

## Medical Policy



### Title: Tumor Treating Fields Therapy

#### Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: • With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment	Interventions of interest are: • Tumor treating fields therapy as an adjunct to standard maintenance therapy	Comparators of interest are: • Standard maintenance therapy alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With progressive or recurrent glioblastoma multiforme	Interventions of interest are: • Tumor treating fields therapy as an adjunct or alternative to medical therapy	Comparators of interest are: • Standard medical therapy (e.g., bevacizumab, nitrosoureas, temozolomide rechallenge)	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With unresectable, locally advanced or metastatic, malignant pleural mesothelioma	Interventions of interest are: • Tumor treating fields therapy as an adjunct or alternative to medical therapy	Comparators of interest are: • Standard medical therapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity

**DESCRIPTION**

Tumor treatment fields (TTF) therapy is a noninvasive technology intended to treat glioblastoma and malignant pleural mesothelioma on an outpatient basis and at home using electric fields. Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Malignant pleural mesothelioma is an aggressive tumor with few treatment options that is associated with significant morbidity and mortality.

**OBJECTIVE**

The objective of this evidence review is to determine whether the use of tumor treating fields therapy improves the net health outcome for patients with solid tumors including glioblastoma multiforme and malignant pleural mesothelioma.

**BACKGROUND****Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.<sup>1</sup> GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors. The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in 1 report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.<sup>2</sup>

**Treatment of Newly Diagnosed Glioblastoma Multiforme**

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).<sup>3</sup> For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur in essentially all patients.

### **Treatment of Recurrent Glioblastoma Multiforme**

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.<sup>4</sup> There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

### **Malignant Pleural Mesothelioma**

Malignant pleural mesothelioma (MPM) is an aggressive tumor that is associated with significant morbidity and mortality. It is associated with asbestos exposure and has a latency period of about 40 years after asbestos exposure. Recommendations for treatment are mainly chemotherapy as first line with pemetrexed plus platinum. Surgical cytoreduction is also recommended in selected patients with early-stage disease. Adjuvant radiation can be offered for patients who have resection of intervention tracts found to be histologically positive or for palliation of symptomatic patients.

### **Regulatory Status**

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.<sup>5</sup> The FDA approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.<sup>6</sup>

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.<sup>7</sup> The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

In May 2019, FDA approved a modified version of the Optune System (NovoTTF-100A System), which is now called the Optune Lua™ System (NovoTTF™-100L System), for "treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy. The indication was modified from that granted for the Humanitarian Device Exemption designation to more clearly identify the patient population the device is intended to treat and in which the safety and probable benefit of the device is supported by the available clinical data." <sup>8</sup>,

To date, all of the existing tumor treating fields products fall under the brand name Optune®. In March 2020, the manufacturer of Optune products announced a plan to include a suffix after the brand name for newly approved indications to further delineate specific indications for individual products (e.g., Optune Lua).<sup>9</sup>

FDA product codes: NZK; QGZ.

**POLICY**

- A. Tumor treating fields therapy to treat glioblastoma multiforme may be considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:
1. Adult patients  $\geq 18$  years of age
  2. Supratentorial tumor
  3. Karnofsky Performance Status score  $\geq 70\%$
  4. Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).
- B. Tumor treating fields therapy is considered **experimental / investigational** in all other conditions including, but not limited to, the following situations:
1. As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
  2. As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
  3. For brain metastases
  4. For cancer in areas other than the brain
  5. As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for patients with malignant pleural mesothelioma.

**Policy Guidelines**

1. Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth  $>25\%$  compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).
2. The Food and Drug Administration label includes the following notices:
  - a. Patients should use Optune for at least 18 hours a day to get the best response to treatment
  - b. Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

**RATIONALE**

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through May 28, 2021.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed glioblastoma multiforme (GBM) patients following initial treatment with surgery, radiotherapy and chemotherapy; (2) TTF as an adjunct or alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent GBM; and (3) as treatment of adult patients with unresectable, locally advanced or metastatic malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy.

