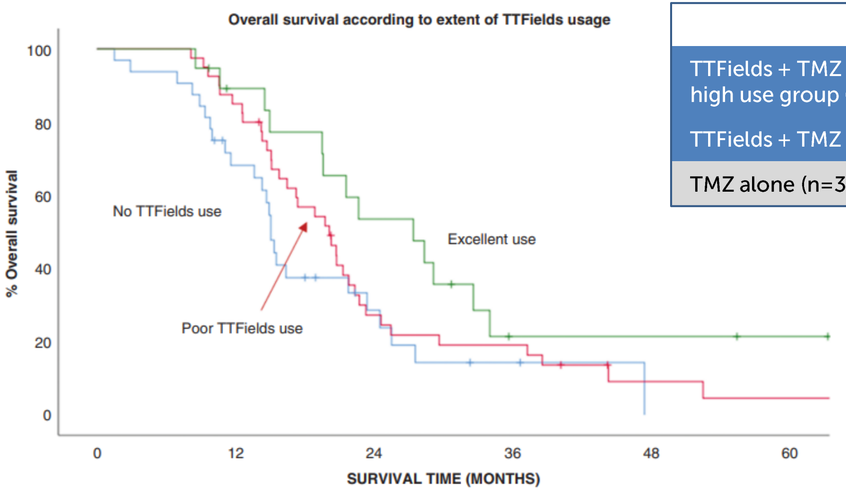
real-world and routine clinical care study evidence

real-world evidence showed ndGBM median overall survival extension by over 12 months in the high use TTFields group

FOR MORE INFORMATION, USE THE QR CODE:



	Median OS
TTFields + TMZ high use group (n=19)	28.0 mo
TTFields + TMZ (n=40)	20.0 mo
TMZ alone (n=32)	15.0 mo

Neuro-Oncology Advances

4(1), 1–8, 2022 | https://doi.org/10.1093/noajnl/vdac150 | Advance Access date 15 September 2022

Determinants of tumor treating field usage in patients with primary glioblastoma: A single institutional experience

Matthew T. Ballo, Kaitlin W. Qualls, L. Madison Michael, Jeffrey M. Sorenson, Brandon Baughman, Saradasri Karri-Wellikoff, and Manjari Pandey

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Abstract

Background. Determinates of tumor treating fields (TTFields) usage in patients receiving combined modality therapy for primary IDH wild-type glioblastoma are currently unknown.

Methods. Ninety-one patients underwent maximal debulking surgical resection, completed external beam radiotherapy with concurrent Temozolomide (TMZ), and initiated adjuvant TMZ with or without TTFields. We performed a retrospective analysis of patient, tumor, and treatment-related factors that affected TTFields usage.

Results. We identified three TTFields usage subgroups: 32 patients that declined TTFields, 40 patients that started, but had monthly compliance of less than 75% or used it for less than 2 months, and 19 patients who used TTFields for 2 or more months and maintained average monthly compliance greater than 75%. With 26.5 months median follow-up for surviving patients, the 1- and 3-year actuarial overall survival for all patients was 80% and 18%, respectively. On multivariate analysis TTFields use (P = .03), extent of surgical resection (P = 0.02), and MGMT methylation status (P = .01) were significantly associated with overall survival. TTFields usage was explored as a continuous variable and higher average usage was associated with longer overall survival (P = .03). There was no relationship between patient, tumor, or treatment-related factors and a patient's decision to use TTFields.

Conclusions. No subgroup of patients was more or less likely to initiate TTFields therapy and no subgroup was more or less likely to use TTFields as prescribed. The degree of TTFields compliance may be associated with improved survival independent of other factors.

Key Point

- It is reasonable to offer all patients with primary glioblastoma TTFields therapy as we could not identify a group that was more or less likely to discontinue therapy or unable to initiate therapy. Patients benefit from TTFields regardless of tumor or patient characteristics.

Glioblastoma is the most common and aggressive primary malignant brain tumor diagnosed in adults and has a poor prognosis, with only 5%–10% of patients being alive 5 years following diagnosis. Even with the best standard of care, consisting of maximal safe surgical resection, radiation therapy, and temozolomide (TMZ) chemotherapy, median overall survival has historically been only 14.6 months.[1,2]

Tumor treating fields (TTFields) represent a novel therapy in the treatment of glioblastoma. TTFields deliver low-intensity, intermediate-frequency (200 kHz) alternating electric fields

ndGBM, newly diagnosed glioblastoma; OS, overall survival; TMZ, temozolomide, TTFields, Tumor Treating Fields. Mild to moderate skin irritation was the most common device related side effect. High use group >2 months use and ≥75% usage. Low use group <75% usage or <2 months use. Ballo et al. Neuro-Oncology Advances, Volume 4, Issue 1, January-December 2022, vdac150, https://doi.org/10.1093/noajnl/vdac150

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real-world evidence validates EF-14 with statistically significant improvement in PFS and OS in Chinese patients with ndGBM

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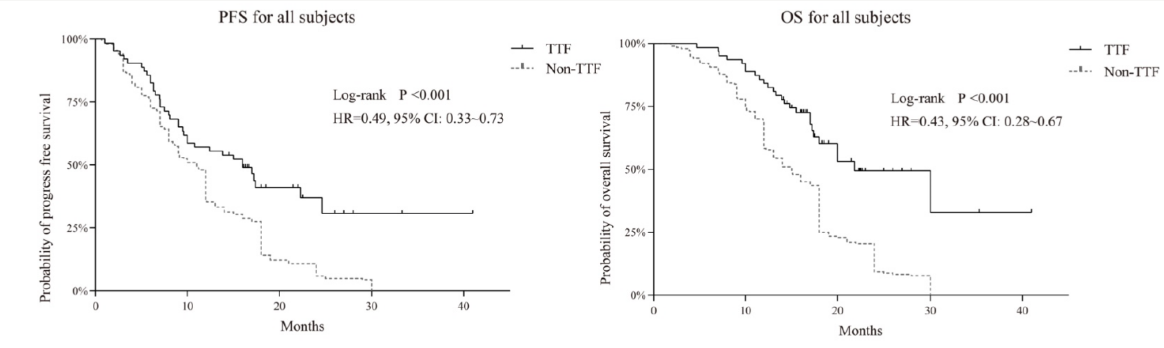
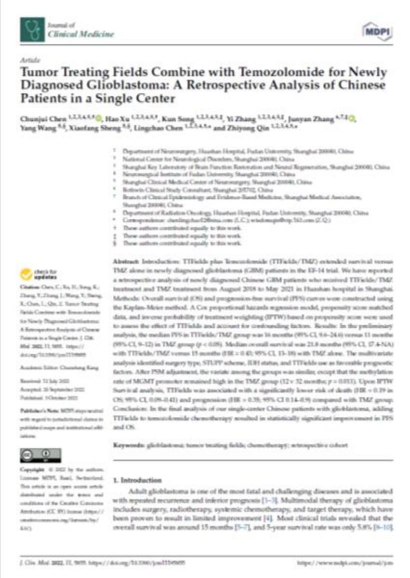


	Median OS	Median PFS
TTFields + TMZ (n=63)	21.8 mo	16.0 mo
TMZ alone (n=204)	15.0 mo	11.0 mo


Journal of Clinical Medicine

Article

Tumor Treating Fields Combine with Temozolomide for Newly Diagnosed Glioblastoma: A Retrospective Analysis of Chinese Patients in a Single Center

MDPI

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide; TTFields, Tumor Treating Fields. Mild to moderate skin irritation was the most common device related side effect. Chen et al. J. Clin. Med. Volume 11, 5855. https://doi.org/10.3390/jcm11195855

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post-approval study supports safety and efficacy profile of TTFields therapy in ndGBM Japanese patients, validating EF-14 improved survival rates

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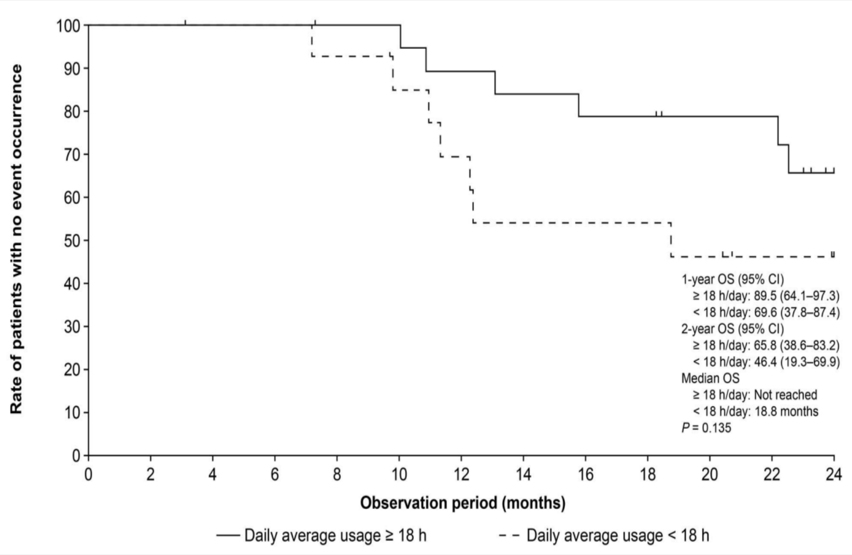
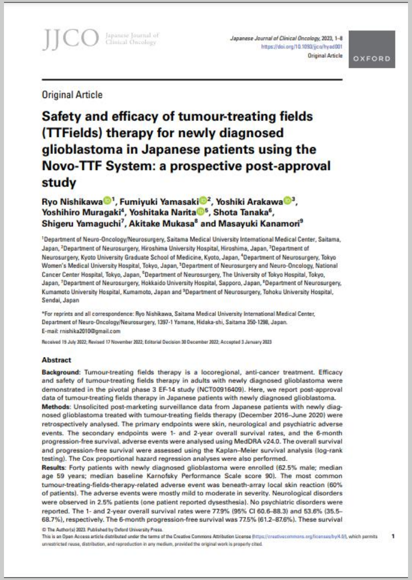


	1-year survival	2-year survival
TMZ alone[1]	65%	31%
TTFields + TMZ (n=14)	77.9%	53.6%
TTFields + TMZ high use group (n=21)	89.5%	65.8%



JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2023, 1–8
https://doi.org/10.1093/jjco/hyad001
Original Article

OXFORD

Original Article

Safety and efficacy of tumour-treating fields (TTFields) therapy for newly diagnosed glioblastoma in Japanese patients using the Novo-TTF System: a prospective post-approval study

Ryo Nishikawa[1], Fumiyuki Yamasaki[2], Yoshiki Arakawa[3], Yoshihiro Muragaki[4], Yoshitaka Narita[5], Shota Tanaka[6], Shigeru Yamaguchi[7], Akitake Mukasa[8] and Masayuki Kanamori[9]

[1]Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Saitama, Japan, [2]Department of Neurosurgery, Hiroshima University Hospital, Hiroshima, Japan, [3]Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, [4]Department of Neurosurgery, Tokyo Women's Medical University Hospital, Tokyo, Japan, [5]Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan, [6]Department of Neurosurgery, The University of Tokyo Hospital, Tokyo, Japan, [7]Department of Neurosurgery, Hokkaido University Hospital, Sapporo, Japan, [8]Department of Neurosurgery, Kumamoto University Hospital, Kumamoto, Japan and [9]Department of Neurosurgery, Tohoku University Hospital, Sendai, Japan

*For reprints and all correspondence: Ryo Nishikawa, Saitama Medical University International Medical Center, Department of Neuro-Oncology/Neurosurgery, 1397-1 Yamane, Hidaka-shi, Saitama 350-1298, Japan.
E-mail: rnishika2010@gmail.com

Received 19 July 2022; Revised 17 November 2022; Editorial Decision 30 December 2022; Accepted 3 January 2023

Abstract

Background: Tumour-treating fields therapy is a locoregional, anti-cancer treatment. Efficacy and safety of tumour-treating fields therapy in adults with newly diagnosed glioblastoma were demonstrated in the pivotal phase 3 EF-14 study (NCT00916409). Here, we report post-approval data of tumour-treating fields therapy in Japanese patients with newly diagnosed glioblastoma.
Methods: Unsolicited post-marketing surveillance data from Japanese patients with newly diagnosed glioblastoma treated with tumour-treating fields therapy (December 2016–June 2020) were retrospectively analysed. The primary endpoints were skin, neurological and psychiatric adverse events. The secondary endpoints were 1- and 2-year overall survival rates, and the 6-month progression-free survival. adverse events were analysed using MedDRA v24.0. The overall survival and progression-free survival were assessed using the Kaplan–Meier survival analysis (log-rank testing). The Cox proportional hazard regression analyses were also performed.
Results: Forty patients with newly diagnosed glioblastoma were enrolled (62.5% male; median age 59 years; median baseline Karnofsky Performance Scale score 90). The most common tumour-treating-fields-therapy-related adverse event was beneath-array local skin reaction (60% of patients). The adverse events were mostly mild to moderate in severity. Neurological disorders were observed in 2.5% patients (one patient reported dysesthesia). No psychiatric disorders were reported. The 1- and 2-year overall survival rates were 77.9% (95% CI 60.6–88.3) and 53.6% (35.5–68.7%), respectively. The 6-month progression-free survival was 77.5% (61.2–87.6%). These survival

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1) Results from the EF-14 study, Stupp R et al. JAMA. 2017;318(23):2306–2316.
ndGBM, newly diagnosed glioblastoma; OS, overall survival;TMZ, temozolomide; TTFields, Tumor Treating Fields. Mild to moderate skin irritation was the most common device related side effect. High use group daily average usage ≥18 hours. Low use group daily average usage <18 hours. Nishikawa et al. Japanese Journal of Clinical Oncology, 2023; https://doi.org/10.1093/jjco/hyad001

long term study of ndGBM patients, covering 18-year period, confirms TTFields' positive effect on PFS and OS

