Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

---

***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Tumor Treating Fields Therapy

Description/Background

Glioblastoma multiforme is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treatment fields (TTF) therapy is a noninvasive technology intended to treat glioblastoma using electrical fields.

Tumor Treating Fields potentially causes cancer cells to die by using alternating electric fields to disrupt cell division, which is believed to inhibit tumor growth. The electrical currents are delivered to a malignant tumor site via insulated electrodes that are placed around the region of the body containing the tumor.

BACKGROUND

GLIOBLASTOME MULTIFORME

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.(1) 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 49.1% of all primary malignant brain tumors. Mean age at GBM diagnosis is 65 years. GBM have the lowest survival rate of any central nervous system tumor; the 5-year survival rate and average length of survival is 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, 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 two 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 for malignant gliomas.

Prognostic factors for therapy success are age, histology, and 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 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 in all patients.

Treatment of Recurrent GBM

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%.(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.

Advanced Heptacellular Cancer

TheraBionic® P1 is a portable battery-driven generator coupled with a spoon shaped antenna. The antenna is placed on the tongue and is purported to deliver tumor specific radiofrequency electromagnetic fields (e.g. liver cancer frequencies which target liver cancer cells). Each treatment episode lasts 28 days and consists of 1-hour sessions 3 times per day at home by the individual until progression of malignancy is documented.

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.(5) 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®.(6)

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed glioblastoma.(7) 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 Humanitarian Device Exemption indication was modified in order 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."(8)

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.(9)

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).(10) Optune was renamed Optune Gio™ in 2023. (11)

In September of 2023, the FDA granted a humanitarian device exemption (HDE) to TheraBionics, Inc for TheraBionic P1. The HDE is contingent upon periodic reports and a post-approval study. Areas of focus include: (1) overall survival representing the period starting at the date of treatment initiation until death; and 2) quality of life and/or (3) other patient reported outcomes. The TheraBionic P1 medical device is intended for the treatment of persons ≥18 years of age with advanced hepatocellular carcinoma who fail first and second line therapy.

The brief FDA overview information indicates that the TheraBionic P1 device shows a probable benefit of overall survival when compared to similar groups of people who receive a placebo treatment. This information populated from a small clinical trial of 41 adults, 14 patients (34.1%) had stable disease for more than 6 months.

FDA product code: NZK, QGZ, QOM

Medical Policy Statement

The safety and effectiveness of tumor-treatment fields (TTF) therapy has been established. It is a useful therapeutic option for individuals meeting specific selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Treatment of newly diagnosed, histologically confirmed supratentorial glioblastoma multiforme when the following criteria are met:

- Adults (22 years of age and older) when one of the following apply:
  - Used as an adjunct therapy to standard treatments that include maximal debulking surgery and completion of radiation together with the chemotherapy drug temozolomide (TMZ)
  - Continued as maintenance therapy, after TMZ completion, in responsive tumors

Monotherapy as an alternative to standard medical therapy in the reoccurrence of histologically or radiologically confirmed supratentorial glioblastoma multiforme tumor

Exclusions:
Tumor treating field therapy with any of the following:

- Combined with chemotherapy other than TMZ
- As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for individuals with malignant pleural mesothelioma
- When used for any indications other than those listed above

---

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

A4555 E0766 95999

Other codes (investigational, not medically necessary, etc.):

A9900 E0767 E1399 77299

Rationale

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or alternative to medical therapy (e.g., bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (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 alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for individuals with newly diagnosed GBM. TTF 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.

Populations

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

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.(4,12,13) TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by two 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.(12,13) 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.

TTF 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, because most GBMs recur, the time to tumor recurrence. 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.

Study Selection
- 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 longer 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 duplicate 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.(13) 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.(15) 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 (QOL) 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 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 at this time. The interim analysis, which the FDA considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).(16) At the time of the interim analysis, data were available for 210 patients 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) EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	• 695 newly diagnosed with GBM and treated by radiochemotherapy • 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 (i.e., temozolomide). PFS increased by 2.7 mo ($p<0.001$) and OS increased by 4.9 mo ($p<0.001$) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ($p<0.01$).

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 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”.(15) 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

	Median PFS	Median OS	Systemic Adverse

Study	Final N (%)	(95% CI), mo	(95% CI), mo	Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), mo
Stupp et al (2017)						
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		<0.001	<0.001	0.58		0.01

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 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. Relevance Limitations

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

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.

