Contractor Advisory Committee for Tumor Treating Fields Therapy (TTFT)

March 6, 2019
Agenda

• Introductions and background
  • Answering the scientific questions
    – Mechanism of action
    – General acceptance by medical community
    – Net positive health outcomes
    – Predictors of success
    – Additional supporting evidence

• Patient perspective
Participants

• Bill Doyle
  – Executive Chairman, Novocure

• Matthew Ballo, M.D.
  – Professor of Radiation Oncology, University of Tennessee Health Science Center
  – Medical Director, Radiation Oncology, West Cancer Center

• Steve W.
  – Tumor Treating Fields patient

• Adrian Kinzel, M.D.
  – Vice President and Medical Director, Novocure
Definitions and abbreviations

- Tumor Treating Fields – common scientific name in the literature
  - TTFFields
  - TTF
  - TTFFields treatment or TTF treatment
- Tumor Treatment Field Therapy (TTFT) – Medicare/MAC name for the therapy
- Optune®
  - Brand name for the TTFFields delivery device for glioblastoma patients
  - Formerly known as the NovoTTF-100A™ device
- EF-14 Trial – Randomized control trial (n=695) for TTFFields in newly diagnosed glioblastoma
- Glioblastoma
  - GBM
  - Glioblastoma multiforme, older name based on a previous WHO classification
Requested coverage for Tumor Treating Fields

• Medicare coverage requested:

“TTFT with temozolomide (TMZ) is covered 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.”

• Requested coverage matches the FDA pre-market approval (PMA) indication for use:

“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.”
FDA premarket approval (PMA) background

• “PMA is the most stringent type of device marketing application required by FDA.”

• “Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.”

• “PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s).”

Medicare standards for local coverage determinations (LCD)

- General acceptance standard for LCDs

“In conducting a review, MACs [Medicare Administrative Contractors] shall use the available evidence of general acceptance by the medical community, such as published original research in peer-reviewed medical journals, systematic reviews and meta-analyses, evidence-based consensus statements and clinical guidelines.”
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- **Answering the scientific questions**
  - Mechanism of action
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  - Additional supporting evidence

- Patient perspective
How confident are you that scientific evidence supports mitotic spindle disruption and cellular apoptosis as the mechanism of action of TTFT?
Substantial research demonstrates the effects of forces on tubulin proteins and the mitotic spindle.


**473 publications in Medline Database on the biophysics of mechanical forces and tubulin function**

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**1980**

“Many models for the mechanism of [microtubules] MT-mediated transport and mitosis postulate an important role for MT polarity because a symmetric fibre could not generate force in one direction along its surface.”

**2018**

“Dynamic microtubules can also engage in mechanical processes, such as exerting forces by pushing or pulling against a load…[microtubule-associated proteins] and forces can modulate microtubule growth and shrinkage.”
Like gravity and magnetic fields, electric fields exert forces at a distance.

**GRAVITATIONAL FIELDS**
exert forces on masses

**MAGNETIC FIELDS**
exert forces on ferromagnetic materials like iron

**ELECTRIC FIELDS**
exert forces on charges & polarized molecules
Electric fields exert forces on charged tubulin proteins, disrupting mitosis

Polar (charged) tubulin dimer proteins orient in direction of electric fields
Mitotic spindle disruption by electric fields has been observed in every cancer cell line tested

Mitotic spindle disruption in fluorescence images of A549 cells exposed to TTFields

A549 cells in lung tissue were treated with Tumor Treating Fields for 24 hours. Tubulin fluorescence images were inverted and pseudocolored so that increasing fluorescence intensity is indicated from blue to red (scale bar represent arbitrary units). Dashed lines define the region between the two spindle poles (white) and overall tubulin fluorescence within the cell (Red). 1. Giladi M., et al. Sci Rep. 2015 Dec 11;5:18046. 2. Kim EH, et al. Oncotarget. 2016; 7:38 2. Additional data on file with Novocure.
Tumor Treating Fields Therapy delivery system

**TRANSDUCER ARRAY**
Sterile, single-use transducer array replaced every 3-4 days

**ELECTRIC FIELD GENERATOR**
2.7 lbs, portable Tumor Treating Fields generator
Independent research confirms TTFields system delivers effective electric field dose to cranium

Electric field intensity (V/cm) models confirm dose deposition in target regions

Electric field distribution within the brain was calculated using the finite element method to solve the quasistatic approximation of the Maxwell’s equations. The model estimates field distribution with consideration for established measurements of permittivity (\(\varepsilon\)) and conductivity (\(\sigma\)) for critical tissue (e.g., skull, white matter, tumor, etc.).

