# Medical Policy

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## Title: Tumor Treating Fields Therapy

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| Related Policies: | ▪ *Stereotactic Radiosurgery and Stereotactic Body Radiotherapy* |

| **Professional / Institutional** |
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| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| Individuals:<br>• With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment | Interventions of interest are:<br>• Tumor treating fields therapy as an adjunct to standard maintenance therapy | Comparators of interest are:<br>• Standard maintenance therapy alone | Relevant outcomes include:<br>• Overall survival<br>• Disease-specific survival<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With progressive or recurrent glioblastoma multiforme | Interventions of interest are:<br>• Tumor treating fields therapy as an adjunct or alternative to medical therapy | Comparators of interest are:<br>• Standard medical therapy (e.g., bevacizumab, nitrosoureas, | Relevant outcomes include:<br>• Overall survival<br>• Disease-specific survival<br>• Quality of life |

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| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| | | temozolomide rechallenge) | • Treatment-related morbidity |
| Individuals:<br>• With unresectable, locally advanced or metastatic, malignant pleural mesothelioma | Interventions of interest are:<br>• Tumor treating fields therapy as an adjunct or alternative to medical therapy | Comparators of interest are:<br>• Standard medical therapy | Relevant outcomes include:<br>• Overall survival<br>• Disease-specific survival<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With metastatic non-small cell lung cancer who are receiving an immune checkpoint inhibitor or docetaxel and have progressed on or after a platinum-based regimen | Interventions of interest are:<br>• Tumor treating fields therapy | Comparators of interest are:<br>• Standard medical therapy | Relevant outcomes include:<br>• Overall survival<br>• Progression-free survival<br>• Quality of life<br>• Treatment-related morbidity |

## DESCRIPTION

Tumor treating fields (TTF) therapy is a noninvasive technology intended to treat glioblastoma, malignant pleural mesothelioma, and non small cell lung cancer on an outpatient basis and at home using electrical fields. Collectively, these cancers are associated with significant morbidity and mortality and additional treatment options are heavily desired.

## OBJECTIVE

The objective of this evidence review is to determine whether the use of tumor treating fields therapy improves the net health outcome for individuals with solid tumors including glioblastoma multiforme, malignant pleural mesothelioma, and non-small cell lung cancer (NSCLC).

## BACKGROUND

### Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.[1,] Glioblastomas are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all primary malignant brain tumors. Mean age at GBM diagnosis is 65 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; the 5-year survival rate and average length of survival are estimated at 6.9% and 8 months, respectively.[2,]

### 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.

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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 (RT), 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 $O^6$-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see 2.04.113 on *MGMT* promotor methylation for malignant gliomas).

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).[3,] For patients with good performance status, the most aggressive treatment (standard 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 RT 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 (eg, 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%.[4,] 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.

**Non-small Cell Lung Cancer**
Lung cancer, including non-small cell lung cancer (NSCLC), is the leading cause of cancer-related death in the United States.[5,] There are numerous treatment options for NSCLC which have improved survival rates. Patients eligible for targeted or immunotherapies now have 5-year survival rates up to 62.5%. Tumor treating fields have been studied in combination with immune

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checkpoint inhibitors (i.e., PD-1/PD-L1 inhibitors) or docetaxel in patients with metastatic NSCLC who progressed with platinum-based therapy.[6,]

**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.[7,] 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®.[8,]

In October 2015, FDA expanded the indication for Optune in combination with temozolomide to include newly diagnosed GBM.[9,] 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, the 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." [10,] In September 2021, the FDA granted breakthrough designation to the NovoTTF-200T System for use together with atezolizumab and bevacizumab for the first-line treatment of patients with unresectable or metastatic liver cancer.[11,]

In October 2024, Optune Lua was approved for "metastatic non-small cell lung cancer along with concurrent drug treatments in adults who have progressed on or after a platinum-based chemotherapy." [6,]

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 (eg, Optune Lua).[12,] Optune was renamed Optune Gio™ in 2023. [13,]

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## POLICY

A. Tumor treating fields therapy to treat glioblastoma multiforme (GBM) may be considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in individuals with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

1. Individuals ≥18 years of age
2. Supratentorial tumor
3. Karnofsky Performance Status score ≥70%
4. Individual understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the U.S. 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 individuals with progressive or recurrent glioblastoma multiforme
2. As an alternative to standard medical therapy for individuals 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 individuals with malignant pleural mesothelioma.
6. As an adjunct to standard medical therapy for individuals with non-small cell lung cancer (NSCLC).