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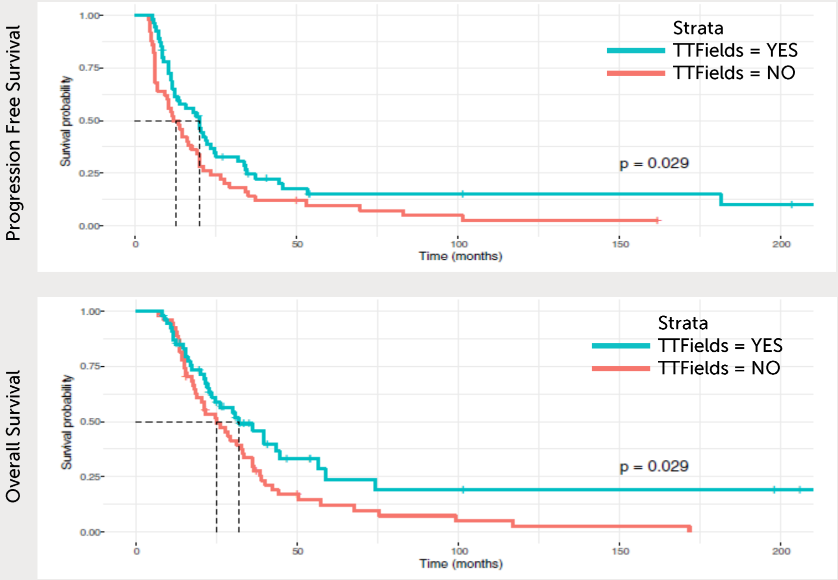


	median PFS	median OS
TTFields + TMZ (n=55)	19.75 mo	31.67 mo
TMZ alone [1]	12.45 mo	24.80 mo


frontiers | Frontiers in Oncology

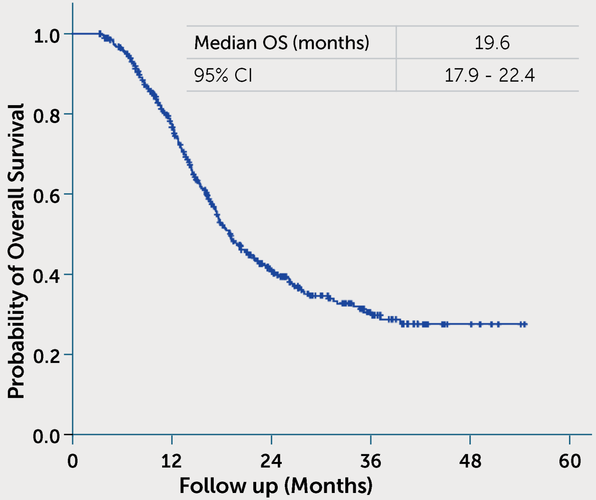
Eighteen years' experience with tumor treating fields in the treatment of newly diagnosed glioblastoma

1) Results from the EF-14 study, Stupp R et al. JAMA. 2017;318(23):2306–2316.
ndGBM, newly diagnosed glioblastoma; OS, median overall survival; PFS, median progression-free survival; TMZ, temozolomide; TTFields, Tumor Treating Fields. Mild to moderate skin irritation was the most common device related side effect. Vymazal J, et al. Front. Oncol. 12:1014455. doi: 10.3389/fonc.2022.1014455

TIGER study of routine clinical care in German ndGBM patients corroborates overall survival and safety outcomes from EF-14

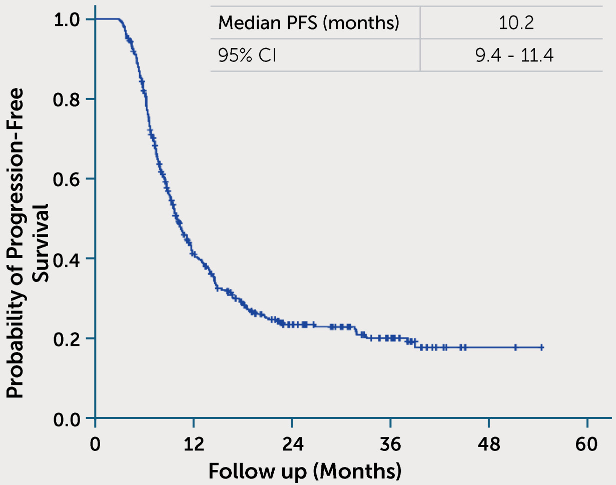
FOR MORE INFORMATION, USE THE QR CODE:

Overall Survival

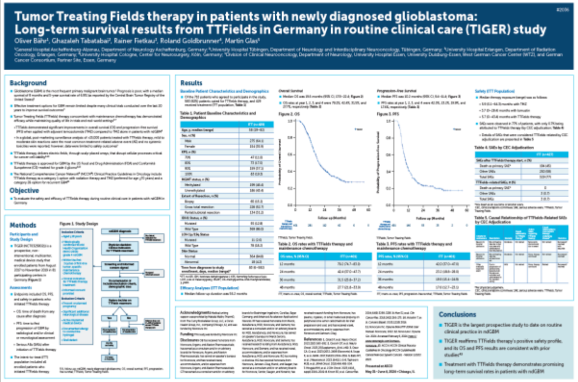


Median OS (months)	19.6
95% CI	17.9 - 22.4

Progression-Free Survival



Median PFS (months)	10.2
95% CI	9.4 - 11.4



ndGBM, newly diagnosed glioblastoma; OS, overall survival; PFS, progression-free survival. Bähr et al. Tumor treating fields (TTFields) therapy in patients with glioblastoma: Long-term survival results from TTFields in Germany in routine clinical care (TIGER) study. JCO 42 2036-2036 (2024)..doi:10.1200/JCO.2024.42.16_suppl.2036

review article identifies TTFields therapy as one of few factors driving increased overall survival in GBM patients since the 2005 Stupp-protocol

FOR MORE INFORMATION, USE THE QR CODE:

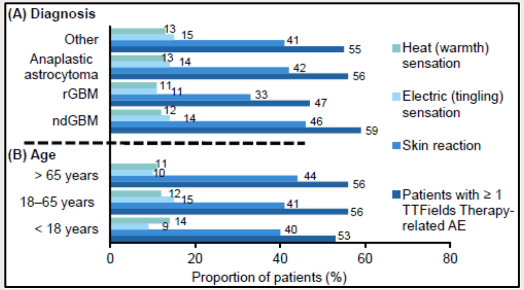
Neff et al.

Characteristic	N	HR[1]	95% CI[1]	p-value
Age (years)	19,414	1.02	1.02, 1.03	<0.001
Sex				
Female	8,046	—	—	reference
Male	11,368	1.10	1.07, 1.14	<0.001
Elixhauser Comorbidity Score	19,414	1.01	1.01, 1.01	<0.001
Tumor-Treating Fields (ever)				
No	16,353	—	—	reference
Yes	3,061	**0.77**	0.73, 0.80	<0.001
Received radiation or radiosurgery (ever)				
No	7,370	—	—	reference
Yes	12,044	**0.88**	0.85, 0.91	<0.001
Bevacizumab (ever)				
No	15,741	—	—	reference
Yes	3,673	**0.85**	0.82, 0.88	<0.001

In this commercially insured dataset, TTFields improved OS to a greater extent (HR=0.77) vs. Bevacizumab (HR=0.85) or Radiation use (HR=0.88)

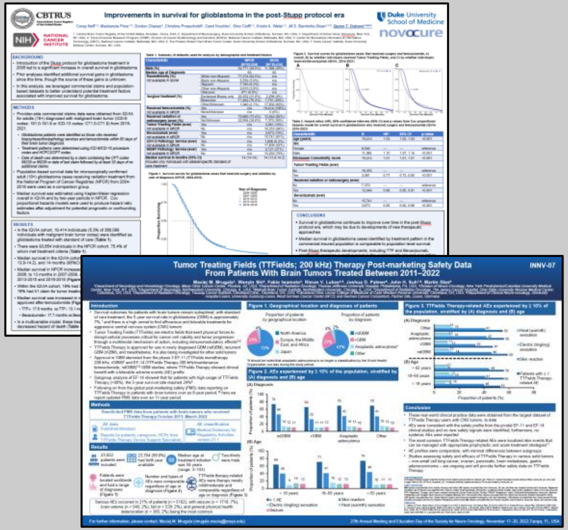
TTFields subset n=3,061 over 6 years

Mrugala et al.



AEs were consistent with the safety profile from the pivotal EF-11 and EF-14 clinical studies

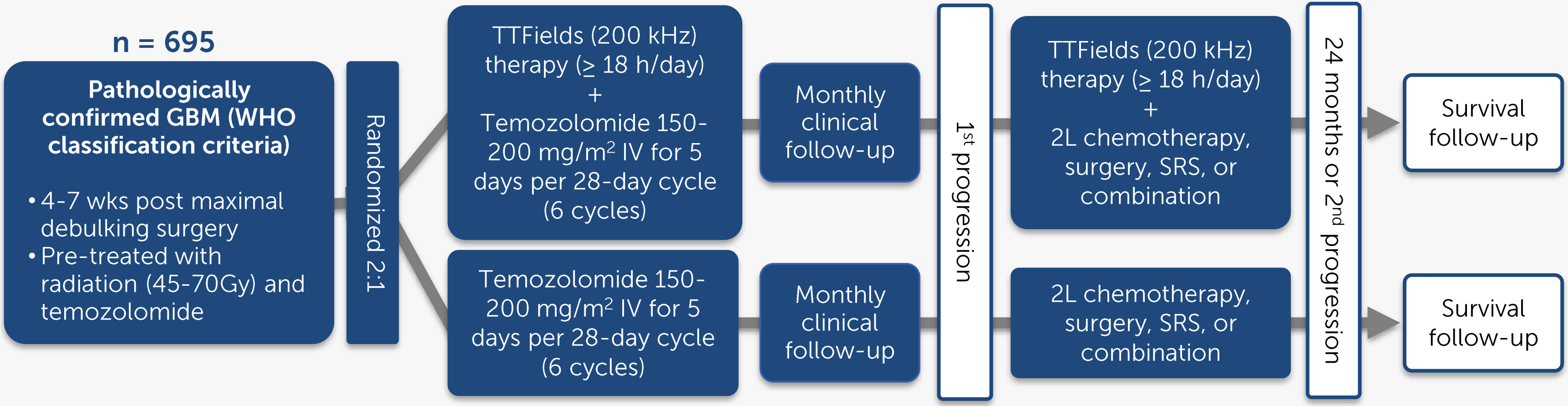
n=23,822 over 11 years



Neff et al. Improvements in Survival for Glioblastoma in the post-Stupp Protocol Era. 27th Annual Meeting and Education Day of the Society for Neuro-Oncology, November 17–20, 2022 , Tampa, FL: SNO; 2022. Abstract EPID-06
Mrugala et al. Tumor Treating Fields (TTFields; 200 kHz) Therapy Post-marketing Safety Data From Patients With Brain Tumors Treated Between 2011–2022. 27th Annual Meeting and Education Day of the Society for Neuro-Oncology, November 17–20, 2022 , Tampa, FL: SNO; 2022. Abstract INNV-07

tumor treating fields clinical evidence appendix

EF-14 phase 3 pivotal trial evaluated Optune Gio + TMZ in 695 patients with ndGBM



Start date: June 2009
Primary completion: December 2016
Study completion: March 2017
Study sites: 83 (global)

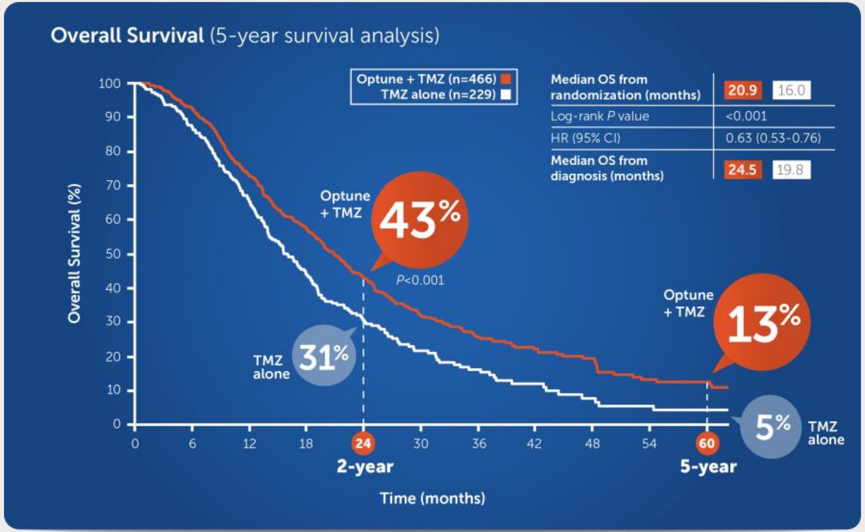
Primary endpoint:
- Progression-free survival

Secondary endpoints:
- Overall survival

GBM, glioblastoma; ndGBM, newly diagnosed glioblastoma; SRS, stereotactic radiosurgery; TMZ, temozolomide; TTFields, Tumor Treating Fields; wks, weeks; WHO, World Health Organization
ClinicalTrials.gov. NCT00916409.

in ndGBM, Optune Gio + TMZ provided an unprecedented long-term survival benefit

FOR MORE INFORMATION, USE THE QR CODE:



Research

JAMA | Original Investigation

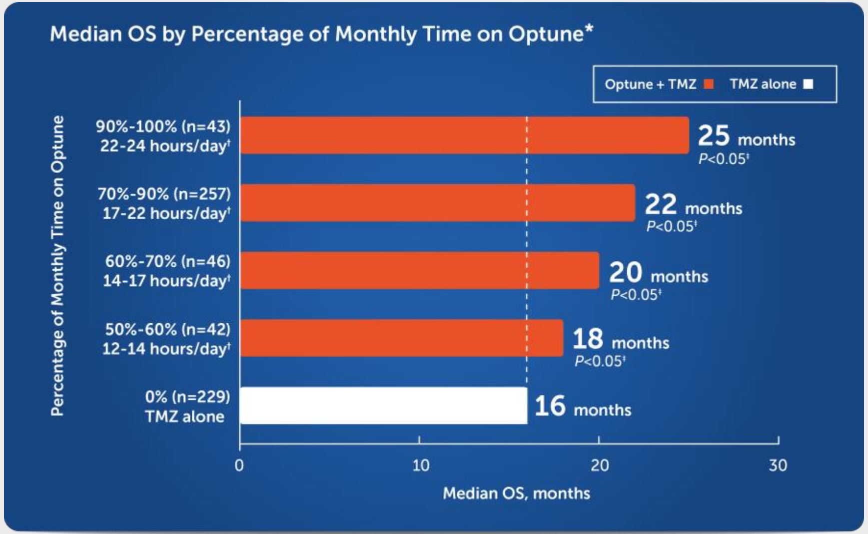
Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

