Washington State Health Care Authority

Health Technology Assessment

Novocure (Tumor Treating Fields)

UPDATED Final Evidence Report

December 26, 2015

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
hca.wa.gov/hta
shtap@hca.wa.gov

Novocure (Tumor Treating Fields)

A Health Technology Assessment
Prepared for Washington State Health Care Authority

FINAL REPORT

December 26, 2015

Acknowledgement
This report was prepared by:

Hayes, Inc.
157 S. Broad Street Suite 200
Lansdale, PA 19446
P: 215.855.0615 F: 215.855.5218

Table of Contents

List of Figures

List of Tables

List of Key Abbreviations

GBM glioblastoma

NSCLC non-small cell lung cancer

OS overall survival

PFS progression-free survival

RCT randomized controlled trial

TMZ temozolomide

TTF tumor treating fields

Executive Summary

The **Executive Summary** summarizes background information, the methods and search results for this report, findings with respect to the Key Questions, and payer policies and practice guidelines. The **Executive Summary** also includes conclusions and an assessment of the quality of the evidence for each Key Question. In general, references are not cited in the **Executive Summary**. The **Executive Summary** ends with an **Overall Summary and Discussion**.

The **Technical Report** provides additional detail, with full citation, regarding background information, study results, and payer policies and guidelines, but does not include conclusions or quality assessment.

Summary of Clinical Background

Epidemiology, Diagnosis, and Treatment of Glioblastoma

Glioblastoma (GBM) is the most prevalent and malignant intracranial tumor, representing as much as 30% of primary brain tumors. The overall prognosis is poor, even with the best standard of care. Even with optimal treatment, the median survival time is approximately 10 to 14 months. Only a third of patients survive for 1 year following diagnosis of GBM, and less than 5% live beyond 5 years. The incidence of GBM has been shown to increase with age, and is more common in men than women. Exposure to therapeutic or high-dose radiation and rare familial syndromes has been linked to GBM. Patients with recurrent GBM have a median survival time of just 5 to 7 months. Longer-term survival has been linked to younger age and more favorable scores on the Karnofsky Performance Scale (KPS), which measures functional impairment.

Current Therapies for GBM

The current standard of care for newly diagnosed GBM patients is surgery, followed by combination chemotherapy using temozolomide (TMZ) and radiation therapy. Virtually all patients with newly diagnosed GBM relapse despite best available treatment, with a median time to recurrence of approximately 7 months.

At the time of disease recurrence, treatment options for GBM patients are limited. Approximately 20% of patients may undergo repeat surgery. It has been suggested that tumor involvement in certain critical brain regions, poor performance score, and large tumor volume are associated with poor repeat surgery outcomes. Carmustine polymer wafers may be placed intraoperatively in the surgical cavity during repeat surgery. However, the carmustine wafers may potentially interact with other agents and cause increased toxicity. Rarely, patients may undergo reirradiation. For the majority of recurrent GBM patients, chemotherapy is indicated. The type of chemotherapy drug used varies widely. In the United States, combination treatment with chemotherapy and the angiogenesis inhibitor bevacizumab has been approved for recurrent GBM and certain other cancers. However, approximately 40% to 60% of recurrent GBM patients are either unresponsive to bevacizumab or experience serious adverse events following treatment. These serious side effects include hemorrhage, thromboembolism, infection,

hypertensive crisis, renal failure, diarrhea, nausea, and vomiting. Furthermore, although some patients may be initially responsive to bevacizumab, the tumor eventually progresses. Novel therapies with a different mechanism of action against GBM and with reduced toxicity are needed. Novocure (rebranded as Optune; Novocure Ltd.) is a portable medical device that generates low-intensity alternating electric fields, called tumor treating fields (TTF), for the treatment of recurrent GBM. Clinical trials have suggested that Novocure may be as effective as chemotherapy with decreased toxic side effects.

Novocure (TTF)

The NovoTTF-100A System, also referred to as Novocure or Optune, approved by the Food and Drug Administration (FDA) in April 2011 for treatment of recurrent GBM, and approved for newly diagnosed GBM in October 2015, is a novel device which emits alternating electric fields that disrupt the rapid cell division exhibited by cancer cells. Alternating electric fields, also called tumor treating fields (TTF), have been shown to be effective when applied externally to patients with recurrent GBM. TTF therapy uses low-intensity, intermediate-frequency electric fields that have an anti-mitotic effect, which acts during late metaphase and anaphase. The mechanism of action has been attributed to interference with the formation of the mitotic spindle microtubules and/or physical destruction of cells during cleavage. Unlike chemotherapy, Novocure therapy does not have a half-life. Therefore, it requires continuous application to be effective. Patients are instructed to use the device at least 18 hours per day. The minimal treatment course duration is 4 weeks.

The Novocure system comprises an electrical field generator device, 4 insulated transducer arrays, a connector cable, and a power source (battery or electrical outlet). Treatment parameters are preset (200 kilohertz [kHz] and a minimal field intensity of 0.7 volts per centimeter [V/cm] in the brain or 1 to 2 V/cm in the chest cavity and upper abdomen) and no electrical output adjustments are available to the patient. TTF are delivered through transducer arrays that are applied to the shaved scalp (or on the thorax in the case of non-small cell lung cancer). The transducer arrays are composed of insulated ceramic discs that are separated from the skin by a layer of conductive hydrogel. The locations of the arrays are calculated for each individual patient to optimize field intensity based on head size and tumor location. Patients or caregivers replace transducer arrays 1 to 2 times per week and re-shave the scalp to maintain optimal contact with the arrays.

Novocure Treatment for Non-Small Cell Lung Cancer

Although the majority of the current published literature on Novocure has been applied to GBM patients, Novocure has recently been investigated for the treatment of advanced stage III or stage IV non-small cell lung cancer (NSCLC). There are several possible strategies for treating patients with stage III NSCLC. These options include induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy. Optimal surgical management involves complete resection. Patients that have a planned lobectomy (as opposed to pneumonectomy) are the best candidates for preoperative chemoradiotherapy. If patients are evaluated as unresectable, 2 to 4 cycles of concurrent chemoradiotherapy is the standard of care. Platinum-based chemotherapy yields the best outcomes. Bevacizumab plus chemotherapy may be indicated in patients with poor performance status and with advanced or recurrent NSCLC.

For the treatment of stage IV NSCLC, the standard first-line chemotherapy is platinum-based chemotherapy. Chemotherapy should be initiated while the patient has a good performance status. Systemic treatment should be offered to all stage IV patients with poor performance status. Four to 6 treatment cycles of chemotherapy are recommended.

Novocure Treatment for Other Cancers

Ongoing clinical trials are currently investigating the use of Novocure in patients with several other conditions. Several studies were found on the ClinicalTrials.gov database on September 19, 2015 (searched for *Novocure* or *TTFields* at: ClinicalTrials.gov). These conditions included malignant pleural mesothelioma, ovarian carcinoma, advanced pancreatic adenocarcinoma, recurrent atypical and anaplastic meningioma, and low-grade gliomas. Several other clinical trials are currently underway to further investigate the safety and efficacy of Novocure in newly diagnosed and recurrent GBM and NSCLC.

Safety of Novocure

Potential adverse effects associated with Novocure exposure are an important factor to consider when utilizing TTF. Kirson et al. (2007) posits that 2 types of toxicities may occur following exposure to alternating electric fields:

- Aggravation of excitable tissues, potentially leading to cardiac arrhythmias or seizures.
- Damage to rapidly dividing normal cells within the body (e.g., bone marrow or small intestine mucosa).

However, the authors state these toxicities are unlikely to occur, due to the specific parameters of the alternating electric fields used during treatment of GBM. The most commonly observed harm associated with Novocure is contact dermatitis beneath the electrodes, which may be a combination of several factors: chronic moisture, heat, and occlusion of the skin; bacterial skin infections; chemical irritation by the hydrogel and medical tape; possible inhibition of cellular replication in the skin; and mechanical erosions from shaving and stripping away the arrays.

Policy Context

Novocure (rebranded as Optune) is a medical device currently approved for use in adult patients with GBM that has recurred following chemotherapy. The device is worn on the head and applies alternating electric field therapy, also referred to as tumor treating fields (TTF). The mechanism of action for this therapy involves interfering with tumor cell replication through application of electric field therapy. Concerns for this treatment are considered low for safety and high for efficacy and cost-effectiveness.

Summary of Review Objectives and Methods

Review Objectives

Population: Adults diagnosed with recurrent glioblastoma multiforme or other forms of cancer (e.g., (non-small cell lung cancer, ovarian carcinoma, nonrecurrent glioblastoma multiforme).

Interventions: Novocure (tumor treating fields).

Comparisons: Chemotherapy; Novocure alone versus Novocure plus adjunctive treatments; placebo; no comparator.

Outcomes: Overall survival; tumor response and progression; health outcomes (e.g., quality of life); adverse events; cost and cost-effectiveness.

Key Questions

1. What is the clinical effectiveness of Novocure for treatment of the following conditions?
    a. What is the clinical effectiveness of Novocure for treatment of glioblastoma?
    b. What is the clinical effectiveness of Novocure for treatment of other cancers?
2. What are the harms associated with Novocure?
3. Does the effectiveness of Novocure or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, gener, prior treatments)?
4. What are the cost implications and cost-effectiveness of Novocure?

Methods

See the **Methods** section of the **Technical Report**, **Appendix I**, and **Appendix II** for additional detail.

Search Strategy and Selection Criteria

Core databases, PubMed, and the websites of relevant specialty societies were searched for systematic reviews, meta-analyses, economic evaluations, and practice guidelines published in the last 10 years. Systematic reviews were selected if they reviewed studies considered eligible for answering the Key Questions or if they provided useful background information. No systematic reviews of direct evidence pertinent to the Key Questions were discovered. The PubMed and OVID-Embase databases (searched on May 28, 2015) were searched for primary studies and economic evaluations designed to answer the Key Questions. Update searches were conducted on September 11, 2015, and November 20, 2015.

Inclusion/Exclusion Criteria

Studies were selected for inclusion if they assessed the safety or efficacy of Novocure treatment, were conducted in patients diagnosed with glioblastoma multiforme (GBM) or other cancer, and were published in English-language journals. Studies were excluded if they contained no quantitative data for assessing impact of Novocure treatment, were conference abstracts, were conducted in nonhumans, or were case studies or series of case reports.

Quality Assessment

The process used by Hayes for assessing the quality of primary studies and bodies of evidence is in alignment with the methods recommended by the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Working Group. Like the GRADE Working Group, Hayes uses the phrase *quality of evidence* to describe bodies of evidence in the same manner that other groups, such as the Agency for Healthcare Research and Quality (AHRQ), use the phrase *strength of evidence*. A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. See the **Methods** section of the **Technical Report** and **Appendix II** for details on quality assessment methods.

Summary of Search Results

Nine studies reported in 12 publications were selected for detailed analysis as evidence pertaining to the Key Questions. **Figure 1** summarizes the systematic identification and selection of these studies. One unique study was identified for Key Question #2 (safety). No unique studies were identified for Key Question #3 (differential effectiveness). No studies were identified for Key Question #4 (cost-effectiveness). See **Appendix III** for a list of 29 studies that were excluded from analysis after full-text review. Eleven relevant practice guidelines published in the last 10 years were identified.

Findings

Summary of Findings tables follow each Key Question. See **Executive Summary**, **Methods**, *Quality Assessment* and the corresponding section in the **Technical Report**, as well as **Appendix II**, for details regarding the assessment of bodies of evidence. See **Appendix IV** for full evidence tables.

Key Question #1

Key Question #1: What is the clinical effectiveness of Novocure for treatment of the following conditions?

#1a: What is the clinical effectiveness of Novocure for treatment of glioblastoma?

#1b: What is the clinical effectiveness of Novocure for treatment of other cancers?

Nine (9) studies reported in 12 articles assessing the effectiveness of Novocure treatment in patients with recurrent or newly diagnosed GBM or other cancers accessible to tumor treating fields (TTF) were selected.

GBM (7 studies)
See **Table 1** for a summary of findings.

Clinical Effectiveness of Novocure for GBM (Key Question #1a)
One fair-quality randomized controlled trial (RCT) found that overall survival and progression-free survival were similar in the Novocure and chemotherapy groups in patients with recurrent GBM. Two studies with historical control groups (1 poor quality, 1 very poor quality) found that for patients with recurrent GBM, Novocure treatment significantly increased overall survival by 3.6 to 7.6 months and increased progression-free survival at 6 months by 6% to 35% compared with chemotherapy. Only 1 study included a measure of quality of life (QOL). No differences were observed in global health and social function between groups. Cognitive and emotional function favored Novocure, but physical function was slightly worse in Novocure patients. The symptom scale was worse in the chemotherapy group, including increased pain and fatigue, which was likely related to chemotherapy administration. A very-poor-quality retrospective cohort study that compared combination Novocure plus bevacizumab treatment with Novocure plus bevacizumab plus a chemotherapy regimen of 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) found that although overall survival and progression-free survival were longer in the Novocure plus bevacizumab plus TCCC group, this difference was not statistically significant. However, this study had a very small sample size in the TCCC group and was likely underpowered. A fifth poor-quality uncontrolled study found that 15% of patients exposed to Novocure monotherapy exhibited a partial or complete radiological response to treatment. Despite the positive findings, the evidence for the effectiveness of Novocure for treating recurrent GBM was considered to

be of low quality because of the small quantity of data, small sample sizes, and lack of concurrent control or comparator groups in most studies.

One fair-quality RCT and 1 very-poor-quality cohort study found that Novocure was superior to chemotherapy for patients with newly diagnosed GBM. In the RCT, progression-free survival for patients in the Novocure plus TMZ group was 3.1 months longer than for patients in the TMZ alone group, and overall survival was 5.1 months longer. The cohort study found that Novocure treatment significantly increased overall survival by 62% and progression-free survival at 6 months by 15% compared with chemotherapy. The evidence for the effectiveness of Novocure for treating newly diagnosed GBM was considered to be of very low quality because of the small quantity of data for this indication.

Please see the Literature Review for in-depth study details, including length of treatment, treatment compliance, and patient characteristics.

Table 1. Summary of Findings, Key Question #1a: GBM

Key: GBM, glioblastoma; grp, group; HR, hazard ratio; NA, not assessed; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; PICO, population-intervention-comparator-outcome; pts, patients; RCT, randomized controlled trial; TCCC, 6-thioguanine, lomustine, capecitabine, and celecoxib; tx, treatment

Number, Size, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ #1a. Effectiveness of Novocure for Recurrent GBM			
5 studies (n=873) Kirson 2007 (trial w/ historical controls, very poor) Stupp 2012 (RCT, fair) Mrugala 2014 (multicenter registry study w/ historical controls, poor) Vymazal and Wong 2014 (subgroup analysis, poor) Wong 2015a (retrospective cohort, very poor)	**OVERALL: LOW** **Study quality:** Very poor-fair **Quantity and precision:** Few studies, some with small sample sizes **Consistency:** Studies consistently demonstrated that Novocure was comparable w/ chemotherapy alone w/ some inconsistency for OS and PFS on whether Novocure was more effective than chemotherapy alone **Applicability to PICO:** ✓ **Publication Bias:** Unknown	Novocure more effective than chemotherapy (2 studies) Novocure equal to chemotherapy (1 study) Novocure plus bevacizumab plus TCCC more effective than Novocure plus bevacizumab only (1 study) No comparison group (1 study)	***Median OS (Novocure grp, chemotherapy grp):*** Kirson 2007: 14.3 mos, 6.7 mos (*P*=NA) Mrugala 2014: 9.6 mos, 6.0 mos (*P*=0.0003) Vymazal and Wong 2014: 6.6 mos, NA ***Median PFS at 6 mos (Novocure grp, chemotherapy grp):*** Kirson 2007: 50%, 15% (*P*=NA) Stupp 2012: 21%, 15% (NS) ***Percentage OS at 6 mos, 1 yr, 2 yrs (Novocure grp, chemotherapy grp):*** Stupp 2012: 52.5%, 48%; 20.0%, 19%; 7.5%, 2.5% (*P*=NA) Mrugala 2014: NA; 44%, 24%; 30%, 7% ***Percentage of pts w/ partial or complete radiological response to tx (Novocure grp, chemotherapy grp):*** Stupp 2012: 14%, 9.6% (NS) Vymazal and Wong 2014: 15%, NA ***Median OS (Novocure plus bevacizumab plus TCCC grp, Novocure plus bevacizumab only grp):*** Wong 2015a: 10.3 mos, 4.1 mos (NS)

Number, Size, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
			Median PFS (Novocure plus bevacizumab plus TCCC grp, Novocure plus bevacizumab only grp): Wong 2015a: 8.1 mos, 2.8 mos (NS)
KQ #1a. Effectiveness of Novocure for Newly Diagnosed GBM			
2 studies (n=325) Kirson 2009 (cohort study, very poor) Stupp 2015 (RCT, fair)	**OVERALL: VERY LOW** **Study quality:** Very poor **Quantity and precision:** Very sparse data **Consistency:** Unknown **Applicability to PICO:** ✓ **Publication Bias:** Unknown	Novocure more effective than chemotherapy	***Stupp 2015 (Novocure plus TMZ grp, TMZ only grp):*** Median PFS: 7.1 mos, 4.0 mos (*P*=0.001), HR 0.62 (98.7% CI, 0.43-0.89) Median OS: 20.5 mos, 15.6 mos (*P*=0.004), HR 0.64 (98.7% CI, 0.43 -0.89) ***Kirson 2009 (Novocure grp, chemotherapy grp):*** Median OS: 39 mos, 14.7 mos (*P*=0.0018) Median PFS: 35.6 mos, 7.1 mos (*P*=0.0002), HR 3.32 (95% CI, 1.9-5.9)

Other Cancers (2 studies)
See **Table 2** for a summary of findings.

Clinical Effectiveness of Novocure for Other Cancers (Key Question #1b)
Overall, 2 case series found that 15% to 17% of patients with cancers other than GBM exhibited partial responses to Novocure treatment. One small case series (41 patients) found that 15% of NSCLC patients exhibited a partial response to Novocure treatment. The daily treatment duration was relatively short compared with other studies, which may have adversely affected treatment outcome. The evidence for the effectiveness of Novocure for treating NSCLC was considered to be of very low quality because of the small quantity of data and lack of control or comparator group.

A second case series investigating Novocure treatment in 6 patients with solid tumors of varying etiologies found that 17% of patients exhibited partial responses to Novocure treatment. Four of these patients had skin lesions (2 patients with invasive ductal breast cancer, 1 patient with adenocarcinoma of the breast, and 1 patient with a malignant melanoma on the thigh). One breast cancer patient (17%) showed a partial response, 3 patients (50%) with skin lesions due to breast cancer or melanoma had stable disease, 1 patient (17%) with GBM exhibited progressive disease, and 1 mesothelioma patient (17%) had a mixed response. The evidence for the effectiveness of Novocure for treating breast cancer was considered to be of very low quality because of the small quantity of data and lack of control or comparator group.

The evidence for the effectiveness of Novocure for treating melanoma was considered to be of very low quality because of the small quantity of data and lack of control or comparator group.

The evidence for the effectiveness of Novocure for treating metastases from a mesothelioma was considered to be of very low quality because of the small quantity of data and lack of control or comparator group.

The evidence for the effectiveness of Novocure for treating cancers other than GBM, NSCLC, breast cancer, melanoma, or mesothelioma was considered to be insufficient because of the lack of studies.

Table 2. Summary of Findings, Key Question #1b: Other Cancers

Key: GBM, glioblastoma; grp, group; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; pt(s), patient(s); tx, treatment

Number, Size & Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results (statistically significant results bolded)
KQ #1b. Effectiveness of Novocure for NSCLC			
1 study (n=41) Pless 2013 (case series, very poor)	**OVERALL: VERY LOW** **Study quality:** Very poor **Quantity and precision:** Very sparse data **Consistency:** Unknown **Applicability to PICO:** ✓ **Publication Bias:** Unknown	No comparison grp	15% of NSCLC pts exhibited a partial response to Novocure tx. ***Median PFS:*** 22.2 wks ***Median OS:*** 13.8 mos ***1-yr survival:*** 57%
KQ #1b. Effectiveness of Novocure for Solid Tumors from Breast Cancer, Melanoma, and Mesothelioma			
1 study (n=6) Salzberg 2008 (case series, very poor)	**OVERALL: VERY LOW** **Study quality:** Very poor **Quantity and precision:** Very sparse data **Consistency:** Unknown **Applicability to PICO:** ✓ **Publication Bias:** Unknown	No comparison grp	1 breast cancer pt (17%) showed a partial response to tx. 3 pts (50%) w/ skin lesions due to breast cancer or melanoma had stable disease. 1 pt (17%) w/ GBM exhibited progressive disease. This pt was not included in the GBM literature review, as it is a case report. 1 mesothelioma pt (17%) had a mixed response.
KQ #1b. Effectiveness of Novocure for Other Cancers: *Insufficient (no studies)*			

Key Question #2

Key Question #2: What are the harms associated with Novocure?

Eight studies reported on adverse events that occurred during Novocure treatment. No serious adverse events related to Novocure treatment were reported. The most common complication reported was mild to moderate dermatitis under the transducer arrays (16% to 90%). Several studies reported that the dermatitis would improve with application of topical corticosteroids, and in some cases repositioning of the electrodes. Three studies reported that the condition would resolve completely after treatment was stopped. Two studies reported 1% to 7% of patients experienced skin ulcers. Proper and sterile shaving and preparation of the scalp and careful removal of arrays can prevent occurrence or

worsening of dermatologic adverse events. Treatments for dermatologic adverse events include topical therapies, relocation of arrays, and avoidance of placing arrays on affected skin whenever possible. Oral antibiotics may be required in the case of more serious dermatologic adverse events.

