Optune in these patients could lead to tissue damage or lower the chance of Optune being effective.

If the patient has an underlying serious skin condition on the scalp, evaluate whether this may prevent or temporarily interfere with Optune treatment.

Indications for use and safety information in Europe:

Newly diagnosed GBM

Optune is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant temozolomide, concomitant to maintenance temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant temozolomide. Treatment may be given together with maintenance temozolomide (according to the prescribing information in the Temodar package insert) and after maintenance temozolomide is stopped.

Recurrent GBM

Optune is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy.

Contraindications

Do not use Optune if you are pregnant, 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. Do not use Optune if you have clinically significant hepatic, renal or hematologic disease. Do not use Optune if you have significant additional neurological disease (primary seizure disorder, dementia, progressive degenerative neurological disorder, meningitis or encephalitis, hydrocephalus associated with increased intracranial pressure). 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 Treatment Kit 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 the device manufacturer (Novocure). All servicing procedures must be performed by qualified and trained personnel.

Do not use Optune Treatment Kit if you are 17 years old or younger. The system has not been tested in persons 17 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

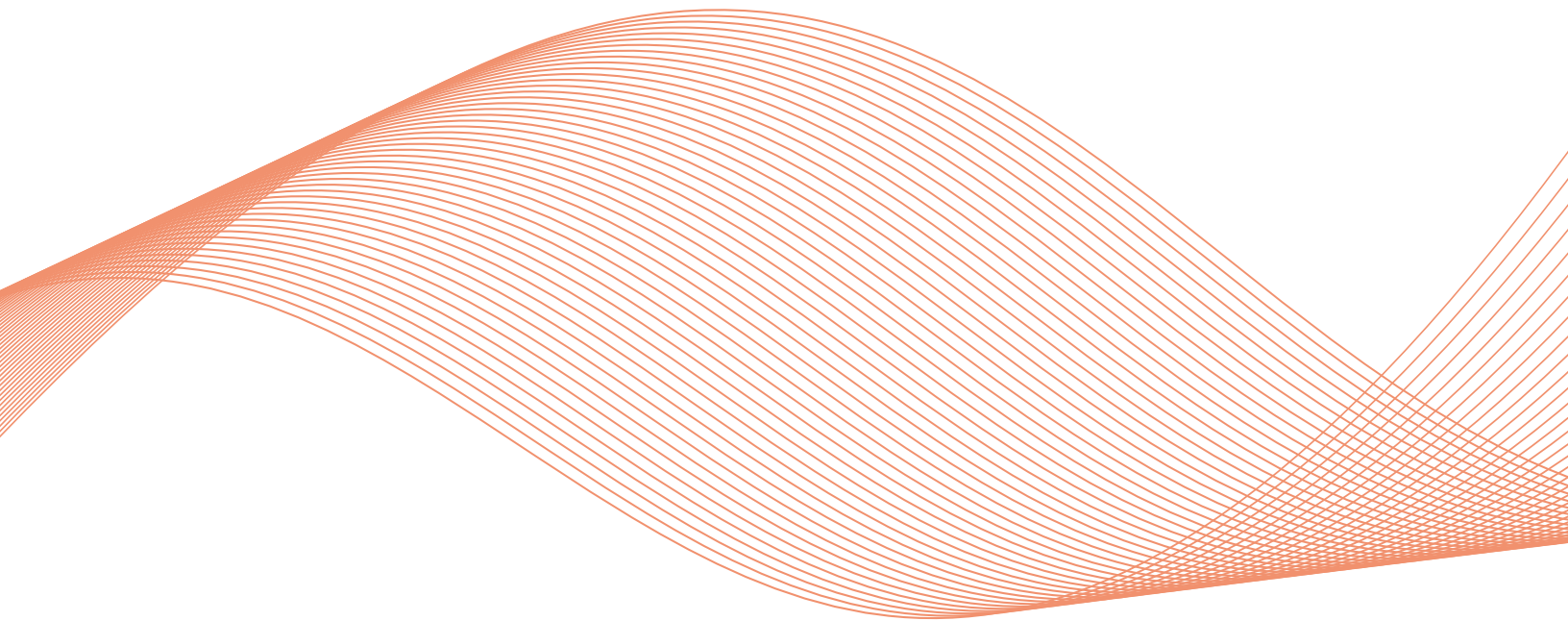
Do not wet the device or the transducer arrays. Do not use any parts that do not come with the Optune treatment kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Optune commonly causes skin irritation beneath the transducer arrays and in rare cases lead to headaches, falls, fatigue, muscle twitching or skin ulcers.