[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) EF-14		1. No sham control and not blinded to treatment assignment				

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; 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: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly diagnosed GBM

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 (i.e., temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but 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.

TTF THERAPY AS AN ADJUNCT OR ALTERNATIVE TO MEDICAL THERAPY FOR PROGRESSIVE OR RECURRENT GBM

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

Populations

The relevant population 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 (e.g., 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.
- 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.

Systematic Reviews

A systematic review by Regev et al (2021) is introduced above.(14) 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%, and19.7%, respectively. As previously noted, statistical comparisons to other treatment modalities were not provided.

Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A system (now called Optune) was based on a phase 3, multinational randomized controlled trial (RCT) (EF11), 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 adult who had relapsed or progressive glioblastoma multiforme (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) EF-11	U.S., E.U., Israel	28	1987-2013	• 237 adults with relapsed or progressive supratentorial glioblastoma • 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]

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.
[a] Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (i.e., carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL 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, QOL, 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 I and II contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade II, III, or IV events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade II or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade II or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades III-IV) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL 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 QOL 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) 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		0.27	0.16	0.13			

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. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]

Stupp et al (2012) EF-11	2. Physician's choice chemotherapy

The evidence 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[d]	Data Completeness[e]	Power[d]	Statistical[f]
Stupp et al (2012) 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 1. 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.
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.

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.(17) 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.(18) 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=0.043).

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).(19) 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 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, p<0.001) (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)	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)	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 mo
Mrugala et al (2014)	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

EU: 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)	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) 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	0.049	0.043	
	Median OS with TTF	**1-Year OS, %**	**2-Year OS, %**
Mrugala et al (2014)			
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	<0.001	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 non-responders in the active treatment and active treatment control.(20) They found that responders had a lower grade of histology and lower daily dexamethasone use than non-responders. 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.(21) The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group (p=0.009). These post hoc analyses are considered to be hypothesis-generating.

Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. 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 heterogenous, 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 QOL data was approximately one-quarter of total enrollment, and the self-reported QOL 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

TTF THERAPY AS AN ADJUNCT OR ALTERNATIVE TO STANDARD MEDICAL THERAPY FOR UNRESECTABLE, LOCALLY ADVANCED, OR METASTATIC MALIGNANT PLEURAL MESOTHELIOMA

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for malignant pleural mesothelioma. TTF has been investigated as an adjunct to pemetrexed and platinum-based chemotherapy for the treatment of unresectable, locally advanced or metastatic, malignant pleural mesothelioma.

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, malignant pleural mesothelioma.

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, malignant pleural mesothelioma: 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
- 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 longer 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
TTF therapy for patients with metastatic, malignant pleural mesothelioma (MPM) has been evaluated in 1 prospective, single-arm study (STELLAR),(22) and a much smaller single-arm retrospective study of 5 patients at a single US center.

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 13 sites outside the U.S. The primary outcome was overall survival as measured from start of study until date of death. Secondary outcomes were progression free survival based on investigator assessment of CT scan imaging, radiological response rate, 1- and 2-year survival rates, and safety.

In STELLAR the median overall survival was 18.2 months and median progression free survival was 7.6 months. Seventy-two of the 80 patients enrolled had at least one 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 FDA (2019) NCT02397928	Prospective, single-arm, multicenter (12 sites)	E.U.	2015-2017	Age 18 years or older, with mesothelioma, Stage IV, not candidate for curative treatment (surgery or radiotherapy), ≥1evaluable lesion, ECOG Performance Status of 0 to 1, at least 4 weeks since last surgery, life expectancy at least 3 months; able to operate the device independently or with help of a caregiver	TT Fields (delivered by the NovoTTF-100L System) for ≥18 hours per day in combination with emetrexed and cisplatin or carboplatin N=80	Protocol specified minimum follow-up of at least 12 months

ECOG: Eastern Cooperative Oncology Group; EU: European Union; TTF: tumor treating fields

Table 12. Summary of The STELLAR Single Arm Study Results

Study	Median Overall Survival (95% CI)	Median Progression-free Survival (95% CI)	One-year Survival (95% CI)	2-year survival (95% CI)	Response
STELLAR FDA (2019) NCT02397928	18.2 months (12.3 to 25.8)	7.6 months (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; 14/70 (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 FDA (2019) 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 FDA (2019) NCT02397928	1. not randomized	1. not blinded	3. not published	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.