Other commonly reported adverse events include headache (2% to 7%), fatigue (2.5% to 24%), pain or discomfort (5% to 12%), gastrointestinal disorders (3% to 12%), nervous system disorders (10% to 30%), infections (1% to 5%), and psychiatric disorders (3% to 5%). An RCT found that significantly more gastrointestinal (4% versus 17%), hematological (3% versus 17%), and infectious (4% versus 8%) adverse events were observed in the chemotherapy group than in the Novocure group. A second RCT noted that mild anxiety, confusion, insomnia, and headaches were reported more frequently in Novocure plus TMZ patients; these complications occurred mainly at the time of treatment initiation.

In summary, use of Novocure to treat GBM and other solid tumors *does not pose major safety concerns*, but evidence of the *harms associated with Novocure* is of low quality because of the quality of individual studies and general lack of statistical comparisons with a control group.

Key Question #3

Key Question #3: Does the effectiveness of Novocure or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, gender, prior treatments)?

Six of the 9 studies analyzed for Key Question #1 reported the number of previous episodes of GBM experienced prior to Novocure treatment. Median overall survival tended to be longer in studies that enrolled a higher number of patients in their first or second episode of GBM. Overall survival was longest in the studies that enrolled patients with newly diagnosed GBM (20.5 months to 39 months). Overall survival was shortest in the study that enrolled only 0% to 18% of patients in their first GBM recurrence in each Novocure group (4.1 months). Overall survival was 9.6 months in a study that enrolled 33% of patients in their first GBM recurrence and was 14.3 months in a study that enrolled 50% of the total patient population in their first GBM recurrence. Another study found that patients treated at their first GBM recurrence had significantly longer overall survival (20 months) compared with patients treated at second recurrence (8.5 months) or third or more recurrence (4.9 months) (P=0.0271). An RCT enrolled only 9% of patients in their first GBM recurrence. Overall survival was 52.5% at 6 months, 20% at 12 months, and 7.5% at 24 months. Median progression-free survival was also longer in studies that enrolled a greater percentage of patients in their first or second episode of GBM. Progression-free survival was 2.8 months in a study that enrolled 0% to 18% of patients in their first GBM recurrence. Progression-free survival was 7.1 months and 35.6 months in the 2 studies that enrolled patients with newly diagnosed GBM. Progression-free survival at 6 months was greater in a study that enrolled 50% of the total patient population in their first GBM recurrence (50%) than the study that enrolled only 9% of patients in their first GBM recurrence (21%).
A post hoc analysis comparing prognostic factors between patients that responded to treatment and those that did not found that mean cumulative dexamethasone dose was significantly lower for responders (35.9 milligrams [mg]) than nonresponders (485.6 mg) in the Novocure group (P<0.0001). This difference was not found in the chemotherapy group. A subsequent post hoc analysis was conducted to further investigate effect of dexamethasone on overall survival. Novocure patients who used a dexamethasone dose of > 4.1 mg per day exhibited a significantly shortened median overall survival of 4.8 months than patients who used a dexamethasone dose of ≤ 4.1 mg per day that had a median overall survival of 11.0 months (P<0.0001). Chemotherapy patients who used dexamethasone >

4.1 mg per day exhibited a significantly shortened median overall survival of 6.0 months than patients who used dexamethasone ≤ 4.1 mg per day that had a median overall survival of 8.9 months (*P*<0.0015).

A registry study found that patients that had received bevacizumab prior to Novocure treatment had significantly shorter overall survival (7.2 months) than those that had not received bevacizumab (13.4 months) (*P*=0.0070). In addition, patients with a Karnofsky Performance Scale (KPS) score of 90 to 100 had a significantly longer overall survival (14.8 months) than patients with a KPS of 70 to 90 (7.7 months) (*P*=0.0070) or KPS less than 70 (6.1 months) (*P*<0.0001). A subgroup analysis of select patients found that although responders to Novocure had favorable prognostic characteristics compared with nonresponders, including higher KPS score (90 versus 80), lower rate of prior bevacizumab treatment (6% versus 19%), higher rate of secondary GBM upgraded from low-grade gliomas (31% versus 8%), and smaller median tumor size (10.0 square centimeters [cm^2] versus 14.4 cm^2), these differences were not significant.

Compliance with Novocure treatment was an important factor related to treatment outcome. An RCT found that median overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (7.7 months) than in patients with a compliance < 75% (4.5 months) (*P*=0.042). A registry study also found that median overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (13.5 months) than in patients with a compliance rate < 75% (4.0 months) (*P*<0.0001). A third study found that response to treatment was correlated with compliance (*P*<0.001). Partial and complete responders had an average compliance of 92%, patients with stable disease had an average compliance of 85%, and patients with progressive disease had an average compliance of 79%.

In summary, evidence for Key Question #3 demonstrated very-low-quality positive evidence of varying clinical efficacy according to the following patient characteristics and clinical history:

- Median overall survival and progression-free survival were longer in studies that enrolled a higher number of patients with fewer prior episodes of GBM (6 studies).
- Patients that required lower daily doses of dexamethasone exhibited longer overall survival (1 study).
- Patients with a more favorable KPS score had significantly longer overall survival (2 studies).
- Patients not exposed to bevacizumab treatment prior to Novocure treatment were more likely to respond to treatment (2 studies).
- Patients with secondary GBM upgraded from low-grade gliomas were more likely to respond to treatment (1 study).
- Patients with a smaller tumor size were more likely to respond to treatment (1 study).
- Patients that were compliant with using their Novocure device had longer overall survival (3 studies).

Key Question #4

Key Question #4: What are the cost implications and cost-effectiveness of Novocure?

Cost of Novocure Device

The literature search did not provide cost information for Novocure. A search of the Internet yielded an estimate of the cost of the device to be $10,907.81 to $16,361.71 per month (Randall, 2010). Another source estimated the cost of the Novocure device to be $21,429.96 per month (Kotz, 2014).

Cost-Effectiveness

No published studies evaluating the cost of Novocure per unit of clinical benefit were available in the reviewed literature. Thus, evidence of the cost-effectiveness of Novocure for treatment of GBM or other cancers is insufficient due to the lack of studies.

Practice Guidelines

The search of the core sources and relevant specialty groups identified 11 guidelines with relevant recommendations regarding treatment of GBM and NSCLC, and published within the past 10 years. The general recommendations provided by the guidelines are summarized in **Table 3**. Additional details, by guideline, are presented in **Appendix V**. See also **Practice Guidelines** in the **Technical Report** for additional background information on guidelines.

Treatment of GBM

Six guidelines addressed treatment of GBM, 4 of which mentioned Novocure. These included guidelines from the American Association of Neuroscience Nurses (AANN), 2 guidelines from the American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS), the European Association of Neuro-Oncology (EANO), the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN).

Three guidelines stated that for newly diagnosed GBM, surgery is the first therapeutic intervention (EANO, ESMO, NCCN). Three guidelines state that Carmustine polymer wafers (Gliadel Wafers) may prolong survival when implanted into the resection cavity at the time of surgery (AANN, AANS/CNS, NCCN). Resection or biopsy should be followed by combined treatment with TMZ and radiotherapy (RT). The AANN recommends that nurses closely monitor patients for postoperative complications and rehabilitation needs following surgery. Two guidelines stated that bevacizumab can be administered to treat GBM recurrence (AANN, AANS/CNS). Patients with progressive GBM should be enrolled in an appropriate clinical trial (AANS/CNS, EANO). Four guidelines mentioned that Novocure (TTF) has been investigated in the treatment of GBM. One guideline stated that Novocure should only be administered in the context of clinical trials (EANO), 1 guideline stated that nurses should be aware that Novocure may be considered a comparable treatment option to chemotherapy in recurrent GBM patients (AANN), 1 guideline stated that GBM failed to prolong survival compared with chemotherapy (ESMO), and 1 guideline mentioned Novocure as an option in the treatment algorithm for recurrent GBM (NCCN).

Treatment of NSCLC

Five guidelines addressed treatment of stage III or stage IV NSCLC. These included guidelines from the ACCP, ASTRO, 2 ESMO guidelines, and the NCCN. None of the guidelines mentioned the use of Novocure

for treating NSCLC. Four guidelines list several possible strategies for treating patients with stage III NSCLC. These options include induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy. Optimal surgical management involves complete resection. Patients that have a planned lobectomy (as opposed to pneumonectomy) are the best candidates for preoperative chemoradiotherapy. The 2 most common concurrent chemotherapy regimens are cisplatin/etoposide and carboplatin/paclitaxel. If patients are evaluated as unresectable, 2 to 4 cycles of concurrent chemoradiotherapy is the standard of care. Platinum-based chemotherapy yields the best outcomes (ACCP, ASTRO, ESMO, NCCN). One guideline states that bevacizumab plus chemotherapy or chemotherapy alone is indicated in patients with poor performance status and with advanced or recurrent NSCLC (NCCN).

One guideline addressed treatment of stage IV NSCLC (ESMO). The standard first-line chemotherapy is platinum-based chemotherapy. Chemotherapy should be initiated while the patient has a good performance status. Systemic treatment should be offered to all stage IV patients with poor performance status. Four to 6 treatment cycles of chemotherapy are recommended.

Table 3. Summary of Practice Guideline Recommendations

Key: AANN, Association of Neuroscience Nurses; AANS, American Association of Neurological Surgeons; ACCP, American College of Chest Physicians; ASTRO, American Society for Radiation Oncology; CNS, Congress of Neurological Surgeons; EANO, European Association of Neuro-Oncology; ESMO, European Society for Medical Oncology; GBM, glioblastoma; GL, guideline; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; pt(s), patient(s); RT, radiotherapy; TMZ, temozolomide; tx, treatment

Quantity of Individual GLs	Individual GL Quality	Recommendations
Tx of GBM		
6 (AANN, AANS/CNS, EANO, ESMO, NCCN)	3 Fair 3 Poor	Newly diagnosed GBM: Resection or biopsy, followed by RT plus concurrent TMZ, followed by adjuvant TMZ. Carmustine polymer wafers (Gliadel Wafers) may prolong survival when implanted into the resection cavity at the time of surgery. Recurrent GBM: Options include re-resection, reirradiation, rechallenge chemotherapy, or bevacizumab. Progressive GBM: Pts w/ progressive GBM should be enrolled in an appropriate clinical trial. Novocure: Novocure should only be administered in the context of clinical trials (EANO); nurses should be aware that Novocure may be considered a comparable tx option to chemotherapy in recurrent GBM pts (AANN); GBM failed to prolong survival compared w/ chemotherapy (ESMO); Novocure is an option in the tx algorithm for recurrent GBM (NCCN).
Tx of NSCLC		
5 (ACCP, ASTRO, ESMO, NCCN)	2 Good 1 Fair 2 poor	Surgery: Optimal surgical management involves complete resection. RT and Chemotherapy: Options include induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent

Quantity of Individual GLs	Individual GL Quality	Recommendations
		definitive chemoradiotherapy. Pts that have a planned lobectomy (as opposed to pneumonectomy) are the best candidates for preoperative chemoradiotherapy. The 2 most common concurrent chemotherapy regimens are cisplatin/etoposide and carboplatin/paclitaxel. If pts are evaluated as unresectable, 2 to 4 cycles of concurrent chemoradiotherapy is the standard of care. Platinum-based chemotherapy yields the best outcomes. Bevacizumab: Bevacizumab plus chemotherapy or chemotherapy alone is indicated in pts with poor performance status and with advanced or recurrent NSCLC (NCCN). Stage IV NSCLC: The standard first-line chemotherapy is platinum-based chemotherapy. Chemotherapy should be initiated while the pt has a good performance status. Systemic tx should be offered to all stage IV pts w/ poor performance status. 4 to 6 tx cycles of chemotherapy are recommended (ESMO). None of the guidelines mentioned the use of Novocure for treating NSCLC.

Selected Payer Policies

No Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) was identified for Novocure/Optune. At the direction of Washington State HCA, the coverage policies for the following organizations were reviewed: Aetna, CMS, Oregon Health Evidence Review Commission (HERC), GroupHealth, and Regence Blue Cross/Blue Shield. The only payers found to have a policy were Aetna, GroupHealth, and Regence Group.

Aetna considers Novocure to be medically necessary as monotherapy for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. GroupHealth states that there is insufficient evidence to show that Novocure is as safe as standard services/therapies and/or provides better long-term outcomes. Regence group considers Novocure to be investigational.

See **Selected Payer Policies** in the **Technical Report** for additional details and links to policy documents.

Overall Summary and Discussion

Evidence-Based Summary Statement

The NovoTTF-100A (Novocure/Optune) device was approved by the Food and Drug Administration (FDA) in April 2011 for the treatment of patients with recurrent GBM, and for newly diagnosed GBM in October 2015. The original approval was based on a single RCT that suggested positive outcomes in patients with recurrent GBM. In this trial, patients with recurrent GBM were randomized to Novocure monotherapy or physician's choice chemotherapy. Treatment outcomes were similar in both groups. Overall survival was approximately 50% at 6 months, 20% at 1 year, and 5% at 2 years in both the Novocure and chemotherapy groups. Progression-free survival at 6 months was 21% in the Novocure group and 15% in the chemotherapy group. The side effect profile appeared to favor Novocure. There were significantly more gastrointestinal, hematological, and infectious adverse events seen in the chemotherapy group than in the Novocure group. One important limitation of this study was that there was a high loss to follow-up in the Novocure group, as 22% of patients did not complete 1 full 4-week treatment cycle. The expanded indication of newly diagnosed GBM was based on results from an interim analysis of an RCT of 315 patients that compared a group that received Novocure plus TMZ with a group that received TMZ alone (Stupp et al., 2015). Patients who received Novocure plus TMZ lived about 7 months with no disease progression, compared with 4 months in the TMZ alone group. The Novocure plus TMZ group survived for an average of 20 months, compared with 15 months for those who were treated with TMZ alone. This study has a high loss to follow-up in the TMZ alone group (20%).

The largest body of evidence available for any indication was recurrent GBM. Overall, low-quality evidence suggests that Novocure is at least comparable with chemotherapy for the treatment of recurrent GBM. In addition to the RCT described above, 4 additional studies provided positive evidence that Novocure has some benefit in patients with recurrent GBM. Two studies with historical control groups found that for patients with recurrent GBM, Novocure treatment significantly increased overall survival by 38% to 53% and progression-free survival at 6 months by 15% compared with chemotherapy. A retrospective cohort study that compared combination Novocure plus bevacizumab treatment with Novocure plus bevacizumab plus TCCC found that although overall survival and progression-free survival were longer in the Novocure plus bevacizumab plus a chemotherapy regimen of 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) group, this difference was not statistically significant. A fifth uncontrolled study found that 15% of patients exposed to Novocure monotherapy exhibited a partial or complete radiological response to treatment.

In addition to the previously discussed RCT, a single cohort study was available investigating efficacy of Novocure in patients with newly diagnosed GBM. Novocure treatment significantly increased overall survival by 62% and progression-free survival at 6 months by 15% compared with chemotherapy.

One small case series investigated the efficacy of Novocure in patients with NSCLC, and found that 15% of NSCLC patients exhibited a partial response to Novocure treatment. The daily treatment duration was relatively short compared to other studies, which may have adversely affected treatment outcome. A second case series investigated Novocure treatment in 6 patients with solid tumors of varying etiologies. One breast cancer patient showed a partial response, 3 patients with skin lesions due to breast cancer or melanoma had stable disease, 1 patient with GBM exhibited progressive disease, and 1 mesothelioma patient had a mixed response.

Several studies provided data suggesting that compliance with Novocure treatment was an important factor related to treatment outcome. An RCT found that median overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (≥ 18 hours per day; 7.7 months) than in patients with a compliance < 75% (4.5 months). Similarly, a registry study found that overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (13.5 months) than in patients with a compliance < 75% (4.0 months). Another study found that whether patients responded to treatment was correlated with compliance. Partial and complete responders had an average compliance of 92%, patients with stable disease had an average compliance of 85%, and patients with progressive disease had an average compliance of 79%. These data suggest the crucial importance of using the device according to manufacturer instructions to ensure almost continuous exposure to the tumor treating fields for optimal efficacy.

The literature provides very little direct evidence of improvements in QOL or functional states attributable to Novocure. Only 1 study, the RCT, included a measure of QOL in patients who had remained on treatment for at least 3 months. No differences were observed in global health and social function between groups. Cognitive and emotional function favored Novocure, but physical function was slightly worse in Novocure patients. The symptom scale was worse in the chemotherapy group, including increased pain and fatigue, which was likely related to chemotherapy administration. More data on QOL and functional states are needed to determine the short- and long-term impact of using the portable device for 18 to 22 hours per day.

Gaps in the Evidence

The following evidence is needed to better answer the Key Questions of this report:

- RCTs and cohort studies of sufficient size and design to further investigate the safety and efficacy of Novocure in patients with recurrent and newly diagnosed GBM, NSCLC, and other cancers compared with chemotherapy or other treatment.
- Studies designed to systematically investigate differential effectiveness and safety according to patient characteristics and previous treatment history.
- Studies investigating the impact of Novocure on QOL and functional status.
- Economic evaluations on the cost-effectiveness of Novocure.

Technical Report

Clinical Background

Epidemiology, Diagnosis, and Treatment of Glioblastoma

Glioblastoma (GBM) is the most prevalent and malignant intracranial tumor, representing as much as 30% of primary brain tumors (Rulseh et al., 2012). The overall prognosis is poor, even with the best standard of care. Even with optimal treatment, the median survival time is approximately 10 to 14 months (Rulseh et al., 2012). Only a third of patients survive for 1 year following diagnosis of GBM, and less than 5% live beyond 5 years (Nabors et al., 2015). The incidence of GBM has been shown to increase with age, and is more common in men than women (Schwartzbaum et al., 2006). Exposure to therapeutic or high-dose radiation and rare familial syndromes has been linked to GBM (Schwartzbaum et al., 2006). Patients with recurrent GBM have a median survival time of just 5 to 7 months. Longer-term survival has been linked to younger age and more favorable scores on the Karnofsky Performance Scale (KPS), which measures functional impairment (Rulseh et al., 2012).

Current Therapies for GBM

The current standard of care for newly diagnosed GBM patients is surgery, followed by combination chemotherapy using temozolomide (TMZ) and radiation therapy (Stupp et al., 2007; Nabors et al., 2015). Virtually all patients with newly diagnosed GBM relapse despite best available treatment, with a median time to recurrence of approximately 7 months (Mrugala et al., 2014).

At the time of disease recurrence, treatment options for GBM patients are limited. Approximately 20% of patients may undergo repeat surgery. It has been suggested that tumor involvement in certain critical brain regions, poor performance score, and large tumor volume are associated with poor repeat surgery outcomes (Nabors et al., 2015). Carmustine polymer wafers may be placed intraoperatively in the surgical cavity during repeat surgery. However, the carmustine wafers may potentially interact with other agents and cause increased toxicity. Rarely, patients may undergo reirradiation. For the majority of recurrent GBM patients, chemotherapy is indicated. The type of chemotherapy drug used varies widely. In the United States, combination treatment with chemotherapy and the angiogenesis inhibitor bevacizumab has been approved for recurrent GBM and certain other cancers (Stupp et al., 2012). However, approximately 40% to 60% of recurrent GBM patients are either unresponsive to bevacizumab or experience serious adverse events following treatment (Kanner et al., 2014). These serious side effects include hemorrhage, thromboembolism, infection, hypertensive crisis, renal failure, diarrhea, nausea, and vomiting. Furthermore, although some patients may be initially responsive to bevacizumab, the tumor eventually progresses (Fonkem and Wong, 2012). Novel therapies with a different mechanism of action against GBM and reduced toxicity are needed. Novocure (rebranded as Optune; Novocure Ltd.) is a portable medical device that generates low-intensity alternating electric fields, called tumor treating fields (TTF), for the treatment of recurrent GBM. Clinical trials have suggested that Novocure may be as effective as chemotherapy with decreased toxic side effects.

Novocure (TTF)

The NovoTTF-100A System, also referred to as Novocure or Optune (Novocure Inc.; Haifa, Israel), approved by the Food and Drug Administration (FDA) in April 2011 for treatment of recurrent GBM, and

approved for an expanded indication to newly diagnosed GBM in October 2015, is a novel device which emits alternating electric fields that disrupt the rapid cell division exhibited by cancer cells. Alternating electric fields, or TTF, have been shown to be effective when applied externally to patients with recurrent GBM (Kirson et al., 2007). TTF therapy uses low-intensity, intermediate-frequency electric fields that have an antimitotic effect, which acts during late metaphase and anaphase (Rulseh et al., 2012). The mechanism of action has been attributed to interference with the formation of the mitotic spindle microtubules and/or physical destruction of cells during cleavage (Kirson et al., 2007). Unlike chemotherapy, Novocure therapy does not have a half-life. Therefore, it requires continuous application to be effective. Patients are instructed to use the device at least 18 hours per day. The minimal treatment course duration is 4 weeks (Novocure, 2013; Mrugala et al., 2014).