Significant and growing body of external research elucidating the mechanism of action for TTFields

Recently published external research

**Korea University**
Comprehensive revalidation of MOA *in vitro* and *in vivo*

**Stanford University**
Effect of combinations with selected systemic agents and recent research on cell membrane permeability under TTFields

**University of Würzburg**
Synergism with checkpoint inhibitors

**UT Southwestern**
Effects of TTFields with ionizing radiation. Identifying a reduction in the DNA repair mechanisms and downregulation of BRCA1

**Aarhus University and Max Planck Institute for Biological Cybernetics**
Advanced techniques to personalize electric field maps and maximize field intensity using alternative array layouts

30+ academic centers performing bench and animal research on TTFields

External authors produce the majority of the peer-reviewed research on Tumor Treating Fields

Refer to bibliography annex for complete list of citations; totals do not include general scientific publications studying the effect of force and biophysical mechanics on mitotic spindle formation; 23 of the external publications were performed entirely independent of Novocure and 7 publications were run independently while relying on a pre-clinical system provided by Novocure.

CAC bibliography does not contain an up-to-date list of relevant external research on effect of electric fields on tubulin or the science of TTFields.
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  – Mechanism of action
  – **General acceptance by medical community**
  – Net positive health outcomes
  – Predictors of success
  – Additional supporting evidence

• Patient perspective
How confident are you that TTFT is generally accepted by the medical community for newly diagnosed GBM?
TTFIELDS development timeline

- **2000**: Company founded
- **2003**: First-in-man study
- **2004**: EF-07 pilot trial in GBM begins
- **2006**: EF-11 pivotal trial in recurrent GBM begins
- **2009**: EF-14 pivotal trial in newly diagnosed GBM begins
- **2011**: Optune FDA approval in newly diagnosed GBM
- **2015**: Optune FDA approval in newly diagnosed GBM
- **2017**: EF-14 pivotal trial in newly diagnosed GBM positive final long-term analysis results published
- **2018**: TTFIELDS Category 1 in NCCN Guidelines® for newly diagnosed GBM
In 2018, 40% of eligible patients received a prescription for TTFields.

New prescriptions written for Tumor Treating Fields in the U.S. by year

Glioblastoma statistics

- 13,800 patients diagnosed annually
- 9,300 patients eligible for TTFields
- 40% of eligible patients received a prescription in 2018

Prescriber base has increased steadily since 2015 FDA approval for newly diagnosed GBM

Unique prescribers in the U.S. by year

2018 Rx Volume by Segment
- 50% neuro-oncologists
- 31% radiation oncologists
- 15% medical oncologists
- 4% neurosurgeons

Novocure data requested by CAC panel. Segments based on volume of prescriptions written.
TTFields has achieved general acceptance in the medical community throughout the United States.

Prescriptions from

50 states +
Washington D.C. and Puerto Rico

Regional acceptance

39 to 42%
of eligible patients receiving a prescription for Optune in East, Central, and West regions

TTFields has achieved general acceptance in the medical community throughout the United States

Prescription distribution

48% of prescriptions from community practices; 52% from academic practices

Certified prescribers at

59 of the 62 NCI-designated cancer centers

Novocure data requested by CAC panel. Novocure 2018 data.
Novocure supplies Optune directly to patients

Optune

0% of the product revenue is received by the physician practice

Infused oncology drugs

4 to 40% of the product revenue is received by the physician practice

TTFields for newly diagnosed GBM is covered by essentially every commercial payer, including every national payer