CI, confidence interval; ndGBM, newly diagnosed glioblastoma; TMZ, temozolomide. Stupp R et al. JAMA. 2017;318(23):2306–2316.

more time on Optune Gio predicted increased significant survival benefit

FOR MORE INFORMATION, USE THE QR CODE:



29.3% vs. 4.5%

5-YEAR PROBABILITY OF SURVIVAL WITH 90% COMPLIANCE (n=43) VS SURVIVAL WITH TMZ ALONE


Journal of Neuro-Oncology (2019) 141:467–473
https://doi.org/10.1007/s11060-018-03057-z

CLINICAL STUDY

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

S. A. Toms[1] · C. Y. Kim[2] · G. Nicholas[3] · Z. Ram[4]

Received: 30 August 2018 / Accepted: 21 November 2018 / Published online: 1 December 2018
© The Author(s) 2018

Abstract

OS, overall survival; TMZ, temozolomide. Toms SA et al. J Neurooncol. 2019; 141(2): 467–473.

higher TTFields therapy dose can lead to increased efficacy

FOR MORE INFORMATION, USE THE QR CODES:

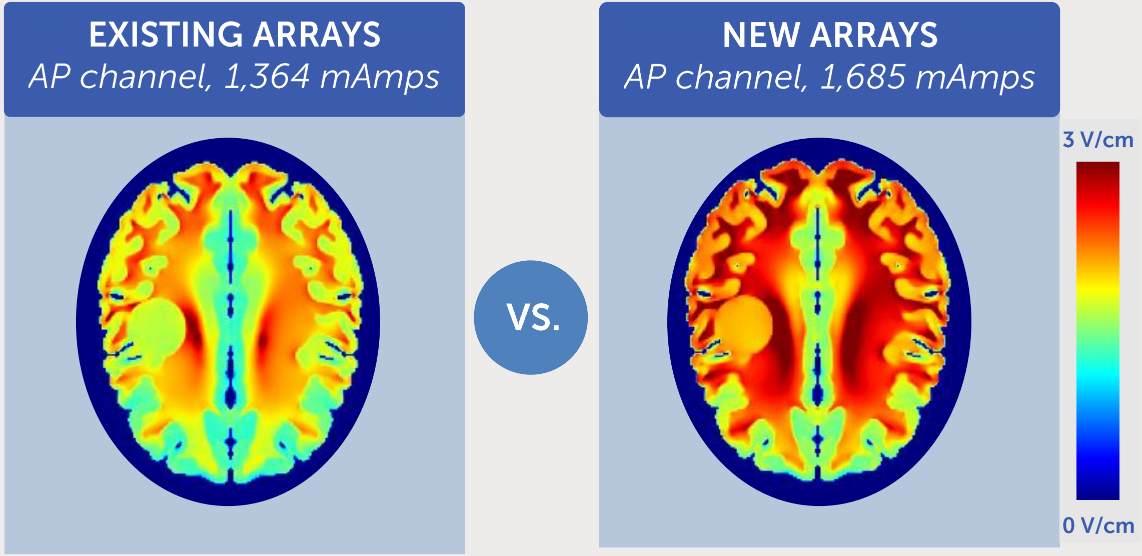
Clinical Investigation

Correlation of Tumor Treating Fields Dosimetry to Survival Outcomes in Newly Diagnosed Glioblastoma: A Large-Scale Numerical Simulation-Based Analysis of Data from the Phase 3 EF-14 Randomized Trial

Matthew T. Ballo, MD,* Noa Urman, MSc,† Gitit Lavy-Shahaf, PhD,† Jai Grewal, MD,‡ Ze'ev Bomzon, PhD,† and Steven Toms, MD§

*Department of Radiation Oncology, West Cancer Center, Germantown, Tennessee; †Novocure Ltd, Haifa, Israel; ‡Novocure Inc, Portsmouth, New Hampshire; and §Warren Alpert Medical School of Brown University and Lifespan Health System, Providence, Rhode Island

Received Dec 28, 2018. Accepted for publication Apr 14, 2019.



Glas et al. Red Journal. 2021;112(5):1269-1278. Ballo et al. Red Journal. 2019;104(5):1106-1113.
Data on file. Simulation of electric field distribution in healthy brain model. Flex arrays are the next generation arrays planned for a limited launch in Europe in late 2022.

all analyzed subgroups experienced a benefit when adding Optune Gio to TMZ

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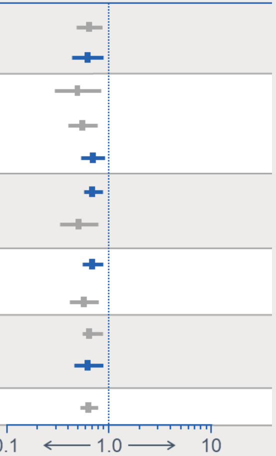
Median survival (months)

Subgroup		Optune + TMZ	TMZ	Hazard ratio (95% CI)
MGMT promoter methylation	Unmethylated	16.9	14.7	
	» Methylated	31.6	21.2	
Resection	Biopsy	16.5	11.6	
	Partial	21.4	15.1	
	» Gross total	22.6	18.5	
Age	» <65 years	21.6	17.3	
	≥65 years	17.4	13.7	
KPS	» 90-100	23.3	17.8	
	≤80	14.9	11.0	
Sex	Women	24.6	18.5	
	» Men	19.1	15.5	
	Total	20.9	16.0	




Research

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Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

CI, confidence interval; KPS, Karnofsky Performance Status; MGMT, O-6-methylguanine-DNA methyltransferase; TMZ, temozolomide; TTFields, Tumor Treating Fields. Stupp R et al. *JAMA*. 2017;318(23):2306–2316.

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Optune Gio was associated with increased survival in patients 65 years and older

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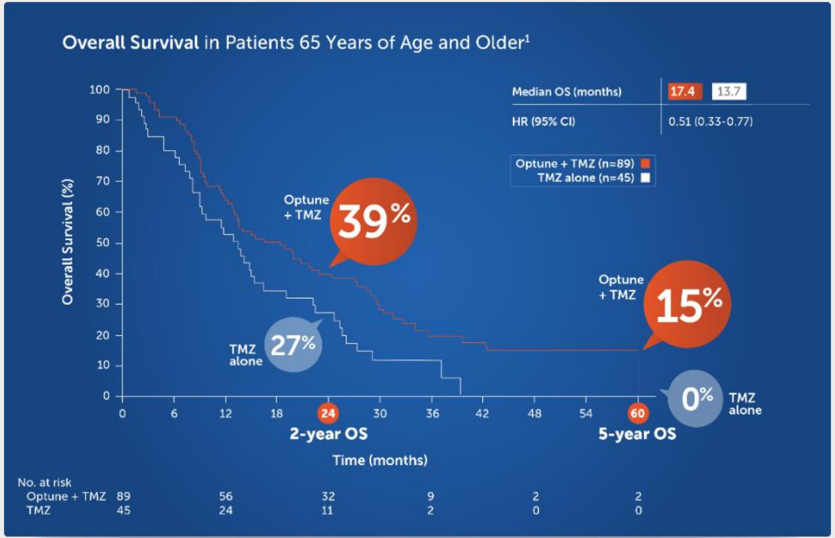

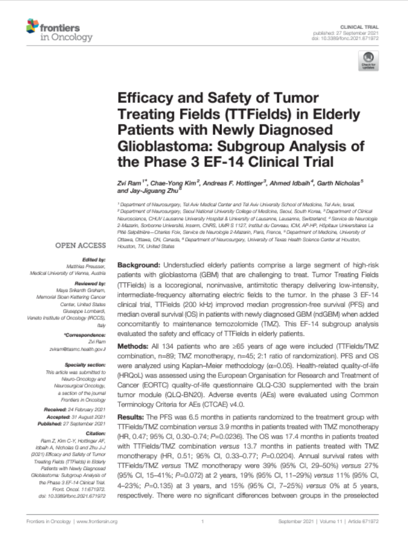

frontiers in Oncology
CLINICAL TRIAL
published: 27 September 2021
doi: 10.3389/fonc.2021.671972

Efficacy and Safety of Tumor Treating Fields (TTFields) in Elderly Patients with Newly Diagnosed Glioblastoma: Subgroup Analysis of the Phase 3 EF-14 Clinical Trial

Zvi Ram[1]*, Chae-Yong Kim[2], Andreas F. Hottinger[3], Ahmed Idbaih[4], Garth Nicholas[5] and Jay-Jiguang Zhu[6]

[1] Department of Neurosurgery, Tel Aviv Medical Center and Tel Aviv University School of Medicine, Tel Aviv, Israel, [2] Department of Neurosurgery, Seoul National University College of Medicine, Seoul, South Korea, [3] Department of Clinical Neuroscience, CHUV Lausanne University Hospital & University of Lausanne, Lausanne, Switzerland, [4] Service de Neurologie 2-Mazarin, Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau, ICM, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière—Charles Foix, Service de Neurologie 2-Mazarin, Paris, France, [5] Department of Medicine, University of Ottawa, Ottawa, ON, Canada, [6] Department of Neurosurgery, University of Texas Health Science Center at Houston, Houston, TX, United States

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Ram Z, Kim C-Y, Hottinger AF, Idbaih A, Nicholas G and Zhu J-J (2021) Efficacy and Safety of Tumor Treating Fields (TTFields) in Elderly Patients with Newly Diagnosed Glioblastoma: Subgroup Analysis of the Phase 3 EF-14 Clinical Trial. Front. Oncol. 11:671972. doi: 10.3389/fonc.2021.671972

Background: Understudied elderly patients comprise a large segment of high-risk patients with glioblastoma (GBM) that are challenging to treat. Tumor Treating Fields (TTFields) is a locoregional, noninvasive, antimitotic therapy delivering low-intensity, intermediate-frequency alternating electric fields to the tumor. In the phase 3 EF-14 clinical trial, TTFields (200 kHz) improved median progression-free survival (PFS) and median overall survival (OS) in patients with newly diagnosed GBM (ndGBM) when added concomitantly to maintenance temozolomide (TMZ). This EF-14 subgroup analysis evaluated the safety and efficacy of TTFields in elderly patients.

Methods: All 134 patients who are ≥65 years of age were included (TTFields/TMZ combination, n=89; TMZ monotherapy, n=45; 2:1 ratio of randomization). PFS and OS were analyzed using Kaplan–Meier methodology (α=0.05). Health-related quality-of-life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire QLQ-C30 supplemented with the brain tumor module (QLQ-BN20). Adverse events (AEs) were evaluated using Common Terminology Criteria for AEs (CTCAE) v4.0.

Results: The PFS was 6.5 months in patients randomized to the treatment group with TTFields/TMZ combination *versus* 3.9 months in patients treated with TMZ monotherapy (HR, 0.47; 95% CI, 0.30–0.74; *P*=0.0236). The OS was 17.4 months in patients treated with TTFields/TMZ combination *versus* 13.7 months in patients treated with TMZ monotherapy (HR, 0.51; 95% CI, 0.33–0.77; *P*=0.0204). Annual survival rates with TTFields/TMZ *versus* TMZ monotherapy were 39% (95% CI, 29–50%) *versus* 27% (95% CI, 15–41%; *P*=0.072) at 2 years, 19% (95% CI, 11–29%) *versus* 11% (95% CI, 4–23%; *P*=0.135) at 3 years, and 15% (95% CI, 7–25%) *versus* 0% at 5 years, respectively. There were no significant differences between groups in the preselected

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CI, confidence interval; TMZ, temozolomide. Ram Z et al. Frontiers in Oncology. 2022; 12: 902929.

biopsy-only patients using Optune Gio had longer median overall survival

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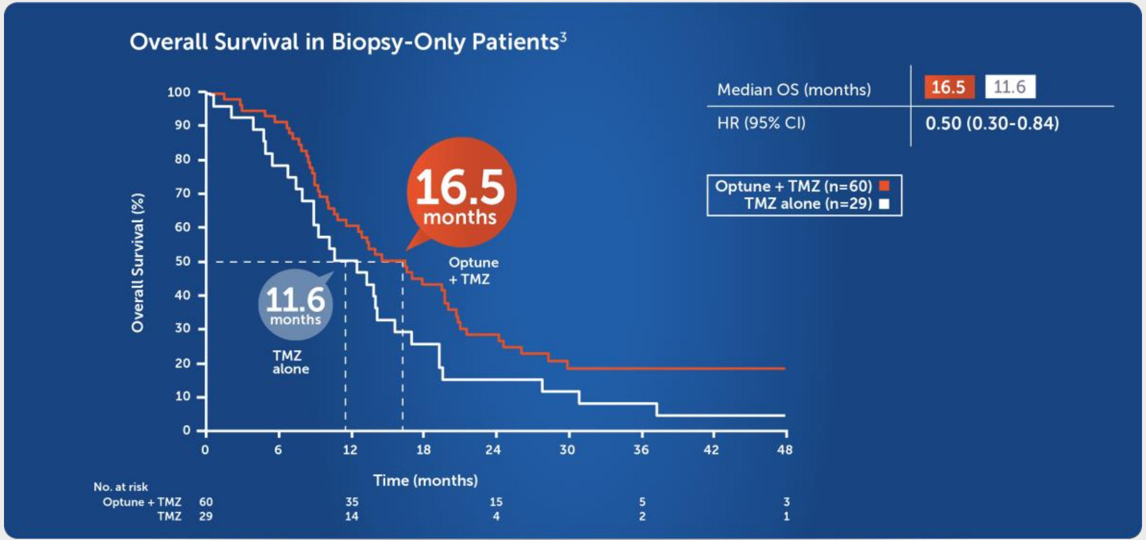



Research

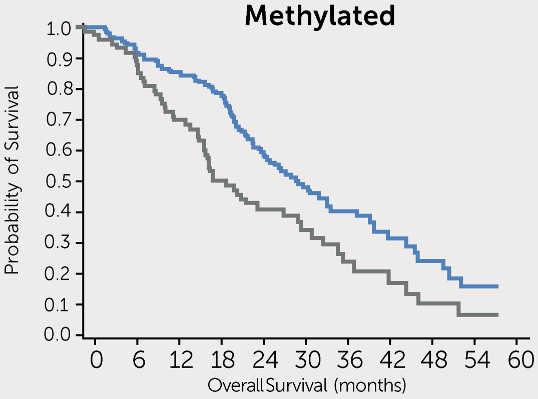
JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma
A Randomized Clinical Trial

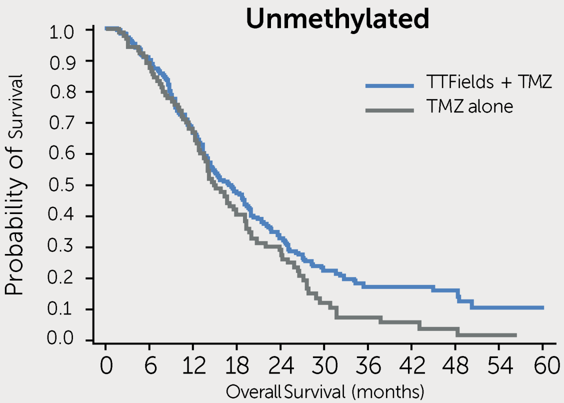
CI, confidence interval; TMZ, temozolomide. Stupp R et al. JAMA. 2017;318(23):2306–2316.

survival benefit occurred independently of MGMT methylation status

FOR MORE INFORMATION, USE THE QR CODE:



	TTFields + TMZ (n = 137)	TMZ Alone (n = 77)
Median OS, months	31.6	21.2
Range, months	21.1–48.5	12.3–37.9
HR (95% CI)[1]	0.62 (0.43–0.88)	



	TTFields + TMZ (n = 209)	TMZ Alone (n = 95)
Median OS, months	16.9	14.7
Range, months	9.7–28.2	9.8–24.8
HR (95% CI)[1]	0.66 (0.49–0.85)	


Research

JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

CI, confidence interval; KPS, Karnofsky Performance Status; MGMT, O-6-methylguanine-DNA methyltransferase; TMZ, temozolomide; TTFields, Tumor Treating Fields. Stupp R et al. JAMA. 2017;318(23):2306–2316.