The Novocure system comprises an electrical field generator device, 4 insulated transducer arrays, a connector cable, and a power source (battery or electrical outlet). Treatment parameters are preset (200 kilohertz [kHz] and a minimal field intensity of 0.7 volts per centimeter [V/cm] in the brain or 1 to 2 V/cm in the chest cavity and upper abdomen) and no electrical output adjustments are available to the patient. TTF are delivered through transducer arrays that are applied to the shaved scalp (or on the thorax in the case of non-small cell lung cancer). The transducer arrays are composed of insulated ceramic discs that are separated from the skin by a layer of conductive hydrogel. The locations of the arrays are calculated for each individual patient to optimize field intensity based on head size and tumor location. Patients or caregivers replace transducer arrays 1 to 2 times per week and re-shave the scalp to maintain optimal contact with the arrays (Novocure, 2013; Pless et al., 2013; Lacouture et al., 2014).

Novocure Treatment for Non-Small Cell Lung Cancer

Although the majority of the current published literature on Novocure has been applied to GBM patients, Novocure has recently been investigated for the treatment of advanced stage III or stage IV non-small cell lung cancer (NSCLC). There are several possible strategies for treating patients with stage III NSCLC. These options include induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy. Optimal surgical management involves complete resection. Patients that have a planned lobectomy (as opposed to pneumonectomy) are the best candidates for preoperative chemoradiotherapy. If patients are evaluated as unresectable, 2 to 4 cycles of concurrent chemoradiotherapy is the standard of care. Platinum-based chemotherapy yields the best outcomes (Kozower et al., 2013; Eberhardt et al., 2015; Ettinger et al., 2015; Rodrigues et al., 2015). Bevacizumab plus chemotherapy may be indicated in patients with poor performance status and with advanced or recurrent NSCLC (Ettinger et al., 2015).

For the treatment of stage IV NSCLC, the standard first-line chemotherapy is platinum-based chemotherapy. Chemotherapy should be initiated while the patient has a good performance status. Systemic treatment should be offered to all stage IV patients with poor performance status. Four to 6 treatment cycles of chemotherapy are recommended (Reck et al., 2014).

Novocure Treatment for Other Cancers

Ongoing clinical trials are currently investigating the use of Novocure in patients with several other conditions. Several studies were found on the ClinicalTrials.gov database on September 19, 2015 (searched for *Novocure* or *TTFields* at: ClinicalTrials.gov).

- Trial Safety and Efficacy of TTFields Concomitant With Pemetrexed and Cisplatin or Carboplatin in Malignant Pleural Mesothelioma (STELLAR) (NCT02397928):

  - Primary sponsor: Novocure Ltd.
  - Trial design and phase: Nonrandomized, single-assignment, open-label; currently recruiting
  - Number of expected enrollees: 80
  - Primary outcome measure: Overall survival
  - Date of completion: February 2018

- Safety, Feasibility and Effect of TTFields Concomitant With Weekly Paclitaxel in Recurrent Ovarian Carcinoma (INNOVATE) (NCT02244502):
  - Primary sponsor: Novocure Ltd.
  - Trial design and phase: Nonrandomized, single-assignment, open-label; currently recruiting
  - Number of expected enrollees: 30
  - Primary outcome measure: Incidence of adverse events, number of patients discontinuing due to skin toxicity
  - Date of completion: July 2016

- Safety Feasibility and Effect of NovoTTF-100L Together With Gemcitabine for Front-line Therapy of Advanced Pancreatic Adenocarcinoma (PANOVA) (NCT01971281):
  - Primary sponsor: Novocure Ltd.
  - Trial design and phase: Nonrandomized, single-assignment, open-label; currently recruiting
  - Number of expected enrollees: 20
  - Primary outcome measure: Adverse events, feasibility based on compliance
  - Date of completion: June 2015

- Pilot Study of Optune (NovoTTF-100A) for Recurrent Atypical and Anaplastic Meningioma (NCT01892397):
  - Primary sponsor: Memorial Sloan Kettering Cancer Center
  - Trial design and phase: Nonrandomized, single-assignment, open-label; currently recruiting
  - Number of expected enrollees: 21
  - Primary outcome measure: Progression-free survival
  - Date of completion: June 2016

- A Phase II Study of NovoTTF-100A Alone and With Temozolomide in Patients With Low-Grade Gliomas (NCT02507232):
  - Primary sponsor: University of California, San Diego
  - Trial design and phase: Randomized, parallel-assignment; not yet recruiting
  - Number of expected enrollees: 42
  - Primary outcome measure: Objective response rate
  - Date of completion: September 2019

In addition, several ongoing trials are further investigating indications for which there is published evidence:

- Effect of NovoTTF-100A Together With Temozolomide in Newly Diagnosed Glioblastoma Multiforme (GBM) (NCT00916409):

  - Primary sponsor: Novocure Ltd.
  - Trial design and phase: Randomized, parallel-assignment; not currently recruiting
  - Number of expected enrollees: 700
  - Primary outcome measure: Progression-free survival
  - Date of completion: July 2016

- Effect of NovoTTF-100A in Non-small Cell Lung Cancer (NSCLC) Patients With 1-5 Brain Metastases Following Optimal Standard Local Treatment (NCT01755624):
  - Primary sponsor: Novocure Ltd.
  - Trial design and phase: Randomized, parallel-assignment; currently recruiting
  - Number of expected enrollees: 60
  - Primary outcome measure: Time to local and distant progression in the brain
  - Date of completion: July 2017

- Optune (NOVOTTF-100A)+ Bevacizumab+ Hypofractionated Stereotactic Irradiation Bevacizumab-Naive Recurrent Glioblastoma (GCC 1344) (NCT01925573):
  - Primary sponsor: University of Maryland
  - Trial design and phase: Nonrandomized, single-assignment, open-label; currently recruiting
  - Number of expected enrollees: 27
  - Primary outcome measure: Adverse events, ability to complete protocol without acute toxicity
  - Date of completion: December 2020

- Post-approval Study of NovoTTF-100A in Recurrent GBM Patients (NCT01756729):
  - Primary sponsor: Novocure Ltd.
  - Trial design and phase: Nonrandomized, concurrent control, open-label; currently recruiting
  - Number of expected enrollees: 486
  - Primary outcome measure: Overall survival
  - Date of completion: January 2018

- Tryptophan Metabolism in Human Brain Tumors (NCT02367482):
  - Primary sponsor: Wayne State University
  - Trial design and phase: Prospective, observational; currently recruiting
  - Number of expected enrollees: 10
  - Primary outcome measure: Interval changes of tumoral metabolism
  - Date of completion: December 2015

- NovoTTF Therapy in Treating Patients With Recurrent Glioblastoma Multiforme (NCT01954576):
  - Primary sponsor: Washington University School of Medicine
  - Trial design and phase: Nonrandomized, single-assignment, open-label; currently recruiting
  - Number of expected enrollees: 30
  - Primary outcome measure: Objective response rate
  - Date of completion: May 2018

- NovoTTF-100A With Bevacizumab and Carmustine in Treating Patients With Glioblastoma Multiforme in First Relapse (NCT02348255):
  - Primary sponsor: University of California, Davis
  - Trial design and phase: Nonrandomized, single-assignment, open-label; not yet recruiting
  - Number of expected enrollees: 20
  - Primary outcome measure: Adverse events, progression-free survival, overall survival, quality of life, change in tumor volume, change in magnetic resonance imaging (MRI)
  - Date of completion: December 2019

- A Phase II Study of NovoTTF-100A in Combination With Bevacizumab (BEV) and Temozolomide (TMZ) in Patients With Newly Diagnosed Unresectable Glioblastoma (NCT02343549):
  - Primary sponsor: Carolinas Healthcare System
  - Trial design and phase: Nonrandomized, single-assignment, open-label; currently recruiting
  - Number of expected enrollees: 46
  - Primary outcome measure: Overall survival
  - Date of completion: June 2017

- NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma (NCT01894061):
  - Primary sponsor: Case Comprehensive Cancer Center
  - Trial design and phase: Nonrandomized, single-assignment, open-label; currently recruiting
  - Number of expected enrollees: 40
  - Primary outcome measure: Progression-free survival
  - Date of completion: October 2016

Safety of Novocure

Potential adverse effects associated with Novocure exposure are an important factor to consider when utilizing TTF. Kirson et al. (2007) posits that 2 types of toxicities may occur following exposure to alternating electric fields:

- Aggravation of excitable tissues, potentially leading to cardiac arrhythmias or seizures.
- Damage to rapidly dividing normal cells within the body (e.g., bone marrow or small intestine mucosa).

However, the authors state these toxicities are unlikely due to the specific parameters of the alternating electric fields used during treatment of GBM. The most commonly observed harm associated with Novocure is contact dermatitis beneath the electrodes, which may be a combination of several factors: chronic moisture, heat, and occlusion of the skin; bacterial skin infections; chemical irritation by the hydrogel and medical tape; possible inhibition of cellular replication in the skin; and mechanical erosions from shaving and stripping away the arrays (Kirson et al., 2007; Lacouture et al., 2014).

Washington Agency Utilization Data

No data are available for this technology.

Review Objectives and Analytic Framework

Scope

The scope of this report is defined as:

Population: Adults diagnosed with recurrent GBM or other forms of cancer (e.g., (NSCLC, ovarian carcinoma, nonrecurrent GBM).

Interventions: Novocure (tumor treating fields).

Comparisons: Chemotherapy; Novocure alone versus Novocure plus adjunctive treatments; placebo; no comparator.

Outcomes: Overall survival; tumor response and progression; health outcomes (e.g., quality of life); adverse events; cost and cost-effectiveness.

Key Questions

The following key questions will be addressed:

1. What is the clinical effectiveness of Novocure for treatment of the following conditions?
   1a. What is the clinical effectiveness of Novocure for treatment of glioblastoma?
   1b. What is the clinical effectiveness of Novocure for treatment of other cancers?
2. What are the harms associated with Novocure?
3. Does the effectiveness of Novocure or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, gender, prior treatments)?
4. What are the cost implications and cost-effectiveness of Novocure?

Methods

Search Strategy and Selection Criteria

See **Appendix I** for additional search details.

Systematic Reviews and Guidelines

These sources were searched on May 27, 2015, for systematic reviews, meta-analyses, economic evaluations, and practice guidelines:

- Core online databases such as the Agency for Healthcare Research and Quality (AHRQ), Centre for Reviews and Dissemination (York University), and National Guidelines Clearinghouse (NGC).
- Websites of relevant professional societies.
- PubMed, using filters for Practice Guidelines, Guidelines, Meta-analyses, and Systematic Reviews.

Systematic reviews were selected if they reviewed studies considered eligible for answering the Key Questions or if they provided useful background information. However, no systematic reviews of direct evidence pertinent to the Key Questions were discovered.

Primary Studies

The PubMed and OVID-Embase databases were searched on May 28, 2015, for primary studies and economic evaluations designed to answer the Key Questions. Update searches were conducted on September 11, 2015, and November 20, 2015. Specific search strings are documented in **Appendix I**. Additional studies were identified through manual searching of bibliographies of reviews and primary articles.

Inclusion/Exclusion Criteria

Studies were selected for inclusion if they:

- Assessed the safety or efficacy of Novocure treatment
- Were conducted in patients diagnosed with GBM or other cancer
- Were published in English-language journals

Studies were excluded if they:

- Contained no quantitative data for assessing impact of Novocure treatment
- Were conference abstracts
- Were conducted in nonhumans
- Were case studies or series of case reports

Quality Assessment

Clinical Studies

Appendix II outlines the process used by Hayes for assessing the quality of individual primary studies and the quality of bodies of evidence. This process is in alignment with the methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Quality checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *good*, *fair*, *poor*, or *very poor*. For individual studies included in systematic reviews, this report relies on the quality assessment by review authors. To aid in interpreting the assessment by review authors, a systematic review quality checklist, the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007), was used.

Like the GRADE Working Group, Hayes uses the phrase *quality of evidence* to describe bodies of evidence in the same manner that other groups, such as AHRQ, use the phrase *strength of evidence*. The

Hayes Evidence-Grading Guides ensure that assessment of the quality of bodies of evidence takes into account the following considerations:

- Methodological quality of individual studies, with an emphasis on the risk of bias within studies.
- Applicability to the population(s), intervention(s), comparator(s), and outcome(s) of interest, i.e., applicability to the PICO statement.
- Consistency of the results across studies.
- Quantity of data (number of studies and sample sizes).
- Publication bias, if relevant information or analysis is available.

NOTE: Two terms related to applicability are *directness* and *generalizability*. *Directness* refers to how applicable the evidence is to the outcomes of interest (i.e., health outcomes versus surrogate or intermediate outcomes) or to the comparator of interest (indirect comparison of 2 treatments versus head-to-head trials). *Generalizability* usually refers to whether study results are applicable to real-world practice. If the setting is not specified in a PICO (population-interventions-comparator-outcomes) statement, the issue of generalizability to real-world settings is not typically treated as an evidence quality issue. Another term used by some organizations is *imprecision*, which refers to findings based on such a small quantity of data that the CI surrounding a pooled estimate includes both clinically important benefits and clinically important harms, or such a small quantity of data that any results other than large statistically significant effects should be considered unreliable.

Bodies of evidence for particular outcomes are labeled as being of *high*, *moderate*, *or low quality*, or they are deemed to be *insufficient* to permit conclusions. These labels can be interpreted in the following manner:

High: Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.

Moderate: Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies.

Low: We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and possibly the direction of the results.

Insufficient: Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

Economic Evaluations

A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. Sources are listed in **Appendix II**.

Guidelines

The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Enterprise, 2013), along with a consideration of the items related to commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. Use of the AGREE tool was limited to these areas because they relate most directly to the link between guideline recommendations and evidence.

Search Results

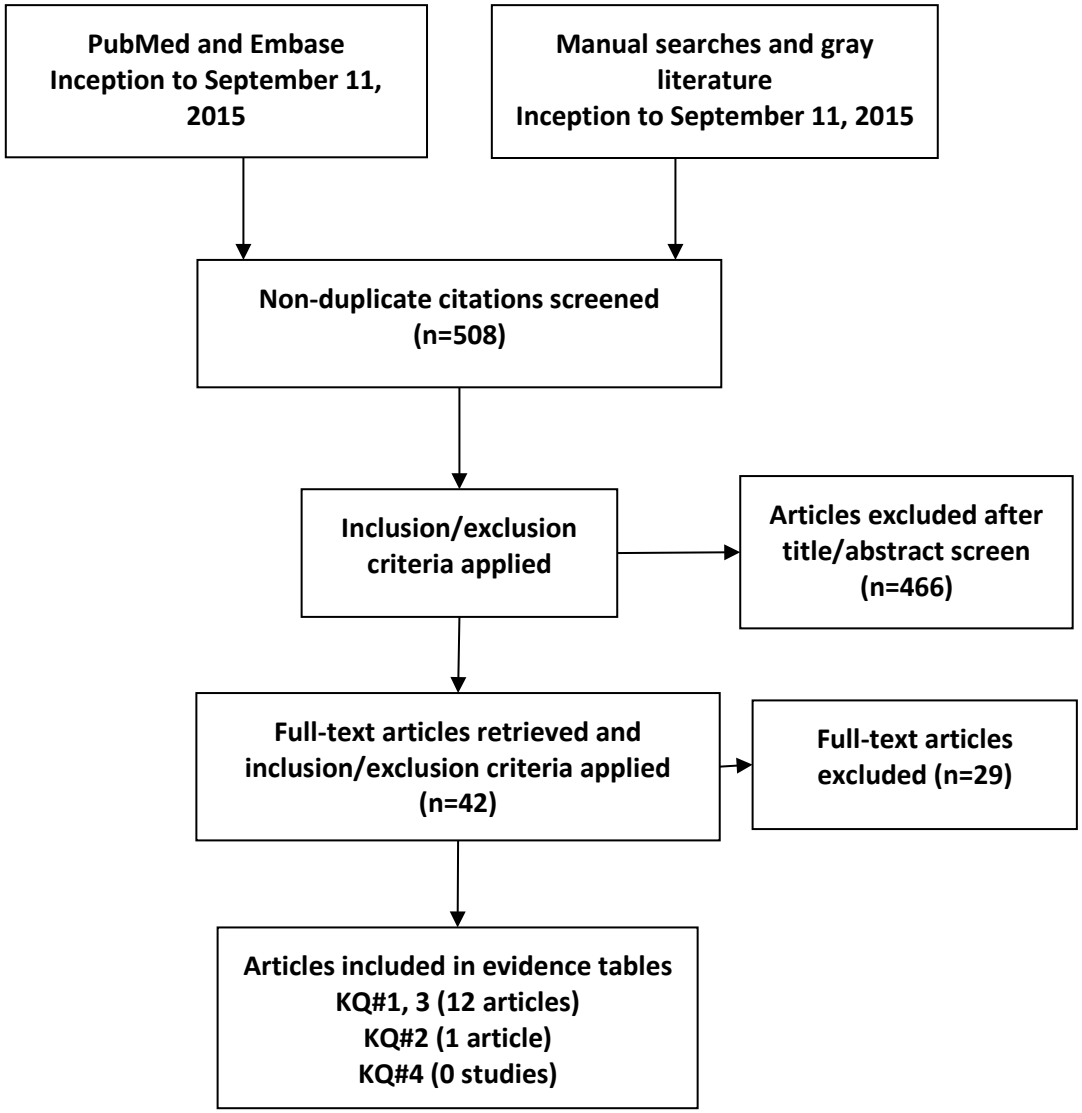
Included Studies

Ten studies reported in 13 publications were selected for detailed analysis as evidence pertaining to the Key Questions. **Figure 1** summarizes the systematic identification and selection of these studies. One unique study was identified for Key Question #2 (safety). No unique studies were identified for Key Question #3 (differential effectiveness). No studies were identified for Key Question #4 (cost-effectiveness).

Excluded Studies

See **Appendix III** for a listing of the 29 studies that were excluded from analysis after full-text review.

Figure 1. Summary of Search Results



Literature Review

Key Question #1

Key Question #1: What is the clinical effectiveness of Novocure for treatment of the following conditions?

#1a: What is the clinical effectiveness of Novocure for treatment of glioblastoma?

#1b: What is the clinical effectiveness of Novocure for treatment of other cancers?

The searches identified a total of 9 studies (reported in 12 articles) that evaluated the effectiveness of Novocure treatment in patients with glioblastoma multiforme (GBM) or other cancers accessible to tumor treating fields (TTF) (Kirson et al., 2007; Salzberg et al., 2008; Kirson et al., 2009; Stupp et al., 2012; Pless et al., 2013; Kanner et al., 2014; Mrugala et al., 2014; Vymazal and Wong, 2014; Wong et al., 2014; Stupp et al., 2015; Wong et al., 2015a; Wong et al., 2015b). The body of evidence comprised 2 fair-quality randomized controlled trials (RCTs), 1 very-poor-quality trial with historical controls, 2 very-poor-quality cohort studies, 1 poor-quality multicenter registry study with historical controls, 1 poor-quality subgroup analysis of selected patients from 2 clinical trials, and 2 very-poor-quality case series. Overall, results for Novocure for treating recurrent GBM were positive and suggest that Novocure increases overall survival and progression-free survival (5 studies). In addition, 2 studies suggest that Novocure increases overall survival and progression-free survival in patients with newly diagnosed GBM. See **Appendix IV** for details regarding selected studies.

GBM (7 studies)

Clinical Effectiveness of Novocure for GBM (Key Question #1a)

Five studies (reported in 8 publications) reported consistently positive results for the effectiveness of Novocure treatment in patients with recurrent GBM (Kirson et al., 2007; Stupp et al., 2012; Kanner et al., 2014; Mrugala et al., 2014; Vymazal and Wong, 2014; Wong et al., 2014; Wong et al., 2015a; Wong et al., 2015b). In addition, 1 RCT and 1 cohort study reported positive results for Novocure in patients with newly diagnosed GBM (Kirson et al., 2009; Stupp et al., 2015).

KQ#1a, GBM:
Recurrent GBM: Kirson 2007, Stupp 2012, Kanner 2014, Mrugala 2014, Vymazal and Wong 2014, Wong 2014, Wong 2015a, Wong 2015b
Newly diagnosed GBM: Kirson 2009; Stupp 2015

Four studies compared Novocure treatment with chemotherapy (Kirson et al., 2007; Kirson et al., 2009; Stupp et al., 2012; Kanner et al., 2014; Mrugala et al., 2014; Wong et al., 2014; Wong et al., 2015b). One study compared combination Novocure plus bevacizumab treatment with Novocure plus bevacizumab plus a chemotherapy regimen of 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) (Wong et al., 2015a). One study was a subgroup analysis of selected patients from Stupp et al. (2012) and Kirson et al. (2007) and did not include a control or comparison group (Vymazal and Wong, 2014). In general, patients were instructed to use the Novocure device for at least 18 to 22 hours per day during the 4-week treatment cycle. Where reported, actual device use ranged from 16.8 to 20.6 hours per day. Sample sizes ranged from 10 to 686 patients. Median patient age ranged from 51 to 57 years. Prior treatments included debulking surgery, chemotherapy, radiotherapy with or without concomitant temozolomide (TMZ), and bevacizumab. Common inclusion criteria included age 18 years or older,

World Health Organization (WHO) Grade IV glioblastoma, Karnofsky Performance Status (KPS) of at least 70, and at least 4 weeks from surgery or radiotherapy. Common exclusion criteria included patients with an electronic implanted medical device (e.g., pacemaker); arrhythmia; infratentorial tumor; significant renal, hepatic, or hematologic disease; or neurological or seizure disorder. Outcome measures included overall survival, progression-free survival, time to disease progression, response to treatment, and quality of life (QOL). Survival curves for overall survival and progression-free survival were generated using the Kaplan-Meier method. Study details are presented in **Appendix IVa**.