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.(23) 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: TTF Therapy as an Adjunct or Alternative to Standard Medical Therapy for Unresectable, Locally Advanced, or Metastatic Malignant Pleural Mesothelioma

For patients with metastatic, malignant pleural mesothelioma TTF therapy has been evaluated in 1 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 overall survival was 18.2 months and median progression free survival 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.

Radiofrequency Electromagnetic Field Exposure as an Adjunct to Hepatocellular Carcinoma Treatment

Hepatocellular carcinoma (HCC) not only has a poor prognosis but is one of the world's deadliest and fastest-growing tumors. Standard of care for HCC consists of curative resection, surgery (liver transplantation), trans-arterial chemoembolization, radioembolization, radiofrequency ablation and chemotherapy; however, only a very limited percentage of individuals benefit from these modalities. Current treatments for advanced HCC are also known to exacerbate the existing liver condition, which in turn may decrease both quality and

quantity of life. Despite promising preclinical and early-phase clinical trials for some drugs, existing systemic therapeutic methods for advanced tumor stages remain limited, and advanced hepatocellular carcinoma remains an incurable cancer. The TheraBionic P1 device is currently undergoing clinical trials in the treatment of advanced hepatocellular carcinoma. It is an at-home treatment that emits low levels of radio-frequency electromagnetic fields that block the growth of tumor cells without affecting healthy tissue. The device is FDA approved for treating patients 18 years of age and older who fail first- and second-line therapies. The delivery of radiofrequency electromagnetic fields, frequencies may stop cancer cells from dividing and making more cancer cells. The TheraBionic website quotes multiple studies as indicating that individuals who were currently undergoing standard liver cancer treatment did not experience the debilitating side effects associated with the cancer-fighting therapies while using the TheraBionic P1 device. Peer reviewed studies are lacking that explore the safety and effectiveness of radiofrequency electromagnetic field treatments in advanced hepatocellular carcinoma, alone or as an adjunct to care.

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 and a systematic review. Relevant outcome include overall survival, 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 and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival 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 a meaningful 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 overall survival, 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 (overall survival) 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. 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 the effects of the technology on health outcomes.

For individuals who have unresectable, locally advanced or metastatic, malignant pleural mesothelioma 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 U.S. patients. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The study has not been published but is described in the FDA Summary associated with its Humanitarian Device Exemption designation. In patients who received TTF therapy in combination with pemetrexed and cisplatin or carboplatin, median overall survival was 18.2 months (95% CI 12.3 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 a meaningful improvement in the net health outcome.

For individuals who have advanced hepatocellular carcinoma and receive radiofrequency electromagnetic field exposure as an adjunct to care, peer reviewed literature is lacking. Food and Drug Administration approvals are based on small studies in individuals without other options for treatment. Clinical trials are ongoing to evaluate the safety and effectiveness of electromagnetic fields in individuals with hepatocellular carcinoma. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT RECEIVED 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 for input on the use of TTF for treatment of GBM in 2016, BCBSA received input from 1 academic medical center and 3 physician specialty societies, with a total of 9 individual responses. There was majority support, but not consensus, for use of TTF therapy as an adjunct to maintenance treatment following initial therapy for GBM. There was mixed support for use of TTF as an alternative to chemotherapy in advanced or recurrent GBM.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Cancer Society

Acknowledges the use of TTF in unresectable mesotheliomas but indicates that it is not clear if the device improves quality or quantity of life.

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on central nervous system cancers include recommendations for the treatment of glioblastoma (see Table 15).(3) For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O^6 –ethylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric currents 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 2B recommendation.

Table 15. 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) • 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 • Temozolomide alone • Palliative/best supportive care	2A
>70	≥60	• Hypofractionated RT plus concurrent and adjuvant temozolomide[a] (for methylated or indeterminate MGMT promoter status only) • Standard RT plus concurrent and adjuvant temozolomide plus TTF • Temozolomide alone • Hypofractionated brain RT alone	1
>70	≥60	• Standard RT plus concurrent and adjuvant temozolomide • Temozolomide alone (for methylated or indeterminate MGMT promoter status only) • Hypofractionated RT alone (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 • Temozolomide alone • Palliative/best supportive care	2A

KPS: Karnofsky Performance Status; MGMT: O6-methylguanine-DNA-methyltransferase; RT: radiotherapy; TTF: tumor treating fields

The National Comprehensive Cancer Network guidelines on malignant pleural mesothelioma do not address tumor treating fields as a treatment option for malignant pleural mesothelioma.(24)