For complete information regarding Optune's indication, contraindication, warnings and precautions please see the [Instructions for Use \(IFU\)](http://www.optune.com/deutsch/materialien/schulungen.aspx). (<http://www.optune.com/deutsch/materialien/schulungen.aspx>)



INSTRUCTIONS FOR USE



- Patient Information and Operation Manual

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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 21 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Warning - Do not use Optune 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 been 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 cells¹.

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.

TFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TField technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TFields. 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 TFields 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 TFields. 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 TFields 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, TField 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 TFields. 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 telophase².

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 time³.

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).

Clinical Data

NEWLY DIAGNOSED GLIOBLASTOMA (see page 17 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 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 $< 100 \times 10^3/\mu\text{L}$)
 - 2) Neutropenia (absolute neutrophil count $< 1.5 \times 10^3/\mu\text{L}$)
 - 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 > 5 mm, 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	TMZ Alone	
	(N=210)	(N=105)	
	n(%)	n(%)	
Gender			
Male	140 (66.67)	67 (63.81)	
Female	70 (33.33)	38 (36.19)	
Central MGMT Assessment			
Invalid	24 (11.43)	11 (10.48)	
Unknown	58 (27.62)	30 (28.57)	
Methylated	49 (23.33)	26 (24.76)	
Unmethylated	79 (37.62)	38 (36.19)	
Extent of Resection			
Biopsy	23 (10.95)	11 (10.48)	
Gross Total Resection	135 (64.29)	67 (63.81)	
Partial Resection	52 (24.76)	27 (25.71)	
Area			
ROW	83 (39.52)	41 (39.05)	
USA	127 (60.48)	64 (60.95)	
Tumor Position			
Missing	0 (0)	3 (2.86)	
Corpus Callosum	12 (5.71)	3 (2.86)	
Frontal Lobe	64 (30.48)	32 (30.48)	
Occipital Lobe	7 (3.33)	4 (3.81)	
Parietal Lobe	35 (16.67)	27 (25.71)	
Temporal Lobe	92 (43.81)	36 (34.29)	
Tumor Location			
Missing	0 (0)	1 (0.95)	
Both	2 (0.95)	1 (0.95)	
Corpus Callosum	8 (3.81)	3 (2.86)	
Left	93 (44.29)	41 (39.05)	
Right	107 (50.95)	59 (56.19)	
Karnofsky Performance Score	Median	90	90
	Min, Max	60, 100	70, 100
Age in Years	Median	57	58
	Min, Max	20, 83	21, 80
No. of Cycles of TMZ Received	Median	6	4
	Min, Max	1, 26	1, 24
No. of Cycles of Optune 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	TMZ Alone	
	(N=446)	(N=229)	
	n(%)	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