**TUMOR TREATING FIELDS THERAPY AS AN ADJUNCT TO STANDARD MAINTENANCE CARE FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME****Clinical Context and Therapy Purpose**

The purpose of tumor treating fields (TTF) therapy, also referred to as alternating electrical field therapy, is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with newly diagnosed GBM. Tumor treating fields therapy has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

The questions addressed in this evidence review is: Does the use of TTF therapy as an adjunct to standard maintenance therapy improve the net health outcome in patients with newly diagnosed GBM?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant populations of interest is patients who have newly diagnosed GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, radiotherapy (RT), and chemotherapy and be receiving maintenance chemotherapy.

### ***Interventions***

Tumor treating fields therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.<sup>4,10,11</sup> Tumor treating fields therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. Tumor treating fields therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.<sup>10,11</sup> Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune branded products (formerly NovoTTF-100A System) are the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

### ***Comparators***

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

Tumor treating fields therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.<sup>4</sup>

### ***Outcomes***

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and the time to tumor recurrence because most GBMs recur. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment, such as side effects of chemotherapy and the possibility of seizures, need to be assessed.

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

### **Study Selection Criteria**

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## REVIEW OF EVIDENCE

### Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.<sup>12</sup> The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The U.S. Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the U.S. Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).<sup>13</sup> At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

**Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2017) <sup>12</sup> ; EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	<ul style="list-style-type: none"> <li>• 695 newly diagnosed with GBM and treated by radiochemotherapy</li> <li>• KPS score <math>\geq</math>70</li> </ul>	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

E.U.: European Union; GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). Progression free survival increased by 2.7 months ( $p < .001$ )



and OS increased by 4.9 months ( $p < .001$ ) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ( $p < .01$ ).

There was a similar percentage of dropouts at the final analysis with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In a secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from "itchy skin".<sup>12</sup> Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

**Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma**

Study	Final N (%)	Median PFS (95% CI), months	Median OS (95% CI), months	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), months
Stupp et al (2017) <sup>12</sup> ,						
TTF + temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
P value		<.001	<.001	.58		.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable limitations identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment, and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

**Table 3. Study Relevance Limitations**

Study; Trial	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2017) <sup>12</sup> ; EF-14			3. Possible differences in post-progression treatment affecting overall survival		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 4. Study Design and Conduct Limitations**

Study; Trial	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Stupp et al (2017) <sup>12</sup> ; EF-14		1. No sham control and not blinded to treatment assignment				

The study imitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2.

Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### **Section Summary: Tumor Treating Fields Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed Glioblastoma Multiforme**

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment. However, PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

### **TUMOR TREATING FIELDS THERAPY AS AN ADJUNCT OR ALTERNATIVE TO MEDICAL THERAPY FOR PROGRESSIVE OR RECURRENT GLIOBLASTOMA MULTIFORME Clinical Context and Therapy Purpose**

The purpose of tumor treating fields (TTF) therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with progressive or recurrent

GBM. Tumor treating fields therapy has been investigated as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

The questions addressed in this evidence review is: Does the use of TTF therapy as an adjunct or alternative to standard medical therapy improve the net health outcome in patients with progressive or recurrent GBM?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant populations of interest is patients who have recurrent GBM with good performance status.

### ***Interventions***

The therapy being considered is TTF therapy as an adjunct or alternative to standard medical therapy.

### ***Comparators***

The following practice is currently being used to make decisions about progressive or recurrent GBM: standard medical therapy (eg, bevacizumab, nitrosoureas, temozolomide rechallenge).