The selected studies included 2 fair-quality RCTs, 1 very-poor-quality trial with historical controls, 2 very-poor-quality cohort studies, 1 poor-quality multicenter registry study with historical controls, and 1 poor-quality subgroup analysis of selected patients from 2 clinical trials. The following sections are organized by study type.

RCTs: A single fair-quality RCT compared Novocure monotherapy (120 patients) with physician's choice chemotherapy (117 patients) in patients with recurrent GBM (Stupp et al., 2012). Median age of patients was 54 years, median KPS score was 80, and median time from initial GBM diagnosis was 11 months. A minority of patients were in their first GBM recurrence (9% in the Novocure group, 15% in the chemotherapy group). The majority of patients were in their second recurrence of GBM (38% in the Novocure group, 46% in the chemotherapy group). In the Novocure group, patients were instructed to use the device continuously with up to two 1-hour breaks per day (i.e., at least 22 hours of use per day) for each 4-week treatment cycle. Median Novocure compliance was 86% (range, 41% to 98%) of the time in each treatment cycle. On average, patients used the device for 20.6 hours per day. In the chemotherapy group, patients received a single agent or combination chemotherapy containing bevacizumab (31%), irinotecan (31%), nitrosoureas (25%), carboplatin (13%), TMZ (11%), or other agents (5%). There was a high loss to follow-up in the Novocure group, as 22% of patients did not complete 1 full 4-week treatment cycle.

Treatment outcomes were similar between the Novocure and chemotherapy groups. Overall survival was 52.5% and 47% at 6 months, 20% and 19% at 1 year, and 7.5% and 5% at 2 years in the Novocure and chemotherapy groups, respectively. Progression-free survival at 6 months was 21% in the Novocure group and 15% in the chemotherapy group. There were similar rates of partial or complete radiological responses to treatment in the Novocure (14%) and chemotherapy (10%) groups. These differences were not statistically significant (P>0.10). However, a subsequent non-inferiority analysis found that the hazard ratio (HR) for death in the Novocure group compared with the chemotherapy group was below 1.0 (HR, 0.86; 95% CI, 0.66 to 1.12; P=0.27). This suggests that Novocure may be at least as effective as active chemotherapy. Median overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (≥ 18 hours per day; overall survival, 7.7 months) than in patients with a compliance < 75% (overall survival, 4.5 months) (P=0.042). QOL data were available in 63 patients (27%) who had remained on treatment for at least 3 months. No differences were observed in global health and social function between groups. Cognitive and emotional function favored Novocure, but physical function was slightly worse in Novocure patients. The symptom scale was worse in the chemotherapy group, including increased pain and fatigue, which was likely related to chemotherapy administration.

A post hoc analysis of patients in the trial that had received at least 1 full 4-week course of Novocure treatment or full course of chemotherapy (which usually requires 4 to 6 weeks) was conducted (Kanner et al., 2014). This modified intention-to-treat (mITT) analysis found that median overall survival in mITT Novocure patients (7.8 months) was significantly longer than mITT chemotherapy patients (6.0 months) (HR, 0.69; 95% CI, 0.52 to 0.92; P=0.0093). An additional post hoc analysis compared several prognostic

and treatment outcome factors between patients that responded to treatment versus patients that did not respond to treatment (Wong et al., 2014). This analysis found that median overall survival (24.8 versus 6.2 months; *P*<0.0001) and adjusted progression-free survival (17.8 versus 10.5 months; *P*=0.0007) were longer for responders than nonresponders in the Novocure group, respectively. Median overall survival (20.0 versus 6.8 months; *P*=0.0235) and adjusted progression-free survival (11.5 versus 7.9 months; *P*=0.0222) were longer for responders than nonresponders in the chemotherapy group, respectively. Response to treatment was correlated with overall survival in Novocure patients (*P*=0.0002) but not in chemotherapy patients (*P*=0.2900). Mean cumulative dexamethasone dose was significantly lower for responders (35.9 mg) than nonresponders (485.6 mg) in the Novocure group (*P*<0.0001). This difference was not found in the chemotherapy group.

A subsequent post hoc analysis was conducted to further investigate the effect of dexamethasone on overall survival (Wong et al., 2015b). Using an unsupervised binary partitioning algorithm, cohorts were separated according to the dexamethasone dose that yielded the greatest statistical difference in overall survival. Novocure patients who used a dexamethasone dose of > 4.1 mg per day (64 patients) exhibited a significantly shortened median overall survival of 4.8 months (95% CI, 3.9 to 6.0) than patients who used a dexamethasone dose of ≤ 4.1 mg per day (56 patients) that had a median overall survival of 11.0 months (95% CI, 8.8 to 16.6) (*P*<0.0001). Chemotherapy patients who used dexamethasone > 4.1 mg per day (54 patients) exhibited a significantly shortened median overall survival of 6.0 months (95% CI, 3.5 to 8.3) than patients who used dexamethasone ≤ 4.1 mg per day (63 patients) that had a median overall survival of 8.9 months (95% CI, 7.2 to 16.1) (*P*<0.0015).

A single RCT investigated Novocure treatment plus TMZ treatment compared with TMZ alone in patients with newly diagnosed GBM (Stupp et al., 2015). The trial enrolled 695 patients into either the Novocure plus TMZ group (466 patients) or the TMZ only group (229 patients). The study was terminated early based on the results of this planned interim analysis. Stupp et al. (2015) reported results from the interim analysis of the RCT; a publication based on the full data set is pending. Patients randomized to Novocure plus TMZ (210 patients) had significantly longer median progression-free survival and overall survival than those randomized to TMZ alone (105 patients). Median progression-free survival in the intention-to-treat population was 7.1 months and 4.0 months in the Novocure plus TMZ and TMZ alone groups, respectively (HR, 0.62; 98.7% CI, 0.43 to 0.89; *P*=0.001). Overall survival in the per-protocol population was 20.5 months and 15.6 months (HR, 0.64; 99.4% CI, 0.42 to 0.98; *P*=0.004) in the Novocure plus TMZ and TMZ alone groups, respectively. Although combination Novocure and TMZ treatment was not associated with a significant increase in systemic toxic effects, there was a higher incidence of irritation under the transducer arrays, as well as anxiety, confusion, insomnia, and headaches.

Nonrandomized Comparison Studies: Overall, the evidence from the nonrandomized comparison studies suggests that Novocure treatment increases overall survival and progression-free survival compared with chemotherapy. One very-poor-quality small trial compared Novocure treatment (at least 18 hours per day) in 12 recurrent GBM patients with historical control data of recurrent GBM patients that had received chemotherapy (Kirson et al., 2007). Median overall survival was doubled in Novocure patients (62 weeks) compared with historical control patients (29 weeks). Progression-free survival at 6 months was greater in Novocure patients (50%) than historical control patients (15%). Median time to progression was 26 and 9.5 weeks in the Novocure and chemotherapy groups, respectively.

A very-poor-quality cohort study compared Novocure plus TMZ treatment in 10 patients with newly diagnosed GBM with historical control patients who had received chemotherapy (for the outcome measure of overall survival) or a matched group of concurrent control patients receiving TMZ (for the outcome measure of progression-free survival) (Kirson et al., 2009). The authors did not provide details on the variables used to match the concurrent control group for the outcome measure of progression-free survival. Hours of device use per day were not reported. Median overall survival was significantly greater in the Novocure patients (39 months) than the historical chemotherapy patients (15 months) (*P*=0.0018). Median progression-free survival was greater in the Novocure patients (155 weeks) than the concurrent TMZ patients (31 weeks) (HR, 3.32; 95% CI, 1.9 to 5.9; *P*=0.0002).

A poor-quality multicenter registry study compared Novocure treatment in 457 patients with recurrent GBM with historical Novocure and chemotherapy group data from Stupp et al. (2012) (Mrugala et al., 2014). Mean age was 55 years and mean KPS score was 80. The majority of patients were in their first GBM recurrence (33%), 27% were in their second recurrence, 27% were in their third to fifth recurrence, and 13% had unknown recurrence status. Median overall survival was longer in the Novocure registry patients (9.6 months) than in the Stupp et al. Novocure patients (6.6 months) and chemotherapy patients (6.0 months). This may have been due in part to the longer treatment duration in the Novocure registry patients (4.1 months) than in the Stupp et al. Novocure (2.3 months) and chemotherapy groups (2.1 months). In addition, registry patients were more likely to be treated during their first GBM recurrence (33%) than patients in the Stupp et al. trial (9%). Compliance data were available for 287 (63%) of the registry patients. Median daily compliance was 70% (16.8 hours per day; range, 12% to 99%). One-hundred-twenty-seven patients (44%) had ≥75% compliance per day. Median overall survival was significantly longer in registry patients with a monthly compliance rate ≥75% (13.5 months) than in patients with a compliance rate of <75% (4.0 months) (*P*<0.0001).

A very-poor-quality retrospective cohort study compared combination Novocure plus bevacizumab treatment (34 patients) with Novocure plus bevacizumab plus a chemotherapy regimen of 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) (3 patients) in patients with recurrent GBM (Wong et al., 2015a). Median overall survival was longer in the Novocure plus bevacizumab plus TCCC group (10.3 months) than in the Novocure plus bevacizumab only group (4.1 months). There was a nonsignificant trend in favor of the group that received TCCC (*P*=0.0951). Median progression-free survival was also longer in the Novocure plus bevacizumab plus TCCC group (8.1 months) than in the Novocure plus bevacizumab only group (2.8 months). There was a nonsignificant trend in favor of the group that received TCCC (*P*=0.0585). Average compliance was higher in the Novocure plus bevacizumab only group (83.5%) than in the Novocure plus bevacizumab plus TCCC group (66.7%) (*P*=0.0670). Because there were very few patients in the TCCC group, the study was underpowered to detect significant differences between groups. Because this study investigates Novocure as an adjunct treatment to other treatments, as opposed to comparing Novocure alone with a control treatment, this study cannot contribute to the analysis of the effectiveness of Novocure compared with other treatments.

Uncontrolled Studies: One poor-quality subgroup analysis analyzed 130 patients with recurrent GBM that had received Novocure monotherapy in Stupp et al. (2012) and Kirson et al. (2007) (Vymazal and Wong, 2014). Only patients who had received magnetic resonance imaging (MRI) at baseline and at least 1 follow-up MRI were included in the analysis. One-hundred-ten of 130 patients (85%) met this criterion. Sixteen of 110 patients (15%) exhibited a partial or complete radiological response to Novocure treatment. Although responders to Novocure had favorable prognostic characteristics compared with nonresponders, including higher KPS score (90 versus 80), lower rate of prior bevacizumab treatment

(6% versus 19%), higher rate of secondary GBM upgraded from low-grade gliomas (31% versus 8%), and smaller median tumor size (10.0 cm^2 versus 14.4 cm^2), these differences were not significant. Response duration was highly correlated with overall survival (*P*<0.0001). Average daily compliance was 83% (19.9 hours per day). Response to treatment was correlated with compliance (*P*<0.001). Partial and complete responders (14 patients) had an average compliance of 92%, patients with stable disease (34 patients) had an average compliance of 85% (34 patients), and patients with progressive disease had an average compliance of 79% (59 patients).

Summary of Clinical Effectiveness of Novocure for GBM (Key Question #1a)

Overall, low-quality evidence suggests that Novocure is at least comparable with chemotherapy for the treatment of recurrent GBM. One RCT found that overall survival and progression-free survival were similar in the Novocure and chemotherapy groups. Two studies with historical control groups found that for patients with recurrent GBM, Novocure treatment significantly increased overall survival by 38% to 53% and progression-free survival at 6 months by 15% compared with chemotherapy. A retrospective cohort study that compared combination Novocure plus bevacizumab treatment with Novocure plus bevacizumab plus TCCC found that although overall survival and progression-free survival were longer in the Novocure plus bevacizumab plus TCCC group, this difference was not statistically significant. However, this study had a very small sample size in the TCCC group and was likely underpowered. A fifth uncontrolled study found that 15% of patients exposed to Novocure monotherapy exhibited a partial or complete radiological response to treatment. The evidence for the effectiveness of Novocure for treating recurrent GBM was considered to be of low quality because of the small quantity of data, small sample sizes, and lack of concurrent control or comparator groups in most studies.

One RCT and one cohort study found that Novocure was superior to chemotherapy for patients with newly diagnosed GBM. In the RCT, progression-free survival for patients in the Novocure plus TMZ group was 3.1 months longer than for patients in the TMZ alone group, and overall survival was 5.1 months longer. The cohort study found that Novocure treatment significantly increased overall survival by 62% and progression-free survival at 6 months by 15% compared with chemotherapy. The evidence for the effectiveness of Novocure for treating newly diagnosed GBM was considered to be of very low quality because of the small quantity of data for this indication.

Other Cancers (2 studies)

Clinical Effectiveness of Novocure for Other Cancers (Key Question #1b)

Two studies reported that 15% to 17% of patients with cancers other than GBM exhibited partial responses to Novocure treatment (Salzberg et al., 2008; Pless et al., 2013). Both studies were very-poor-quality case series.

KQ#1b, Other Cancers:
Non-Small Lung Cancer: Pless 2013
Breast Cancer: Salzberg 2008
Melanoma: Salzberg 2008
Mesothelioma: Salzberg 2008

One study enrolled 6 patients with recurrent solid tumors (Salzberg et al., 2008). Four of these patients had skin lesions (2 patients with invasive ductal breast cancer, 1 patient with adenocarcinoma of the breast, and 1 patient with a malignant melanoma on the thigh). A fifth patient had metastases from a mesothelioma in the retroperitoneal cavity. A sixth patient had recurrent GBM. Because this single patient with GBM was a case report, this study was not included in the literature review on Novocure treatment for GBM. Median patient age was 66 years, and all patients had received several prior lines of treatment. Patients were instructed to use Novocure daily for 23 hours per day for 2 to 4 weeks. Device

compliance was more than 80%; 4 pts (67%) exhibited a partial response or stable disease following 2 to 4 weeks of Novocure treatment. Objective tumor assessment was performed by digital photography (for skin lesion patients) or computed tomography (CT) scan. One breast cancer patient had a 51% reduction in tumor size (17% of patients showed a partial response) while 3 patients with skin lesions due to breast cancer or melanoma had an arrest of tumor growth (50% of patients had stable disease). The GBM patient exhibited progressive disease. The mesothelioma patient had some tumor regression in the area of the tumor which was exposed to electrodes, while the other portions of the tumor were stable or progressive. The lack of a control or comparator group, as well as the very small sample size, precludes drawing any definitive conclusions.

A case series that investigated the efficacy of Novocure plus pemetrexed treatment enrolled 41 patients with stage IIIB (with pleural effusion; 24% of patients) or stage IV (76% of patients) non-small cell lung cancer (NSCLC). Median patient age was 63 years. Median time from NSCLC diagnosis was 10.6 months. All patients had received 1 to 5 lines of chemotherapy, 12% had received surgery, and 24% had received radiation. Median time from last dose of chemotherapy was 14.9 weeks. Patients were instructed to use Novocure for at least 12 hours per day, which is the shortest daily treatment duration reported. Patients received an average of 18 weeks of Novocure (range, 1 to 32 weeks). Average Novocure daily use was 11.2 hours per day. All patients received concomitant standard pemetrexed treatment of 500 milligrams per square meter (mg/m^2) every 3 weeks with adequate supportive treatment. Six patients (15%) showed a partial response to treatment, and 20 patients (49%) had stable disease. Ten patients (24%) exhibited progression outside of TTF. Median daily treatment in patients who had a partial remission was longer than the average daily Novocure use (13.5 hours per day). Median overall survival was 13.8 months. Median time to disease progression inside of TTF was 28 weeks. Median progression-free survival was 22.2 weeks; 57% of patients were still alive at 1-year follow-up. Study details are presented in **Appendix IVb**.

Summary of Clinical Effectiveness of Novocure for Other Cancers (Key Question #1b)
Two case series found that 15% to 17% of patients with cancers other than GBM exhibited partial responses to Novocure treatment. One small case series (41 patients) found that 15% of NSCLC patients exhibited a partial response to Novocure treatment. The daily treatment duration was relatively short compared to other studies, which may have adversely affected treatment outcome. The evidence for the effectiveness of Novocure for treating NSCLC was considered to be of very low quality because of the small quantity of data and lack of control or comparator group.

A second case series investigating Novocure treatment in 6 patients with solid tumors of varying etiologies found that 17% of patients exhibited partial responses to Novocure treatment. Four of these patients had skin lesions (2 patients with invasive ductal breast cancer, 1 patient with adenocarcinoma of the breast, and 1 patient with a malignant melanoma on the thigh). One breast cancer patient (17%) showed a partial response, 3 patients with skin lesions due to breast cancer or melanoma (50%) had stable disease, 1 patient with GBM (17%) exhibited progressive disease, and 1 mesothelioma patient (17%) had a mixed response. The evidence for the effectiveness of Novocure for treating breast cancer was considered to be of very low quality because of the small quantity of data and lack of control or comparator group.

The evidence for the effectiveness of Novocure for treating melanoma was considered to be of very low quality because of the small quantity of data and lack of control or comparator group.

The evidence for the effectiveness of Novocure for treating metastases from a mesothelioma was considered to be of very low quality because of the small quantity of data and lack of control or comparator group.

The evidence for the effectiveness of Novocure for treating cancers other than GBM, NSCLC, breast cancer, melanoma, or mesothelioma was considered to be insufficient because of the lack of studies.

Key Question #2

Key Question #2: What are the harms associated with Novocure?

Eight studies reported on adverse events that occurred during Novocure treatment. These studies included 2 fair-quality RCTs (Stupp et al., 2012; Stupp et al., 2015), 1 poor-quality multicenter registry study with historical controls (Mrugala et al., 2014), 1 very-poor-quality trial with historical controls (Kirson et al., 2007), 1 very-poor-quality cohort study (Kirson et al., 2009), and 3 very-poor-quality case series (Salzberg et al., 2008; Pless et al., 2013; Lacouture et al., 2014).

No serious adverse events related to Novocure treatment were reported. The most common complication reported was mild to moderate dermatitis under the transducer arrays (16% to 90%). Several studies reported that the dermatitis improved with application of topical corticosteroids, and in some cases repositioning of the electrodes (Kirson et al., 2007; Salzberg et al., 2008; Kirson et al., 2009; Stupp et al., 2012; Pless et al., 2013; Mrugala et al., 2014). Three studies reported that the condition resolved completely after treatment was stopped (Kirson et al., 2009; Stupp et al., 2012; Pless et al., 2013). Two studies reported 1% to 7% of patients experienced skin ulcers (Pless et al., 2013; Lacouture et al., 2014). Proper and sterile shaving and preparation of the scalp and careful removal of arrays can prevent occurrence or worsening of dermatologic adverse events (Lacouture et al., 2014). Treatments for dermatologic adverse events include topical therapies, relocation of arrays, and avoidance of placing arrays on affected skin whenever possible. Oral antibiotics may be required in the case of more serious dermatologic adverse events.

Other commonly reported adverse events include headache (2% to 7%), fatigue (2.5% to 24%), pain or discomfort (5% to 12%), gastrointestinal disorders (3% to 12%), nervous system disorders (10% to 30%), infections (1% to 5%), and psychiatric disorders (3% to 5%). Stupp et al. (2012) found that significantly more gastrointestinal (4% versus 17%), hematological (3% versus 17%), and infectious (4% versus 8%) adverse events were observed in the chemotherapy group than in the Novocure group. Stupp et al. (2015) noted that mild anxiety, confusion, insomnia, and headaches were reported more frequently in Novocure plus TMZ patients; these complications occurred mainly at the time of treatment initiation.

In summary, use of Novocure to treat GBM and other solid tumors *does not pose major safety concerns*, but evidence of the *harms associated with Novocure* is of low quality because of the quality of individual studies and general lack of statistical comparisons with a control group.

Key Question #3

Key Question #3: Does the effectiveness of Novocure or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, gender, prior treatments)?

Six of the 9 studies analyzed for Key Question #1 reported the number of previous episodes of GBM experienced prior to Novocure treatment (Kirson et al., 2007; Kirson et al., 2009; Stupp et al., 2012; Mrugala et al., 2014; Stupp et al., 2015; Wong et al., 2015a). Median overall survival tended to be longer in studies that enrolled a higher number of patients in their first or second episode of GBM. Overall survival was longest in studies that enrolled patients with newly diagnosed GBM (20.5 months to 39 months) (Kirson et al., 2009; Stupp et al., 2015). Overall survival was shortest in the study that enrolled only 0% to 18% of patients in their first GBM recurrence in each Novocure group (4.1 months) (Wong et al., 2015a). Overall survival was 9.6 months in a study that enrolled 33% of patients in their first GBM recurrence (Mrugala et al., 2014) and 14.3 months in a study that enrolled 50% of the total patient population in their first GBM recurrence (Kirson et al., 2007). Mrugala et al. (2014) found that patients treated at their first GBM recurrence had significantly longer overall survival (20 months) compared with patients treated at second recurrence (8.5 months) or third or more recurrence (4.9 months) (P=0.0271). Stupp et al. (2012) enrolled only 9% of patients in their first GBM recurrence. Overall survival was 52.5% at 6 months, 20% at 12 months, and 7.5% at 24 months. Median progression-free survival was also longer in studies that enrolled a greater percentage of patients in their first or second episode of GBM. Progression-free survival was 2.8 months in a study that enrolled 0% to 18% of patients in their first GBM recurrence (Wong et al., 2015a). Progression-free survival was 7.1 months and 35.6 months in the 2 studies that enrolled patients with newly diagnosed GBM (Kirson et al., 2009; Stupp et al., 2015). Progression-free survival at 6 months was greater in a study that enrolled 50% of the total patient population in their first GBM recurrence (50%) (Kirson et al., 2007) than the study that enrolled only 9% of patients in their first GBM recurrence (21%) (Stupp et al., 2012).