## POLICY GUIDELINES

A. 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 individual during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

B. Per the pivotal trial, individuals ≥18 years of age were eligible for enrollment. The median individual age was about 56 years with a range of 19 to 83 years; subgroup analyses for younger age groups were not provided.

C. The recommended Karnofsky Performance Status (KPS) varies from the NCCN guideline (score ≥60). In the pivotal trial the median KPS score at baseline was 90.0, with a range from 60 to 100. Subgroup analyses for individuals with score 60 to 70 were not provided.

D. The U.S. Food and Drug Administration label includes the following notices:

1. Individuals should use Optune for at least 18 hours a day to get the best response to treatment
2. Individuals 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.

E. A Karnofsky score of ≥70% is comparable to an ECOG score of 0 to 1.

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## RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through April 6, 2026.

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, 5 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 (RT) and chemotherapy; (2) TTF as an adjunct or alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent GBM; (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; and (4) TTF with an immune checkpoint inhibitor or docetaxel after progression on or after a platinum-based regimen in metastatic NSCLC.

## TUMOR TREATING FIELDS THERAPY AS AN ADJUNCT TO STANDARD MAINTENANCE CARE FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

### Clinical Context and Therapy Purpose

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

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### *Populations*
The relevant population of interest is individuals who have newly diagnosed GBM and good performance status. Newly diagnosed individuals would have undergone initial treatment with surgery, 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.[4,14,15,] Tumor treating fields therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (150 or 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.[14,15,] 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.[4,]

### *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 (PFS) and overall survival (OS) is months.

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**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.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

## REVIEW OF EVIDENCE

### *Systematic Reviews*

Regev et al (2021) conducted a systematic review of studies describing the use of TTF therapy for the treatment of GBM.[16,] The authors included a total of 20 studies of patients with newly diagnosed GBM and recurrent GBM. For newly diagnosed GBM (n=542), only 1 RCT was identified (Stupp et al, 2017), which is described in further detail in the section below. The remainder of the data for newly diagnosed GBM was observational. The pooled median OS and PFS in newly diagnosed patients was 21.7 months (95% confidence interval [CI], 19.6 to 23.8) and 7.2 months (95% CI, 6.1 to 8.2) months, respectively. The pooled rate of OS at 1, 2, and 3 years was 73.5%, 45.1%, and 29.3%, respectively. The pooled rate of PFS at 6, 12, and 18 months was 55.9%, 32.4%, and 21.7%, respectively. Statistical comparisons to other treatment modalities were not provided.

### *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.[17,] 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 RT 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 PFS, and the secondary outcome was 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 (FDA) 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

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at this time. The interim analysis, which the U.S. FDA considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).[18,] 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)[17,]; EF-14 | U.S., E.U., South Korea, Israel | 83 | 2009-2016 | • 695 newly diagnosed with GBM and treated by radiochemotherapy<br>• KPS score ≥70 | 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). PFS 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".[17,] 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.

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**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)[17,] | | | | | | |
| 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; a 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 measurement 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[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| Stupp et al (2017)[17,]; EF-14 | | | 3. Possible differences in post-progression treatment affecting OS | | |

OS: overall survival.
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. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

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[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

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

| Study; Trial | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Stupp et al (2017)[17]; 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.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

### 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. In a systematic review that included the EF-14 trial along with other observational studies, the pooled median OS and PFS in newly diagnosed patients who received TTF therapy was 21.7 months and 7.2 months, respectively.