Optune Gio has a strong safety profile with no significant increase in serious AEs compared with TMZ alone

FOR MORE INFORMATION, USE THE QR CODES:

Incidence of grade 3/4 AEs occurring in ≥5% of patients during 5 years of follow-up	Optune + TMZ (n=456) %	TMZ alone (n=216) %
≥1 AE	48	44
Blood and lymphatic system disorders	13	11
Thrombocytopenia	9	5
Gastrointestinal disorders	5	4
Asthenia, fatigue, and gait disturbance	9	6
Infections	7	5
Injury, poisoning, and procedural complications (falls and medical device site reaction)	5	3
Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)	4	5
Musculoskeletal and connective tissue disorders	5	4
Nervous system disorders	24	20
Seizures	6	6
Respiratory, thoracic, and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)	5	5


Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-020-03540-6

CLINICAL STUDY

Global post-marketing safety surveillance of Tumor Treating Fields (TTFields) in patients with high-grade glioma in clinical practice

Wenyin Shi[1] · Deborah T. Blumenthal[2] · Nancy Ann Oberheim Bush[3] · Sied Kebir[4,5] · Rimas V. Lukas[6,7] · Yoshihiro Muragaki[8,9] · Jay-Jiguang Zhu[10] · Martin Glas[4,5]

Received: 8 April 2020 / Accepted: 21 May 2020
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Abstract

Introduction Tumor Treating Fields (TTFields; antimitotic treatment) delivers low-intensity, intermediate-frequency, alternating electric fields through skin-applied transducer arrays. TTFields (200 kHz) was FDA-approved in glioblastoma (GBM), based on the phase 3 EF-11 (recurrent GBM, rGBM) and EF-14 (newly diagnosed GBM, ndGBM) trials. The most common TTFields-related adverse event (AE) in both trials was array-associated skin irritation. We now report on TTFields-related AEs in the real-world, clinical practice setting.
Methods Unsolicited, post-marketing surveillance data from TTFields-treated patients (October 2011–February 2019) were retrospectively analyzed using MedDRA v21.1 preferred terms, stratified by region (US, EMEA [Europe, Middle East, Africa], Japan), diagnosis (ndGBM, rGBM, anaplastic astrocytoma/oligodendroglioma, other brain tumors), and age (< 18 [pediatric], 18–64 [adults], ≥ 65 [elderly]; years of age).
Results Of 11,029 patients, 53% were diagnosed with ndGBM and 39% were diagnosed with rGBM at any line of disease recurrence. Most were adults (73%), 26% were elderly, and the male-to-female ratio was ~2:1 (close to published ratios of typical GBM populations). The most commonly reported TTFields-related AE was array-associated skin reaction, occurring in patients with ndGBM (38%), rGBM (29%), anaplastic astrocytoma/oligodendroglioma (38%), and other brain tumors (31%); as well as 37% of pediatric, 34% of adult, and 36% of elderly patients. Most skin AEs were mild/moderate and manageable. Other TTFields-related AEs in patients with ndGBM/rGBM included under-array heat sensation (warmth; 11%, 10%, respectively) and electric sensation (tingling; 11%, 9%, respectively), and headache (7%, 6%, respectively).
Conclusions This TTFields safety surveillance analysis in > 11,000 patients revealed no new safety concerns, with a favorable safety profile comparable with published TTFields/GBM trials. The safety profile remained consistent among subgroups, suggesting feasibility in multiple populations, including elderly patients.

Keywords TTFields · Glioblastoma · Real-world · Safety surveillance · Tolerability · Skin adverse events

Introduction

The most common primary brain/central nervous system (CNS) cancers in adults are malignant gliomas, including glioblastoma (GBM), anaplastic astrocytoma, and anaplastic oligodendroglioma [1]. GBM is an aggressive glioma that accounts for 15% of all primary brain/CNS tumors, 48% of primary malignant CNS tumors, and 57% of all gliomas in the United States (US) [2]. Although GBM is a rare tumor type with an estimated global GBM incidence of < 10 per 100,000, it has high mortality and an extremely poor prognosis [3, 4]. Moreover, GBM incidence is generally higher in men, with a male-to-female ratio ranging from 1.0 to 1.9 [2, 5]. In 2020, 13,140 new cases of GBM are projected in the US, including 6950 cases among people ≥ 65 years of age [2].

Prior to Tumor Treating Fields (TTFields), the first-line, standard of care (SOC) treatment for patients with newly diagnosed GBM (ndGBM) consisted of maximal safe resection followed by adjuvant radiotherapy (RT) plus concomitant and maintenance temozolomide (TMZ) chemotherapy [6–8]. Median overall survival (OS) for GBM ranges from 6.0 to 19.6 months, despite treatment advances in neurosurgery, RT, and chemotherapy [9]. The 1-year survival rate

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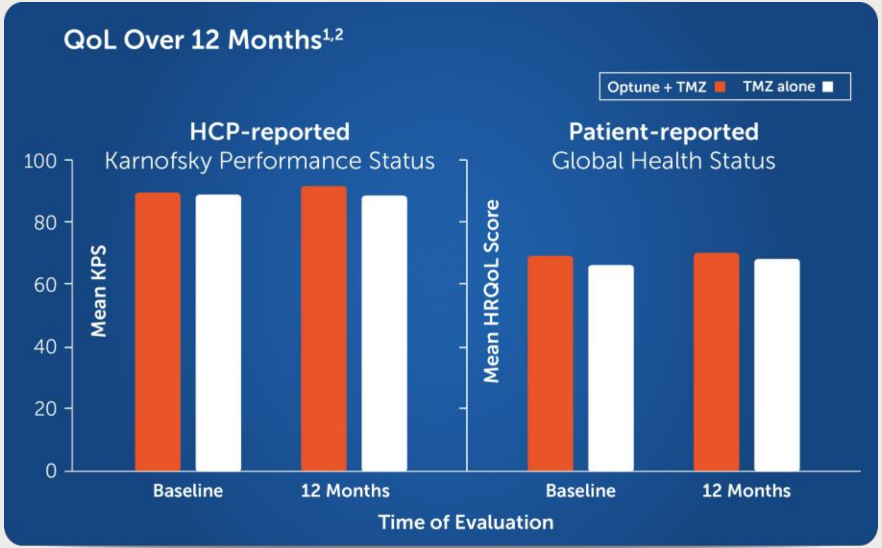
AE, adverse event; TMZ, temozolomide. Stupp R et al. JAMA. 2017;318(23):2306–2316. Shi et al. J Neurooncol. 2020;148:489-500.
Mild to moderate skin irritation was the only device related adverse event

HCPs and patients reported stable quality of life up to 1 year of Optune Gio use

FOR MORE INFORMATION, USE THE QR CODES:

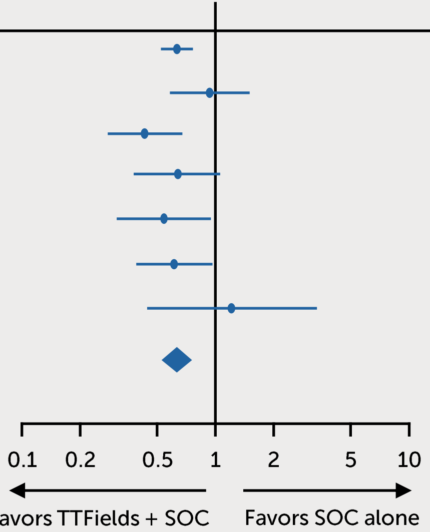


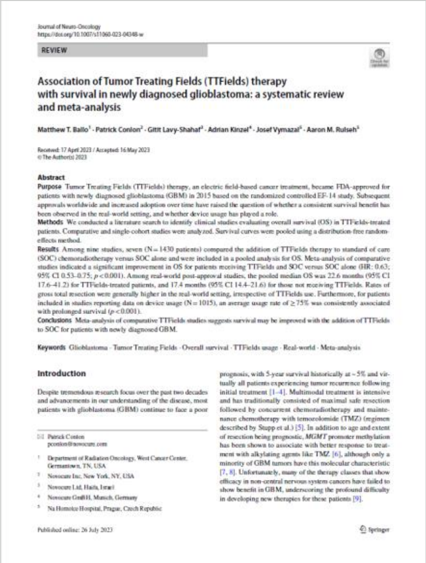
QoL, qualitory of life; HRQoL, health-related quality of life; TMZ, temozolomide. Taphoorn et al. JAMA Oncol. 2018;4(4):495-504. Palmer et al. Front. Oncol 2021;11:772261.

meta-analysis in ndGBM showed significant improvement in OS, and usage ≥75% consistently prolonged survival, corroborating pivotal trial data

FOR MORE INFORMATION, USE THE QR CODE:

Source	TTFields + SOC (N)	SOC alone (N)	HR (95% CI)	W
Stupp et al. 2017	466	229	0.63 (0.53–0.76)	39.8
Liu et al. 2020	37	67	0.93 (0.58–1.47)	11.9
Chen et al. 2022	63	204	0.43 (0.28–0.67)	13.2
Ballo et al. 2022	59	32	0.63 (0.38–1.05)	10.3
Pandey et al. 2022	55	57	0.54 (0.31–0.94)	8.9
Vymazal et al. 2023	55	54	0.61 (0.39–0.95)	12.8
She et al. 2023	13	39	1.21 (0.45–3.29)	3.0
Overall	**748**	**682**	**0.63 (0.53–0.75) (*P*<0.001)**	**100.0**





Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-023-04348-w

REVIEW

Association of Tumor Treating Fields (TTFields) therapy with survival in newly diagnosed glioblastoma: a systematic review and meta-analysis

Matthew T. Ballo[1] · Patrick Conlon[2] · Gitit Lavy-Shahaf[3] · Adrian Kinzel[4] · Josef Vymazal[5] · Aaron M. Rulseh[5]

Received: 17 April 2023 / Accepted: 16 May 2023
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Abstract

Purpose Tumor Treating Fields (TTFields) therapy, an electric field-based cancer treatment, became FDA-approved for patients with newly diagnosed glioblastoma (GBM) in 2015 based on the randomized controlled EF-14 study. Subsequent approvals worldwide and increased adoption over time have raised the question of whether a consistent survival benefit has been observed in the real-world setting, and whether device usage has played a role.

Methods We conducted a literature search to identify clinical studies evaluating overall survival (OS) in TTFields-treated patients. Comparative and single-cohort studies were analyzed. Survival curves were pooled using a distribution-free random-effects method.

Results Among nine studies, seven (N = 1430 patients) compared the addition of TTFields therapy to standard of care (SOC) chemoradiotherapy versus SOC alone and were included in a pooled analysis for OS. Meta-analysis of comparative studies indicated a significant improvement in OS for patients receiving TTFields and SOC versus SOC alone (HR: 0.63; 95% CI 0.53–0.75; $p < 0.001$). Among real-world post-approval studies, the pooled median OS was 22.6 months (95% CI 17.6–41.2) for TTFields-treated patients, and 17.4 months (95% CI 14.4–21.6) for those not receiving TTFields. Rates of gross total resection were generally higher in the real-world setting, irrespective of TTFields use. Furthermore, for patients included in studies reporting data on device usage (N = 1015), an average usage rate of ≥ 75% was consistently associated with prolonged survival ($p < 0.001$).

Conclusions Meta-analysis of comparative TTFields studies suggests survival may be improved with the addition of TTFields to SOC for patients with newly diagnosed GBM.

Keywords Glioblastoma · Tumor Treating Fields · Overall survival · TTFields usage · Real-world · Meta-analysis

Introduction

Despite tremendous research focus over the past two decades and advancements in our understanding of the disease, most patients with glioblastoma (GBM) continue to face a poor prognosis, with 5-year survival historically at ~5% and virtually all patients experiencing tumor recurrence following initial treatment [1–4]. Multimodal treatment is intensive and has traditionally consisted of maximal safe resection followed by concurrent chemoradiotherapy and maintenance chemotherapy with temozolomide (TMZ) (regimen described by Stupp et al.) [5]. In addition to age and extent of resection being prognostic, *MGMT* promoter methylation has been shown to associate with better response to treatment with alkylating agents like TMZ [6], although only a minority of GBM tumors have this molecular characteristic [7, 8]. Unfortunately, many of the therapy classes that show efficacy in non-central nervous system cancers have failed to show benefit in GBM, underscoring the profound difficulty in developing new therapies for these patients [9].