<table>
<thead>
<tr>
<th>2</th>
<th>THE PARENT CORPORATIONS OF CGS AND NORIDIAN, THE MEDICARE MACS ORGANIZING THIS PANEL, BOTH COVER TTFIELDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5+</td>
<td>ALL FIVE OF THE LARGEST COMMERCIAL PAYERS AND THE BCBSA COVER TTFIELDS</td>
</tr>
<tr>
<td>85</td>
<td>HEALTHCARE PAYERS IN THE UNITED STATES HAVE ISSUED POSITIVE COVERAGE POLICIES</td>
</tr>
<tr>
<td>243</td>
<td>MILLION AMERICANS COVERED UNDER PRIVATE HEALTH PLANS</td>
</tr>
</tbody>
</table>

Medicare’s current negative LCD is:

- Non-conforming with U.S. payers
- Out of step with reimbursement decisions by other major governments around the world
- Putting Medicare beneficiaries at risk for inequitable access to oncology care*

*Novocure has to date provided Optune to Medicare beneficiaries

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  – *Net positive health outcomes*
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  – Additional supporting evidence

• Patient perspective
How confident are you that there is sufficient evidence to determine that TTFT for newly diagnosed GBM can provide net positive health outcomes in the Medicare-eligible population?
Medicare-eligible population definition

• Medicare eligibility
  – Over age 65; or
  – End-stage renal disease; or
  – Permanently disabled regardless of age

• Glioblastoma often leads to debilitating side-effects, rendering patients unable to function independently

Review of clinical data for TTFT in newly diagnosed GBM

Matthew Ballo, M.D.

Professor of Radiation Oncology, University of Tennessee Health Science Center, Medical Director, Radiation Oncology, West Cancer Center
Glioblastoma

- Most prevalent and aggressive central nervous system cancer in adults

- Disease prognosis depends on
  - Age
  - Extent of surgical resection
  - Tumor location
  - Genetics
  - Functional status

- Treatment options are limited and survival can be measured in months without aggressive treatment

FDA-approved therapies for glioblastoma

- **Carmustine Injection** Palliative Therapy (1977)
- **Carmustine Polymer Wafers** Newly Diagnosed GBM (1996)
- **TMZ** Newly Diagnosed and Maintenance (2003)
- **Carmustine Polymer Wafers** Recurrent GBM (2005)
- **Bevacizumab** Recurrent GBM (2009)
- **Optune + TMZ** Newly Diagnosed GBM (2011)
- **FDA approved expanded label for Optune to include final long term analysis** Newly Diagnosed GBM (2015)
- **Optune** Recurrent GBM (2015)
- **FDA approved therapies for glioblastoma** Newly Diagnosed GBM (2018)

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The success of the EF-14 trial for TTFields provided a much needed advance in clinical outcomes in glioblastoma

Methods. We queried ClinicalTrials.gov for interventional clinical trials for patients with GBM initiated between January 2005 and December 2016 and abstracted data regarding phase, status, start and end dates, testing locations, endpoints, experimental interventions, sample size, clinical presentation/indication, and design to better understand the clinical trials landscape.

Results. Only approximately 8%-11% of patients with newly diagnosed GBM enroll on clinical trials with a similar estimate for all patients with GBM. Trial duration was similar across phases with median time to completion between 3 and 4 years. While 93% of clinical trials were in phases I-II, 26% of the overall clinical trial patient population was enrolled on phase III studies. Of the 8 completed phase III trials, only 1 reported positive results. Although 58% of the phase III trials were supported by phase II data with a similar endpoint, only 25% of these phase II trials were randomized.
The results of the EF-14 Randomized Control Trial (n=695) have been reported in multiple JAMA publications:

EF-14: phase 3 pivotal trial design

*Primary endpoint: PFS
*Powered secondary endpoint: OS
*Additional secondary endpoints: PFS6, 1-y/2-y survival, ORR, safety, QoL

Stratification by:
1. Resection (biopsy vs partial vs gross total)
2. MGMT promoter methylation status

EF-14 Protocol: “Central MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient.”