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.(25) 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 16. Of particular note are the phase III trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

Table 16. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02831959 [a]	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	Dec 2024
NCT02973789[a]	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	276	Sep 2023
NCT03377491[a]	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 2024
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	950	Aug 2026
NCT03448757	Determination of Autonomic Responses to the Exposure of Low Energy Electromagnetic Fields With Frequency Modulation in Patients With Advanced Hepatocellular Carcinoma and Healthy Individuals.	60	Dec 2023 (ongoing)
NCT04797884	A Phase 2 and Phase 3 Randomized Study of Intrabucally Administered Electromagnetic Fields Versus Placebo for Patients With Child-Pugh A or B With Advanced Hepatocellular Carcinoma	Estimate 166	Oct 2024 (ongoing)
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	18	Mar 2022 (terminated)
NCT03940196[a]	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	May 2023 (completed)
NCT01971281[a]	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[a]	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma	40	Jul 2019 (completed)

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

Government Regulations

National:

There is no national coverage determination for TTF.

Local:

Tumor Treatment Field Therapy
L34823; Effective: October 2015, Revised 1/1/20

INITIAL COVERAGE FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME:
TUMOR TREATMENT FIELD therapy (E0766) is covered for the treatment of newly diagnosed Glioblastoma Multiforme (GBM) only when all of the following criteria are met:

1. The beneficiary has histologically confirmed (World Health Organization (WHO) grade IV astrocytoma), newly diagnosed, supratentorial GBM; and,
2. The beneficiary has received initial treatment with maximal debulking surgery (when feasible), followed by chemotherapy and radiotherapy; and,
3. **TUMOR TREATMENT FIELD** therapy is initiated within 7 weeks from the last dose of concomitant chemotherapy or radiotherapy, whichever is later; and,
4. The beneficiary has no evidence of progression by Response Assessment in Neuro-Oncology (RANO) criteria; and,
5. The beneficiary has a Karnofsky Performance Score (KPS) of at least 70; and,
6. The beneficiary will use TTFT for an average of 18 hours per day.

If all of the coverage criteria above are not met, claims for code E0766 will be denied as not reasonable and necessary.

CONTINUED COVERAGE FOR NEWLY DIAGNOSED GBM BEYOND THE FIRST THREE MONTHS OF THERAPY:
Continued coverage of TTFT (E0766) beyond the first three months of therapy requires that no sooner than the 60th day but no later than the 91st day after initiating therapy, the treating practitioner must conduct a clinical re-evaluation and document that the beneficiary is continuing to use and is benefiting from TTFT.
Documentation of clinical benefit is demonstrated by:

1. Face-to-face clinical re-evaluation by the treating practitioner; and,
2. Objective evidence of adherence to therapy, reviewed by the treating practitioner.

Adherence to therapy is defined as the use of TTFT for an average of 18 hours per day (excluding days the treating practitioner has documented a medical need to limit or interrupt treatment).

If the above criteria are not met, continued coverage of TTFT will be denied as not reasonable and necessary.

If the practitioner re-evaluation does not occur until after the 91st day but the evaluation demonstrates that the beneficiary is benefiting from TTFT as defined in criteria 1 and 2 above, continued coverage of TTFT will commence with the date of that re-evaluation. See Policy Specific Documentation Requirements in the LCD-related Policy Article, located in the Related Local Coverage Documents section of this LCD, for information about KX modifier use.

RECURRENT GBM
TUMOR TREATMENT FIELD therapy (E0766) will be denied as not reasonable and necessary for the treatment of recurrent GBM.

OTHER USES
The use of TTFT for any indications other than newly diagnosed GBM will be denied as not reasonable and necessary.

BENEFICIARIES ENTERING MEDICARE
For beneficiaries who are undergoing treatment with TTFT for newly diagnosed, supratentorial GBM prior to enrollment in Fee-For-Service (FFS) Medicare and are seeking Medicare coverage of TTFT, coverage will be provided if all of the following coverage requirements are met:

a. The beneficiary has been receiving TTFT following initial maximal debulking surgery (if feasible) followed by chemotherapy/radiotherapy for histologically confirmed newly diagnosed GBM; and,
b. Clinical Evaluation – Following enrollment in FFS Medicare, the beneficiary must have a face-to-face evaluation by their treating practitioner who documents in the beneficiary's medical record that:
    1. The beneficiary is adherent with the use of TTFT for an average of 18 hours per day; and,
    2. The beneficiary is deriving benefit from the therapy.