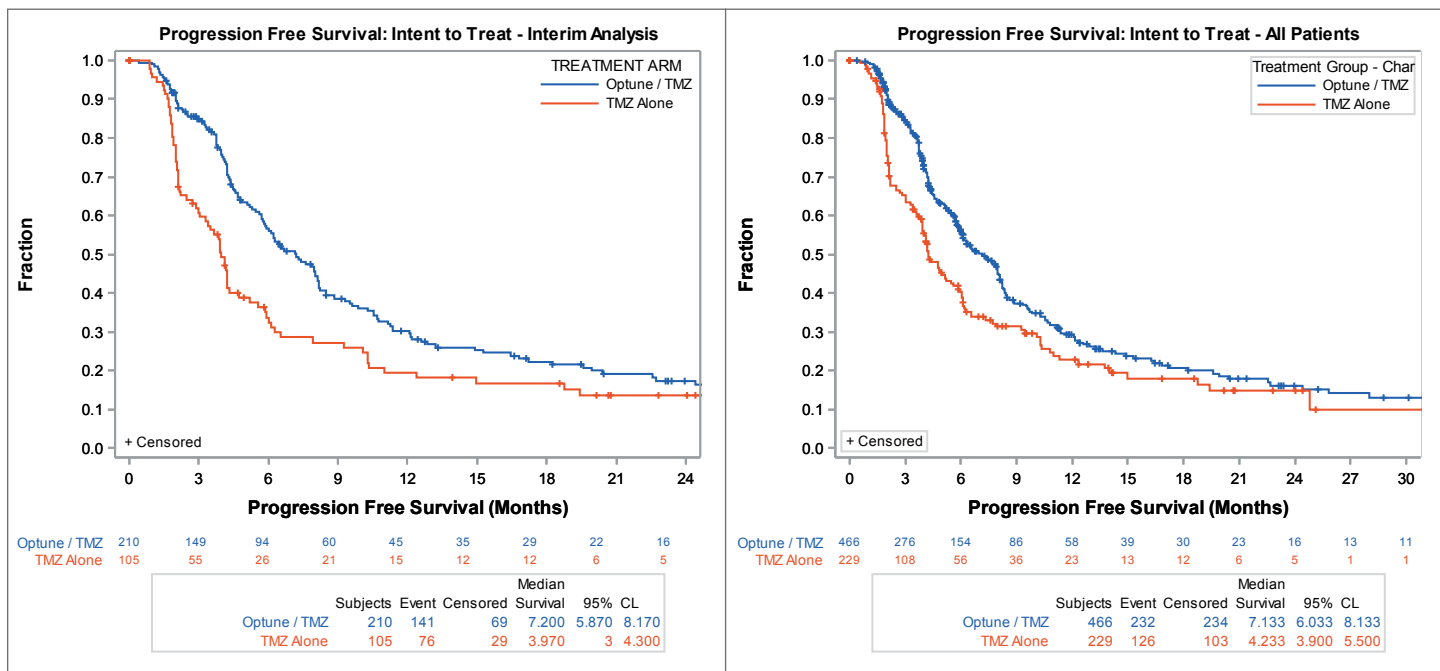
As seen above, all baseline characteristics are well balanced between arms in the ITT population at the final analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 64 patients (9.21%) had tissue that was not evaluable,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



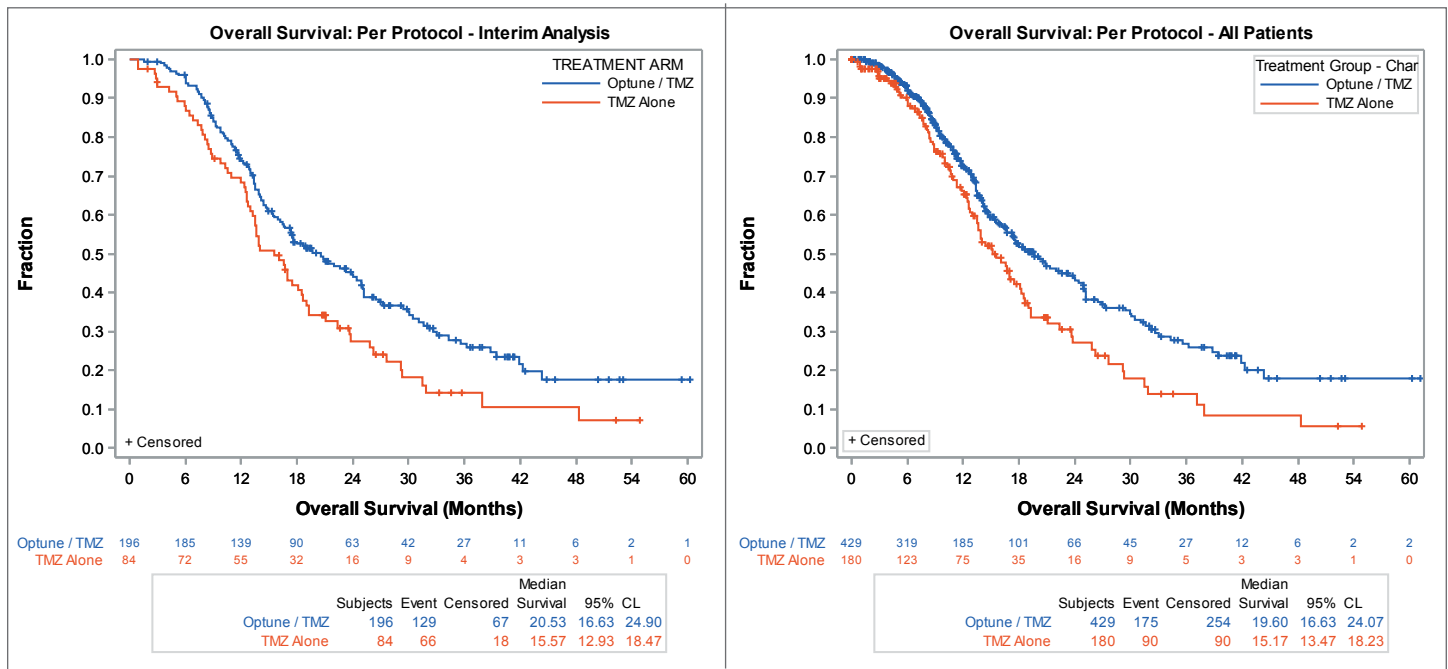
	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	7.2 (5.9, 8.2)	4.0 (3.0, 4.3)	7.1 (6.0, 8.1)	4.2 (3.9, 5.5)
Log-rank test	$p=0.0013$		$p=0.0010$	
Hazard Ratio (95% CI)	0.621 (0.468, 0.823)		0.694 (0.558, 0.823)	