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5 Na Homolce Hospital, Prague, Czech Republic

Published online: 26 July 2023

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Ballo et al. J Neurooncol (2023). Published 26 July 2023. https://doi.org/10.1007/s11060-023-04348-w

TTFields therapy provide consistent activity for patients with GBM irrespective of molecular alterations

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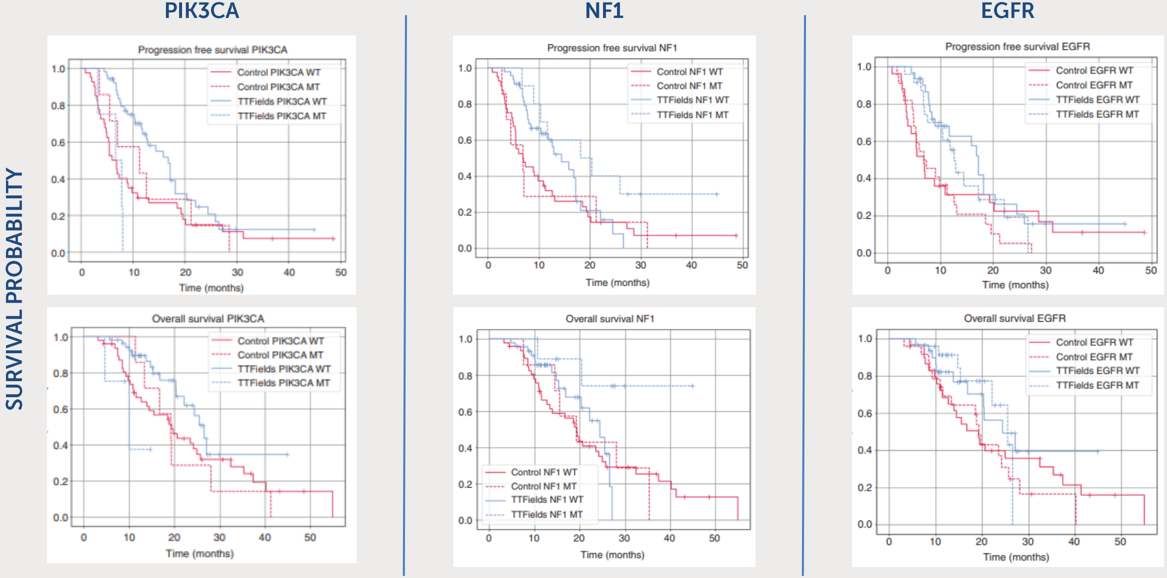


Neuro-Oncology Advances

Molecular alterations associated with improved outcome in patients with glioblastoma treated with Tumor-Treating Fields

Manjari Pandey, Joanne Xiu, Sandeep Mittal, Jia Zeng, Michelle Saul, Santosh Kesari, Amir Azadi, Herbert Newton, Karina Deniz, Katherine Ladner, Ashley Sumrall, W. Michael Korn, and Emil Lou

Key Points

- Alterations in NF1 were associated with increased benefit from TTFields.
- Wild-type PIK3CA and EGFR also aligned with increased benefit from this approach.
- These results provide insight into molecular differences that can be validated to tailor treatment.

Pandey et al. Neuro-Oncology Advances. Volume 4, Issue 1, January-December 2022. https://doi.org/10.1093/noajnl/vdac096

the therapeutic potential of TTFields therapy becoming a research "hotspot"

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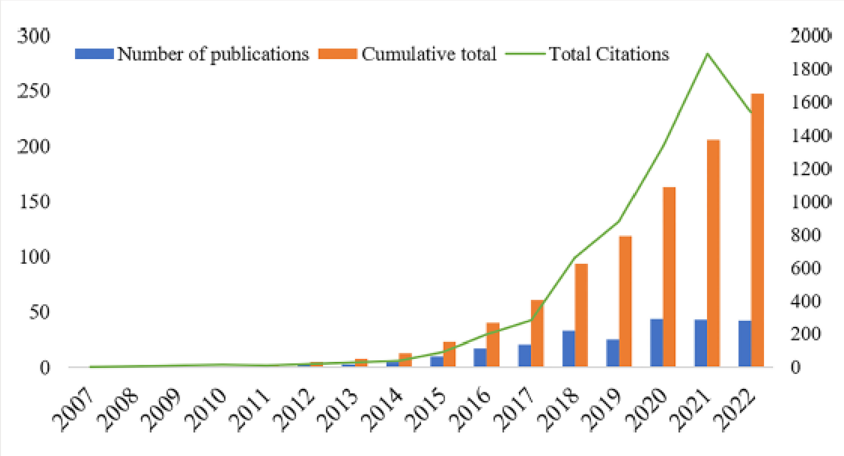

Number of annual publications, annual cumulative number of publications and annual total citations of TTFields related literature from 2007 to September 2022.
(Decline in 2022 citations due to partial year)

28.5%

AVERAGE INCREASE IN THE CUMULATIVE NUMBER OF PUBLICATIONS RELATED TO TTFIELDS

frontiers | Frontiers in Oncology

Research on application of tumor treating fields in glioblastoma: A bibliometric and visual analysis

Xue Du[1,2], Chunbao Chen[2], Yu Xiao[3], Yu Cui[1,2], Lu Yang[1,2], Xiaochun Li[1,2], Xueping Liu[1,2], Ruisi Wang[1,2] and Bangxian Tan[1,2]*

[1]Department of Oncology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China, [2]Department of Clinical Medicine, North Sichuan Medical College, Nanchong Sichuan, China, [3]Department of Radiation Oncology, Fujian Cancer Hospital, Fujian Medical University, Fuzhou, China

Background: Glioblastoma, one of the common tumors of the central nervous system (CNS), is prone to recurrence even after standard treatment protocols. As an innovative physiotherapy method emerging in recent years, the tumor treating fields (TTFields) technique has been approved for the treatment of glioblastoma due to its non-invasive and portable features. The purpose of this study is to visualize and analyze the scientific results and research trends in TTFields therapy for glioblastoma.

Methods: Publications related to TTFields therapy for glioblastoma were searched in the Web of Science Core Collection (WoSCC) database in September 2022. A bibliometric and visual analysis of publications in this field was performed mainly using CiteSpace and R software for country/region, author, journal, reference and keyword.

Results: A total of 618 publications in this field were retrieved, and 248 were finally obtained according to the search criteria, including 159 articles (64.11%) and 89 reviews (37.89%). The cumulative number of publications increased year by year, with an average growth rate (AGR) of 28.50%. The test results of Pearson correlation coefficient showed a high positive correlation between publications and citations (r=0.937, p<0.001). The USA had the largest number of publications (123, 49.60%), followed by Germany (32, 12.90%) and China (30, 12.10%). As for the country/region collaborations, the USA cooperated most closely with other countries/regions, followed by Germany and China. The degree of collaboration (DC) between countries/regions was 25.81%. The institutions with the largest number of publications were Tel Aviv Univ (10), Harvard Med Sch (10) and Novocure Ltd (10). Moreover, Wong E (18) possessed the greatest number of publications, followed by Weinberg U (11) and Kirson E (10). The DC between authors was 97.58%. STUPP R (236) was the most cited author followed by KIRSON ED (164) and GILADI M (104). JOURNAL OF NEURO-ONCOLOGY (22) was the journal with the largest number of published publications (75), followed by FRONTIERS IN ONCOLOGY (15) and

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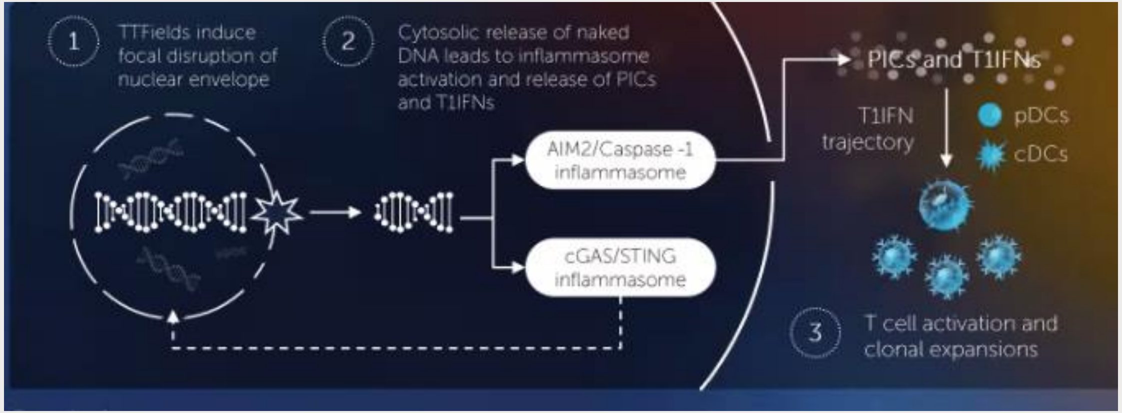
Du et al. Front. Oncol., 10 November 2022 Sec. Neuro-Oncology and Neurosurgical Oncology; https://doi.org/10.3389/fonc.2022.1055366

TTFields therapy activates inflammasomes to induce adjuvant immunity in GBM

FOR MORE INFORMATION, USE THE QR CODE:



The Journal of Clinical Investigation

RESEARCH ARTICLE

Tumor Treating Fields dually activate STING and AIM2 inflammasomes to induce adjuvant immunity in glioblastoma

Dongjiang Chen,[1] Son B. Le,[1] Tarun E. Hutchinson,[1] Anda-Alexandra Calinescu,[1] Mathew Sebastian,[2] Dan Jin,[1] Tianyi Liu,[1] Ashley Ghiaseddin,[1] Maryam Rahman,[1] and David D. Tran[1]

[1]Division of Neuro-Oncology and Preston A. Wells, Jr. Center for Brain Tumor Therapy, Lillian S. Wells Department of Neurosurgery and [2]Medical Scientist Training Program, University of Florida College of Medicine, Gainesville, Florida, USA.

Tumor Treating Fields (TTFields), an approved therapy for glioblastoma (GBM) and malignant mesothelioma, employ noninvasive application of low-intensity, intermediate-frequency, alternating electric fields to disrupt the mitotic spindle, leading to chromosome missegregation and apoptosis. Emerging evidence suggests that TTFields may also induce inflammation. However, the mechanism underlying this property and whether it can be harnessed therapeutically are unclear. Here, we report that TTFields induced focal disruption of the nuclear envelope, leading to cytosolic release of large micronuclei clusters that intensely recruited and activated 2 major DNA sensors — cyclic GMP-AMP synthase (cGAS) and absent in melanoma 2 (AIM2) — and their cognate cGAS/stimulator of interferon genes (STING) and AIM2/caspase 1 inflammasomes to produce proinflammatory cytokines, type 1 interferons (T1IFNs), and T1IFN-responsive genes. In syngeneic murine GBM models, TTFields-treated GBM cells induced antitumor memory immunity and a cure rate of 42% to 66% in a *STING*- and *AIM2*-dependent manner. Using single-cell and bulk RNA sequencing of peripheral blood mononuclear cells, we detected robust post-TTFields activation of adaptive immunity in patients with GBM via a T1IFN-based trajectory and identified a gene panel signature of TTFields effects on T cell activation and clonal expansion. Collectively, these studies defined a therapeutic strategy using TTFields as cancer immunotherapy in GBM and potentially other solid tumors.

Introduction

Glioblastoma (GBM) is the most common and lethal brain cancer in adults and one of the least immunogenic tumors (1). Recent work has revealed striking immune dysregulation and functional impairment in patients with GBM. Besides systemic T lymphopenia and anergy and dysfunctional cytokine profiles among others, GBM tumors also possess a profoundly immunosuppressed or cold tumor microenvironment (TME), characterized by scant tumor-infiltrating lymphocytes (TILs) and an abundance of inhibitory cells, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). The cold GBM TME expresses high levels of immune checkpoint proteins (2), and is further complicated by tumor cells' profound genetic heterogeneity (3). In addition, the blood brain barrier (BBB) prevents exposure of tumor-associated neoantigens to immune cells and vice versa, severely hindering immunotherapeutic efforts (2). Overcoming these hurdles promises a long-lasting, multilayered, immune-mediated tumor control. To "heat up" the cold GBM TME, recent efforts have focused on tumor cell–extrinsic pathways with mixed results, such as dendritic cell–based (DC-based) vaccination, immune checkpoint blockade, rewiring the cytokine milieu, or disrupting BBB integrity to recruit tumor-specific cytotoxic T lymphocytes (CTLs) (4). However, it remains a challenge to leverage a direct, active role of tumor cells in reversing the immunosuppressive state of the GBM TME.

By targeting the motility, alignment, and assembly of macromolecules required for the mitotic spindle structure during metaphase and the contractile ring during anaphase, telophase, and cytokinesis of the cell cycle, Tumor Treating Fields (TTFields) cause chromosome missegregation and breakage and incomplete cytoplasmic separation, respectively, leading to mitotic catastrophe and p53-dependent and -independent apoptosis (5-7). TTFields have also been demonstrated to target the DNA damage repair and breast cancer 1–mediated (BRCA1-mediated) homologous recombination pathways by interfering with DNA fork replication (8-10) and induce endoplasmic reticulum stress during mitosis to trigger adenosine monophosphate–activated protein kinase–dependent autophagosome formation, through increased lipidation of protein light chain 3 α/β-I (LC3A/B-I) to form LC3A/B-II (11). Recent reports also revealed TTFields' ability to electroporate the plasma membrane of GBM cells, allowing particles up to 20 kDa to pass

Conflict of interest: DDT has received research grants, personal honoraria (<$10,000 annually), and the Inovitro system from Novocure to support parts of the work reported here. The conceptualization, design, data collection, analysis, interpretation, decision to publish, and manuscript preparation were performed by the authors independently of Novocure. DC and DDT are inventors of 2 patent applications (nos. 63172862 and 63015093) based on the data. All rights were transferred to Novocure. DDT has received research funding in the last 12 months from Merck, Sarepta, and Lacerta.

Submitted: March 3, 2021; **Accepted:** February 16, 2022; **Published:** April 15, 2022.
Reference information: *J Clin Invest*. 2022;132(8):e149258.
https://doi.org/10.1172/JCI149258.