*Treatment with Optune was continued for 24 months or until second progression, whichever occurred first unless prohibited by the patient’s clinical condition. GBM, glioblastoma multiforme; TMZ, temozolomide; RT, radiation therapy; 2L, second-line; SRS, stereotactic radiosurgery; PFS, progression-free survival; OS, overall survival; PFS6, the percentage of patients alive and progression-free at 6 months; ORR, objective response rate; QoL, quality of life; MGMT, O6-methylguanine-DNA methyltransferase. 1. Stupp R, et al. JAMA. 2017;318(23):2306-2316. 2. Stupp R, et al. JAMA. 2017;318(23 suppl 1):S1-S213.
### EF-14: key baseline characteristics

Baseline characteristics were well balanced between the two treatment arms.

<table>
<thead>
<tr>
<th>ITT Population</th>
<th>Optune + TMZ (n=466)</th>
<th>TMZ Alone (n=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Median age, years (range) | 56 (19-83) | 57 (19-80)
| Female sex, % | 32 | 31 |
| Median KPS (range) | 90 (60-100) | 90 (70-100) |
| Extent of resection, % | | |
| Gross total resection | 53 | 54 |
| Partial resection | 34 | 33 |
| Biopsy | 13 | 13 |
| Median time from diagnosis to randomization, mo (range) | 3.8 (1.7-6.2) | 3.7 (1.4-6.3) |
| **Duration of therapy with TMZ, mo** |
| Median (range) | 6 (0-51) | 5 (0-33) |
| **Duration of therapy with Optune, mo** |
| Median (range) | 8.2 (0-82) |  

EF-14: key baseline characteristics (cont’d)

<table>
<thead>
<tr>
<th>ITT Population</th>
<th>Optune + TMZ (n=466)</th>
<th>TMZ Alone (n=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular Profiles, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGMT status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue available and tested</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>Methylated</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td>Insufficient for testing</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>IDH1 R132H mutation status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue available and tested</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>Positive</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td><strong>Medications, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Average daily usage of TTFields*, %</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Baseline characteristics were well balanced between the two treatment arms

*Defined as use of Optune ≥75% of the time, or ≥18 hours per day, in the first 3 months of treatment. ITT, intent-to-treat; TMZ, temozolomide; MGMT, O6-methylguanine-DNA methyltransferase; IDH1, isocitrate dehydrogenase 1.Stupp R, et al. JAMA. 2017;318(23):2306-2316.
At the time of the final survival analysis, PFS was reported out to 30 months.

EF-14: Overall Survival (ITT)

**ITT Population**

<table>
<thead>
<tr>
<th></th>
<th>Optune + TMZ (n=466)</th>
<th>TMZ Alone (n=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS from randomization, mo</td>
<td>20.9</td>
<td>16.0</td>
</tr>
<tr>
<td>95% CI, mo</td>
<td>19.3-22.7</td>
<td>14.0-18.4</td>
</tr>
<tr>
<td>Stratified log-rank</td>
<td></td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63 (0.53-0.76)</td>
<td></td>
</tr>
<tr>
<td>Median OS from diagnosis, mo</td>
<td>24.5</td>
<td>19.8</td>
</tr>
<tr>
<td>2-year OS</td>
<td>43%</td>
<td>31%</td>
</tr>
</tbody>
</table>

**Graph**

EF-14 safety summary: incidence of grade 3/4 adverse events in ≥5% of patients

<table>
<thead>
<tr>
<th>Safety Population</th>
<th>Grade 3-4 Events, No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optune + TMZ (n=456)</td>
</tr>
<tr>
<td>≥1 Adverse event</td>
<td>218 (48)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorder*</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>59 (13)</td>
</tr>
<tr>
<td></td>
<td>39 (9)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Asthenia, fatigue, and gait disturbance</td>
<td>42 (9)</td>
</tr>
<tr>
<td>Infections</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications (falls and medical device site reaction)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>109 (24)</td>
</tr>
<tr>
<td>Seizures</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)</td>
<td>24 (5)</td>
</tr>
</tbody>
</table>

*The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group. The differences disappear when data are normalized to treatment duration. TMZ, temozolomide. 1. Stupp R, et al. JAMA. 2017;318(23):2306-2316. 2. Optune Instructions for Use.
EF-14 overall survival: magnitude of benefit was comparable to Stupp/EORTC trial in 2005 for temozolomide

