Tumor Treating Fields Therapy

Policy # 00391
Original Effective Date: 11/20/2013
Current Effective Date: 11/11/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Stereotactic Radiosurgery and Stereotactic Body Radiotherapy is addressed separately in medical policy 00045.

Note: Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain is addressed separately in medical policy 00434.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider an initial 3 months of tumor treating fields (TTF) therapy to treat glioblastoma multiforme (GBM) as an adjunct to standard maintenance therapy with temozolomide in individuals with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be met for TTF therapy to treat GBM as an adjunct to standard maintenance therapy with temozolomide in individuals with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions (**ALL** criteria must be met):

- Individuals ≥18 years of age; **AND**
- Supratentorial tumor following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy; **AND**
- Karnofsky Performance Status (KPS) score ≥70%; **AND**
- Individual understands device use, including the requirement for a shaved head, and is willing to use Optune for at least 18 hours a day.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Tumor Treating Fields Therapy

Policy # 00391
Original Effective Date: 11/20/2013
Current Effective Date: 11/11/2024

Based on review of available data, the Company may consider continuation of tumor treating fields (TTF) therapy to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility will be met for continuation of TTF therapy for 3 months if **ALL** of the following criteria are met:

- Evidence of no documented disease progression by magnetic resonance imaging (MRI) done at a minimum of every 2-4 months (see Policy Guidelines). This includes a completed MRI scan report submitted as part of any request for continuation; **AND**
- Karnofsky Performance Status (KPS) score of 70% or greater; **AND**
- Documentation that the individual has agreed to use Optune for at least 18 hours a day and has used it at least 75% of the time for 18 hours per day.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers tumor treating fields (TTF) therapy to be **investigational*** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for individuals with progressive or recurrent glioblastoma multiforme (GBM);
- As an alternative to standard medical therapy for patients with progressive or recurrent GBM;
- For brain metastases;
- For cancer in areas other than the brain.
- As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for individuals with malignant pleural mesothelioma

The use of tumor treating fields (TTF) therapy when patient selection criteria are not met is considered to be **investigational.***

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Tumor Treating Fields Therapy

Policy # 00391
Original Effective Date: 11/20/2013
Current Effective Date: 11/11/2024

Policy Guidelines

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).

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.

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.

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

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

The Optune device is designed to be used at least 18 hours every day in order to maximize treatment benefit. Continuous application is needed to reach and maintain therapeutic efficacy. The compliance rate, the number of days in which the minimum 18 hours daily use is reached, is an independent predictor of overall survival. In a systematic review and meta-analysis reported on the pooled effect of compliance on OS rates of those with a TTF use daily compliance of 75% or more (10.3 months) compared to those with a TTF daily compliance of less than 75% (5.7 months). The 6-, 9-, and 12-month OS rates of those who used the TTF device 75% or more improved compared to those who used the TTF device less than 75% (73.5% [95% CI = 67.5-80], 54.3% [95% CI = 47.7-61.9], and 44.4% [95% CI = 37.9-51.9] compared to 48% [95% CI = 41-56.2], 40.6% [95% CI = 33.7-49], and 32.5% [95% CI = 25.8-40.9], respectively). An internal log file monitors compliance with therapy.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Tumor Treating Fields Therapy

Policy # 00391
Original Effective Date: 11/20/2013
Current Effective Date: 11/11/2024

Background/Overview

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. 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 49.1% of all primary malignant brain tumors 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 is estimated at 6.9% and 8 months, respectively.

Treatment of Newly Diagnosed Glioblastoma Multiforme

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy (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). 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.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

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%. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. 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®‡.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

In October 2015, FDA expanded the indication for Optune in combination with temozolomide to include newly diagnosed GBM. 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."

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.

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). Optune was renamed Optune Gio™‡ in 2023.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Description

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

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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. 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.

Supplemental Information

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.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

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.1.2023) include recommendations for the treatment of glioblastoma (see Table 1). 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 is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

NCCN notes that "alternating electric field therapy is also FDA approved for treating recurrent glioblastoma based on the safety results of this medical device from the EF-11 clinical trial. This phase III study randomized 237 patients with recurrent glioblastoma to alternating electric field therapy or the treating oncologist's choice of chemotherapy. The study did not meet its primary endpoint of demonstrating an improvement in survival in the cohort of patients treated with alternating electric field therapy. Although median OS was similar in both of the treatment arms (6.6 vs. 6 months), the study had not been powered for a non-inferiority determination. Due to lack of clear efficacy data for alternating electric field therapy in EF-11, the panel is divided about recommending it for the treatment of recurrent glioblastoma."