Wong et al. (2014) conducted a post hoc analysis of Stupp et al. (2012) comparing prognostic factors between patients that responded to treatment and those that did not. Mean cumulative dexamethasone dose was significantly lower for responders (35.9 mg) than nonresponders (485.6 mg) in the Novocure group (P<0.0001). This difference was not found in the chemotherapy group. A subsequent post hoc analysis was conducted to further investigate effect of dexamethasone on overall survival (Wong et al., 2015b). Novocure patients who used a dexamethasone dose of > 4.1 mg per day exhibited a significantly shortened median overall survival of 4.8 months (95% CI, 3.9 to 6.0) than patients who used a dexamethasone dose of ≤ 4.1 mg per day that had a median overall survival of 11.0 months (95% CI, 8.8 to 16.6) (P<0.0001). Chemotherapy patients who used dexamethasone > 4.1 mg per day exhibited a significantly shortened median overall survival of 6.0 months (95% CI, 3.5 to 8.3) than patients who used dexamethasone ≤ 4.1 mg per day that had a median overall survival of 8.9 months (95% CI, 7.2 to 16.1) (P<0.0015).

Mrugala et al. (2014) found that patients that had received bevacizumab prior to Novocure treatment had significantly shorter overall survival (7.2 months) than those that had not received bevacizumab (13.4 months) (P=0.0070). In addition, patients with a KPS score of 90 to 100 had a significantly longer overall survival (14.8 months) than patients with a KPS of 70 to 90 (7.7 months) (P=0.0070) or KPS less than 70 (6.1 months) (P<0.0001).

Vymazal and Wong (2014) conducted a subgroup analysis of select patients from Stupp et al. (2012) and Kirson et al. (2007). Although responders to Novocure had favorable prognostic characteristics compared with nonresponders, including higher KPS score (90 versus 80), lower rate of prior bevacizumab treatment (6% versus 19%), higher rate of secondary GBM upgraded from low-grade gliomas (31% versus 8%), and smaller median tumor size (10.0 cm^2 versus 14.4 cm^2), these differences were not significant.

Compliance with Novocure treatment was an important factor related to treatment outcome. Stupp et al. (2012) found that median overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (≥ 18 hours per day; overall survival, 7.7 months) than in patients with a compliance < 75% (overall survival, 4.5 months) (*P*=0.042). Mrugala et al. (2014) also found that median overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (13.5 months) than in patients with a compliance < 75% (4.0 months) (*P*<0.0001). Vymazal and Wong (2014) found that response to treatment was correlated with compliance (*P*<0.001). Partial and complete responders had an average compliance of 92%, patients with stable disease had an average compliance of 85%, and patients with progressive disease had an average compliance of 79%.

In summary, evidence for Key Question #1 demonstrated very-low-quality positive evidence of varying clinical efficacy according to the following patient characteristics and clinical history:

- Median overall survival and progression-free survival were longer in studies that enrolled a higher number of patients with fewer prior episodes of GBM (6 studies).
- Patients that required lower daily doses of dexamethasone exhibited longer overall survival (1 study).
- Patients with a more favorable KPS score had significantly longer overall survival (2 studies).
- Patients not exposed to bevacizumab treatment prior to Novocure treatment were more likely to respond to treatment (2 studies).
- Patients with a secondary GBM upgraded from low-grade gliomas were more likely to respond to treatment (1 study).
- Patients with a smaller tumor size were more likely to respond to treatment (1 study).
- Patients that were compliant with using their Novocure device had longer overall survival (3 studies).

Key Question #4

Key Question #4: What are the cost implications and cost-effectiveness of Novocure?

Cost of Novocure Device

The literature search did not provide cost information for Novocure. A search of the Internet yielded an estimate of the cost of the device to be $10,907.81 to $16,361.71 per month (Randall, 2010). Another source estimated the cost of the Novocure device to be $21,429.96 per month (Kotz, 2014).

NOTE: These currency conversions are based on use of the CCEMG-EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values. The cost convertor was used on September 15, 2015, with 2010 or 2014 as the price year and 2015 as the target price year: CCEMG-EPPI-Centre Cost Converter (last updated on January 27, 2014) (Shemilt et al., 2010). These conversions represent an *approximate* translation of the procedural cost and/or product price *values* to current U.S. *values*. These conversions do NOT provide an estimate of the current cost and do not directly reflect the U.S. healthcare system.

Cost-Effectiveness

No published studies evaluating the cost of Novocure per unit of clinical benefit were available in the reviewed literature. Thus, evidence of the *cost-effectiveness of Novocure for treatment of GBM or other cancers* is insufficient due to the lack of studies.

Overall Summary and Discussion

Evidence-Based Summary Statement

The NovoTTF-100A (Novocure/Optune) device was approved by the Food and Drug Administration (FDA) in April 2011 for the treatment of patients with recurrent GBM, and expanded indication for this device to newly diagnosed GBM in October 2015. The original approval was based on a single RCT that suggested positive outcomes in patients with recurrent GBM. In this trial, patients with recurrent GBM were randomized to Novocure monotherapy or physician's choice chemotherapy. Treatment outcomes were similar in both groups. Overall survival was approximately 50% at 6 months, 20% at 1 year, and 5% at 2 years in both the Novocure and chemotherapy groups. Progression-free survival at 6 months was 21% in the Novocure group and 15% in the chemotherapy group. The side effect profile appeared to favor Novocure. There were significantly more gastrointestinal, hematological, and infectious adverse events seen in the chemotherapy group than in the Novocure group. One important limitation of this study was that there was a high loss to follow-up in the Novocure group, as 22% of patients did not complete 1 full 4-week treatment cycle. The expanded indication of newly diagnosed GBM was based on results from an interim analysis of anRCT of 315 patients that compared a group that received Novocure plus TMZ with a group that received TMZ alone (Stupp et al., 2015). Patients who received Novocure plus TMZ lived about 7 months with no disease progression, compared with 4 months in the TMZ alone group. The Novocure plus TMZ group survived for an average of 20 months, compared with 15 months for those who were treated with TMZ alone. This study had a high loss to follow-up in the TMZ alone group (20%).

The largest body of evidence available for any indication was recurrent GBM. Overall, low-quality evidence suggests that Novocure is at least comparable with chemotherapy for the treatment of recurrent GBM. In addition to the RCT described above, 4 additional studies provided positive evidence that Novocure has some benefit in patients with recurrent GBM. Two studies with historical control groups found that for patients with recurrent GBM, Novocure treatment significantly increased overall survival by 38% to 53% and progression-free survival at 6 months by 15% compared with chemotherapy. A retrospective cohort study that compared combination Novocure plus bevacizumab treatment with Novocure plus bevacizumab plus a chemotherapy regimen of 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) found that although overall survival and progression-free survival were longer in the Novocure plus bevacizumab plus TCCC group, this difference was not statistically significant. A fifth uncontrolled study found that 15% of patients exposed to Novocure monotherapy exhibited a partial or complete radiological response to treatment.

In addition to the previously discussed RCT, a single cohort study was available investigating efficacy of Novocure in patients with newly diagnosed GBM. Novocure treatment significantly increased overall survival by 62% and progression-free survival at 6 months by 15% compared with chemotherapy.

One small case series investigated the efficacy of Novocure in patients with NSCLC and found that 15% of NSCLC patients exhibited a partial response to Novocure treatment. The daily treatment duration was relatively short compared to other studies, which may have adversely affected treatment outcome. A second case series investigated Novocure treatment in 6 patients with solid tumors of varying etiologies. One breast cancer patient showed a partial response, 3 patients with skin lesions due to breast cancer or melanoma had stable disease, 1 patient with GBM exhibited progressive disease, and 1 mesothelioma patient had a mixed response.

Several studies provided data suggesting that compliance with Novocure treatment was an important factor related to treatment outcome. An RCT found that median overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (≥ 18 hours per day; 7.7 months) than in patients with a compliance < 75% (4.5 months). Similarly, a registry study found that overall survival was significantly longer in Novocure patients with a monthly compliance rate ≥ 75% (13.5 months) than in patients with a compliance < 75% (4.0 months). Another study found that whether patients responded to treatment was correlated with compliance. Partial and complete responders had an average compliance of 92%, patients with stable disease had an average compliance of 85%, and patients with progressive disease had an average compliance of 79%. These data suggest the crucial importance of using the device according to manufacturer instructions to ensure almost continuous exposure to TTF for optimal efficacy.

The literature provides very little direct evidence of improvements in QOL or functional states attributable to Novocure. Only 1 study, the RCT, included a measure of QOL in patients who had remained on treatment for at least 3 months. No differences were observed in global health and social function between groups. Cognitive and emotional function favored Novocure, but physical function was slightly worse in Novocure patients. The symptom scale was worse in the chemotherapy group, including increased pain and fatigue, which was likely related to chemotherapy administration. More data on QOL and functional states are needed to determine the short- and long-term impact of using the portable device for 18 to 22 hours per day.

Gaps in the Evidence

The following evidence is needed to better answer the Key Questions of this report:

- RCTs and cohort studies of sufficient size and design to further investigate the safety and efficacy of Novocure in patients with recurrent and newly diagnosed GBM, NSCLC, and other cancers compared with chemotherapy or other treatment.
- Studies designed to systematically investigate differential effectiveness and safety according to patient characteristics and previous treatment history.
- Studies investigating the impact of Novocure on QOL and functional status.
- Economic evaluations on the cost-effectiveness of Novocure.

Practice Guidelines

Eleven practice guidelines with relevant recommendations were identified: 6 guidelines addressing treatment strategies for GBM, and 5 guidelines addressing treatment of NSCLC. **Appendix V** presents the recommendations of each guideline.

Selected Payer Policies

The following payer sites were searched on September 9 and 10, 2015, using the keywords *novocure* or *a4555* or *tumor* or *glioblastoma* or *field* or *e0766*.

Aetna

Aetna considers devices to generate electric tumor treatment fields (ETTF) medically necessary as monotherapy for persons with histologically confirmed glioblastoma (WHO grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. Aetna considers devices to generate ETTFs experimental and investigational for the treatment of other malignant tumors and for all other indications because their effectiveness has not been established.

See Electric Tumor Treatment Fields: Aetna Clinical Policy Bulletin No. 0827.

Centers for Medicare & Medicaid Services (CMS)

No CMS National Coverage Determination (NCD) was identified for Novocure/Optune on September 8, 2015 (search National Coverage Documents in National Coverage Determinations and Medicare Coverage Documents at: CMS Advanced Search Database). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

GroupHealth

Group Health states in their Clinical Review Criteria that there is insufficient evidence in the published medical literature to show TTF therapy is as safe as standard services/therapies and/or provides better long-term outcomes.

See Group Health Clinical Review Criteria: Tumor Treatment Fields Therapy.

Oregon Health Evidence Review Commission (HERC)

No coverage policy for Novocure/Optune was identified on the Oregon HERC website (HERC Coverage Guidances).

Regence Group

Regence Group considers TTF therapy to treat glioblastoma to be investigational.

See Tumor-Treatment Fields Therapy for Glioblastoma: Regence Group Medical Policy No. 85.

References

Appraisal of Guidelines Research & Evaluation (AGREE) Enterprise. Appraisal of Guidelines for Research and Evaluation II Instrument. Updated September 2013. Available at: http://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf. Accessed September 16, 2015.

Eberhardt WEE, De Ruysscher D, Weder W, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. *Ann Oncol*. 2015;26(8):1573-1588. PMID: 25897013.

Ettinger DS, Wood DE, Akerley W, et al. Non-Small Cell Lung Cancer, Version 6.2015. *J Natl Compr Canc Netw*. 2015;13(5):515-524. PMID: 25964637.

Fonkem E, Wong ET. NovoTTF-100A: a new treatment modality for recurrent glioblastoma. *Expert Rev Neurother*. 2012;12(8):895-899. PMID: 22708931.

Kanner AA, Wong ET, Villano JL, Ram Z, EF-11 Investigators. Post Hoc analyses of intention-to-treat population in phase III comparison of NovoTTF-100A™ system versus best physician's choice chemotherapy. *Semin Oncol*. 2014;41(Suppl 6):S25-S34. PMID: 25213871.

Kirson ED, Dbalý V, Tovarys F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A*. 2007;104(24):10152-10157. PMID: 17551011.

Kirson ED, Schneiderman RS, Dbaly V, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). *BMC Med Phy*. 2009. PMID: 19133110.

Kotz D. Scalp device might help patients with brain tumors. December 27, 2014. *Boston Globe* [website]. Available at: https://www.bostonglobe.com/lifestyle/health-wellness/2014/12/26/scalp-device-might-help-patients-with-brain-tumors/Z0K4lhiSXm52q5E9AM7kOK/story.html. Accessed September 15, 2015.

Kozower BD, Larner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e369S-e399S. PMID: 23649447.

Lacouture ME, Davis ME, Elzinga G, et al. Characterization and management of dermatologic adverse events with the NovoTTF-100A System, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. *Semin Oncol*. 2014;41(Suppl 4):S1-14. PMID: 24794308.

Lewis SZ, Diekemper R, Addrizzo-Harris DJ. Methodology for development of guidelines for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):41S-50S. PMID: 23649432.

Lovely MP, Stewart-Amidei C, Arzbaecher J, et al. American Association of Neuroscience Nurses (AANN). Care of the adult patient with a brain tumor. Chicago, IL: American Association of Neuroscience Nurses (AANN); 2014. National Guideline Clearinghouse [website]. Available at: http://www.guideline.gov/content.aspx?id=48105. Accessed September 16, 2015.

Macdonald DR, Cascino TL, Schold SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol*. 1990;8(7):1277-1280. PMID: 2358840.

Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A™ system for glioblastoma: The Patient Registry Dataset (PRiDe). *Semin Oncol*. 2014;41(Suppl 6):S4-S13. PMID: 25213869.

Nabors LB, Portnow J, Ammirati M, et al. Central nervous system cancers, version 2.2014. Featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw*. 2014;12(11):1517-1523. PMID: 25361798.

National Comprehensive Cancer Network (NCCN). Development and Update of the NCCN Guidelines. 2015. Available at: http://www.nccn.org/professionals/development.aspx. Accessed September 17, 2015.

Novocure (USA) Inc. Instructions for use. NovoTFF- 100A system. 2013. http://www.optune.com/Content/pdfs/Novocure_IFU.pdf. Accessed September 16, 2015.

Olson JJ, Nayak L, Ormond DR, Wen PY, Kalkanis SN; AANS/CNS Joint Guidelines Committee. The role of cytotoxic chemotherapy in the management of progressive glioblastoma : a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2014a;118(3):501-555. PMID: 24740194.

Olson JJ, Nayak L, Ormond DR, et al. The role of targeted therapies in the management of progressive glioblastoma : a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2014b;118(3):557-599. PMID: 24740195.

Pless M, Droege C, von Moos R, Salzberg M, Betticher D. A phase I/II trial of Tumor Treating Fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. *Lung Cancer*. 2013;81(3):445-450. PMID: 23891283.

Randall T. Electric Helmet Slows Brain Tumors Without Chemo Side Effects [news article]. June 5, 2010. Available at: http://www.bloomberg.com/news/articles/2010-06-05/electric-helmet-slows-brain-tumors-without-chemotherapy-s-side-effects. Accessed September 15, 2015.

Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;(25 Suppl 3):iii27-iii39. PMID: 25115305.

Rodrigues G, Choy H, Bradley J, et al. Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. *Pract Radiat Oncol*. 2015;5(3):141-148. PMID: 25957184.

Rulseh AM, Keller J, Klener J, et al. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. *World J Surg Oncol*. 2012;10:220. PMID: 23095807.

Salzberg M, Kirson E, Palti Y, Rochlitz C. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. *Onkologie*. 2008;31(7):362-365. PMID: 18596382.

Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. *Nat Clin Pract Neurol*. 2006;2(9):494-503. PMID: 16932614.

Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10. PMID: 17302989.

Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evid Policy*. 2010;6(1):51-59.

Stupp R, Brada M, van den Bent MJ, Tonn J-C, Pentheroudakis G, ESMO Guidelines Working Group. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25(Suppl 3):iii93-iii101. PMID: 24782454.

Stupp R, Hegi ME, Gilbert MR, Chakravarti A. Chemoradiotherapy in malignant glioma: standard of care and future directions. *J Clin Oncol*. 2007;25(26):4127-4136. PMID: 17827463.

Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996. PMID: 15758009.

Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA*. 2015;314(23):2535-2543. PMID: 26670971.

Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer*. 2012;48(14):2192-2202. PMID: 22608262.

Vymazal J, Wong ET. Response patterns of recurrent glioblastomas treated with tumor-treating fields. *Semin Oncol*. 2014;(41 Suppl 6):S14-S24. PMID: 25213870.

Weller M, van den Bent M, Hopkins K, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. *Lancet Oncol*. 2014;15(9):e395-403. PMID: 25079102.

Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol*. 1999;17(8):2572-2578. PMID: 10561324.

Wong ET, Lok E, Swanson KD. Clinical benefit in recurrent glioblastoma from adjuvant NovoTTF-100A and TCCC after temozolomide and bevacizumab failure: a preliminary observation. *Cancer Med*. 2015a;4(3):383-391. PMID: 25620708.

Wong ET, Lok E, Gautam S, Swanson KD. Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma. *Br J Cancer*. 2015b;113(2):232-241. PMID: 26125449.

Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. *Cancer Med*. 2014;3(3):592-602. PMID: 24574359.

Appendices

Appendix I. Search Strategy

Initial Search, Systematic Reviews And Practice Guidelines (conducted May 27, 2015)
Initially, evidence for this report was obtained by searching for systematic reviews, meta-analyses, practice guidelines, and economic evaluations that had been published in the past 10 years. Searches were conducted in the following databases using the terms *Novocure* or *Optune* or *NovoTTF* or *"tumor treating fields"* or *"tumor treatment fields"* or *TTfield* or *TTfields* or *"alternating electric field"*: Agency for Healthcare Research and Quality (AHRQ), Blue Cross Blue Shield TEC Assessments, Canadian Agency for Drugs and Technology in Health (CADTH), Centre for Reviews and Dissemination (CRD) (York University), Hayes Knowledge Center, Institute for Clinical Systems Improvement (ICSI), National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (UK), U.S. Preventive Services Task Force (USPSTF), National Guidelines Clearinghouse (NGC), National Institute for Health and Care Excellence (NICE), and Veterans Affairs Technology Assessment Program (VA TAP). (NOTE: The CRD search strategy includes a search for Cochrane Reviews.)

The websites for the National Comprehensive Cancer Network (NCCN), American Association of Neurological Surgeons (AANS), and Congress of Neurological Surgeons (CNS) were also searched.

Additional systematic reviews were sought from a search of the PubMed database using filters for Practice Guidelines, Guidelines, Meta-analyses, and Systematic Reviews, according to this search:

1. Novocure or Optune or NovoTTF or "tumor treating fields" or “tumor treatment fields” or TTfield or TTfields or “alternating electric field”

   Filters: Meta-Analysis; Systematic Reviews; Publication date from 2005/01/01 to 2015/12/31; English

Search For Primary Clinical Studies And Economic Evaluations

Since no systematic reviews were identified that addressed the Key Questions for this report, the main literature search was designed to identify all relevant primary studies.

PubMed search on May 28, 2014

Combined using “or”

1. Novocure
2. Optune
3. NovoTTF
4. tumor treating fields
5. tumor treatment fields
6. TTfield
7. TTfields

8. alternating electric field

   Filters: English

OVID-Embase search on May 28, 2014

The following search was run in both the Embase and MEDLINE databases. Only search results in Embase were reviewed.

1. Novocure
2. Optune
3. NovoTTF
4. tumor treating fields
5. tumor treatment fields
6. TTfield*
7. alternating electric field
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. remove duplicates from 8
10. limit 9 to human
11. limit 10 to humans

Update Searches

Update searches were conducted on September 11, 2015, and November 20, 2015.

Appendix II. Overview of Evidence Quality Assessment Methods

Clinical Studies

Tools used include internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, a checklist for judging the adequacy of systematic reviews used instead of de novo analysis, and Hayes Evidence-Grading Guides for evaluating bodies of evidence for different types of technologies. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body.