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)

System Organ Class	Optune/TMZ (N=437)			TMZ Alone (N=207)		
	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 Disorder	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
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 recurrent 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 GBM¹

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
- 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 $< 100 \times 10^3/\mu\text{L}$)
 - 6) Neutropenia (absolute neutrophil count $< 1 \times 10^3/\mu\text{L}$)
 - 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 > 5 mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

¹Stupp, 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.

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 (cm²): 16.2±12.4; progression number: 1.4±0.9; re-operated: 26%; male: 70%; previous low grade: 10%; prior bevacizumab failure: 19%. Baseline characteristics were similar between treatment groups with slightly more men in the Optune 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)	88 (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

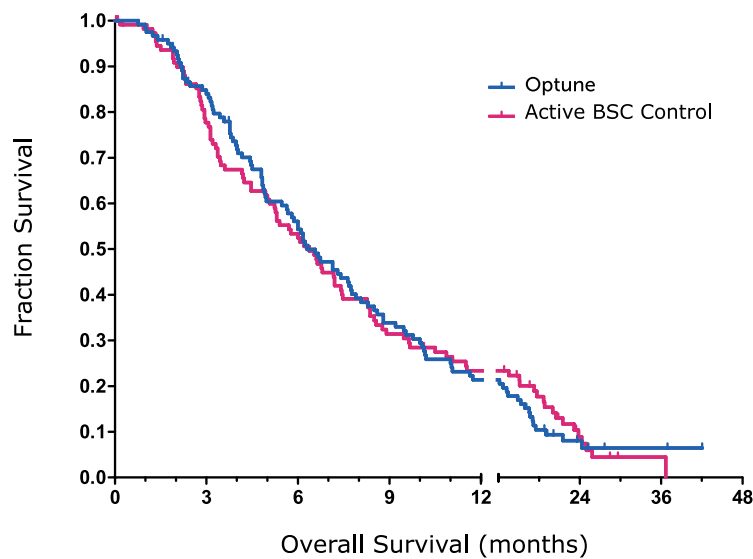
Effectiveness Results:

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.



	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 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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Health Technology Clinical Committee Findings and Decision

Topic: Cardiac Stents
Meeting Date: January 15, 2016
Final Adoption:

Meeting materials and transcript are available on the HTA website:
www.hca.wa.gov/hta/meetingmaterials/Forms/ExtMeetingMaterials.aspx

Number and Coverage Topic:

20160115B – Cardiac Stents

HTCC Coverage Determination:

Cardiac stents for stable angina are a **covered benefit with conditions**.

Drug eluting or bare metal cardiac stents are **covered** when cardiac stents are indicated for treatment.

HTCC Reimbursement Determination:

Limitations of Coverage:

For patients with **stable angina** cardiac stents are covered for the following:

1. Angina refractory to optimal medical therapy, and
2. Objective evidence of myocardial ischemia.

Non-Covered Indicators:

N/A

Agency Contact Information:

Agency	Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

Draft

HTCC Coverage Vote and Formal Action

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee concluded that the current evidence for newer generation cardiac stents is sufficient to make a determination on this topic. The committee discussed and voted on the evidence for use of cardiac stents compared to current medical management strategies for stable angina. The committee then considered the evidence of newer generation drug eluting stents versus bare metal stents for stable or unstable angina. The committee considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover with conditions cardiac stents for unstable angina. The committee voted separately to cover with no conditions the use of drug eluting stents or bare metal stents when appropriate for stable or unstable angina.