If all of the above are not met, the claim will be denied as not reasonable and necessary.

Tumor Treatment Field – Policy Article
A52711: Effective date: 10/01/15, Revised 1/1/20
NON-MEDICAL NECESSITY COVERAGE AND PAYMENT RULES:
For any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements.

Information provided in this policy article relates to determinations other than those based on Social Security Act §1862(a)(1)(A) provisions (i.e. "reasonable and necessary"). TUMOR TREATMENT FIELD therapy devices are covered under the Durable Medical Equipment benefit (Social Security Act §1861(s)[6]). In order for a beneficiary's equipment to be eligible for reimbursement the reasonable and necessary (R&N) requirements set out in the related Local Coverage Determination must be met. In addition, there are specific statutory payment policy requirements, discussed below, that also must be met.

Code E0766 is in the frequent and substantial service payment category. Items included in this payment category are reimbursed a single monthly fee schedule amount for the device and all related supplies and accessories. Separate billing of supplies and/or accessories will be denied as unbundling.

Code A4555 is not valid for billing to Medicare. If code A4555 is billed, it will be denied as an invalid code.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

1. National Cancer Institute (NCI) - Adult Central Nervous System Tumors Treatment (PDQ®) – Health Professional Version. 2022; https://www.cancer.gov/types/brain/hp/adult-brain-treatment-pdq#cit/section_1.1. Accessed May 10, 2024.
2. National Brain Tumor Society. Glioblastoma Facts & Figures. https://braintumor.org/take-action/about-gbm/. Accessed May 31, 2023.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 3.2024; http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed November 27, 2024.
4. Stupp R, Wong ET, Kanner AA et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer 2012; 48(14):2192-202.
5. U.S. Food and Drug Administration (FDA). Tumor treatment fields. NovoTTF-10A System. Summary of safety and effectiveness data (SSED). Premarket Approval Application (PMA) No. P100034. 2011; http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034b.pdf. Accessed May 11, 2024.
6. U.S. Food and Drug Administration (FDA). Supplemental application for device name change. 2014; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p100034s010. Accessed May 13, 2024.
7. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Optune™ (formerly NovoTTF-100ATM System) 2015; https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013B.pdf. Accessed May 10, 2024.
8. US Food and Drug Administration. NovoTTF 100L System: Summary of Safety and Probable Benefit. May 12, 2024. https://www.accessdata.fda.gov/cdrh_docs/pdf18/H180002B.pdf. Accessed May 31, 2023.
9. FDA Grants Breakthrough Device Designation to the NovoTTF-200T System for Advanced Liver Cancer. September 9, 2021. https://www.novocure.com/fda-grants-breakthrough-device-designation-to-the-novottf-200t-system-for-advanced-liver-cancer/. Accessed May 11, 2024.
10. Novocure. Novocure announces Optune Lua as the brand name for the NovoTTF-100L system. March 19, 2020; https://www.novocure.com/novocure-announces-optune-lua-as-the-brand-name-for-the-novottf-100l-system/. Accessed November 27, 2024.
11. Novocure Announces Presentations on Tumor Treating Fields Therapy, Including New Clinical Data and Real-World Evidence, at 2023 Society for Neuro-Oncology Annual Meeting. Novocure. Published November 10, 2023. https://www.novocure.com/novocure-announces-presentations-on-tumor-treating-fields-therapy-including-new-clinical-data-and-