Step 1	Individual study appraisal: a. Initial rating according to study design *Good:* Randomized Controlled Trials *Fair:* Nonrandomized Trial (controlled, parallel-group, quasi-randomized) *Poor:* Observational Analytic Studies (prospective or retrospective trials involving historical controls, pretest-posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group) *Very Poor:* Descriptive Uncontrolled Studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data]) b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist c. Repeat for each study
Step 2	Evaluation of each body of evidence by outcome, key question, or application: a. Initial quality designation according to best study design in a body of evidence b. Downgrade/upgrade *Downgrade factors:* Study weaknesses (Quality Checklists), small quantity of evidence, lack of applicability, inconsistency of results, publication bias *Possible upgrade factors:* Strong association, dose-response effect, bias favoring no effect c. Assign final rating: High-Moderate-Low-Insufficient d. Repeat for each outcome/question/application
Step 3	Evaluation of overall evidence: a. Rank outcomes by clinical importance b. Consider overall quality of evidence for each critical outcome c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Insufficient
Step 4	Evidence-based conclusion: Overall quality of evidence plus balance of benefits and harms

Practice Guidelines (checklist taken from AGREE Tool and approach to scoring used in this report)

Rank each item on a scale of 1 to 7.
Decide on overall quality (1 = lowest to 7 = highest), giving strongest weight to items 7 to 14 (Rigor of Development Domain) and items 22 to 23 (Editorial Independence).

For qualitative labels:

Very poor = 1
Poor = 2-3
Fair = 4-5
Good = 6-7

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

Appendix III. Excluded Studies

The following 29 studies were excluded during full-text review.

Case reports

Elzinga G, Wong ET. Resolution of cystic enhancement to add-on tumor treating electric fields for recurrent glioblastoma after incomplete response to bevacizumab. *Case Rep Neurol*. 2014;6(1):109-115. PMID: 24847254.

Rulseh AM, Keller J, Klener J, et al. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. *World J Surg Oncol*. 2012;10:220. PMID: 23095807.

Turner SG, Gergel T, Wu H, Lacroix M, Toms SA. The effect of field strength on glioblastoma multiforme response in patients treated with the NovoTTF™-100A system. *World J Surg Oncol*. 2014;12:162. PMID: 24884522.

Villano JL, Williams LE, Watson KS, et al. Delayed response and survival from NovoTTF-100A in recurrent GBM. *Med Oncol*. 2013;30(1):338. PMID: 23307238.

Conference abstracts not published in peer-reviewed journal (duplicate abstracts not reported)

Elzinga G, Chung A, Wong ET. Safety analysis of bevacizumab plus NovoTTF-100a in patients with recurrent malignant gliomas. 4th Quadrennial Meeting of the World Federation of Neuro-Oncology held in Conjunction with the 18th Annual Meeting of the Society for Neuro-Oncology. 2013. San Francisco, CA.

Kanner AA, Wong ET, Villano JL, et al. Tumor treating fields (TTFIELDS) in recurrent GBM. An updated subgroup analysis of the phase III data. 4th Quadrennial Meeting of the World Federation of Neuro-Oncology held in Conjunction with the 18th Annual Meeting of the Society for Neuro-Oncology. 2013. San Francisco, CA. Results published in peer-reviewed journal (study analyzed in present report).

Kesari S, Taillibert S, Kanner A. Phase III trial of tumor-treating fields (TTFields) together with temozolomide compared with temozolomide (TMZ) alone in patients with newly diagnosed glioblastoma multiforme (NCT00916409). Annual Meeting of the American Society of Clinical Oncology. 2012. Chicago, IL. Study design only.

Lacouture M, Elizabeth Davis M, Elzinga G. Dermatologic event characteristics and management with the novottf-100a system, a novel anti-mitotic device for the treatment of recurrent glioblastoma (rGBM). 4th Quadrennial Meeting of the World Federation of Neuro-Oncology held in Conjunction with the 18th Annual Meeting of the Society for Neuro-Oncology. 2013. San Francisco, CA.

Majd P, O'Connell D, Kim R, et al. Case of glioblastoma patient treated with NovoTTF therapy at recurrence degenerating to sarcoma. 19th Annual Scientific Meeting of the Society for Neuro-Oncology. 2014. Miami, FL. Case report.

Mrugala MM, Graham CA, Rockhill JK. Novo-TTF 100A system used successfully in a patient with a ventriculo-peritoneal shunt. 11th Congress of the European Association of Neuro-Oncology. 2014. Turin, Italy. Case report.

Muragaki Y, Nitta M, Okumura T, et al. Early Japanese experience with NovoTTF-100A system for recurrent GBM. 19th Annual Scientific Meeting of the Society for Neuro-Oncology. 2014. Miami, FL.

New P, Powell S. Pathology of cases of imaging progression in patients diagnosed with glioblastoma who have been treated with the novocure - TTF device in the EF-14 trial. 19th Annual Scientific Meeting of the Society for Neuro-Oncology. 2014. Miami, FL. Series of case reports.

Pless M, Betticher DC, Droege CM. A phase II clinical trial of tumor-treating field (TTF) therapy concomitant to pemetrexed for advanced non-small cell lung cancer (NSCLC). Annual Meeting of the American Society of Clinical Oncology. 2012. Chicago, IL.

Ram Z, Wong ET, Gutin PH. Comparing the effect of novottf to bevacizumab in recurrent GBM: A post-HOC sub-analysis of the phase III trial data. 6th Annual Scientific Meeting of the Society for Neuro-Oncology in Conjunction with the AANS/CNS Section on Tumors. 2011. Orange Country, CA.

Schaff L, Armentano F, Harrison C. Radiographic response of an incidental meningioma in a patient with glioblastoma on novoTTF therapy. 4th Quadrennial Meeting of the World Federation of Neuro-Oncology held in Conjunction with the 18th Annual Meeting of the Society for Neuro-Oncology. 2013. San Francisco, CA. Case report.

Stupp R, Wong E, Scott C. Interim analysis of the EF-14 trial: A prospective, multi-center trial of NovoTTF-100a together with temozolomide compared to temozolomide alone in patients with newly diagnosed GBM. 19th Annual Scientific Meeting of the Society for Neuro-Oncology. 2014. Miami, FL.

Sumrall A, Haggstrom D, Crimaldi A. Use of novoTTF-100a TM in heavily pre-treated patients with relapsed high grade glioma: A retrospective chart review. 4th Quadrennial Meeting of the World Federation of Neuro-Oncology held in Conjunction with the 18th Annual Meeting of the Society for Neuro-Oncology. 2013. San Francisco, CA.

Turner S, Gergel T, Lacroix M. The effect of field strength on GBM response in patients treated with novocure-ttf. 4th Quadrennial Meeting of the World Federation of Neuro-Oncology held in Conjunction with the 18th Annual Meeting of the Society for Neuro-Oncology. 2013. San Francisco, CA. Results published in peer-reviewed journal (study analyzed in present report).

Weinberg U, Kirson E, Farber O, et al. A phase II randomized study of NovoTTF therapy versus supportive care in non-small cell lung cancer patients with 1-5 brain metastases following optimal standard local treatment. 19th Annual Scientific Meeting of the Society for Neuro-Oncology. 2014. Miami, FL. Study design only.

Weinberg U, Kirson E, Farber O, et al. An open label pilot study of NovoTTF Therapy concomitant with gemcitabine for front-line therapy of advanced pancreatic adenocarcinoma (NCT01971281). 105th Annual Meeting of the American Association for Cancer Research. 2015. San Diego, CA. Study design only.

Wong E, Barron L, Hwong J, et al. Antimitotic NovoTTF therapy for a progressive glioblastoma patient with fournier gangrene: Non-interference with wound healing and why it works. 67th American Academy of Neurology Annual Meeting. 2015. Washington, DC. Case report.

Wong ET, Engelhard HH, Tran DD. An updated analysis of patient registry data on NovoTTF-100A alternating electric fields therapy for recurrent glioblastoma. 19th Annual Scientific Meeting of the Society for Neuro-Oncology. 2014. Miami, FL. Results published in peer-reviewed journal (study analyzed in present report).

Wong ET, Elzinga G, Chung A. Objective response in recurrent glioblastoma from adjuvant NovoTTF-100a and TCCC after temozolomide and bevacizumab failure. 138th Annual Meeting of the American Neurological Association. 2013. New Orleans, LA. Case report.

Wong ET, Lok E, Gautam S. Dexamethasone exerts profound interference on treatment efficacy for recurrent glioblastoma. 19th Annual Scientific Meeting of the Society for Neuro-Oncology. 2014. Miami, FL. Results published in peer-reviewed journal (study analyzed in present report).

Conducted in nonhuman animals

Castellví Q, Ginestà MM, Capellà G, Ivorra A. Tumor growth delay by adjuvant alternating electric fields which appears non-thermally mediated. *Bioelectrochemistry*. 2015;105:16-24. PMID: 25955102.

Giladi M, Weinberg U, Schneiderman RS, et al. Alternating electric fields (tumor-treating fields therapy) can improve chemotherapy treatment efficacy in non-small cell lung cancer both in vitro and in vivo. *Semin Oncol*. 2014;41 Suppl 6:S35-S41. PMID: 25213867.

Kirson ED, Giladi M, Gurvich Z, et al. Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs. *Clin Exp Metastasis*. 2009;26(7):633-640. PMID: 19387848.

Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. *Cancer Res*. 2004;64(9):3288-3295. PMID: 15126372.

Schneiderman RS, Shmueli E, Kirson ED, Palti Y. TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters. *BMC Cancer*. 2010;10:229. PMID: 20492723.

Appendix IV. Evidence Tables

Appendix IVa. Studies Assessing the Clinical Performance of Novocure for Glioblastoma

Key: AE(s), adverse event(s); BL, baseline; btwn, between; dx, diagnosis; dx'd, diagnosed; f/u, follow-up; fxn, function; GBM, glioblastoma; grp(s), group(s); HR(s), hazard ratio(s); hx, history; ITT, intention to treat; KPS, Karnofsky performance scale; mITT, modified ITT; MRI, magnetic resonance imaging; NA, not assessed; NR, not reported; OS, overall survival; PFS, progression-free survival; pt(s), patient(s); QOL, quality of life; RCT, randomized controlled trial; sx, symptom(s); TCCC, 6-thioguanine, lomustine, capecitabine, and celecoxib; TMZ, temozolomide; tx, treatment; WHO, World Health Organization

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
Kirson et al. (2007) ***Study design:*** Trial w/ historical controls ***Control/comparator:*** Historical control data (chemotherapy pts) ***Novocure tx:*** Novocure was applied daily for an average of 18 hrs per day until disease progression or for a maximum of 18 mos. ***Assessment of tumor response:*** Objective tumor assessment was performed by MRI based on criteria defined by Macdonald et al. (1990). ***Data analysis:*** Kaplan-Meier survival curves were generated for time to progression and OS. ***Funding source:*** Novocure Ltd. ***Conflict of interest:*** Study authors are either employees or stakeholders of Novocure or receive consulting fees from Novocure.	12 pts w/ recurrent GBM (mean age 51 yrs; mean KPS score 87) Historical control data were based on a large meta-analysis (Wong et al., 1999) as well as data from 4 prospective trials that included >50 recurrent GBM pts that had received chemotherapy. ***Inclusion criteria:*** Age >18 yrs; had histologically established GBM (WHO grade IV); recurrence based on Macdonald criteria; KPS score ≥70; ≥4 wks from brain surgery and ≥8 wks from radiotherapy ***Exclusion criteria:*** Significant comorbidities; infratentorial tumors; implanted pacemakers or clinically significant arrhythmias ***Setting:*** NR ***Previous tx:*** All pts had received adjuvant TMZ ***Number of previous episodes:*** NR ***Concurrent tx:*** NR	1 pt excluded due to failure to meet histological criteria for grade IV glioma; 1 pt withdrew consent immediately following BL visit. 10 pts were included in efficacy analysis. ***Median (range) time to disease progression:*** Novocure pts: 26.1 wks (3-124 wks) Historical control: 9.5 ± 1.6 wks Increase of 63.6% compared to historical controls. ***PFS at 6 mos (%, 95% CI):*** Novocure pts: 50% (23%-77%) Historical control: 15.3% ± 3.8% Increase of 69.4% compared to historical controls. ***Median (range) OS:*** Novocure pts: 62.2 wks (20.3-124.0 wks) Historical control: 29.3 ± 6 wks Increase of 52.9% compared to historical controls. ***Safety:*** No serious AEs occurred. Elevated liver enzymes were attributed to anti-epileptic drug usage. 2 pts had partial seizures unrelated to tx. No abnormal cardiac or neurologic activities were detected. 90% of pts had mild to moderate contact dermatitis beneath the electrode gel.	Very poor Small sample size. No btwn-grp statistical analyses. No concurrent control or comparator grp.
Kirson et al. (2009)	10 newly dx'd GBM pts (pt characteristics NR)	***Median PFS:*** Novocure pts: 155 wks	Very poor

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
Study design: Unclear: different design used for PFS and OS. For the outcome of PFS, a prospective cohort grp was matched w/ a concurrent cohort grp (no details on what was matched). For the outcome of OS, a prospective cohort grp was matched for age and KPS w/ a historical cohort grp. ***Control/comparator:*** TMZ only ***Novocure tx:*** Multiple 4-wk courses of continuous Novocure tx until progression (average 1 yr, range 2.5-24 mos). Pts received Novocure plus TMZ. ***Assessment of tumor response:*** Objective tumor assessment was performed by MRI based on criteria defined by Macdonald et al. (1990). ***Data analysis:*** Kaplan-Meier survival curves were generated for PFS and OS. Log-rank tests were used to detect significant differences btwn grps. ***Funding source:*** Novocure Ltd. ***Conflict of interest:*** Study authors are either employees or stakeholders of Novocure.	NOTE: This study also reports some data from 10 recurrent GBM pts that was previously reported in Kirson et al. (2007). PFS was compared to a matched grp of concurrent control pts who received TMZ only (n=32). OS was compared to matched historical control pts who received chemotherapy w/ the same KPS score (>60) and age (origin of historical control data NR). Details for matching NR. ***Inclusion criteria:*** Age ≥18 yrs; had histologically established GBM; KPS score ≥70; ≥4 wks from radiotherapy ***Exclusion criteria:*** Actively participating in another clinical trial; received anti-tumor tx in previous 4 wks; suspected radiation necrosis; implanted pacemakers or documented arrhythmias; significant renal, hepatic or hematologic disease; significant additional neurological disorder; seizure disorder unrelated to tumor; preexisting dementia; progressive degenerative neurological disorder; meningitis or encephalitis; hydrocephalus associated w/ increased intracranial pressure ***Setting:*** NR ***Previous tx:*** All pts had received radiotherapy ≥4 wks prior to study ***Number of previous episodes:*** None ***Concurrent tx:*** TMZ	Concurrent TMZ pts: 31 wks The difference btwn grps is significant (*P*=0.0002), HR 3.32 (95% CI, 1.9-5.9). ***Median OS:*** Novocure pts: 39 mos Historical control pts: 14.7 mos The difference btwn grps is significant (*P*=0.0018). ***Safety:*** No serious device-related AEs occurred. Dermatitis (grade 1-grade 2) occurred in 90% of pts, and appeared most often during the 2nd mo of tx. No increases in toxicity in TMZ were observed.	Small sample size. Origin of historical control data NR. Methods for recruiting and collecting data in concurrent TMZ grp NR. Grp characteristics NR.
Stupp et al. (2012); Kanner et al. (2014); Wong et al. (2014); Wong et al. (2015b) ***Study design:*** RCT	237 pts w/ recurrent GBM (median age 54 yrs; median KPS score 80; median time from initial dx 11 mos) ***Inclusion criteria:*** Age ≥18 yrs; had histologically established GBM (WHO grade IV); recurrence	In the Novocure grp, 116 of 120 pts (97%) started tx and 93 pts (78%) completed 4 wks of tx (1 cycle). In the control grp, 113 of 117 pts (97%) started chemotherapy and all but 1 pt completed 1 full tx course. Median (range) compliance for Novocure was 86% (41% to 98%) of the time in each tx cycle. Mean use was 20.6 hrs per day.	Fair Compliance in control grp NR. High loss to f/u in Novocure grp (22%).

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
Control/comparator: Chemotherapy (physician's choice) ***Novocure tx:*** Novocure was applied daily for an average of 20.6 hrs per day for each 4-wk tx cycle until disease progression or intolerance. Pts were instructed to use Novocure continuously w/ ≤2 1-hr breaks per day (≥22 hrs per day). Median f/u was 39 mos. ***Chemotherapy:*** Single agent or a combination chemotherapy containing bevacizumab (31%), irinotecan (31%), nitrosoureas (25%), carboplatin (13%), TMZ (11%), or other agents (5%) ***Assessment of tumor response:*** Objective tumor assessment was performed by MRI based on criteria defined by Macdonald et al. (1990). When an MRI could not be obtained, progression was assessed clinically based on neurological status, steroid dosing, AEs and investigator assessment of progression. ***Data analysis:*** Kaplan-Meier survival curves were generated for PFS and OS. Log-rank tests were used to detect significant differences btwn grps. All analyses were ITT. ***mITT post hoc analysis (Kanner et al., 2014):*** The mITT population included all Novocure pts that underwent ≥1 tx course (28 days), and all chemotherapy pts receiving ≥1 tx course of chemotherapy	based on Macdonald criteria; KPS score ≥70; adequate hematologic, renal and hepatic fxn; prior tx w/ radiotherapy ***Exclusion criteria:*** Infratentorial tumors; implanted pacemakers or clinically significant arrhythmias or programmable shunt ***Setting:*** 28 institutions in 7 countries ***Previous tx (Novocure grp, control grp):*** Debulking surgery: 79%, 85% Biopsy only: 21%, 15% Radiotherapy w/ TMZ: 86%, 82% Radiotherapy w/o TMZ: 13%, 17% Prior bevacizumab: 19%, 18% ***Number of previous episodes (Novocure grp, control grp):*** 1st recurrence: 9%, 15% 2nd recurrence: 48%, 46% ≥3rd recurrence: 43%, 39% ***Concurrent tx:*** None	***Partial or complete radiological response to tx:*** Novocure pts: 14.0% (95% CI, 7.9%-22.4%) Control pts: 9.6% (95% CI, 3.9%-18.8%) Btwn-grp difference NS (*P*=0.19) A non-inferiority analysis comparing chemotherapy to Novocure monotherapy found that the HR for death in the Novocure grp compared to the chemotherapy grp was below 1.0 (0.86; 95% CI 0.66–1.12), *P*=0.27, indicating that Novocure may be at least equivalent to active chemotherapy. ***PFS at 6 mos (%, 95% CI):*** Novocure pts: 21.4% (13.5%-29.3%) Control pts: 15.1% (7.8%-22.3%) Btwn-grp difference NS (*P*=0.13) ***OS at 6 mos, 12 mos, 24 mos*:*** Novocure pts: 63 pts (52.5%), 24 pts (20%), 9 pts (7.5%) Control pts: 56 pts (48%), 22 pts (19%), 6 pts (5%) In the active chemotherapy control grp, survival was not significantly affected by the choice of chemotherapy (Cox proportional hazards test; *P*=0.66). ***QOL:*** QOL data were available in 63 pts (27%) who had remained on tx for >3 mos. No meaningful differences were observed in global health and social fxn btwn grps. Cognitive and emotional fxn favored Novocure. Physical fxn was slightly worse w/ Novocure, while role fxn favored Novocure. A worse sx scale was directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy grp and not in the Novocure grp. Significance levels NR. ***mITT post hoc analysis:*** Median OS in mITT Novocure pts (7.8 mos) was significantly longer than mITT control pts (6.0 mos); HR 0.69; 95% CI, 0.52-0.92; *P*=0.0093. ***Responders vs nonresponders subgrp analysis:*** Median response duration was longer in Novocure pts (7.3 mos) than in chemotherapy pts (5.6 mos) (*P*=0.0009). Median OS was longer for responders than	

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
(delivery of the drug until recovery of blood counts or side effects, which usually requires 4 to 6 wks). ***Responders vs nonresponders post hoc analysis (Wong et al., 2014):*** Time to response, response duration, PFS, OS, prognostic factors, and relative HRs were compared btwn responders and nonresponders. ***High vs low daily dexamethasone dose post hoc analysis (Wong et al., 2015b):*** Using an unsupervised binary partitioning algorithm, cohorts were determined based on the dexamethasone dose that yielded the greatest statistical difference in OS to further investigate whether there was a threshold dose of dexamethasone that affected outcome. ***Funding source:*** Novocure Ltd. ***Conflict of interest:*** Several of the study authors are either employees of Novocure or receive consulting fees and/or research funding from Novocure.		nonresponders tx'd w/ Novocure (*P*<0.0001) and chemotherapy (*P*=0.0235). Response to tx was correlated w/ OS in Novocure pts (*P*=0.0002) but not in chemotherapy pts (*P*=0.2900). Hazard analysis showed delayed tumor progression in responders compared to nonresponders in both Novocure and control grps. Adjusted PFS was longer in responders than in nonresponders tx/d w/ Novocure (*P*=0.0007) or chemotherapy (*P*=0.0222). Mean cumulative dexamethasone dose was lower in responders (35.9 mg) than nonresponders (485.6 mg) in the Novocure cohort (*P*<0.0001). 5 of 14 responders in the Novocure cohort and 0 of 7 responders in the chemotherapy cohort had prior low-grade histology. ***High vs low daily dexamethasone dose post hoc analysis:*** Novocure pts who used dexamethasone >4.1 mg per day (64 pts) exhibited a significantly shortened median OS of 4.8 mos (95% CI, 3.9-6.0) than pts who used dexamethasone ≤4.1 mg per day (56 pts) that had a median OS of 11.0 mos (95% CI, 8.8-16.6). Chemotherapy pts who used dexamethasone >4.1 mg per day (54 pts) exhibited a significantly shortened median OS of 6.0 mos (95% CI, 3.5-8.3) than pts who used dexamethasone ≤4.1 mg per day (63 pts) that had a median OS of 8.9 mos (95% CI, 7.2-16.1). ***Compliance:*** Median OS was significantly higher in Novocure pts w/ a monthly compliance rate ≥75% (≥18 hrs per day; OS 7.7 mos) than in pts w/ a compliance <75% (OS 4.5 mos); *P*=0.042. ***Percentage of pts reporting AEs grade ≥2 (Novocure grp, chemotherapy grp):*** Leucopenia: 0%, 5% Neutropenia: 0%, 2% Thrombocytopenia: 1%, 7% Abdominal pain: 0%, 3% Diarrhea: 0%, 6% Nausea/vomiting: 2%, 7% General deterioration and malaise: 5%, 6% Infections: 4%, 8% Skin rash (transducer arrays): 2%, 0% Metabolism and nutrition disorders: 4%, 6% Musculoskeletal disorders: 2%, 5% Nervous system disorders: 30%, 28% Brain edema: 0%, 2%	