<table>
<thead>
<tr>
<th></th>
<th>RT alone vs. TMZ+RT</th>
<th>TMZ alone vs. Optune+TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.63 (0.52 – 0.75)</td>
<td>0.63 (0.53 – 0.76)</td>
</tr>
<tr>
<td>Median survival</td>
<td>12.1 months → 14.6 months Δ 2.5 months</td>
<td>16.0 months → 20.9 months Δ 4.9 months</td>
</tr>
<tr>
<td></td>
<td>Two-year survival rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10% → 27% Δ 17%</td>
<td>31% → 43% Δ 12%</td>
</tr>
<tr>
<td></td>
<td>Five-year survival rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2% → 10% Δ 8%</td>
<td>5% → 13% Δ 8%</td>
</tr>
</tbody>
</table>

The EF-14 control arm survival was consistent with prior trials, specifically the RTOG-0525 trial randomized post RT

### Overall Survival (months)

<table>
<thead>
<tr>
<th></th>
<th>Control arm of EF-14 (n=266)</th>
<th>Control arm of RTOG0525 (n=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>From randomization</td>
<td>Median</td>
<td>16.0</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>14.0-18.4</td>
</tr>
<tr>
<td>Two year survival</td>
<td>Median</td>
<td>30.7%</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>25-38</td>
</tr>
<tr>
<td>From registration</td>
<td>Median</td>
<td>19.8</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>17.6-22.1</td>
</tr>
</tbody>
</table>

### National Comprehensive Cancer Network® (NCCN®)

**Category 1* Adjuvant Treatment Recommendations for Newly Diagnosed GBM**

<table>
<thead>
<tr>
<th>Postoperative</th>
<th>Newly diagnosed GBM</th>
<th>Age ≤ 70 years, KPS ≥ 60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MGMT</strong></td>
<td><strong>Standard brain RT + concurrent TMZ and adjuvant TMZ + alternating electric field therapy (Optune)</strong>†,‡,§</td>
<td></td>
</tr>
<tr>
<td>promoter</td>
<td>OR</td>
<td>Standard brain RT + concurrent TMZ and adjuvant TMZ†,‡</td>
</tr>
<tr>
<td>methylated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard brain RT + concurrent TMZ and adjuvant TMZ†,‡,‖ + alternating electric field therapy (Optune)</strong>†,‡,§</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard brain RT + concurrent TMZ†,‡,‖ and adjuvant TMZ†,‡,‖ + alternating electric field therapy (Optune)</strong>†,‡,§</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MGMT</strong></td>
<td><strong>Standard brain RT + concurrent TMZ‖ and adjuvant TMZ‖ + alternating electric field therapy (Optune)</strong>†,‡,§</td>
<td></td>
</tr>
<tr>
<td>promoter</td>
<td>OR</td>
<td>Standard brain RT + concurrent TMZ‖ and adjuvant TMZ‖†,‡,‖</td>
</tr>
<tr>
<td>unmethylated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or indeterminate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*There is uniform NCCN consensus for this recommendation based on high-level evidence (Category 1). †Combination of agents may lead to increased toxicity or radiographic changes. ‡ Benefit of treatment with TMZ for GBM beyond 6 months is unknown. §Alternating electric field therapy is only indicated for patients with supratentorial disease. ‖Clinical benefit from TMZ is likely to be lower in patients whose tumors lack MGMT promoter methylation. Note: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is preferred for eligible patients. See the NCCN Guidelines for Central Nervous System Cancers for the complete list of adjuvant treatment recommendations for newly diagnosed glioblastoma. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. GBM, glioblastoma; KPS, Karnofsky Performance Score; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiation therapy; TMZ, temozolomide. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers. V.1.2018. ©2018 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.
Category 1* Adjuvant Treatment Recommendations for Newly Diagnosed GBM (cont’d)