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Table 1. 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 (for methylated or indeterminate MGMT promoter status only) • Standard RT plus concurrent and adjuvant temozolomide plus TTF	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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

>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: O^6-methylguanine-DNA-methyltransferase; RT: radiotherapy; TTF: tumor treating fields.

The National Comprehensive Cancer Network guidelines on malignant pleural mesothelioma (v.1. 2024) do not address tumor treating fields (TTF) as a treatment option for malignant pleural mesothelioma.

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. 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.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. Tumor treating fields therapy is an active area of research for mechanisms underlying its effects on cancer cells.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Table 2. 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	Oct 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
Unpublished			
NCT02663271[a]	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the	18	Mar 2022 (terminated)

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma		
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.

References

1. National Cancer Institute (NCI). Adult Central Nervous System Tumors Treatment (PDQ)Health Professional Version. Updated March 6, 2024; https://www.cancer.gov/types/brain/hp/adult-brain-treatment-pdq#cit/section_1.1.
2. National Brain Tumor Society. Glioblastoma Facts & Figures. https://braintumor.org/take-action/about-gbm/.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
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. Sep 2012; 48(14): 2192-202. PMID 22608262
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.
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.
7. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): OptuneTM (formerly NovoTTF-100ATM System) 2015; https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013B.pdf.
8. U.S. Food and Drug Administration (FDA). NovoTTF 100L System: Summary of Safety and Probable Benefit. May 23, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf18/H180002B.pdf.
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/.
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/.
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/.
12. Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. Ann N Y Acad Sci. Jul 2013; 1291: 86-95. PMID 23659608
13. Pless M, Weinberg U. Tumor treating fields: concept, evidence and future. Expert Opin Investig Drugs. Aug 2011; 20(8): 1099-106. PMID 21548832

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

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. Toms SA, Kim CY, Nicholas G, Ram Z. Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: A subgroup analysis of the EF-14 phase III trial. J Neurooncol. 2019; 141(2):467-473.
16. 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
17. 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): 2535-43. PMID 26670971
18. 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
19. Kesari S, Ram Z. 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
20. 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
21. 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
22. 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
23. Ceresoli GL, Aerts JG, Dziadziuszko R, et al. Tumour Treating Fields in combination with pemetrexed and cisplatin or 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

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

24. 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
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Mesothelioma: Pleural. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf.
26. 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 Neurooncol. Jun 2022; 158(2): 225-253. PMID 35195819

Policy History

Original Effective Date: 11/20/2013
Current Effective Date: 11/11/2024

11/07/2013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. New policy.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. This policy was retired on 3/16/2016 and has been returned to active status. Title changed from "Tumor-Treatment Fields Therapy for Glioblastoma" to "Tumor Treating Fields Therapy". Added that an initial 6 months of TTF therapy will be eligible for coverage when criteria are met to treat GBM as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy. Added that continuation of TTF therapy may be eligible for coverage with criteria.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Tumor Treating Fields Therapy

Policy # 00391
Original Effective Date: 11/20/2013
Current Effective Date: 11/11/2024

09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. Malignant pleural mesothelioma added to list of conditions for which the therapy is considered investigational. Revised investigational statement to cover when ALL criteria are not met.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. FDA section updated to include information differentiating between Optune and Optune Lua products.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/01/2022	Medical Policy Committee review
09/14/2022	Medical Policy Implementation Committee approval. Replaced "patients" with "individuals" in the coverage section. Added "following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy" to the criteria bullet for supratentorial tumor. Edited criteria for continuation of tumor treating fields to include individuals being willing to use Optune for at least 18 hours a day and has attempted to use it at least 75% of the time for 18 hours per day.
09/07/2023	Medical Policy Committee review
09/13/2023	Medical Policy Implementation Committee approval. Changed the eligible for coverage statement from an initial 6 months to an initial 3 months to treat glioblastoma multiforme (GBM) as an adjunct to standard maintenance therapy with temozolomide in individuals with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy. Referenced the Policy Guidelines in the coverage criteria for continuation of tumor treating fields therapy. Added a paragraph on the Optune device in the Policy Guidelines. Added a paragraph in the Supplemental Information section from the NCCN 1.2023 Version on the FDA approved alternating electric field therapy for treating recurrent glioblastoma.
10/03/2024	Medical Policy Committee review
10/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Tumor Treating Fields Therapy

Policy # 00391
Original Effective Date: 11/20/2013
Current Effective Date: 11/11/2024

Next Scheduled Review Date: 10/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	A4555, E0766
ICD-10 Diagnosis	C71.0-C71.9, Z85.841

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Tumor Treating Fields Therapy

Policy # 00391
Original Effective Date: 11/20/2013
Current Effective Date: 11/11/2024

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

©2024 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.