### ***Outcomes***

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and the time to tumor recurrence because most GBMs recur. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment, such as side effects of chemotherapy and the possibility of seizures, need to be assessed. Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

### **Study Selection Criteria**

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## **REVIEW OF EVIDENCE**

### **Randomized Controlled Trials**

The 2011 U.S. Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).<sup>4</sup> This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term

chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

**Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2012) <sup>4</sup> ; EF-11	U.S., E.U., Israel	28	1987-2013	<ul style="list-style-type: none"> <li>• 237 adults with relapsed or progressive supratentorial glioblastoma</li> <li>• KPS score <math>\geq 70\%</math></li> </ul>	120 patients treated with TTF alone, 93 (78%) completed 1 cycle	117 patients treated with physician's choice of medical therapy <sup>a</sup>

E.U.: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

<sup>a</sup> Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, which included laboratory tests. Magnetic resonance images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. Quality of life questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, quality of life, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3 to 4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal quality of life data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control

group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal quality of life could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

**Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma**

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012) <sup>4</sup> ; EF-11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		.27	.16	.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; OS: overall survival; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

**Table 7. Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Stupp et al (2012) <sup>4</sup> ; EF-11			2. Physician's choice chemotherapy		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8. Study Design and Conduct Limitations**

<b>Study; Trial</b>	<b>Allocation<sup>a</sup></b>	<b>Blinding<sup>b</sup></b>	<b>Selective Reporting<sup>c</sup></b>	<b>Data Completeness<sup>d</sup></b>	<b>Power<sup>e</sup></b>	<b>Statistical<sup>f</sup></b>
Stupp et al (2012) <sup>4</sup> ; EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up; longitudinal QOL data were available for 27% of patients		1. Not designed as a noninferiority trial

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life; TTF: tumor treating fields.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.<sup>14</sup> Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ( $p=.043$ ).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).<sup>15</sup> Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 months) was reported as superior to that attained in the EF-11 pivotal trial (6.6 months,  $p<.001$ ) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

**Table 9. Characteristics of Key Nonrandomized Trial Results**

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017) <sup>14</sup> ,	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 months
Mrugala et al (2014) <sup>15</sup> ,	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	NR

E.U.: European Union; FU: follow-up; GBM: glioblastoma; NR: not reported; TTF: tumor treating fields.

**Table 10. Summary of Key Nonrandomized Trial Results**

Study	Median OS, months	Additional OS outcomes	
Kesari et al (2017) <sup>14</sup> ; EF-14	Median OS without bevacizumab, months	Median OS with bevacizumab, months	
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
Hazard ratio (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
P value	.049	.043	
Mrugala et al (2014) <sup>15</sup> ,	Median OS with TTF	1-Year OS, %	2-Year OS, %
PRiDe Registry	9.6	44	30
EF-11	6.6	20	9
Hazard ratio (95% CI)	0.66 (0.05 to 0.86)	NR	NR
P value	<.001	NR	NR

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.<sup>16</sup> They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.<sup>17</sup> The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group (p=.009). These post hoc analyses are considered to be hypothesis-generating.

### Section Summary: Tumor Treating Fields Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent Glioblastoma Multiforme

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared

with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogeneous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed quality of life data was approximately one-quarter of total enrollment, and the self-reported quality of life indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

## **TUMOR TREATING FIELDS THERAPY AS AN ADJUNCT TO PEMETREXED AND PLATINUM-BASED CHEMOTHERAPY FOR UNRESECTABLE, LOCALLY ADVANCED, OR METASTATIC MALIGNANT PLEURAL MESOTHELIOMA**

### **Clinical Context and Therapy Purpose**

The purpose of TTF therapy as an adjunct or alternative to standard medical therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with malignant pleural mesothelioma. Tumor treating fields has been investigated as an adjunct to pemetrexed and platinum-based chemotherapy for the treatment of unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM).

The question addressed in this evidence review is: Does the use of TTF therapy as an adjunct or alternative to standard medical therapy improve the net health outcome in patients with unresectable, locally advanced or metastatic, MPM.

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is patients with unresectable, locally advanced or metastatic, MPM.

### ***Interventions***

The therapy being considered is TTF as an adjunct or alternative to standard medical therapy.

Optune branded products (formerly NovoTTF-100A System) are the only legally marketed TTF delivery system available in the United States. For the treatment of malignant pleural mesothelioma, the Optune Lua system is used in the same way as the Optune system is used for glioblastoma; however, the 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved chest and back.