- **Postoperative Newly diagnosed GBM**
  - Age >70 years, KPS ≥ 60
  - **MGMT**
  - promoter methylated
    - Hypofractionated brain RT + concurrent and adjuvant TMZ†,‡
    - OR
    - Standard RT + concurrent TMZ and adjuvant TMZ + alternating electric field therapy (Optune)†,‡,§
  - **MGMT**
  - promoter unmethylated or indeterminate
    - Standard RT + concurrent TMZ† and adjuvant TMZ† + alternating electric field therapy (Optune)†,‡,§

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*There is uniform NCCN consensus for this recommendation based on high-level evidence (Category 1). †Combination of agents may lead to increased toxicity or radiographic changes. ‡ Benefit of treatment with TMZ for GBM beyond 6 months is unknown. §Alternating electric field therapy is only indicated for patients with supratentorial disease. †Clinical benefit from TMZ is likely to be lower in patients whose tumors lack MGMT promoter methylation. Note: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is preferred for eligible patients. See the NCCN Guidelines for Central Nervous System Cancers for the complete list of adjuvant treatment recommendations for newly diagnosed glioblastoma. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. GBM, glioblastoma; KPS, Karnofsky Performance Score; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiation therapy; TMZ, temozolomide. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers, V.1.2018. ©2018 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.
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  - **Predictors of success**
  - Additional supporting evidence

- Patient perspective
How confident are you that the available evidence demonstrates adequate predictors of success in Medicare-eligible population?
EF-14 trial subgroup analysis for overall survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Hazard Ratio</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>695 (100)</td>
<td></td>
<td>20.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16.0</td>
</tr>
<tr>
<td>MGMT (central)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmethylated</td>
<td>304 (44)</td>
<td>16.9</td>
<td>14.7</td>
</tr>
<tr>
<td>Methylated</td>
<td>214 (31)</td>
<td>31.6</td>
<td>21.2</td>
</tr>
<tr>
<td>Resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>89 (13)</td>
<td>16.5</td>
<td>11.6</td>
</tr>
<tr>
<td>Partial</td>
<td>234 (34)</td>
<td>21.4</td>
<td>15.1</td>
</tr>
<tr>
<td>Gross total</td>
<td>372 (54)</td>
<td>22.6</td>
<td>18.5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>561 (81)</td>
<td>21.6</td>
<td>17.3</td>
</tr>
<tr>
<td>≥65 y</td>
<td>134 (19)</td>
<td>17.4</td>
<td>13.7</td>
</tr>
<tr>
<td>KPS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td>457 (66)</td>
<td>23.3</td>
<td>17.8</td>
</tr>
<tr>
<td>≤80</td>
<td>228 (33)</td>
<td>14.9</td>
<td>11.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>222 (32)</td>
<td>24.6</td>
<td>18.5</td>
</tr>
<tr>
<td>Male</td>
<td>473 (68)</td>
<td>19.1</td>
<td>15.5</td>
</tr>
</tbody>
</table>

Understanding dose and measuring dose-response in EF-14
In vitro evidence of mechanism of action: field frequency must be titrated to tumor cell size

- Multiple cancer cell lines were exposed to TTFields at various frequencies (50–500 kHz)
- Inhibition of cellular proliferation by TTFields was frequency dependent
- Optimal frequency was inversely proportional to cell size
  - Smaller cells were inhibited at higher frequencies
  - Larger cells were inhibited at lower frequencies
- The optimal frequency for inhibiting GBM cells was 200 kHz

In vitro evidence of mechanism of action: time-dependent effects of TTFields (more is better)

<table>
<thead>
<tr>
<th>Glioma Cell Line</th>
<th>Doubling Time (hours)</th>
<th>Number of Cells Following TTFields Application (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st Cell Cycle</td>
</tr>
<tr>
<td>U-87 MG</td>
<td>35</td>
<td>79</td>
</tr>
<tr>
<td>A-172</td>
<td>32</td>
<td>81</td>
</tr>
<tr>
<td>U-118 MG</td>
<td>19</td>
<td>85</td>
</tr>
<tr>
<td>F-98</td>
<td>25</td>
<td>78</td>
</tr>
</tbody>
</table>