## 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 TTF therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with progressive or recurrent GBM. Tumor

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

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

***Populations***
The relevant populations of interest is individuals 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 PFS and OS 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.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

**REVIEW OF EVIDENCE**

***Systematic Reviews***
A systematic review by Regev et al (2021) is introduced above.[16,] For patients with recurrent GBM (n=1094), only 2 RCTs were identified (Stupp et al [2012] and post hoc analysis of Kesari et al [2017]), which are described in further detail in the section below. The remainder of the data for recurrent GBM was observational. For patients with recurrent GBM, the pooled median OS and PFS were 10.3 months (95% CI, 8.3 to 12.8) and 5.7 (95% CI, 2.8 to 10) months, respectively. The pooled rate of OS at 1, 2, and 3 years was 43.7%, 21.3%, and 14%, respectively. The pooled rate of PFS at 6, 12, and 18 months was 47.8%, 29.3%, and 19.7%, respectively. As previously noted, statistical comparisons to other treatment modalities were not provided.

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### *Randomized Controlled Trials*

The 2011 U.S. FDA 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).[4,] 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 RT, 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)[4,]; EF-11 | U.S., E.U., Israel | 28 | 1987-2013 | • 237 adults with relapsed or progressive supratentorial glioblastoma<br>• KPS score ≥70% | 120 patients treated with TTF alone, 93 (78%) completed 1 cycle | 117 patients treated with physician's choice of medical therapy[a] |

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

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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), which 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 | PFS | | OS (95% CI), % | | |
|---|---|---|---|---|---|---|---|
| | | | Median, mo | Rate at 6 Months (95% CI), % | 1 Year | 2 Years | 3 Years |
| Stupp et al (2012)[4]; 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; PFS: progression-free survival; TTF: tumor treating fields.

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## Table 7. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| Stupp et al (2012)[4]; 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.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

## Table 8. Study Design and Conduct Limitations

| Study; Trial | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Stupp et al (2012)[4]; 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.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

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### *Nonrandomized Comparative Studies*

Zhu et al (2022) conducted a prospective, post-marketing registry study (the EF-19 study) to evaluate the safety and efficacy of TTF versus physician's choice standard of care in patients from the EF-11 study with recurrent glioblastoma.[19,] The patient population was comprised of patients already enrolled in the PRiDe registry and included a total of 309 patients. Primary and secondary endpoints assessed included OS in the intention-to-treat (ITT) and per-protocol (PP) populations. In the ITT population, median OS in patients treated with TTF was comparable to physician's choice of standard of care (7.4 vs 6.4 months, respectively; log-rank test p=.053). The Cox test HR was 0.66 (95% CI, 0.47 to 0.92; p=.016). In the PP population, median OS in patients treated with TTF was significantly longer than patients treated with standard of care (8.1 vs 6.4 months; log-rank test p=.017). The Cox test HR was 0.60 (95% CI, 0.42 to 0.85; p=.004). Tumor treating fields therapy showed a favorable safety profile as well.

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.[20,] 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).[21,] 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 |
|---|---|---|---|---|---|---|---|
| Zhu et al (2022)[19,] | Registry | U.S | 2016 - 2018 | 309 patients with recurrent GBM | 192 patients treated with TTF already enrolled in the PRiDe registry | 117 patients in the SOC cohort from the EF-11 study | 12 months |
| Kesari et al (2017)[20,] | 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 |

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| Study | Study Type | Country | Dates | Participants | TTF | Controls | FU |
|---|---|---|---|---|---|---|---|
| Mrugala et al (2014)[21,] | 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; SOC: standard of care; TTF: tumor treating fields.

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

| Study | Median OS, months | Additional OS outcomes | |
|---|---|---|---|
| Zhu et al (2022)[19,] | Median OS with TTF (ITT population), months | Median OS with TTF (PP population), months | |
| TTF monotherapy | 7.4 | 8.1 | |
| Physician's choice SOC | 6.4 | 6.4 | |
| HR (95%, CI) | 0.66 (0.47 to 0.92) | 0.60 (0.42 to 0.85) | |
| p-value | .016 | .004 | |
| Kesari et al (2017)[20,]; 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 | |
| HR (95% CI) | 0.70 (0.48 to 1.00) | 0.61 (0.37 to 0.99) | |
| p-value | .049 | .043 | |
| Mrugala et al (2014)[21,] | Median OS with TTF | 1-Year OS, % | 2-Year OS, % |
| PRiDe Registry | 9.6 | 44 | 30 |