GBM, glioblastoma; Chen et al. J Clin Invest. 2022;132(8):e149258. https://doi.org/10.1172/JCI149258.

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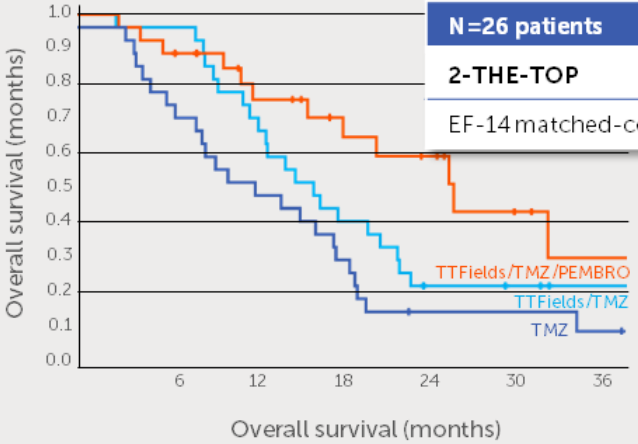
there is early evidence of efficacy in newly diagnosed GBM patients when TTFields therapy is added to immune checkpoint inhibitors

FOR MORE INFORMATION, USE THE QR CODE:

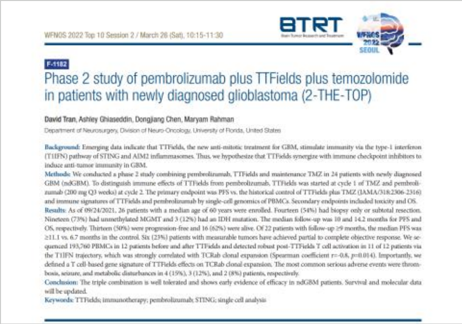
Overall Survival

2-THE-TOP single arm study vs. external controls



N=26 patients	Median OS
2-THE-TOP	**25.2 mos.**
EF-14 matched-control	15.9 mos.

(HR = 0.38; p=0.020)



WFNOS 2022 Top 10 Session 2 / March 26 (Sat), 10:15-11:30

F-1182

Phase 2 study of pembrolizumab plus TTFields plus temozolomide in patients with newly diagnosed glioblastoma (2-THE-TOP)

David Tran, Ashley Ghiaseddin, Dongjiang Chen, Maryam Rahman

Department of Neurosurgery, Division of Neuro-Oncology, University of Florida, United States

Background: Emerging data indicate that TTFields, the new anti-mitotic treatment for GBM, stimulate immunity via the type-1 interferon (T1IFN) pathway of STING and AIM2 inflammasomes. Thus, we hypothesize that TTFields synergize with immune checkpoint inhibitors to induce anti-tumor immunity in GBM.

Methods: We conducted a phase 2 study combining pembrolizumab, TTFields and maintenance TMZ in 24 patients with newly diagnosed GBM (ndGBM). To distinguish immune effects of TTFields from pembrolizumab, TTFields was started at cycle 1 of TMZ and pembrolizumab (200 mg Q3 weeks) at cycle 2. The primary endpoint was PFS vs. the historical control of TTFields plus TMZ (JAMA/318:2306-2316) and immune signatures of TTFields and pembrolizumab by single-cell genomics of PBMCs. Secondary endpoints included toxicity and OS.

Results: As of 09/24/2021, 26 patients with a median age of 60 years were enrolled. Fourteen (54%) had biopsy only or subtotal resection. Nineteen (73%) had unmethylated MGMT and 3 (12%) had an IDH mutation. The median follow-up was 10 and 14.2 months for PFS and OS, respectively. Thirteen (50%) were progression-free and 16 (62%) were alive. Of 22 patients with follow-up ≥9 months, the median PFS was ≥11.1 vs. 6.7 months in the control. Six (23%) patients with measurable tumors have achieved partial to complete objective response. We sequenced 193,760 PBMCs in 12 patients before and after TTFields and detected robust post-TTFields T cell activation in 11 of 12 patients via the T1IFN trajectory, which was strongly correlated with TCRab clonal expansion (Spearman coefficient r=-0.8, p=0.014). Importantly, we defined a T cell-based gene signature of TTFields effects on TCRab clonal expansion. The most common serious adverse events were thrombosis, seizure, and metabolic disturbances in 4 (15%), 3 (12%), and 2 (8%) patients, respectively.

Conclusion: The triple combination is well tolerated and shows early evidence of efficacy in ndGBM patients. Survival and molecular data will be updated.

Keywords: TTFields; immunotherapy; pembrolizumab; STING; single cell analysis

Tran et al. Oral presentation at WFNOS 2022 Top 10 Session 2 / March 26 (Sat), 10:15-11:30

STELLAR phase 2 trial evaluated TTFields therapy + pemetrexed and cisplatin or carboplatin in MPM

N = 80

Previously Untreated, Unresectable MPM

- Pathological or histological evidence of MPM
- Locally advanced or metastatic disease
- ECOG performance status of 0 or 1

Baseline

TTFields (150 kHz, ≥ 18 h/day)
+
Pemetrexed/cisplatin or pemetrexed/carboplatin
(up to 6 cycles)

TTFields alone until disease progression

Follow-up for survival

Start date: February 2015
Primary completion: April 2018
Study completion: April 2018
Study sites: 13 (Europe)

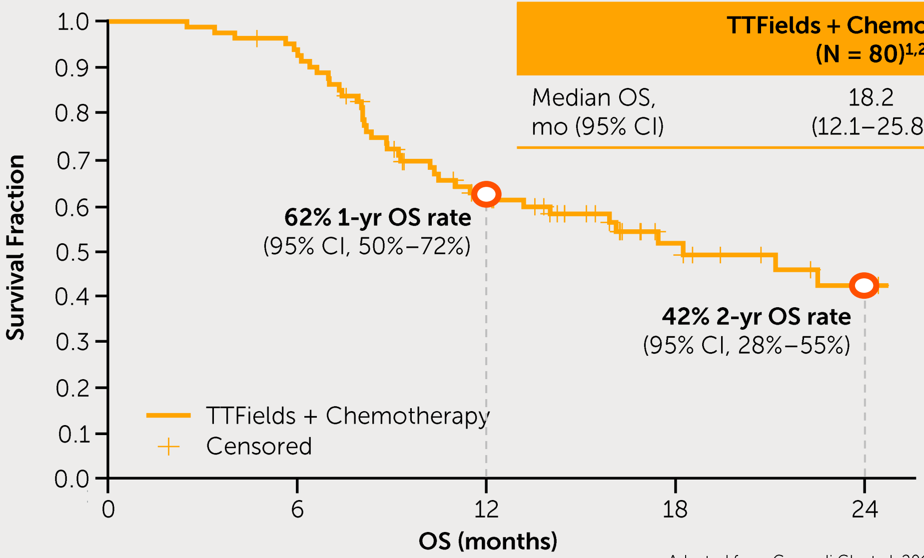
Primary endpoints:
- OS

Secondary endpoints:
- PFS, ORR (modified RECIST criteria for MPM), safety

ECOG, Eastern Cooperative Oncology Group; MPM, malignant pleural mesothelioma; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TTFields, Tumor Treating Fields.
ClinicalTrials.gov. NCT02397928. Accessed June 15, 2022.

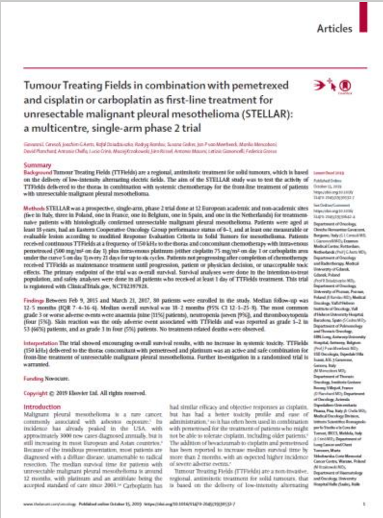
MPM patients who used Optune Lua first line achieved 18.2 months median OS

FOR MORE INFORMATION, USE THE QR CODE:



	TTFields + Chemotherapy (N = 80)[1,2]
Median OS, mo (95% CI)	18.2 (12.1–25.8)

Adapted from Ceresoli GL et al. 2019

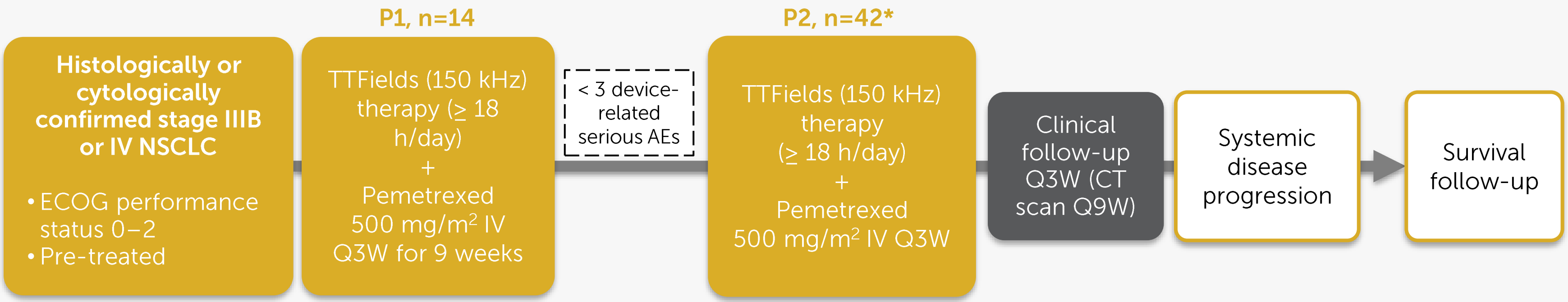


Articles

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

CI, confidence interval; OS, overall survival; TTFields, Tumor Treating Fields. Reference: Ceresoli GL et al. Lancet Oncol. 2019;20(12):1702–1709.

EF-15 phase 2 trial evaluated TTFields therapy + pemetrexed in NSCLC



Start date: May 2008
Primary completion: July 2011
Study completion: July 2011
Study sites: 4 (Switzerland)

Primary endpoints:
- Device related toxicity (P1), Time to in-field progression (P2)

Secondary endpoints:
- OS, ORR, time to systemic progression, safety

*One out of the 42 patients enrolled was excluded from the analysis due to brain metastasis on screening.
AE, adverse event; CT, computerized tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; P, phase; Q3W, every 3 weeks; Q9W, every 9 weeks; TTFields, Tumor Treating Fields.
ClinicalTrials.gov. NCT00749346. Accessed June 15, 2022.

TTFields therapy together with pemetrexed improved disease control within the treatment field in second line NSCLC

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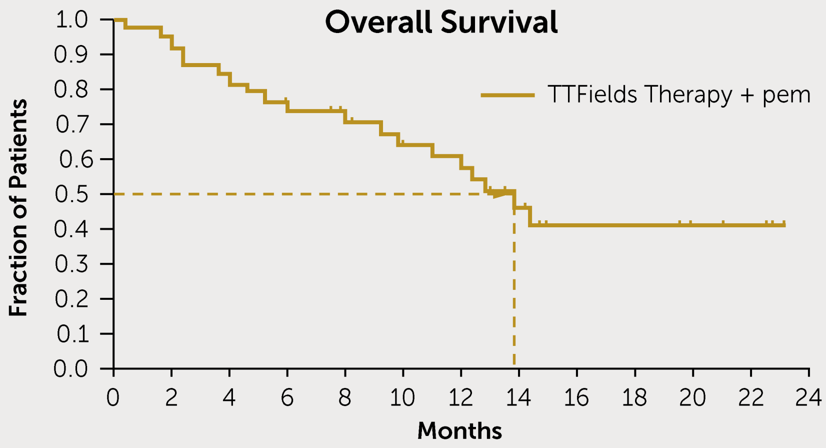

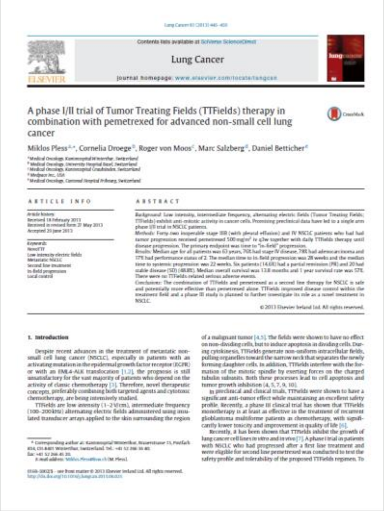
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Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

A phase I/II trial of Tumor Treating Fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer

Miklos Pless, Cornelia Droege, Roger von Moos, Marc Salzberg, Daniel Betticher

ARTICLE INFO

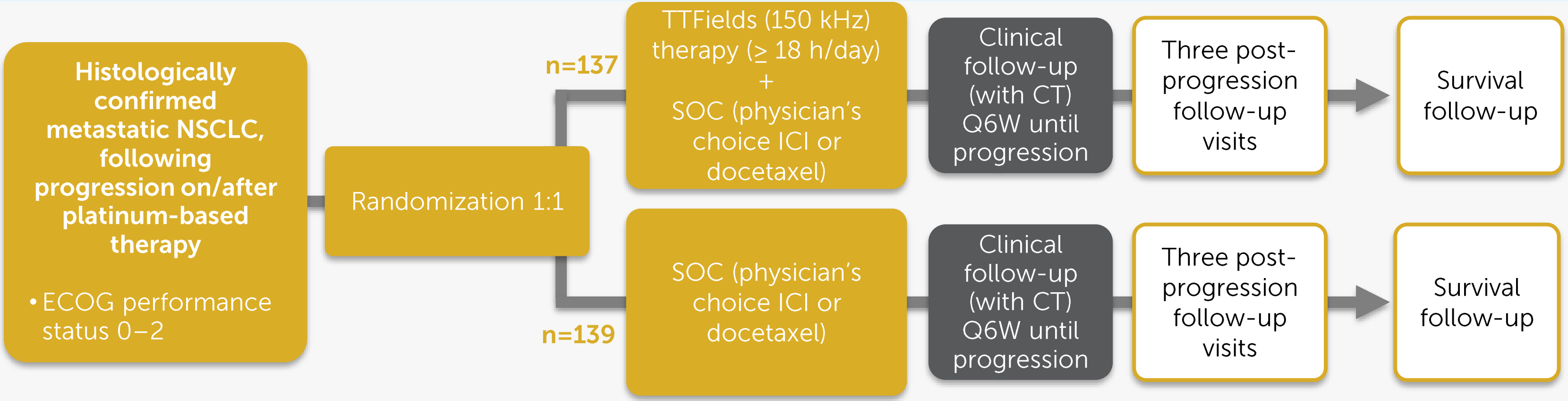
ABSTRACT

	Median in-field PFS	Median PFS	Median OS	1yr Survival
TTFields + Pemetrexed	6.5 mo	5.0 mo	13.8 mo	57.0%
Pemetrexed alone	n/a	2.9 mo	8.3 mo	29.7%

Pem, pemetrexed; TTFields, Tumor Treating Fields; PFS, progression-free survival; OS overall survival.
Pless M et al. *Lung Cancer*. 2013;81(3):445-450.