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
		Cognitive disorder: 2%, 2% Convulsion: 7%, 5% Dysphasia: 2%, 1% Headache: 8%, 6% Hemianopia: 1%, 3% Hemiparesis: 3%, 2% Neuropathy peripheral: 2%, 2% Psychiatric disorders: 5%, 4% Renal and urinary disorders: 3%, 3% Respiratory disorders: 1%, 3% Vascular disorders: 3%, 4% Pulmonary embolism: 1%, 2% Hypertension: 1%, 1% Deep vein thrombosis: 1%, 1% Significantly more gastrointestinal, hematological, and infectious AEs were seen in the chemotherapy grp than in the Novocure grp. ***Dermatologic AEs:*** 18 of 116 pts (16%) had grade 1 or grade 2 dermatologic AEs; 1 of 116 pts (1%) had a skin ulcer; no pts had grade 3 or grade 4 dermatologic AEs. Time to dermatologic AE onset was 2-6 wks from beginning of Novocure tx.	
Lacouture et al. (2014) ***Study design:*** Case series ***Control/comparator:*** None ***Novocure tx:*** NR ***Assessment of tumor response:*** NA ***Data analysis:*** Descriptive statistics only ***Funding source:*** NR ***Conflict of interest:*** Several study authors are consultants or employees of Novocure.	570 pts w/ AEs submitted in the postmarketing surveillance program ***Inclusion criteria:*** NR ***Exclusion criteria:*** NR ***Setting:*** NR ***Previous tx:*** NR ***Number of previous episodes:*** NR ***Concurrent tx:*** NR	***Postmarketing surveillance program:*** 156 of 570 pts (21.8%) had non-serious dermatologic AEs; 4 of 570 pts (0.7%) had a skin ulcer. The median time to dermatologic AE was 32.5 days (range 2-520). ***Potential risk factors for dermatologic AEs:*** Placement of ceramic disc(s) from the transducer arrays on the scalp overlying scars or craniotomy hardware; hx of contact dermatitis to tape adhesive or hydrogel; excessive sweating from hot, humid weather, fever, or occlusive wigs; previous skin exposure to ultraviolet or ionizing radiation; high doses or recent change in systemic corticosteroids; concurrent administration of systemic anticancer agent (e.g., chemotherapeutics, biologics, or targeted therapeutics). ***Proposed grading for dermatologic AEs:*** Grade 1: Asymptomatic or mild sx; topical antibiotic or corticosteroid indicated. Grade 2: Moderate sx, topical and systemic antibiotic or corticosteroid indicated; device application interruption; temporary relocation of device to avoid affected skin areas; or isolation by dressings of affected	Very poor No control or comparator grp. Postmarketing surveillance program was self-report data only. Duration of tx and pt characteristics NR.

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
		areas indicated. Grade 3: Severe or medically significant but not immediately life-threatening, topical and systemic antibiotic or corticosteroid indicated; operative intervention indicated; hospitalization or prolongation of existing hospitalization indicated; device application interruption indicated. Grade 4: Life-threatening consequences; urgent intervention indicated; device discontinuation indicated.	
Mrugala et al. (2014) ***Study design:*** Multicenter registry study w/ historical control data from Stupp et al. 2012 ***Control/comparator:*** None ***Novocure tx:*** ≥18 hrs per day for each 4-wk tx cycle ***Assessment of tumor response:*** NA ***Data analysis:*** Kaplan-Meier survival curves were generated for OS. Log-rank tests were used to detect significant differences btwn registry pts and historical control data. A log-rank test was used to compare relationship btwn OS and compliance, prior debulking surgery, recurrence number, and prior bevacizumab use. ***Funding source:*** Novocure Ltd. ***Conflict of interest:*** Study authors have received research funding from Novocure and/or served on advisory board for Novocure.	457 pts w/ recurrent GBM (mean age 55 yrs; mean KPS score 80) ***Inclusion criteria:*** Age ≥18 yrs; had histologically established GBM (WHO grade IV); recurrence based on Macdonald criteria; received tx w/ radiotherapy w/ or w/out chemotherapy ***Exclusion criteria:*** NR ***Setting:*** 91 oncology centers in the United States ***Previous tx:*** 55% had received bevacizumab, 78% had received radiotherapy plus TMZ, 64% had undergone debulking surgery, 4% had received carmustine wafers ***Number of previous episodes:*** 33% in 1st recurrence, 27% in 2nd recurrence, 27% in 3rd to 5th recurrence, 12.5% unknown ***Concurrent tx:*** NR	Median tx duration for the Novocure registry pts was 4.1 mos. Median tx duration in the Stupp et al. (2012) study was 2.3 mos for Novocure and 2.1 mos for chemotherapy. Historical data were from Novocure and chemotherapy control pts in Stupp et al. (2012). ***Median OS duration:*** Novocure registry pts: 9.6 mos Historical Novocure pts: 6.6 mos Historical chemotherapy pts: 6.0 mos Median OS was significantly longer in registry pts than in the historical Novocure grp and historical chemotherapy grp (*P*=0.0003). ***Median % OS at 1 yr, 2 yrs:*** Novocure registry pts: 44%, 30% Historical Novocure pts: 20%, 9% Historical chemotherapy pts: 20%, 7% ***Compliance*:*** Compliance data were available for 287 of the 457 registry pts (63%). Median daily compliance was 70% (of a 24-hr period; 16.8 hrs per day) for registry pts (range 12% to 99%). 127 pts (44%) had ≥75% compliance per day. Median OS was significantly longer in registry pts w/ a monthly compliance rate ≥75% (13.5 mos) than in pts w/ a compliance <75% (4.0 mos); *P*<0.0001. ***Other prognostic factors:*** Registry pts treated at their 1st GBM recurrence (20 mos) had a significantly longer OS compared w/ pts treated at 2nd recurrence (8.5 mos) or >2nd recurrence (4.9 mos) (*P*=0.0271). Registry pts that had received bevacizumab (7.2 mos) has significantly shorter OS than those that had not received bevacizumab (13.4 mos) (*P*=0.0070). Pts w/ a KPS of 90-100 had a significantly longer OS (14.8 mos) than pts w/ a KPS of 70-90 (7.7 mos) (*P*=0.0070) or KPS	Poor No concurrent control or comparator grp. Data on concomitant tx NR. Registry data is self-report.

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
		<70 (6.1 mos) (*P*<0.0001). ***% of pts reporting AEs:*** Skin reaction: 24.3% Heat sensation: 11.3% Neurological disorder: 10.4% Seizure: 8.9% Electric sensation: 7.7% Headache: 5.7% Pain/discomfort: 4.7% Fall: 3.9% Psychiatric disorder: 2.9% Gastrointestinal disorder: 2.9% Fatigue: 2.5% Vascular disorder: 1.6% Weakness: 1.4% Infections: 1.4% Eye disorder: 1.3%	
Vymazal and Wong (2014) ***Study design:*** Subgroup analysis of selected pts from Stupp et al. (2012) and Kirson et al. (2007) ***Control/comparator:*** None ***Novocure tx:*** Pts were instructed to use Novocure continuously w/ ≤2 1-hr breaks per day (≥22 hrs per day) for each 4-wk tx cycle ***Assessment of tumor response:*** Tumor response and progression were determined by blinded MRI review, according to Macdonald criteria ***Data analysis:*** Time to response, response duration, and OS were calculated using the Kaplan-Meier method. Pearson correlations were	130 pts w/ recurrent GBM that received Novocure monotherapy: 120 pts from Stupp et al. (2012) (mean age 54 yrs; mean KPS score 80; 77% male), 10 pts from Kirson et al. (2007) (mean age 53 yrs; mean KPS score 90; 70% male) ***Inclusion criteria:*** Age ≥18 yrs; histologically established GBM (WHO grade IV); recurrence based on Macdonald criteria; KPS score ≥70%; adequate hematologic, renal, and hepatic fxn; received prior radiotherapy w/ or w/o TMZ ***Exclusion criteria:*** Infratentorial tumor; implanted electronic medical devices ***Setting:*** NA (post-hoc analysis of 2 trials) ***Previous tx (Stupp et al. study, Kirson et al. study):*** Prior bevacizumab: 19%, 0% Median (range) number of prior lines of tx: 2 (1-5), 1 (1-3)	Only pts w/ a BL and ≥1 f/u MRI were included in the assessment. 110 of 130 pts (85%) met this criterion. ***Radiologic response to Novocure tx:*** Response: 16 of 110 pts (15%) Complete response: 4 of 110 pts (4%) ***Prognostic characteristics at BL (responders, nonresponders):*** KPS: 90, 80 Prior bevacizumab tx: 6%, 19% Secondary GBM upgraded from prior low-grade gliomas: 31%, 8% Median tumor size: 10.0 cm^2, 14.4 cm^2 Although prognostic characteristics were favorable in pts that responded to Novocure tx, differences btwn responders and nonresponders were NS. ***Median time to response:*** Responders: 5.2 mos Nonresponders: NA ***Median response duration:*** Responders: 12.9 mos Nonresponders: NA	Poor Retrospective design. No concurrent control or comparator grp. No btwn-grp statistical analyses.

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
conducted btwn response times and OS. ***Funding source:*** Novocure Ltd. ***Conflict of interest:*** Study author has received research funding from Novocure.	***Number of previous episodes:*** Kirson et al. (2007) pts: 50% at 1st recurrence Stupp et al. (2012) pts: 9% at 1st recurrence ***Concurrent tx:*** None	Response duration was highly correlated w/ OS (r^2=0.97; *P*<0.0001). ***Median OS:*** Partial and complete responders: 24.7 mos Stable disease: 7.6 mos Progressive disease: 5.5 mos All pts: 6.6 mos For 7 of the 16 responders (44%), MRI showed initial tumor growth. Median time to reversal of tumor growth in delayed responders was 4 mos. ***Compliance*:*** Average daily compliance was 83% (of a 24-hr period; 19.9 hrs per day). Response to tx was correlated w/ compliance (*P*<0.001). Partial and complete responders (14 pts) had an average compliance of 92%, pts w/ stable disease (34 pts) had an average compliance of 85% (34 pts), and pts w/ progressive disease had an average compliance of 79% (59 pts).	
Wong et al. (2015a) ***Study design:*** Retrospective cohort study ***Control/comparator:*** Novocure plus bevacizumab only vs. Novocure plus bevacizumab plus TCCC chemotherapy ***Novocure tx:*** NR ***TCCC chemotherapy:*** TCCC consists of administration of 6-thioguanine (80 mg/m^2 every 6 h from days 1-3), followed by lomustine (100 mg/m^2 orally on day 4), followed by capecitabine (825 mg/m^2 every 12 h) and celecoxib (400 mg every 12 h from days 11-24). The cycle is repeated every 42 days or 6 wks. ***Assessment of tumor response:*** MRI	37 pts w/ recurrent GBM that received either Novocure plus bevacizumab only (n=34) or Novocure plus bevacizumab plus TCCC (n=3) Novocure plus bevacizumab only grp: Median age 57 yrs; median KPS score 70; median dexamethasone dose 3.0 mg daily Novocure plus bevacizumab plus TCCC grp: Median age 56 yrs; median KPS score 70; median dexamethasone dose 2.8 mg daily ***Inclusion criteria:*** Recurrent GBM pts tx'd w/ Novocure and bevacizumab ***Exclusion criteria:*** NR ***Setting:*** Neuro-oncology clinic ***Previous tx:*** 70% of Novocure plus bevacizumab only pts and 100% of Novocure plus bevacizumab plus TCCC pts had received prior bevacizumab	***Median (range) PFS:*** Novocure plus bevacizumab only grp: 2.8 mos (0.1-20.7) Novocure plus bevacizumab plus TCCC grp: 8.1 mos (6.4-13.2) There was a NS trend found in favor of the TCCC grp (*P*=0.0585). ***Median (range) OS:*** Novocure plus bevacizumab only grp: 4.1 mos (0.3-22.7) Novocure plus bevacizumab plus TCCC grp: 10.3 mos (7.7-13.6) There was a NS trend found in favor of the TCCC grp (*P*=0.0951). ***Compliance:*** Average compliance was higher in the Novocure plus bevacizumab only grp (83.5%) than the Novocure plus bevacizumab plus TCCC grp (66.7%) (*P*=0.0670). ***Safety:*** NR	Very poor Retrospective. No concurrent control or comparator grp. Very small number of pts in TCCC grp (study was underpowered). Effect of Novocure cannot be isolated from bevacizumab.

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
Data analysis: 2-tailed Wilcoxon Rank Sum test w/ continuity correction was used to determine significant btwn-grp differences. ***Funding source:*** Novocure Ltd. ***Conflict of interest:*** Study authors have received research funding from Novocure.	***Number of previous episodes:*** Novocure plus bevacizumab only grp: 18% at 1st recurrence, 26% at 2nd recurrence, 26% at 3rd recurrence, 15% at 4th recurrence, and 15% at 5th recurrence Novocure plus bevacizumab plus TCCC grp: 67% at 2nd recurrence, 33% at 4th recurrence ***Concurrent tx:*** Bevacizumab only or bevacizumab plus TCCC tx		
Stupp et al. (2015) ***Study design:*** RCT ***TMZ tx:*** 150-200 mg/m^2/day was given for 5 days of each 28-day cycle for 6-12 cycles. If a pt experienced tumor progression, 2nd-line chemotherapy was offered per local practice. ***Novocure tx:*** Novocure was applied daily for ≥18 hrs/day for each 4-wk tx cycle until the 2nd radiological progression or clinical deterioration. Novocure was administered in combination w/ TMZ tx. Maximum tx was 24 mos. Median duration of Novocure tx was 9 mos (range 1-58) ***Control grp:*** Received TMZ tx alone ***Assessment of tumor response:*** Objective tumor assessment was performed by MRI based on criteria defined by Macdonald et al. (1990), and evaluated separately by 2 blinded radiologists ***Data analysis:*** PFS in the ITT	315 pts w/ newly dx'd GBM randomized to TMZ alone (n=105 pts) or TMZ plus Novocure (n=210 pts) (median age 57 yrs; median KPS score 90; median time from initial dx 3.8 mos) NOTE: This is an interim analysis. Publication of the full data set of 695 pts is pending. ***Inclusion criteria:*** Age ≥18 yrs; had histologically established GBM (WHO grade IV); progression free after having undergone maximal safe debulking surgery when feasible, or biopsy; had completed standard concomitant chemoradiotherapy w/ TMZ; KPS score ≥70; adequate bone marrow, renal, and hepatic fxn ***Exclusion criteria:*** Infratentorial tumors; severe comorbidities ***Setting:*** 83 institutions in the United States, Canada, Europe, Israel, and South Korea ***Previous tx (Novocure plus TMZ grp, TMZ only grp):*** Biopsy only: 11%, 11% Partial resection: 25%, 26% Gross total resection: 64%, 64% Carmustine wafers: 2%, 3% ***Number of previous episodes:*** None	196/210 (93%) Novocure plus TMZ pts completed at least 1 cycle of Novocure and TMZ tx; 84/105 (80%) TMZ only pts completed at least 1 cycle of TMZ. The median number of TMZ cycles until 1st tumor progression was 6 cycles (range 1-26) in the Novocure plus TMZ grp and 4 cycles (range 1-24) in the TMZ only grp. Two-thirds (n=141) of pts in the Novocure plus TMZ grp continued tx after 1st tumor progression. ***Median PFS (95% CI):*** Novocure plus TMZ grp: 7.1 mos (5.9-8.2 mos) TMZ only grp: 4.0 mos (3.3-5.2 mos) The Novocure plus TMZ grp had significantly longer PFS than the TMZ only grp (HR 0.62; 98.7% CI, 0.43-0.89; *P*=0.001) ***Median OS (95% CI) in the per-protocol analysis:*** Novocure plus TMZ grp (n=196): 20.5 mos (16.7-25.0 mos) TMZ only grp (n=84): 15.6 mos (13.3-19.1 mos) The Novocure plus TMZ grp had significantly longer OS than the TMZ only grp (HR 0.64; 99.4% CI, 0.42-0.98; *P*=0.004) ***Median OS (95% CI) in the ITT analysis:*** Novocure plus TMZ grp: 19.6 mos (16.6-24.4 mos) TMZ only grp: 16.6 mos (13.6-19.2 mos) The Novocure plus TMZ grp had significantly longer OS than the TMZ only grp (HR 0.74; 95% CI, 0.56-0.98; *P*=0.03) ***OS at 2 yrs:*** There were significantly more pts in the Novocure plus TMZ grp (43%) alive at 2 yrs f/u than in the TMZ only grp (29%) (*P*=0.006). ***Compliance:*** About 75% (n=157) of Novocure plus TMZ pts were	Fair Interim analysis. Compliance in control grp NR. High attrition in TMZ only grp (20%).

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
population (significance threshold of 0.01) and OS in the per-protocol population (significance threshold of 0.006) ***Per-protocol population:*** Defined as all pts who do not have any major protocol violations that would affect the endpoints being assessed; TMZ only pts who cross over to Novocure plus TMZ grp at progression will be excluded; all pts randomized to Novocure plus TMZ grp who received ≥1 full tx courses as defined in the protocol (1 maintenance cycle of TMZ and 28 days of Novocure tx); all pts randomized to TMZ only tx that received ≥1 TMZ cycles. (NOTE: This definition was derived from online supplemental material.) ***Funding source:*** Novocure Ltd. ***Conflict of interest:*** Several of the study authors are either employees of Novocure or receive consulting fees and/or research funding from Novocure.	***Concurrent tx:*** TMZ. If a pt experienced tumor progression, 2nd-line tx such as nitrosoureas, TMZ rechallenge, and bevacizumab were offered per local practice. Second-line tx was received by 67% of pts in the Novocure plus TMZ grp compared w/ 57% in the TMZ only grp. ~40% of 2nd-line tx included bevacizumab and ~40% included nitrosoureas. The type of chemotherapy used at recurrence was balanced between tx grps.	adherent to tx (i.e., wore the device >18 hrs/day during the first 3 tx mos). ***% of pts reporting AEs grade ≥3 (Novocure plus TMZ grp, TMZ only grp):*** Hematological disorders: 12%, 9% Cardiac disorders: 1%, 3% Eye disorders: 1%, 1% Gastrointestinal disorders: 5%, 2% Abdominal pain: 1%, 0% Constipation: 1%, 0% Diarrhea: 1%, 2% Vomiting: 1%, 1% General disorders: 8%, 5% Fatigue: 4%, 4% Infections: 5%, 5% Metabolism and nutrition disorders: 3%, 3% Musculoskeletal disorders: 4%, 3% Nervous system disorders: 22%, 25% Seizure: 7%, 8% Headache: 2%, 2% Psychiatric disorders: 4%, 3% Respiratory disorders: 2%, 1% Vascular disorders: 4%, 8% Mild anxiety, confusion, insomnia, and headaches were reported more frequently in Novocure plus TMZ pts and occurred mainly at the time of tx initiation. ***Dermatologic AEs:*** Mild to moderate skin irritation was observed in 43% of Novocure plus TMZ pts. Severe skin reaction (grades 3-4) was observed in 2% of pts. ***Mortality****:* 12 pts died of causes considered unrelated to tx; 8 (3.9%) pts died in the Novocure plus TMZ grp and 4 (4.0%) in the TMZ only grp.	

*Median duration of daily Novocure tx and percent (%) OS were calculated from data provided in the study.