	Not Covered	Covered Under Certain Conditions	Covered Unconditionally
Cardiac stents for stable angina	0	10	1
Cardiac stents, drug eluting vs bare metal	1	0	10

Discussion

The committee reviewed and discussed the evidence for use of cardiac stents compared to medical management for stable angina and discussed the meaning, quality and methodology of the available studies for stents vs medical management. The committee determined that coverage with conditions for the question of stable angina when compared to medical management. Limitations are for this condition and question only. For the question of drug eluting stents versus bare metal stents when stents are indicated the committee determined to cover without conditions. Therefore there are no limitations on the use of drug eluting or bare metal stents when intervention with cardiac stents is appropriate.

Limitations

For patients with **stable angina** cardiac stents are covered for the following:

1. Angina refractory to optimal medical therapy, and
2. Objective evidence of myocardial ischemia.

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). There is a NCD (National Coverage Determination Manual: 20.7 (2014)) for percutaneous transluminal angioplasty with and without stent. The HTCC coverage determination is similar to the CMS decision.

Draft

The committee discussed and reviewed treatment criteria from clinical guidelines identified for treatment of stable angina and revascularization from the following organizations:

- American College of Cardiology and American Heart Association;
- American Association for Thoracic Surgery;
- American College of Cardiology Foundation;
- American College of Physicians;
- American Diabetes Association;
- Council on Clinical Cardiology;
- Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure;
- National Cholesterol Education Program (NCEP);
- Preventive Cardiovascular Nurses Association;
- Society for Cardiovascular Angiography and Interventions;
- Society of Thoracic Surgeons

The chair noted consistency with existing guidelines that include risk identification, risk reduction, medical and revascularization treatment criteria.

The committee chair directed HTA staff to prepare a findings and decision document on Cardiac Stents reflective of the majority vote for final approval at the next public meeting.

Health Technology Clinical Committee Authority:

Washington State's legislature believes it is important to use a science-based, clinician-centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority (HCA), through its Health Technology Assessment (HTA) program, to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and that takes public input at all stages.

Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State HTCC determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.

Health Technology Clinical Committee Findings and Decision

Topic: Cardiac Stents
Meeting Date: January 15, 2016
Final Adoption:

Meeting materials and transcript are available on the HTA website:
www.hca.wa.gov/hta/meetingmaterials/Forms/ExtMeetingMaterials.aspx

Number and Coverage Topic:

20160115B – Cardiac Stents

HTCC Coverage Determination:

Either drug eluting or bare metal cardiac stents are a **covered benefit** when cardiac stents are indicated for treatment (includes stable angina, unstable angina).

For patients being treated for stable angina, Cardiac stents are a **covered benefit with conditions**.

Conditions include:

1. Angina refractory to optimal medical therapy, and
2. Objective evidence of myocardial ischemia

HTCC Reimbursement Determination:

Limitations of Coverage:

See above conditions for treatment of stable angina.

Non-Covered Indicators:

N/A

Agency Contact Information:

Agency	Phone Number
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HTCC Coverage Vote and Formal Action

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Cardiac Stents Re-review

Draft Findings & Decision
 Timeline and Overview of Comments

The Health Technology Assessment (HTA) program received no comments in response to the posted Health Technology Clinical Committee (HTCC) draft findings and decision on **Cardiac Stents – Re-review**.

Timeline

Phase	Date	Public Comment Days
Technology recommendations published	January 5, 2015	
Public comments	January 5 to January 20, 2015	16
Selected technologies published	February 4, 2015	
Public comments	February 4 to March 5, 2015	30
Draft key questions published	July 10, 2015	
Public comments	July 10 to 24, 2015	15
Final key questions published	August 31, 2015	
Draft report published	October 20, 2015	
Public comments	October 20 to November 18, 2015	30
Final report published	December 14, 2015	
Public meeting	January 15, 2016	
Draft findings & decision published	February 4, 2016	
Public comments	February 4 – 18, 2016	15

Overview

Category	Comment Period	
	February 4 – 18, 2016	Cited Evidence
Patient, relative, and citizen	0	0
Legislator and public official	0	0
Health care professional	0	0
Industry & manufacturer	0	0
Professional society & advocacy organization	0	0
Total	0	0