TTFields are experimental for the treatment of patients with non-small cell lung cancer and have not been approved by the US Food and Drug Administration for this indication nor received a CE mark in Europe.

LUNAR phase 3 trial evaluated TTFields therapy + SOC in metastatic NSCLC, post-platinum



Start date: December 2016
Primary completion: December 2022
Study completion: December 2022
Study sites: 124

Primary endpoints:
- OS

Secondary endpoints:
- OS (by cohort), PFS, ORR, QoL, safety

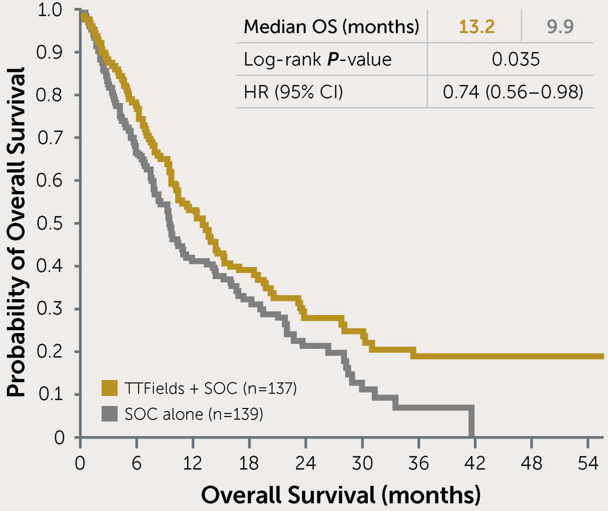
CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; TTFields, Tumor Treating Fields.
ClinicalTrials.gov. NCT02973789.

TTFields therapy together with either standard of care therapies or immune checkpoint inhibitor improved overall survival in second-line NSCLC

FOR MORE INFORMATION, USE THE QR CODE:

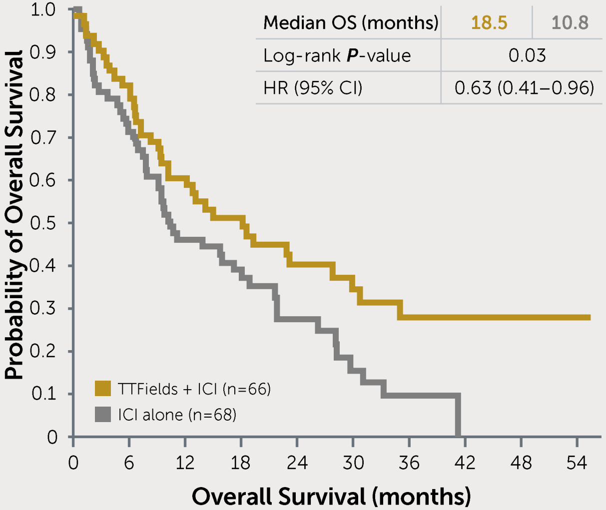
Overall survival (ITT population)

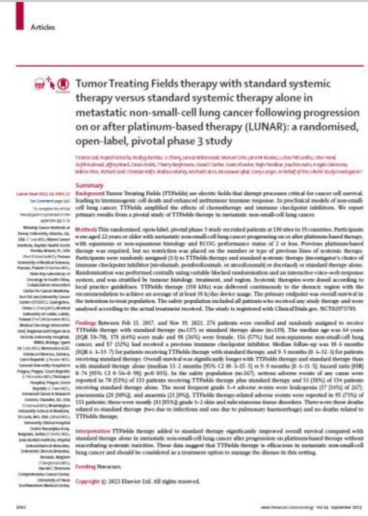
Median OS (months)	13.2	9.9
Log-rank *P*-value	0.035	
HR (95% CI)	0.74 (0.56–0.98)	



Overall survival (ICI-treated patients)

Median OS (months)	18.5	10.8
Log-rank *P*-value	0.03	
HR (95% CI)	0.63 (0.41–0.96)	




Articles

Tumor Treating Fields therapy with standard systemic therapy versus standard systemic therapy alone in metastatic non-small-cell lung cancer following progression on or after platinum-based therapy (LUNAR): a randomised, open-label, pivotal phase 3 study

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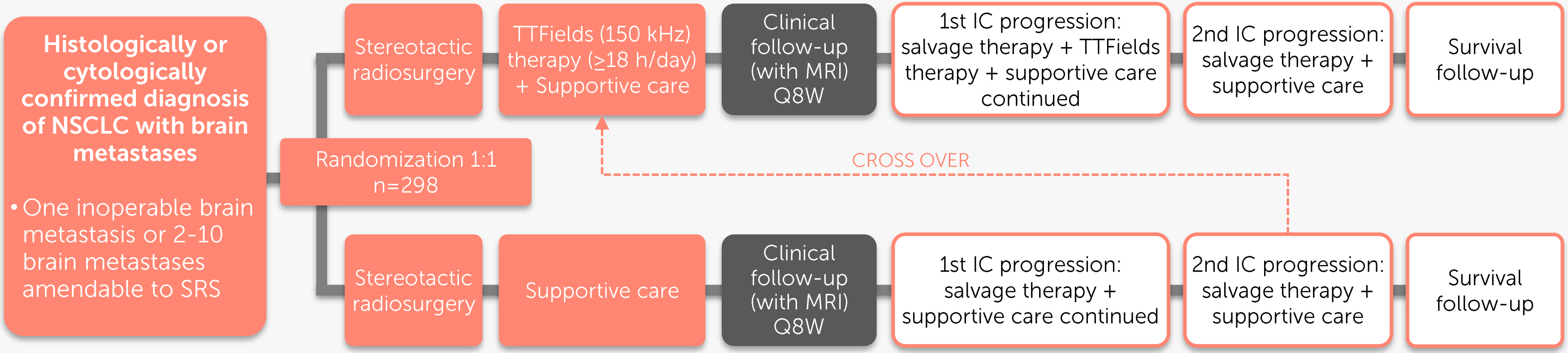
ICI, immune checkpoint inhibitor; ITT, intent to treat; NSCLC, non-small cell lung cancer; TTFields, Tumor Treating Fields.
Leal et al. *Lancet Oncol* 2023; 24: 1002-17.

METIS phase 3 trial evaluated TTFields therapy + supportive care in NSCLC brain metastases, following SRS



Start date: October 2016
Primary completion: March 2023
Study sites: 125

Primary endpoints:

- Time to intracranial progression

Secondary endpoints:

- Time to neurocognitive failure, OS, radiological response rate, time to 2nd intracranial progression, time to 1st and 2nd progression by cohort (1-4 metastases, 5-10 metastases), rate of intracranial progression at two-month intervals, time to distant progression, rate of cognitive decline, neurocognitive failure-free survival, quality of life, adverse events

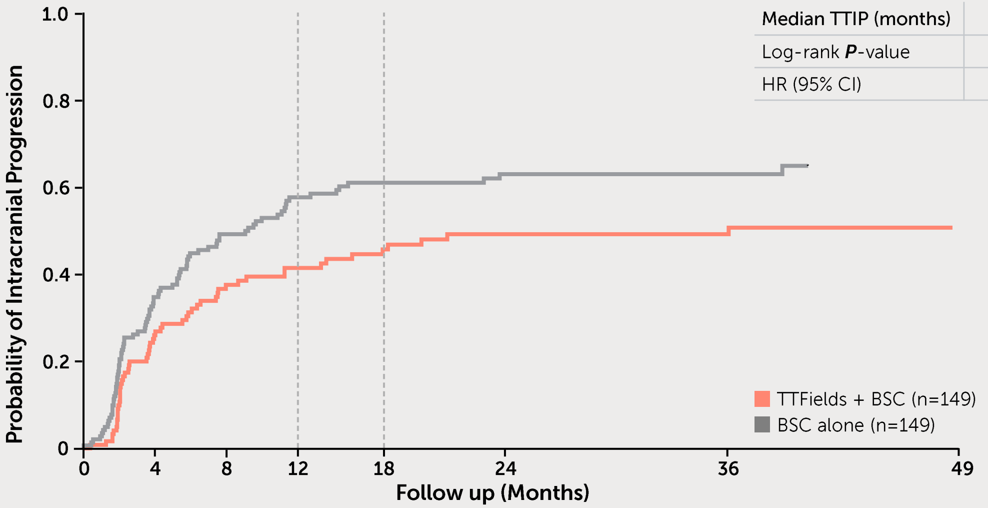
IC, intracranial; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; Q8W, every 8 weeks; SRS, stereotactic radiosurgery; TTFields, Tumor Treating Fields. ClinicalTrials.gov. NCT02831959.

TTFields therapy with supportive care following SRS improved time to intracranial progression in patients with brain metastases from NSCLC

FOR MORE INFORMATION, USE THE QR CODE:

Time to Intracranial Progression

Median TTIP (months)	21.9	11.3
Log-rank ***P***-value	0.016	
HR (95% CI)	0.67	




CENTRAL NERVOUS SYSTEM TUMORS

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Oral Abstract Session

Results from METIS (EF-25), an international, multicenter phase III randomized study evaluating the efficacy and safety of tumor treating fields (TTFields) therapy in NSCLC patients with brain metastases.

Minesh P. Mehta, Vinai Gondi, Manmeet Singh Ahluwalia, David Roberge, Rosanda Ilic, Terence Tai Weng Sio, Daniel Michael Trifiletti, Thierry Muanza, Ana Mair Krpan, Naren R Ramakrishna, John B. Fiveash, Philippe Metellus, Chiachien Jake Wang, Loïc Feuvret, Christian Freyschlag, Tibor Csöszi, Paul D. Brown, Maciej Harat; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Northwestern Medicine Cancer Center Warrenville and Northwestern Medicine Proton Center, Warrenville, IL; CHUM, Montreal, QC, Canada; Clinical Center of Serbia, Neurosurgery Clinic-Department for Neurooncology, Belgrade, Serbia; Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ; Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL; Montreal Neurological Institute McGill University, Montreal, QC, Canada; Radiochirurgia Zagreb, Zagreb, Croatia; Orlando Health Cancer Institute, Orlando, FL; The University of Alabama at Birmingham, Birmingham, AL; Hôpital Prive Clairval, Marseille, France; Willis Knighton Cancer Center, Shreveport, LA; Lyon HCL, Lyon, France; Medizinische Universität Innsbruck, Innsbruck, Austria; Jász-Nagykun-Szolnok Megyei Hetényi Géza Kórház-Rendelőintézet, Szolnok, Hungary; Department of Radiation Oncology, Mayo Clinic, Rochester, MN; Department of Neurooncology and Radiosurgery, Franciszek Lukaszczyk Memorial Oncology Center, Bydgoszcz, Poland

Background: For non-small cell lung cancer (NSCLC) with brain metastases (BM) stereotactic radiosurgery (SRS) is the current preferred therapy. Due to frequent intracranial failures, there is a high unmet need for salvage therapies. Whole brain radiotherapy (WBRT) reduces intracranial failure but used less frequently due to cognitive consequences. Tumor Treating Fields (TTFields) are electric fields that disrupt cancer cell division and have shown improved survival and safety in patients with glioblastoma and metastatic NSCLC. Phase 3 METIS trial [NCT02831959] aimed to evaluate the efficacy and safety of TTFields therapy in NSCLC patients with BM treated with SRS, specifically in terms of lengthening time to intracranial progression without cognitive decline. **Methods:** Mutation negative (M-) NSCLC patients with 1–10 BM were randomized 1:1 to receive stereotactic radiosurgery (SRS) followed by Tumor Treating Fields (TTFields; 150 kHz) therapy with best supportive care (BSC) or SRS followed by BSC. Patients with Karnofsky Performance Status (KPS) ≥70, newly diagnosed with one inoperable or 2–10 supra-/infratentorial brain metastases suitable for SRS and receiving optimal extracranial disease therapy were included. Exclusions were prior WBRT and single operable or recurrent brain metastases. Primary endpoint was time to first intracranial progression (RANO-BM) based on cumulative risk. Patients were followed every two months until second intracranial progression. Cognition and patient quality of life (QoL) were evaluated. **Results:** Between July 2016 and September 2022, 298 patients were randomized. Baseline characteristics were balanced: median age was 63.5 (range 37–84) years, 37.6% females, majority of patients had a KPS ≥ 80, median time from initial NSCLC diagnosis was 1.8 months (range: 0.2–55.7), 77% had adenocarcinoma. Median treatment duration of TTFields was 16 weeks, with a median usage time of 67%. Primary endpoint, time to intracranial progression from SRS, was significantly prolonged with SRS followed by TTFields therapy with BSC vs. TTFields plus BSC arm (median of 21.9 vs. 11.3 months); HR=0.67 [0.48–0.93], p=0.02. TTFields-related AEs were mainly dermatological, and Grade ≤2. TTFields therapy also improved deterioration-free survival of global health status, physical functioning, and fatigue according to QoL, and did not negatively impact cognition. **Conclusions:** METIS study met its primary endpoint, demonstrating that TTFields therapy following SRS in mutation negative NSCLC patients with BM, significantly prolongs time to intracranial progression and could postpone WBRT, without QoL and cognition decline. Clinical trial information: NCT02831959. Research Sponsor: Novocure GmbH.