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| Study | Median OS, months | Additional OS outcomes | |
|---|---|---|---|
| EF-11 | 6.6 | 20 | 9 |
| HR (95% CI) | 0.66 (0.05 to 0.86) | NR | NR |
| p-value | <.001 | NR | NR |

CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR: not reported; OS: overall survival; PP: per-protocol;SOC: standard of care; 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.[22,] 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.[23,] 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. Two registry studies also evaluated real-world outcomes in patients enrolled in the PRiDe registry compared to patients in the EF-11 study. In a systematic review that included the RCT and post hoc analysis of the EF-14 trial, along with other observational studies, the pooled median OS and PFS in patients with recurrent GBM who received TTF therapy was 10.3 months and 5.7 months, respectively

## TUMOR TREATING FIELDS THERAPY AS AN ADJUNCT OR ALTERNATIVE TO STANDARD MEDICAL THERAPY FOR UNRESECTABLE, LOCALLY ADVANCED, OR METASTATIC MALIGNANT PLEURAL MESOTHELIOMA

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## 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 individuals 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 following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest is individuals 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 PFS and OS 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.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

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## Review of Evidence

Tumor treatment fields therapy for patients with metastatic, MPM has been evaluated in 1 prospective, single-arm study (STELLAR)[24,] and a much smaller single-arm retrospective study of 5 patients at a single US center.[25,]

### *Prospective Single-Arm Study*

The STELLAR study enrolled 80 patients with inoperable, previously untreated MPM. Study characteristics and results are summarized in Tables 11 and 12. 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.

In STELLAR the 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)[24]; 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 RT), ≥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<br>N=80 | TTF (delivered by the NovoTTF-100L System) for ≥18 hours per day in combination with pemetrexed and cisplatin or carboplatin | Protocol specified minimum follow-up of at least 12 months |

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

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**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)[24]; 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[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| STELLAR (2019)[24]; 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. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

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

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| STELLAR (2019)[24]; 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.

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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.

### Retrospective Studies

Kutuk et al (2022) published a single-arm retrospective study of 5 patients with unresectable MPM who received TTF therapy from 2019 to 2021 at a single center in the US.[25,] The median follow-up was 5.4 months (range, 1.1 to 20.9). All patients were also treated with pemetrexed plus platinum-based chemotherapy. The median number of 4-week TTF cycles was 5 (range, 2 to 7) and the median TTF device usage in the first 3 months was 12.5 hours per day (range, 5 to 16.8). Treatment-related dermatitis was the only side effect associated with TTF and was reported as grade 1 to 2 in all patients; no patient had grade 3+ device-related toxicities. The authors note that this was the first publication of real-world implementation of TTF for MPM.

### Section Summary: Tumor Treating Fields Therapy as an Adjunct or Alternative to Standard Medical Therapy for Unresectable, Locally Advanced, or Metastatic Malignant Pleural Mesothelioma

For patients with metastatic MPM, TTF therapy has been evaluated in a prospective, single-arm study conducted in 80 patients (STELLAR) and a retrospective study of 5 US patients. 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. The retrospective study is the first publication of real-world implementation of TTF for MPM.

## TUMOR TREATING FIELDS THERAPY WITH CONCURRENT STANDARD CARE FOR METASTATIC NON-SMALL CELL LUNG CANCER

### Clinical Context and Therapy Purpose

The purpose of 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 individuals with metastatic NSCLC. Tumor treating fields therapy has been investigated with a concurrent immune checkpoint inhibitor (i.e., a PD-1/PD-L1 inhibitor) or docetaxel after progression on or after a platinum-based regimen.

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

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### *Populations*
The relevant population of interest is individuals who have metastatic NSCLC and are concurrently treated with an immune checkpoint inhibitor or docetaxel and have progressed on or after a platinum-based regimen.

### *Interventions*
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 bag while carrying out activities of daily living. For the treatment of NSCLC, transducer arrays with insulated electrodes are applied to the patient's chest cavity. The transducer array layout is typically determined using specialized software. The minimum daily treatment for NSCLC is 12 hours.