### ***Comparators***

The following practice is currently being used to make decisions about unresectable, locally advanced or metastatic, MPM: standard medical therapy with pemetrexed and platinum-based chemotherapy.



### Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment.

The time of interest for both progression-free survival and overall survival is months to years.

### Study Selection Criteria

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## REVIEW OF EVIDENCE

### Prospective Single-Arm Study

Tumor treatment fields therapy for patients with metastatic, MPM has been evaluated in 1 prospective, single-arm study (STELLAR).<sup>18</sup> Study characteristics and results are summarized in Tables 11 and 12.

The STELLAR study enrolled 80 patients with inoperable, previously untreated MPM. Patients were treated with cisplatin or carboplatin in combination with TTF therapy delivered by the NovoTTF-100L System at 12 sites outside the U.S. The primary outcome was OS as measured from start of study treatment until date of death. Secondary outcomes were PFS based on investigator assessment of computed tomography (CT) scan imaging, radiological response rate, 1 and 2 year survival rates, and safety.

Median OS was 18.2 months and median PFS was 7.6 months. Seventy-two of the 80 patients enrolled had at least 1 follow-up CT scan. Of those, 40% had a partial response, 57% had stable disease, and 3% progressed. The only adverse event associated with TTF treatment was skin reaction; this adverse event was mild to moderate for the majority of patients who experienced it (66%). The limitations of the STELLAR study are summarized in Tables 13 and 14. Because there was no control group, it is not possible to draw conclusions about the effectiveness of TTF therapy compared to standard medical care alone. Additional limitations include the small sample size and no reporting of symptoms or quality of life outcomes.

**Table 11. Summary of The STELLAR Single Arm Study**

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
STELLAR (2019) <sup>18</sup> ; NCT02397928	Prospective, single-arm, multicenter (12 sites)	E.U.	2015-2017	Age 18 years or older, with mesothelioma, not candidate for curative treatment (surgery or radiotherapy),	TTF (delivered by the NovoTTF-100L System) for ≥18 hours per day in combination with	Protocol specified minimum follow-up of at least 12 months

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
				≥1 evaluable lesion, ECOG Performance Status of 0 to 1, at least 4 weeks since last surgery, life expectancy at least 3 months, and able to operate the device independently or with help of a caregiver	pemetrexed and cisplatin or carboplatin  N=80	

ECOG: Eastern Cooperative Oncology Group; E.U.: European Union; TTF: tumor treating fields

**Table 12. Summary of The STELLAR Single Arm Study Results**

Study	Median OS (95% CI), months	Median PFS (95% CI), months	One-year Survival (95% CI)	2-year survival (95% CI)	Response
STELLAR (2019) <sup>18</sup> , NCT02397928	18.2 (12.1 to 25.8)	7.6 (6.7 to 8.6)	62.2% (50.3% to 72.0%)	41.9% (28.0% to 55.2%)	Of 72 who had a follow-up CT scan: 29/70 (40%) partial response 41 /70 (57%) stable disease 2/70 (3%) progressed

CI: confidence interval; CT: computed tomography; OS: overall survival; PFS: progression free survival

**Table 13. Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
STELLAR (2019) <sup>18</sup> , NCT02397928			2. No comparator	1. Quality of life not assessed	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 14. Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
STELLAR (2019) <sup>18</sup> , NCT02397928	1. Not randomized	1. Not blinded		1. 8 patients lost to follow-up (10%)		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### **Section Summary: Tumor Treating Fields Therapy as an Adjunct to Pemetrexed and Platinum-based Chemotherapy for Unresectable, Locally Advanced, or Metastatic Malignant Pleural Mesothelioma**

For patients with metastatic MPM, TTF therapy has been evaluated in 1 prospective, single-arm study conducted in 80 patients (STELLAR). The STELLAR study enrolled 80 patients with inoperable, previously untreated MPM who were treated with cisplatin or carboplatin in combination with TTF therapy at 12 sites outside the U.S. Median OS was 18.2 months and median PFS was 7.6 months. Seventy-two of the 80 patients enrolled had at least 1 follow-up CT scan. Of those, 40% had a partial response, 57% had stable disease, and 3% progressed. Because there was no control group, it is not possible to draw conclusions about the effectiveness of TTF therapy compared to standard medical care alone. Additional limitations include the small sample size and no reporting of symptoms or quality of life outcomes.