0.05 >*P >0.01, 0.01 >†P >0.001, ‡P <0.001. Adapted from Schneiderman RS, et al. Poster presented at: 2015 Society for NeuroOncology (SNO) Annual Meeting; November 19-22, 2015; San Antonio, TX. Poster no ATPS-25.
*In vitro* evidence of mechanism of action: increased force (field intensity, V/cm) = increased kill rate

- Multiple cancer cell lines subjected to TTFields at various electric field intensities
- Inhibition of cellular proliferation by TTFields is dose dependent
- Effective inhibition of cell culture growth seen at intensities >1.0 V/cm

**Optimal frequency (kHz)**
- 100: Mouse melanoma (B16F1)
- 150: Human breast carcinoma (MDA-MB-231)
- 200: Rat glioma (F-98)
- 200: Human NSCLC (H1299)

Personalizing the array layout: changing the layout changes field distribution and resulting dose delivered to tumor

- Field strength within a tumor did not correlate with its size and shape
- Field strength always increased when the arrays were adapted to the tumor's location
  - Compared with a default layout, the largest increase in field strength was 184%
  - The highest average field strength induced in a tumor was 2.21 V/cm

Correlation of TTFields dose density and survival outcomes in newly diagnosed glioblastoma: A numerical simulation-based analysis of patient data from the EF-14 randomized trial

Matthew T. Ballo¹, Noa Urman², Gitit Lavy-Shahaf², Ze’ev Bomzon² and Steven Toms³

¹West Cancer Center Center, Memphis Tennessee; ²Novocure Ltd, Haifa, Israel; ³Warren Alpert Medical School of Brown University
Background

Rationale:
• Preclinical investigations have defined a relationship between TTFields antimitotic effects and exposure time (in hours), frequency (in kHz) and field intensity (in V/cm).
• The randomized clinical phase III trial (EF-14) of TTFields in Glioblastoma showed improved overall survival.
• The overall survival benefit was associated with the degree of TTFields compliance (% monthly use).

Hypothesis:
• Overall survival and Progression free survival are higher in patients who receive higher doses of TTFields at the tumor bed.
Methods:
Step 1: Contouring of tumor on MRI
Step 2: Head model creation & Transducer placement
Step 3: Intensity Distribution calculation
  • Assign electric properties to model tissue types
  • Calculate 3D electric field distribution numerically (Finite Difference Method).
  • Analyze Field distribution by gross tumor volumes & peritumoral boundary zones (3mm around GTV and Resection cavity)

Local Minimum Field Intensity (LMiFI) :
The lower of the two field intensities delivered to each point (Volts/cm)

Local Minimum Power Density (LMiPD):
The lower of the two power densities delivered to each point (milliWatts/cm³)

Patient data EF-14 TTFields txt arm: N=466
Treatment duration >2 mths: n=379
Sufficient MRI quality: n=340
Total number for analysis: 340 patients
Higher TTFields intensity (≥1.0 Volts/cm) and power density (≥1.1 mW/cm³) are associated with improved overall survival and independent of compliance.
Summary:

**Dose Density = Power Density X Compliance**

- Higher TTFields intensity (≥1.0 Volts/cm) and power density (≥1.1 mW/cm³) are associated with improved overall survival and independent of compliance.

- Calculating, visualizing and manipulating TTFields dose distributions to maximize TTFields dose in the tumor bed is expected to improve patient outcome further.

- A new term, **Dose Density**, expresses the two most important variables associated with TTFields use and Overall Survival as a single variable.
Increased dose correlated with increased survival

Overall Survival by dose in newly diagnosed GBM

- **TMZ alone**: median overall survival, months 16
  - n=229

- **lower energy***: median overall survival, months 21
  - n=195

- **higher energy* and <18 hours/day**: median overall survival, months 23
  - n=42

- **higher energy* and 18-20 hours/day**: median overall survival, months 25
  - n=44

- **higher energy* and 20-24 hours/day**: median overall survival, months 37
  - n=36

---

TMZ, temozolomide; CI, confidence interval. Dose density defined as a factor of both power loss density and monthly usage of therapy. * Higher energy defined as power loss densities greater than or equal to 1.1 mW/cm². Lower energy defined as power loss densities less than 1.1 mW/cm²

1 95% CI 21-48; 23 events, 13 censored
2 95% CI 18-39; 29 events, 15 censored
3 95% CI 19-44; 24 events, 18 censored
4 95% CI 17-24; 153 events, 42 censored

Post-hoc analysis of EF-14 treatment arm patient data. Of the 466 EF-14 treatment arm patients, the analysis reviewed 317 patients with treatment duration >2 months and sufficient MRI quality.