### *Comparators*
The following practice is currently being used to make decisions about metastatic NSCLC in individuals who have progressed on or after a platinum-based regimen: PD-1/PD-L1 inhibitors or docetaxel alone.

### *Outcomes*
The general outcomes of interest are whether TTF improves survival or quality of life.

The time of interest for both PFS and OS 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.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

## REVIEW OF EVIDENCE

### *Randomized Controlled Trials*
Leal et al (2023) published results of LUNAR (NCT02973789), a randomized, open-label phase 3 RCT that evaluated TTF for metastatic NSCLC.[26,] The trial included 276 patients from 130 sites who had metastatic NSCLC and were receiving an immune checkpoint inhibitor (nivolumab, pembrolizumab, or atezolizumab) or docetaxel following progression on or after platinum-based therapy (see Table 15). Patients were at least 22 years of age and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. The primary endpoint was OS with key secondary endpoints of PFS and overall response rate. Median follow-up was 10.6 months (interquartile range [IQR, 6.1-33.7) for patients receiving TTF therapy with standard therapy, and 9.5 months (IQR, 0.1-32.1) for patients receiving standard therapy. Results are summarized in Table 16.

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**Table 15. Key Randomized Controlled Trial Characteristics for Metastatic NSCLC**

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | *Active* | *Comparator* |
| Leal et al (2023)[26]; LUNAR | Countries in North America, Europe, and Asia | 130 | 2017-2021 | 276 patients with metastatic NSCLC who had progression on or after platinum-based therapy | TTF to achieve an average of at least 18 h/d plus immune checkpoint inhibitor or docetaxel (n=137) | Immune checkpoint inhibitor or docetaxel alone (n=139) |

NSCLC: non-small cell lung cancer; TTF: tumor treatment fields.

**Table 16. Key Randomized Controlled Trial Results for Metastatic NSCLC**

| Study | Median OS (95% CI), months | Median PFS (95% CI), months | Overall response rate (95% CI), % | Overall AEs, % | Serious AEs, % |
|---|---|---|---|---|---|
| Leal et al (2023)[26]; LUNAR | | | | | |
| TTF + standard therapy | 13.2 (10.3 to 15.5) | 4.8 (4.1 to 5.7) | 20.4 (14.0 to 28.2) | 97 | 19 |
| Standard therapy alone | 9.9 (8.1 to 11.5) | 4.1 (3.1 to 4.6) | 17.3 (11.4 to 24.6) | 91 | 15 |
| HR (95% CI) | 0.74 (0.56 to 0.98) | 0.85 (0.67 to 1.11) | NR | NR | NR |
| p-value | .035 | .23 | .5 | NR | NR |

AEs: adverse events; CI: confidence interval; HR: hazard ratio; NR: not reported; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 17 and 18 display notable limitations identified in this trial; a major limitation is the lack of patient blinding to treatment assignment. In addition, due to the rapidly changing landscape in

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the treatment of NSCLC, many of the patients did not receive current standard of care immunotherapy.

**Table 17. Study Relevance Limitations**

| Study; Trial | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| Leal et al (2023)[26]; LUNAR | 3. Enrolled population did not fully reflect treatment with current baseline testing and medical therapy standard of care | | | | |

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. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

**Table 18. Study Design and Conduct Limitations**

| Study; Trial | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Leal et al (2023)[26]; LUNAR | | 1. No sham control and not blinded to treatment assignment | | | 4. Original sample size of 534 patients was reduced to 276 at an unplanned interim analysis | |

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The study imitations 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; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

**Section Summary: Tumor Treating Fields Therapy with Concurrent Standard Care for Metastatic Non-small Cell Lung Cancer**
Analysis of the LUNAR trial, a phase 3, open-label RCT in 267 patients, found a significant 3.3-month OS improvement when TTF was added to standard care (immune checkpoint inhibitor or docetaxel) compared to standard care alone. Overall response rates and PFS were not significantly different between groups, and serious AEs were more common in the group treated with TTF. The trial is limited by the lack of a sham comparator, a lack of baseline molecular testing, and changes in standard of care.