### **Summary of Evidence**

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, PFS was assessed by blinded evaluators, and the placebo effects on the objective measure of OS are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized

comparative studies. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (OS) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable, locally advanced or metastatic, MPM who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes 1 single-arm observational study conducted in 80 patients. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. In patients who received TTF therapy in combination with pemetrexed and cisplatin or carboplatin, median overall survival was 18.2 months (95% CI 12.1 to 25.8 months). Because there was no comparison group, it is not possible to make conclusions about the effectiveness of the intervention compared to medical therapy alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **SUPPLEMENTAL INFORMATION**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

#### **Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

#### **2016 Input**

In response to requests, input was received from 3 physician specialty societies (1 of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

#### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given

to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on central nervous system cancers (v. 5.2020) include recommendations for the treatment of glioblastoma (see Table 15).<sup>3</sup> For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O<sup>6</sup>-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

**Table 15. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status**

Age, y	KPS Score, %	Treatment Options	Category
≤70	≥60	<ul style="list-style-type: none"> <li>Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> <li>Standard RT plus concurrent and adjuvant temozolomide</li> </ul>	1
≤70	<60	<ul style="list-style-type: none"> <li>Hypofractionated RT with/without concurrent or adjuvant temozolomide</li> <li>Temozolomide</li> <li>Palliative/best supportive care</li> </ul>	2A
>70	≥60	<ul style="list-style-type: none"> <li>Hypofractionated RT plus concurrent and adjuvant temozolomide<sup>a</sup></li> <li>Standard RT plus concurrent and adjuvant temozolomide plus TTF</li> </ul>	1
>70	<60	<ul style="list-style-type: none"> <li>Hypofractionated brain RT alone</li> <li>Temozolomide alone</li> <li>Palliative/best supportive care</li> </ul>	2A

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

<sup>a</sup> Hypofractionated RT plus concurrent and adjuvant temozolomide is only a Category 1 recommendation in patients with methylated O<sup>6</sup>-methylguanine-DNA methyltransferase promotor status

The National Comprehensive Cancer Network guidelines on malignant pleural mesothelioma (v. 2.2021) do not address tumor treating fields as a treatment option for malignant pleural mesothelioma.<sup>19</sup>

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 16. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and

pancreatic cancer. Tumor treating fields therapy is an active area of research for mechanisms underlying its effects on cancer cells.

**Table 16. Summary of Key Trials**

<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
<i>Ongoing</i>			
NCT03940196 <sup>a</sup>	ENGOT-ov50 / GOG-3029 / INNOVATE-3: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 200kHz) Concomitant With Weekly Paclitaxel for the Treatment of Platinum-resistant Ovarian Cancer (PROC)	540	Sep 2023
NCT02663271 <sup>a</sup>	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma	18	Mar 2022
NCT02831959 <sup>a</sup>	Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS)	270	Sep 2022
NCT02973789 <sup>a</sup>	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	534	Sep 2023
NCT03377491 <sup>a</sup>	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3)	556	Sep 2023
<i>Unpublished</i>			
NCT01971281 <sup>a</sup>	A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (unknown)
NCT01894061 <sup>a</sup>	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Jul 2019 (completed)

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

**CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.**

**Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.**

**CPT/HCPCS**

A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

**ICD-10 Diagnoses**

C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain

**REVISIONS**

08-01-2018	Policy added to the bcbsks.com web site on 08-01-2018.
09-27-2019	Policy posted to the bcbsks.com website on 08-28-2019 with an effective date of 09-27-2019.
	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item B, added "As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for patients with malignant pleural mesothelioma."</li> </ul>
	Updated Rationale section.
	Updated References section.
04-19-2021	Updated Description section
	Updated Rationale section.
	Updated References section.
09-17-2021	Updated Rationale section.
	Updated References section.

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