TTFields in practice at the West Cancer Center

- Multidisciplinary approach
  - Neurosurgery
  - Radiation oncology
  - Medical/Neuro oncology

- Consistent education of patient by treatment team throughout care

- Offered as national and institutional standard of care for newly diagnosed GBM
Agenda

• Introductions and background

• Answering the scientific questions
  – Mechanism of action
  – General acceptance by medical community
  – Net positive health outcomes
  – Predictors of success
  – Additional supporting evidence

• Patient perspective
How confident are you that there are no significant evidence gaps that may impact positive health outcomes in the Medicare-eligible population?
EF-14: health-related quality of life evaluation

- Quality of life (QoL) was a predefined secondary endpoint in the EF-14 clinical trial

- EORTC QLQ-C30 and QLQ-BN20 questionnaires were completed at baseline and every 3 months thereafter, up to 12 months

- Nine scales and items were preselected based on relevance for patients with glioblastoma and the hypothesized effects of Optune on patients’ QoL
  - Global health status
  - Physical functioning
  - Cognitive functioning
  - Role functioning
  - Social functioning
  - Emotional functioning
  - Itchy skin
  - Pain
  - Weakness of legs

- Patients were using first generation Optune, which when compared with the second generation device is twice the size and weight

**EF-14: Deterioration-Free Survival (DFS)**

DFS: Time to >10-point deterioration in scores from baseline without a subsequent ≥10-point improvement in scores compared with baseline; progressive disease; or death in the absence of a previous definitive deterioration before the next assessment. TMZ, temozolomide; DFS, deterioration-free survival.


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median (months)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deterioration-Free Survival (DFS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status</td>
<td>6.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>4.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>5.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Role functioning</td>
<td>4.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Social functioning</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>4.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Pain</td>
<td>5.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Itchy skin</td>
<td>5.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Weakness of legs</td>
<td>5.6</td>
<td>3.9</td>
</tr>
</tbody>
</table>

DFS was significantly longer with Optune + TMZ vs TMZ alone for global health status, physical and emotional functioning, pain, and weakness of legs.

---

DOS: Time to >10-point deterioration in scores from baseline without a subsequent ≥10-point improvement in scores compared with baseline; progressive disease; or death in the absence of a previous definitive deterioration before the next assessment. TMZ, temozolomide; DFS, deterioration-free survival. 1. Taphoorn MJB, et al. *JAMA Oncol.* 2018;4(4):495-504.
Substantial and growing body of peer-reviewed evidence supports clinical adoption of TTFields

- 132 peer reviewed publications of clinical data on TTFields over the past 11 years in Medline Database
- Bibliography provided to the CAC panel is incomplete

Clinical publications on Tumor Treating Fields by year

- Original clinical research
- Review articles
- Clinical case studies

Bibliography provided to CAC; available through Medline Database.
TTFields has achieved “general acceptance” in the medical community based on gold standard clinical data

Agenda

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  – General acceptance by medical community
  – Net positive health outcomes
  – Predictors of success
  – Additional supporting evidence

• Patient perspective
Living with GBM and Thriving with Optune
TTFields Peer Reviewed Publications


Kim EH, Song HS, Yoo SH, Yoon M. Tumor treating fields inhibit glioblastoma cell migration, invasion and angiogenesis. Oncotarget. 2016; 7:65125-65136


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


Sherman JH, Li G, Cho JM, Choy W, Yang I, and Smith ZA. Key perspectives on auditory outcomes following radiosurgery for vestibular schwannoma, tumor treating fields for


Strowd RE. Electrical Field Therapy for Glioblastoma. *NEJM J Watch.* 2018