Appendix IVb. Studies Assessing the Clinical Performance of Novocure for Cancers other than Glioblastoma

Key: AE(s), adverse event(s); CT, computed tomography; DM, diabetes mellitus; dx, diagnosis; ECOG, Eastern Cooperative Oncology Group; f/u, follow-up; fxn, function; GBM, glioblastoma; grp(s), group(s); hx, history; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; pt(s), patient(s); RECIST, Response Evaluation Criteria in Solid Tumors; tx, treatment

Authors/Study Design/ Protocol	Pt Characteristics	Main Findings	Quality/Comments
Salzberg et al. (2008) ***Study design:*** Case series ***Control/comparator:*** None ***Novocure tx:*** Novocure was applied daily for 23 hrs per day for 2 to 4 wks. ***Assessment of tumor response:*** Objective tumor assessment was performed by digital photography (skin lesion pts) or CT scan. ***Data analysis:*** Descriptive statistics only ***Funding source:*** NR ***Conflict of interest:*** 2 of the study authors are employees of Novocure.	6 pts w/ recurrent solid tumors (median age 66 yrs) 4 pts had skin lesions (2 pts w/ invasive ductal breast cancer, 1 pt w/ adenocarcinoma of the breast, and 1 pt w/ malignant melanoma on the thigh), 1 pt had GBM, and 1 pt had metastases from a mesothelioma in the retroperitoneal cavity. ***Inclusion criteria:*** Age ≥18 yrs; had histologically proven and locally advanced or metastatic malignant tumors; ≥1 measurable lesion; tumor location accessible to externally placed electrodes; ECOG performance ≤2; no additional standard tx available; no concomitant anti-tumor tx ***Exclusion criteria:*** NR ***Setting:*** Department of Oncology ***Previous tx:*** All pts had received several lines of tx (types and number of tx NR) ***Number of previous episodes:*** NR ***Concurrent tx:*** None	Pts were exposed to Novocure tx for 13 to 46 days. Compliance was >80%. ***Efficacy:*** Partial response: 1 pt (16.6%) w/ breast cancer had a 51% reduction in tumor size Stable disease: 3 pts (50%) w/ skin lesions due to breast cancer or melanoma had an arrest of tumor growth Disease progression: 1 pt w/ GBM (16.6%) experienced progressive disease Mixed response: 1 pt w/ mesothelioma (16.6%) had some tumor regression in the area of the tumor which was exposed to electrodes, while the other portions of the tumor were stable or progressive ***Safety:*** AEs were mild for all pts. The only AE related to tx was a reddening of the skin in 3 of 6 pts (50%). These lesions occurred beneath the electrodes and were reversible by repositioning the electrodes and topical steroid-containing ointments. No related abnormal laboratory values or serious AEs occurred.	Very poor Small sample size. No statistical analyses. No control or comparator grp. Relatively short duration of tx. Outcome measures not standardized or well-defined.
Pless et al. (2013) ***Study design:*** Case series ***Control/comparator:*** None ***Novocure tx:*** Novocure was applied daily for ≥12 hrs a day until disease progression or excessive toxicity. Pts received an average of 18 wks of Novocure (range 1-32).	41 pts w/ stage IIIB (w/ pleural effusion; 24%) or stage IV NSCLC (76%) (median age 63 yrs) ***Pt characteristics:*** 32 (78%) had adenocarcinoma, 7 (17%) pts had squamous cell carcinoma, 2 (5%) had large cell carcinoma; 7 (17%) pts had an ECOG performance status of 2; median time from the initial dx of NSCLC was 10.6 mos ***Inclusion criteria:*** Age ≥18 yrs; had histologically or cytologically proven stage IV or IIIB NSCLC, or locally	Median f/u time was 9.5 mos Average Novocure daily use was 11.2 hrs (93% compliance of the recommended 12 hrs per day) ***Efficacy:*** Complete response: 0% Partial response: 6 pts (14.6%) Stable disease: 20 pts (48.8%) Progression outside of tumor treating fields: 10 pts (24%) Progression inside of tumor treating fields: NR	Very poor Small sample size. No control or comparator grp. Relatively short duration of daily exposure to Novocure tx.

Authors/Study Design/ Protocol	Pt Characteristics	Main Findings	Quality/Comments
Pemetrexed tx: Pemetrexed was given at the standard dose of 500 mg/m^2 every 3 wks w/ adequate supportive tx (dexamethasone, folic acid, and vitamin B12). In case of an in-field response or stable disease w/ progression outside of the Novocure tx field, pemetrexed would be stopped and docetaxel could be initiated (35 mg/m^2 wkly). Pts received an average of 6.1 cycles of pemetrexed (range 1-33). ***Assessment of tumor response:*** CT scan of chest and abdomen according to RECIST criteria. ***Data analysis:*** Kaplan-Meier survival curves were generated for OS, PFS, and time to progression. ***Funding source:*** NR ***Conflict of interest:*** 1 study author is a contractor w/ Novocure.	advanced NSCLC not otherwise amenable to local tx (surgery or radiotherapy); ≥1 line of chemotherapy; measurable disease; ECOG performance ≤2; adequate bone marrow, hepatic, and renal fxn; life expectancy ≥12 wks; negative pregnancy test in women of child-bearing potential ***Exclusion criteria:*** Known brain metastases or meningeal carcinomatosis; other serious concomitant illness or medical conditions (e.g., congestive heart failure or angina pectoris unless medically controlled); hx of myocardial infarction w/in 1 yr; uncontrolled hypertension or arrhythmias; implanted electric devices such as pacemaker, defibrillator or deep brain stimulation device; hx of significant neurologic or psychiatric disorders; active infection requiring intravenous antibiotics; active ulcer; unstable DM or other contraindication to corticosteroid tx; concurrent tx w/ other experimental drug ***Setting:*** 4 medical institutions in Switzerland ***Previous tx:*** All pts had received 1-5 lines of chemotherapy; 5 (12%) had received surgery; 10 (24%) had received radiation; median time from last dose of chemotherapy was 14.9 wks ***Number of previous episodes:*** NR ***Concurrent tx:*** All pts received concomitant standard pemetrexed tx	Median daily tx in pts who had a partial remission was 13.5 hrs per day. ***Median PFS:*** 22.2 wks ***Median time to in-field progression:*** 28 wks ***Median OS:*** 13.8 mos ***1-yr survival:*** 57% ***Number (%) of pts reporting common AEs (grades 1-2, grades 3-4):*** Fatigue: 9 (21.9%), 1 (2.4%) Insomnia: 3 (7.3%), 0 (0%) Night sweats: 3 (7.3%), 0 (0%) Rash/dermatitis/erythema: 10 (24%), 1 (2%) Blister: 3 (7.3%), 0 (0%) Anorexia: 3 (7.3%), 2 (4.9%) Nausea: 3 (7.3%), 0 (0%) Constipation: 4 (9.7%), 0 (0%) Vomiting: 3 (7.3%), 0 (0%) Thoracic/chest/rib pain: 3 (7.3%), 2 (4.9%) Limb pain: 4 (9.7%), 0 (0%) Abdominal pain: 3 (7.3%), 0 (0%) Headache: 3 (7.3%), 0 (0%) Dyspnea: 8 (19%), 4 (10%) Cough: 11 (27%), 0 (0%)	

Appendix V. Summary of Practice Guidelines

Key: DVT, deep venous thrombosis; GBM, glioblastoma; KPS, Karnofsky Performance Scale; NSCLC, non-small cell lung cancer; pt(s), patient(s); RT, radiotherapy; TMZ, temozolomide; TTF, tumor treatment fields; tx, treatment/therapy

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
American Association of Neuroscience Nurses (AANN) (Lovely et al., 2014) *Care of the adult patient with a brain tumor*	*Surgery:* Nurses should monitor patients closely postoperatively for neurologic status, blood pressure, deficits and rehabilitation needs, seizure activity, infection, hydrocephalus, cerebrospinal fluid leaks, DVT, postoperative pain (Level 3 recommendation) and meningitis (Level 1 recommendation) *Radiation tx*: Nurses should be educated on radiation tx techniques and on biologic effects of radiation tx (Level 3 recommendation). Nurses should be aware of radiation dose and fractions based upon tumor type (Level 1 recommendation). Nurses should assess patients undergoing brain radiation tx for specific adverse effects (Level 1 recommendation). *Chemotherapy:* Nurses should be aware that bevacizumab can be administered to treat GBM recurrence (Level 2 recommendation) and nurses should monitor urinalysis and blood pressure following administration (Level 3 recommendation). Carmustine polymer wafers (Gliadel Wafers) may prolong survival when implanted into the resection cavity at the time of surgery for high-grade gliomas (Level 2 recommendation). Nurses should monitor patients for seizures and signs of infection and assess for adequate wound healing (Level 3 recommendation). For lomustine, nurses should administer antiemetics as needed; monitor weekly laboratory analysis, especially white blood cells and platelets; obtain periodic chest x-rays; and monitor for respiratory, liver, and kidney dysfunction (Level 3 recommendation). *TTF:* Nurses should be aware that use of electrical TTF may be considered a comparable tx option to chemotherapy for pts w/ recurrent malignant glioma, particularly when hematologic, infectious, or gastrointestinal toxicities limit tx options (Level 1 recommendation). When TTF are used, nurses should assess the skin for topical dermatitis (Level 1 recommendation). Nurses should educate pts about measures to improve comfort and compliance w/ the system (Level 3 recommendation). *Vaccine immunotherapy:* Nurses should also be knowledgeable about immune-based brain tumor tx currently in clinical trials (Level 3 recommendation).	3.5 – Poor (criteria for selecting evidence not described, methods for formulating recommendations not described, not externally reviewed by experts, guideline review and update process not described, conflicts of interest not declared)
American Association of Neurological Surgeons (AANS); Congress of Neurological Surgeons (CNS) (Olson et al., 2014a) *The role of cytotoxic chemotherapy in the management of progressive glioblastoma: a*	TMZ is recommended as superior to procarbazine in pts w/ first GBM relapse after having received nitrosourea chemotherapy or no prior cytotoxic chemotherapy at the time of initial tx (Level 2 recommendation). The use of polymer wafers is recommended in the management of progressive GBM as a surgical adjunct, taking into account the associated toxicities seen w/ this modality (Level 2	4 — Fair (systematic search methods and criteria for selecting evidence not described, methods for formulating recommendations not described, guideline not reviewed by external experts, guideline review and update process not described)

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
systematic review and evidence-based clinical practice guideline	recommendation). Consideration of a variety of cytotoxic chemotherapy agents of uncertain benefit is recommended in progressive GBM based on the judgment of the treating physician on an individual pt basis. It is recommended in such cases that enrollment in available clinical trials be encouraged (Level 3 recommendation). Novocure (TTF) was not mentioned in this guideline.	
American Association of Neurological Surgeons (AANS); Congress of Neurological Surgeons (CNS) (Olson et al., 2014b) *The role of targeted therapies in the management of progressive glioblastoma: a systematic review and evidence-based clinical practice guideline*	Tx w/ bevacizumab is recommended (Level 3 recommendation). Pts w/ progressive GBM should be enrolled in properly designed clinical trial to provide convincing evidence of therapeutic value (Strong recommendation). Novocure (TTF) was not mentioned in this guideline.	4 — Fair (systematic search methods and criteria for selecting evidence not described, methods for formulating recommendations not described, guideline not reviewed by external experts, guideline review and update process not described)
American College of Chest Physicians (ACCP) (Kozower et al., 2013; Lewis et al., 2013) *Special Treatment Issues in NSLC: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*	In general, the primary tx of localized tumors (stages I and II) is complete surgical resection. The majority of pts w/ lung cancer involving the mediastinal lymph nodes (stage III) are treated with chemotherapy and radiation tx. There are unusual presentations of NSCLC for which anatomic and biologic matters require a different approach. In addition, the presence of an isolated 2nd focus of cancer in a pt w/ lung cancer presents a situation where the biology may be unclear, and therefore the approach to tx is difficult. Novocure (TTF) was not mentioned in this guideline.	6—Good (keywords and search strings not specified, strengths and limitations of the body of evidence not clearly described, partial funding from pharmaceutical company)
American Society for Radiation Oncology (ASTRO) (Rodrigues et al., 2015) *Definitive radiation therapy in locally advanced NSCLC: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline*	For curative tx of locally advanced NSCLC, concurrent chemoradiation is recommended (Strong recommendation). There is no role for the routine use of induction chemotherapy before chemoradiotherapy or consolidation chemotherapy after chemoradiotherapy. Consolidation chemotherapy remains an option for pts who did not receive full systemic chemotherapy doses during RT (Strong recommendation). The ideal concurrent chemotherapy regimen has not been determined. The 2 most common regimens are cisplatin/etoposide and carboplatin/paclitaxel (Strong recommendation). For pts who cannot tolerate concurrent chemoradiotherapy, sequential chemotherapy followed by radical (definitive) radiation is recommended. RT alone may be used for pts ineligible for combined modality tx (Strong recommendation). Postoperative RT may be recommended for pts w/ complete resection of N2 (ipsilateral mediastinal nodal metastases) disease to improve local control, but should be delivered	4.5—Fair (criteria for selecting evidence not clearly described, strength and limitations of body of evidence not reported, funding source not disclosed, some members have potential conflicts of interest)

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
	sequentially after adjuvant chemotherapy. Postoperative RT is recommended for pts w/ incomplete resection, to be given either concurrently or sequentially w/ chemotherapy (Strong recommendation). Pts with resectable stage III NSCLC should be managed by a multidisciplinary team that uses best surgical judgment. The best candidates for preoperative chemoradiotherapy have preoperatively planned lobectomy (as opposed to pneumonectomy), no weight loss, female sex, and only 1 involved nodal station (Strong recommendation). Novocure (TTF) was not mentioned in this guideline.	
European Association of Neuro-Oncology (EANO) (Weller et al., 2014) *EANO guideline for the diagnosis and treatment of anaplastic gliomas and GBM*	GBM grade IV (age <65-70 yrs): Newly diagnosed: Resection or biopsy, followed by RT plus concurrent TMZ, followed by adjuvant TMZ Recurrent: Re-resection, reirradiation, rechallenge chemotherapy, or bevacizumab (Level A recommendation) GBM grade IV (age >65-70 yrs): Newly diagnosed: Resection or biopsy, followed by RT, or TMZ w/ or w/o RT Recurrent: Resection and chemotherapy or RT (Level A recommendation) At recurrence, standards of care are less well defined; nitrosourea regimens, TMZ rechallenge, and bevacizumab are options for pharmacotherapy; when available, recruitment into appropriate clinical trials should be considered. (Level B recommendation) New approaches, including suicide gene therapy, immunotherapy, or Novocure (TTF) should only be administered in the context of clinical trials.	3 — Poor (search strategy and criteria for selecting evidence not described, methods for formulating recommendations not described, strength and limitations of body of evidence not clearly described, not externally reviewed by experts, guideline review and update process not described, conflicts of interest not taken into account when forming recommendations)
European Society for Medical Oncology (ESMO) (Stupp et al., 2013) *High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, tx and follow-up*	Histological diagnosis is mandatory and should include sufficient tissue for molecular tumor characterization. Surgery is the first therapeutic intervention for all malignant glioma. For GBM, combined tx w/ TMZ and RT remains the standard of care. Novocure (TTF) compared with physicians' choice of chemotherapy in a randomized trial in recurrent GBM failed to prolong survival compared w/ chemotherapy (Strong recommendation).	3 — Poor (search strategy and criteria for selecting evidence not described, methods for formulating recommendations not described, strength and limitations of body of evidence not clearly described, not externally reviewed by experts, guideline review and update process not described, conflicts of interest not taken into account when forming recommendations)
European Society for Medical Oncology (ESMO) (Reck et al., 2014)	The tx strategy should take into account the histology, molecular pathology, age, performance status, comorbidities, and pt preference. Tx decisions should be discussed within a	3 — Poor (search strategy and criteria for selecting evidence not described, methods for formulating recommendations not

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
Metastatic NSCLC: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	multidisciplinary tumor board. Smoking cessation should be highly encouraged (Grade A recommendation). Systemic tx should be offered to all stage IV pts w/ performance status 0-2 (Grade A recommendation). The standard first-line chemotherapy is platinum-based doublet chemotherapy (Grade A recommendation). Pemetrexed is preferred to gemcitabine or docetaxel in pts w/ non-squamous tumors (Grade A recommendation). Bevacizumab combined with a paclitaxel-carboplatin regimen may be offered to pts w/ non-squamous histology NSCLC and performance status 0-1 after exclusion of contraindications (Grade A recommendation). The combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible pts w/ non-squamous NSCLC in the absence of contraindications (Grade A recommendation). Chemotherapy should be initiated while the pt has a good performance status. For most pts, 4 cycles of chemotherapy are recommended, w/ a maximum of 6 cycles (Grade B recommendation). Novocure (TTF) was not mentioned in this guideline.	described, strength and limitations of body of evidence not clearly described, not externally reviewed by experts, guideline review and update process not described, conflicts of interest not taken into account when forming recommendations)
European Society for Medical Oncology (ESMO) (Eberhardt et al., 2015) *2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III NSCLC*	For curative-intent tx, pts should be able to undergo platinum-based chemotherapy (preferably cisplatin) (Grade A recommendation). If N2 (ipsilateral mediastinal nodal metastases) disease is only documented intraoperatively, surgery should be followed by adjuvant chemotherapy (Grade A recommendation). Possible strategies include several options: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy (Grade A recommendation). In potentially resectable superior sulcus tumors, concurrent chemoradiotherapy induction followed by definitive surgery is the treatment of choice (Grade A recommendation). Concurrent chemoradiotherapy is the treatment of choice in pts evaluated as unresectable in stage IIIA and IIIB (Grade A recommendation). If concurrent chemoradiotherapy is not possible—for any reason—sequential approaches of induction chemotherapy followed by definitive RT represent a valid and effective alternative (Grade A recommendation). There is currently no role for prophylactic cranial irradiation in stage III NSCLC (Grade A recommendation).	3 — Poor (search strategy and criteria for selecting evidence not described, methods for formulating recommendations not described, strength and limitations of body of evidence not clearly described, not externally reviewed by experts, guideline review and update process not described, conflicts of interest not taken into account when forming recommendations)

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
	In the absence of contraindications, the optimal chemotherapy to be combined w/ radiation in stage III NSCLC should be based on cisplatin. There are no firm conclusions supporting single agent carboplatin as a radiation sensitizer (Grade A recommendation). In the stage III disease chemoradiotherapy strategy, 2-4 cycles of concomitant chemotherapy should be delivered (Grade A recommendation). The optimal surgical management aims at complete resection—preserving as much non-involved parenchyma as possible, preferably carried out by lobectomy/sleeve resection (Grade A recommendation). There is currently no role for targeted agents in stage III NSCLC outside clinical trials (Grade A recommendation). Novocure (TTF) was not mentioned in this guideline.	
National Comprehensive Cancer Network (NCCN) (Ettinger et al., 2015) *NSCLC*	Surgery: Resection is the preferred local tx modality. The role of surgery in pts w/ pathologically documented N2 disease remains controversial. RT has a role before or after surgery. Preoperative concurrent chemoradiotherapy is an option for pts w/ resectable stage IIIA (minimal N2 and treatable with lobectomy) and is recommended for resectable superior sulcus tumors. Preoperative chemotherapy and postoperative RT is an alternative for pts w/ resectable stage IIIA. RT: The standard of care for pts w/ inoperable stage II and stage III is concurrent chemoradiation tx. Sequential chemotherapy and RT or RT alone is appropriate for pts unable to tolerate concurrent tx. Accelerated RT regimens may be beneficial, particularly if not concurrent w/ chemotherapy. In pts w/ clinical stage I/II upstaged surgically to N2+, postoperative RT appears to improve survival significantly as an adjunct to postoperative chemotherapy. Postoperative RT is generally administered after postoperative chemotherapy. RT is recommended for local palliation or prevention of symptoms (such as pain, bleeding, or obstruction). Palliative RT should be individualized based on goals of care, symptoms, and performance status. Shorter courses of RT provide similar pain relief as longer courses, but with a higher potential need for retreatment, and are preferred for pts w/ poor performance status and/or shorter life expectancy. Chemotherapy: The drug regimen w/ the highest likelihood of benefit w/ toxicity deemed acceptable to both the physician and the pts should be given as initial tx for advanced lung cancer. Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared w/ best supportive care. Bevacizumab + chemotherapy or chemotherapy alone is indicated in performance status 0-1 pts w/ advanced or recurrent NSCLC. Bevacizumab should be given until disease progression. 2 drug	6 — Good (strengths and limitations of the body of evidence not clearly described, funding source not disclosed)

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
	regimens are preferred; a 3rd cytotoxic drug increases response rate but not survival. Single-agent therapy may be appropriate in select pts. Novocure (TTF) was not mentioned in this guideline.	
National Comprehensive Cancer Network (NCCN) (Nabors et al., 2014; NCCN, 2015) *NCCN Guidelines for Central Nervous System Cancers*	Surgery: Resection or biopsy is first-line tx. If feasible, maximal safe resection + carmustine wafer placed in cavity. If age ≤70 yrs and good KPS (≥60): Standard focal brain RT plus concurrent and adjuvant TMZ (Category 1) If age ≤70 yrs and poor KPS (<60): Standard or hypofractionated focal brain RT or TMZ or palliative care (Category 2A) If age >70 yrs and good KPS (≥60): Hypofractionated focal brain RT alone (Category 1) or standard focal brain RT plus concurrent and adjuvant TMZ or hypofractionated focal brain RT plus concurrent and adjuvant TMZ or TMZ alone (Category 2A) If age >70 yrs and poor KPS (<60): Hypofractionated focal brain RT or TMZ or palliative care (Category 2A) If recurrent GBM and diffuse disease: Palliative care (poor functional status) or systemic chemotherapy or surgery for symptomatic, large lesion or consider Novocure (TTF) tx (Category 2B). If recurrent GBM and local disease: Consider resection plus carmustine wafer if resectable, followed by palliative care (poor functional status) or systemic chemotherapy or consider reirradiation (Category 2B) or consider Novocure (TTF) tx (Category 2B). Novocure (TTF) was mentioned as an option in the tx algorithm for recurrent GBM. However, due to the lack of proven efficacy, not all panelists recommended the tx.	5 — Fair (systematic search methods and criteria for selecting evidence not described, strengths and limitations of the body of evidence not clearly described, source of funding not disclosed)

*According to the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors. Guidelines were scored on scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).