**Summary of Evidence**
For individuals who have newly diagnosed glioblastoma multiforme (GBM) on maintenance therapy after initial treatment who receive tumor treating fields (TTF) therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT) and a systematic review. Relevant outcomes include overall survival (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 progression-free survival (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. In a systematic review that included the EF-14 trial along with other observational studies, the pooled median OS and PFS in newly diagnosed patients who received TTF therapy was 21.7 months and 7.2 months, respectively. 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, nonrandomized comparative studies, and a systematic review of these data. 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

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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. Two registry studies also evaluated real-world outcomes in patients enrolled in the PRiDe registry compared to patients in the EF-11 study. In a systematic review that included the RCT and post hoc analysis of the EF-14 trial, along with other observational studies, the pooled median OS and PFS in patients with recurrent GBM who received TTF therapy was 10.3 months and 5.7 months, respectively. 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, malignant pleural mesothelioma (MPM) who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a single-arm prospective study conducted in 80 patients and a retrospective study of 5 US 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 OS was 18.2 months (95% confidence interval [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 retrospective study is the first publication of real-world implementation of TTF for MPM. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have metastatic non-small cell lung cancer (NSCLC) who receive TTF with concurrent standard care including an immune checkpoint inhibitor or docetaxel and who have progressed on or after platinum-based therapy, the evidence includes an open-label RCT conducted in 276 patients. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The LUNAR trial found a significant increase of 3.3 months in OS with TTF in combination with an immune checkpoint inhibitor or docetaxel, but there was no significant improvement in PFS or overall response rate. The trial is limited by the lack of a sham comparator, a lack of baseline molecular testing, and changes in standard of care. 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.

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### *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.3.2025 ) include recommendations for the treatment of glioblastoma (see Table 23 ).[3,] For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate $O^6$-methylguanine-DNA methyltransferase promoter 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 (i.e., tumor treating fields [TTF]) is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

**Table 23. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status**

| Age, y | KPS Score,% | Treatment Options | Category |
|---|---|---|---|
| ≤70 | ≥60 | • Standard RT plus concurrent and adjuvant temozolomide plus TTF (preferred)<br>• Standard RT plus concurrent and adjuvant temozolomide | 1 |
| ≤70 | ≥60 | • Standard RT alone (for unmethylated MGMT promoter status only) | 2A |
| ≤70 | ≥60 | • Standard RT plus concurrent and adjuvant lomustine and temozolomide (for methylated or indeterminate MGMT promoter status only) | 2B |
| ≤70 | <60 | • Hypofractionated RT with/without concurrent or adjuvant temozolomide<br>• Temozolomide alone<br>• Palliative/best supportive care | 2A |

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| | | | |
|---|---|---|---|
| >70 | ≥60 | • Hypofractionated RT plus concurrent and adjuvant temozolomide (for methylated or indeterminate MGMT promoter status only)<br>• Standard RT plus concurrent and adjuvant temozolomide plus TTF | 1 |
| >70 | ≥60 | • Standard RT plus concurrent and adjuvant temozolomide<br>• Temozolomide alone (for methylated or indeterminate MGMT promoter status only)<br>• Hypofractionated RT alone (for unmethylated MGMT promoter status only)<br>• Hypofractionated RT plus concurrent and adjuvant temozolomide (for unmethylated MGMT promoter status only) | 2A |
| >70 | ≥60 | • Hypofractionated RT alone (for methylated or indeterminate MGMT promoter status only) | 2B |
| >70 | <60 | • Hypofractionated brain RT alone<br>• Temozolomide alone<br>• Palliative/best supportive care | 2A |

KPS: Karnofsky Performance Status; MGMT: $O^6$-methylguanine-DNA-methyltransferase; RT: radiotherapy; TTF: tumor treating fields.