real-world-evidence-at-2023-society-for-neuro-oncology-annual-meeting/. Accessed May 16, 2024.
12. Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. Ann N Y Acad Sci 2013.
13. Pless M, Weinberg U. Tumor treating fields: concept, evidence and future. Expert Opin Investig Drugs 2011; 20(8):1099-106.
14. Regev O, Merkin V, Blumenthal DT, et al. Tumor-Treating Fields for the treatment of glioblastoma: a systematic review and meta-analysis. Neurooncol Pract. Aug 2021; 8(4): 426-440. PMID 34277021
15. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA. Dec 19 2017;318(23):2306-2316. PMID 29260225
16. Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. JAMA. Dec 15 2015;314(23):2535-2543. PMID 26670971
17. Zhu JJ, Goldlust SA, Kleinberg LR, et al. Tumor Treating Fields (TTFields) therapy vs physicians' choice standard-of-care treatment in patients with recurrent glioblastoma: a post-approval registry study (EF-19). *Discov Oncol*. Oct 14 2022; 13(1): 105. PMID 36239858
18. Kesari S, Ram Z, Investigators EFT. Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. CNS Oncol. Jul 2017;6(3):185-193. PMID 28399638
19. Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A system for glioblastoma: The Patient Registry Dataset (PRiDe). Semin Oncol. Oct 2014;41(Suppl 6):S4-S13. PMID 25213869
20. Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. Cancer Med. Jun 2014;3(3):592-602. PMID 24574359
21. Kanner AA, Wong ET, Villano JL, et al. Post Hoc analyses of intention –to-treat population in phase III comparison of NovoTTF-100A system versus best physician's choice chemotherapy. Semin Oncol. Oct 2014;41 Suppl 6:S25-34. PMID 25213871
22. Ceresoli GL, Aerts JG, Dziadziuszko R, et al. Tumour Treating Fields in combination with pemetrexed and cisplatinor carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): a multicentre, single-arm phase 2 trial. Lancet Oncol. Dec 2019; 20(12): 1702-1709. PMID 31628016
23. Kutuk T, Appel H, Avendano MC, et al. Feasibility of Tumor Treating Fields with Pemetrexed and Platinum-Based Chemotherapy for Unresectable Malignant Pleural Mesothelioma: Single-Center, Real-World Data. Cancers(Basel). Apr 16 2022; 14(8). PMID 35454925
24. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Mesothelioma: Pleural. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf. Accessed November 27, 2024.
25. Germano IM, Ziu M, Wen P, et al. Congress of Neurological Surgeons systematic review and evidence-based guidelines update on the role of cytotoxic chemotherapy and other

cytotoxic therapies in the management of progressive glioblastoma in adults. *J Neuro oncol*. Jun 2022; 158(2): 225-253. PMID35195819

26. American Cancer Society. Treatment of Mesothelioma Based on the Extent of the Cancer. Revised May 28, 2019; https://www.cancer.org/cancer/malignant-mesothelioma/treating/by-extent.html. Accessed November 27, 2024.
27. U.S. Food & Drug Administration. "Humanitarian Device Exemption: TheraBionic P1." H220001. 2023. https://www.accessdata.fda.gov/cdrh_docs/pdf22/H220001A.pdf. Accessed December 16, 2024.
28. U.S. Food & Drug Administration. "TheraBionic P1 – H220001." 2024. https://www.fda.gov/medical-devices/recently-approved-devices/therabionic-p1-h220001. Accessed December 19, 2024.
29. Jimenez H, Wang M, Zimmerman JW, et al. "Tumour-specific amplitude-modulated radiofrequency electromagnetic fields induce differentiation of hepatocellular carcinoma via targeting Cav3.2 T-type voltage-gated calcium channels and Ca2+ influx." *EBioMedicine*. 2019 Jun;44:209-224. doi: 10.1016/j.ebiom.2019.05.034. Epub 2019 May 31. PMID: 31160272.
30. TheraBionic. TheraBionic's Technology is a Breakthrough in the War on Cancer." 2024. https://www.therabionic.com/. Accessed December 19, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/27/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/14	4/8/14	4/15/14	Joint policy established
9/1/15	6/19/15	7/16/15	Routine review
5/1/16	2/16/16	2/23/16	• Updated to reflect new FDA indications (2015); • Diverge from BCBSA; • Converted from Investigational to Mixed (per new FDA indications); • Codes added to inclusions and exclusions
5/1/17	3/8/17	3/16/17	• Routine maintenance • 95199 added – placement of Novo-Tal pads • Continue to diverge from BCBSA • References and rationale updated
5/1/18	2/20/18	2/20/18	• Routine maintenance
5/1/19	2/19/19		• Routine maintenance
5/1/20	2/18/20		• Routine maintenance • Updated inclusions to include Optune use as continued maintenance after TMZ has been completed per reversal received from IRO
7/1/20	4/14/20		• Exclusion added regarding use of TTF for mesothelioma
5/1/21	2/16/21		• Routine maintenance
5/1/22	2/15/22		• Routine maintenance
5/1/23	2/21/23		• Routine maintenance (slp) • Vendor Managed: N/A
5/1/24	2/20/24		• Routine management (slp) • Vendor managed: N/A
5/1/25	2/18/25		• Routine management (slp) • Vendor managed: N/A

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TUMOR-TREATMENT FIELDS THERAPY FOR GLIOBLASTOMA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.