The National Comprehensive Cancer Network guidelines on malignant pleural mesothelioma (v.2.2026 ) do not address TTF as a treatment option for malignant pleural mesothelioma.[27,]

The National Comprehensive Cancer Network guidelines on non-small cell lung cancer (NSCLC)(v.5.2026 ) do not address TTF as a treatment option for NSCLC.[5,]

**Congress of Neurological Surgeons**
In 2022, the Congress of Neurological Surgeons released guidelines on role of cytotoxic chemotherapy and other cytotoxic therapies in the management of progressive glioblastoma.[28,] In regard to TTF use in adult patients with progressive glioblastoma, the Congress states that "the use of TTF with other chemotherapy may be considered when treating adult patients with progressive glioblastoma [pGBM]. There is insufficient evidence to recommend TTF to increase overall survival in adult patients with pGBM".

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

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**Table 24. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| *Ongoing* | | | |
| NCT06558799[a] | LUNAR-4: Pilot, Single Arm, Open-Label, Multinational Study of Tumor Treating Fields (TTFields, 150 kHz) Concomitant With Pembrolizumab for the Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Previously Treated With a PD-1/PD-L1 Inhibitor and Platinum-Based Chemotherapy | 69 | Jan 2026 |
| NCT06353360[a] | Tumor-Treating Fields (TTFields) in Combination With Temozolomide and Tislelizumab in The Treatment of Newly Diagnosed Glioblastoma: A Safety and Efficacy Clinical Study | 30 | Mar 2026 (unknown status) |
| NCT06558214 | OPTIMUS PRIME: Safety and Feasibility of OPTune GIO® Integrated With MRI-gUided Laser Ablation Surgery and Pembrolizumab for Recurrent GlIoblastoMa, A randomizEd Trial | 20 | Oct 2029 |
| NCT06556563[a] | A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Optune® (TTFields, 200 kHz) Concomitant With Maintenance Temozolomide and Pembrolizumab Versus Optune® Concomitant With Maintenance Temozolomide and Placebo for the Treatment of Newly Diagnosed Glioblastoma (EF-41/KEYNOTE D58). | 741 | Apr 2029 |
| NCT04471844[a] | EF-32: Pivotal, Randomized, Open-Label Study of Optune® (Tumor Treating Fields, 200kHz) Concomitant With Radiation Therapy and Temozolomide for the Treatment of Newly Diagnosed Glioblastoma | 981 (actual) | Feb 2026 |
| *Unpublished* | | | |
| NCT02663271[a] | 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 | 10 | Jun 2021 (terminated) |

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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## 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 |

| **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:<br>▪ In Item B, added "As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for patients with malignant pleural mesothelioma." |
| | 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. |
| 8-23-2022 | Updated Description Section |
| | Updated Policy Guidelines<br>▪ Added: "A Karnofsky score of ≥70% is comparable to an ECOG score of 0 to 1." |
| | Updated Rationale Section |
| | Updated Coding Section<br>▪ Added ICD-10 code C71.9 and Converted ICD-10 Codes to range |
| | Updated References Section |
| 08-22-2023 | Updated Description Section |
| | Updated Policy Guidelines<br>▪ Added policy guideline B and C<br>"B. Per the pivotal trial, patients ≥18 years of age were eligible for enrollment. The median patient age was about 56 years with a range of 19 to 83 years; subgroup analyses for younger age groups were not provided." |

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| REVISIONS | |
|---|---|
| | "C. The recommended Karnofsky Performance Status (KPS) varies from the NCCN guideline (score ≥60). In the pivotal trial the median KPS score at baseline was 90.0, with a range from 60 to 100. Subgroup analyses for patients with score 60 to 70 were not provided." |
| | Updated Rationale Section |
| | Updated Coding Section<br>▪ Removed ICD-10 Codes |
| | Updated References Section |
| 08-27-2024 | Updated Description Section |
| | Updated Rationale Section |
| | Updated References Section |
| Posted 08-26-2025<br>Effective 09-25-2025 | Updated Description Section |
| | Updated Policy Section<br>Added: Section B.6.<br>1. As an adjunct to standard medical therapy for individuals with non-small cell lung cancer (NSCLC). |
| | Updated Rationale Section |
| | Updated References Section |
| 07-14-2026 | Updated Description Section |
| | Updated Rationale Section |
| | Updated Reference Section |
| 10-27-2026 | Updated Description Section |
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