BSC, best supportive care; HR, hazard ratio; NSCLC, non-small cell lung cancer; SRS, stereotactic radiosurgery; TTFields, Tumor Treating Fields; TTIP, time to intracranial progression. Mehta et al. Results from METIS (EF-25), an international, multicenter phase III randomized study evaluating the efficacy and safety of tumor treating fields (TTFields) therapy in NSCLC patients with brain metastases. *JCO* 42 2008-2008(2024). doi:10.1200/JCO.2024.42.16_suppl.2008

PANOVA phase 2 trial evaluated TTFields therapy + gemcitabine +/- nab-paclitaxel in pancreatic cancer

n = 40

Histologically confirmed, unresectable pancreatic adenocarcinoma

- ECOG performance status 0-1

TTFields (150 kHz, $\geq$ 18 h/day)
+
Gemcitabine 1000 mg/m^2 qw for 7 weeks, 1 week rest, once-weekly infusions on days 1, 8, 15, every 28 days (n = 20)
+/-
nab-paclitaxel 125 mg/m^2 on days 1, 8, 15, every 28 days (n = 20)

Monthly clinical follow-up (CT scan Q8W)

Radiological tumor progression

Survival follow-up

Start date: Nov 2013
Primary completion date: Dec 2017
Study completion date: Dec 2017
Study sites: 6 (Europe)

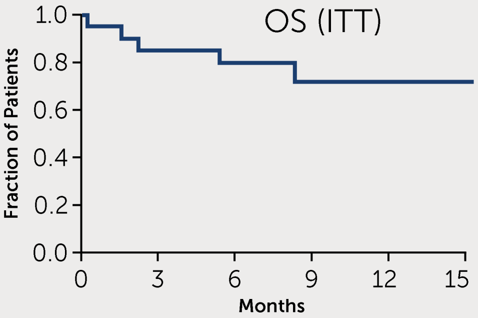
Primary endpoint:
- Safety

Secondary endpoints:
- TTFields monthly usage, PFS, OS

CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS6, progression-free survival rate 6 months; qw, every week; Q8W, every 8 weeks; SR, survival rate.
ClinicalTrials.gov. [NCT01971281]. Accessed December 21, 2020.

TTFields therapy together with chemotherapy were well tolerated for patients with advanced pancreatic cancer

FOR MORE INFORMATION, USE THE QR CODE:



OS	
Median, mo	NR
95% CI	8.4–NA
1-year survival	72%

	Median PFS	Median OS	One-year Survival	Partial Response Rate	Stable Disease
TTFields + gemcitabine	**8.3 mo**	**14.9 mo**	**55%**	**30%**	**30%**
gemcitabine alone	3.7 mo	6.7 mo	22%	7%	28%
TTFields + gemcitabine + nab-paclitaxel	**12.7 mo**	**Not yet reached**	**72%**	**40%**	**47%**
gemcitabine + nab-paclitaxel alone	5.5 mo	8.5 mo	35%	23%	27%

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CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; QW, every week; Q8W, every 8 weeks; TTFields, Tumor Treating Fields.
Rivera F et al. *Pancreatology*. 2019;19(1):64-72.
TTFields are experimental for the treatment of patients with pancreatic cancer and have not been approved by the US Food and Drug Administration for this indication nor received a CE mark in Europe.

encouraging response rate and durability signals in EF-31 phase 2 gastric cancer trial

FOR MORE INFORMATION, USE THE QR CODE:

EF-31 PHASE 2 PILOT TRIAL DESIGN[1]

screening and baseline evaluation (n=26) → TTFields + XELOX (+trastuzumab for HER2+ pts) q3w → CT/MRI scan q9w until progression → survival follow-up q12w

	OBJECTIVE RESPONSE RATE	MEDIAN PROGRESSION-FREE SURVIVAL	DURATION OF RESPONSE	ONE-YEAR SURVIVAL
TTFields + chemotherapy	50%	7.8mo	10.3mo	72%
SOC chemotherapy[2]	41-45%	6.9mo	6.9mo	48%

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clinicaltrials.gov. [NCT04281576]; 2. CheckMate 649, clinicaltrials.gov. [NCT02872116], *Lancet 2021*

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encouraging signals in liver cancer despite poor prognosis and low treatment exposure in HEPANOVA phase 2 trial

FOR MORE INFORMATION, USE THE QR CODE:

HEPANOVA PHASE 2 PILOT TRIAL DESIGN[2]

screening and baseline evaluation → TTFields (150 kHz) + daily sorafenib → follow-up q4w + CT/MRI scan q12w until progression → post-progression follow-up → survival follow-up

76%
DISEASE CONTROL RATE (n=21)
VS. 43% CONTROL[3]

9.5%
OBJECTIVE RESPONSE RATE (n=21)
VS. 4.5% CONTROL

91%
DISEASE CONTROL RATE

18%
OBJECTIVE RESPONSE RATE

patients that received ≥ 12 wks of TTFields (n=11)

1. Gkika E et al. Cancers Cancers (Basel). 2022 Mar 18;14(6):1568. doi: 10.3390/cancers14061568.
2. Novocure, Ltd. Effect of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Sorafenib For Advanced Hepatocellular Carcinoma (HCC) (HEPANOVA) In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 October]. Available from: https://clinicaltrials.gov/ct2/show/NCT03606590. NLM Identifier:NCT03606590
3. Llovet JM et al. N. Engl. J. Med. 2008;359:378–390. doi: 10.1056/NEJMoa0708857.

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platform technology driving robust clinical pipeline

Program	Indication	TRIAL	TTFIELDS THERAPY +	PHASE 2 / PHASE 3 / APPROVED
CNS program	newly diagnosed glioblastoma	EF-14	temozolomide	approved
		TRIDENT	radiation + temozolomide	final data pending
		KEYNOTE D58	pembrolizumab + temozolomide	IND approved
	recurrent glioblastoma	EF-11	monotherapy	approved
thoracic cancer program	brain metastasis	METIS	monotherapy	met primary endpoint
	non-small cell lung cancer	EF-15	pemetrexed	completed
		LUNAR	docetaxel or PD-L1 inhibitor	PMA submitted
		LUNAR-2	pembrolizumab + chemotherapy	IDE approved
		LUNAR-4	immune checkpoint inhibitor	in design
		KEYNOTE B36	pembrolizumab	enrolling
	mesothelioma	STELLAR	pemetrexed + (cisplatin or carboplatin)	approved
gastro-intestinal cancer program	pancreatic cancer	PANOVA	nab-paclitaxel + gemcitabine	completed
		PANOVA-3	nab-paclitaxel + gemcitabine	final data pending
		PANOVA-4	atezolizumab + nab-paclitaxel + gemcitabine	enrolling
	hepatocellular carcinoma	HEPANOVA	sorafenib	completed
	gastric adenocarcinoma	EF-31 / ZL-8301-001	XELOX	completed

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tumor treating fields mechanism of action overview

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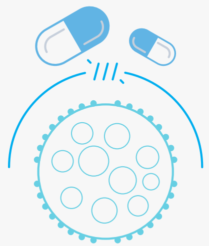
patients with aggressive solid tumors often face suboptimal survival outcomes, despite advancements in treatment modalities

These outcomes are due to diverse treatment challenges, including:



Therapeutic tumor resistance

Drug-to-drug interactions

Additive systemic toxicities

With a poor survival outlook, physicians and patients need additional treatment strategies

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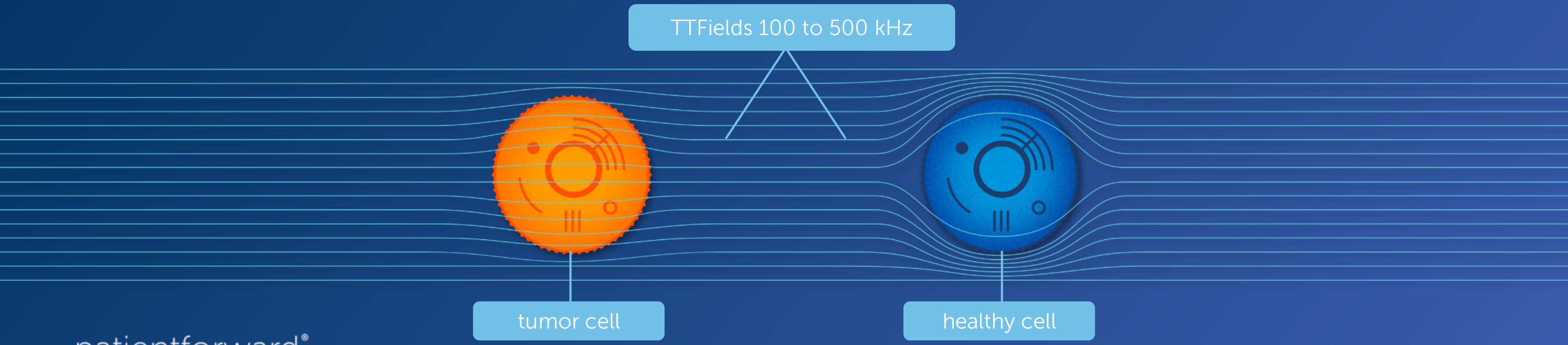
1. Siegel RL, Miller KD, Fuchs HE, Jemal A. *CA Cancer J Clin.* 2021;71(1):7-33. doi:10.3322/caac.21654. **2.** Dagogo-Jack I, Shaw AT. *Nat Rev Clin Oncol.* 2018;15(2):81-94. doi:10.1038/nrclinonc.2017.166. **3.** Gotwals P, Cameron S, Cipolletta D, et al. *Nat Rev Cancer.* 2017;17(5):286-301. doi:10.1038/nrc.2017.17. **4.** Lopez JS, Banerji U. *Nat Rev Clin Oncol.* 2017;14(1):57-66. doi:10.1038/nrclinonc.2016.96. **5.** Bashraheel SS, Domling A, Goda SK. *Biomed Pharmacother.* 2020;125:1-16. doi:10.1016/j.biopha.2020.110009.

Tumor Treating Fields (TTFields) are electric fields that exert physical forces to kill cancer cells via a variety of mechanisms

TTFIELDS
TUMOR TREATING FIELDS THERAPY

TTFields spare healthy cells because they have different properties than cancer cells across a range of tumor types

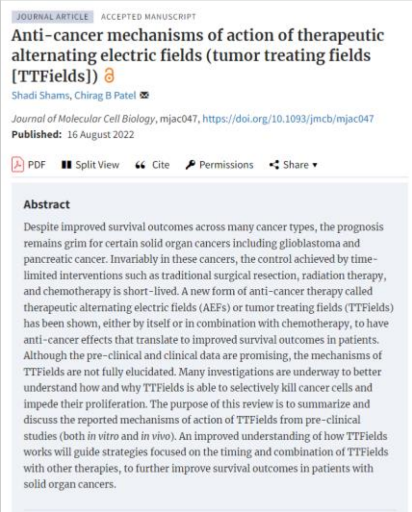


1. Karanam NK, Story MD. *Int J Radiat Biol*. 2021;97(8):1044-1054. 2. Cooper GM. The Cell: A Molecular Approach. 2nd ed. Sinauer Associates; 2000:chap 15. https://www.ncbi.nlm.nih.gov/books/NBK9963/. 3. Baba AI, Câtoi C. Comparative Oncology. The Publishing House of the Romanian Academy; 2007:chap 3. https://www.ncbi.nlm.nih.gov/books/NBK9553/. 4. Trainito CI, Sweeney DC, Čemažar J, et al. *PLoS One*. 2019;14(9):1-18. 5. Haemmerich D, Schutt DJ, Wright AW, Webster JG, Mahvi DM. *Physiol Meas*. 2009;30(5):459-466. 6. Ahmad MA, (IEEE SM), Al Natour Z, Mustafa F, Rizvi TA. *IEEE Access*. 2018;6:25979-25986.

a growing body of evidence supporting multiple mechanisms of action

FOR MORE INFORMATION, USE THE QR CODE:

- Preclinical research has shown interference with cancer cell motility and migration, activation of anti-tumor immunity, downregulation of genes important for DNA damage repair, and other potential mechanisms
- May demonstrate enhanced effects across solid tumor types when used with chemotherapy, radiotherapy, immune checkpoint inhibition, or PARP inhibition in preclinical models


JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Anti-cancer mechanisms of action of therapeutic alternating electric fields (tumor treating fields [TTFields])

Shadi Shams, Chirag B Patel

Journal of Molecular Cell Biology, mjac047, https://doi.org/10.1093/jmcb/mjac047

Published: 16 August 2022

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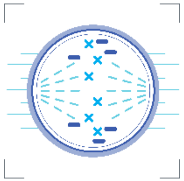
Abstract

Despite improved survival outcomes across many cancer types, the prognosis remains grim for certain solid organ cancers including glioblastoma and pancreatic cancer. Invariably in these cancers, the control achieved by time-limited interventions such as traditional surgical resection, radiation therapy, and chemotherapy is short-lived. A new form of anti-cancer therapy called therapeutic alternating electric fields (AEFs) or tumor treating fields (TTFields) has been shown, either by itself or in combination with chemotherapy, to have anti-cancer effects that translate to improved survival outcomes in patients. Although the pre-clinical and clinical data are promising, the mechanisms of TTFields are not fully elucidated. Many investigations are underway to better understand how and why TTFields is able to selectively kill cancer cells and impede their proliferation. The purpose of this review is to summarize and discuss the reported mechanisms of action of TTFields from pre-clinical studies (both *in vitro* and *in vivo*). An improved understanding of how TTFields works will guide strategies focused on the timing and combination of TTFields with other therapies, to further improve survival outcomes in patients with solid organ cancers.

Chirag B. Patel, et al. Journal of Molecular Cell Biology. *Anti-cancer mechanisms of action of therapeutic alternating electric fields (tumor treating fields [TTFields]).* https://academic.oup.com/jmcb/advance-article/doi/10.1093/jmcb/mjac047/6668799

Tumor Treating Fields have multiple, distinct mechanisms of action

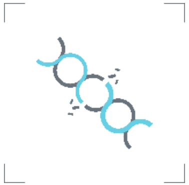
disruption of mitosis



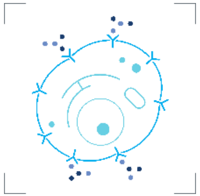
interference of cell movement and migration

TTFields are electric fields that exert physical forces to kill cancer cells via a variety of mechanisms

downregulation of DNA damage response



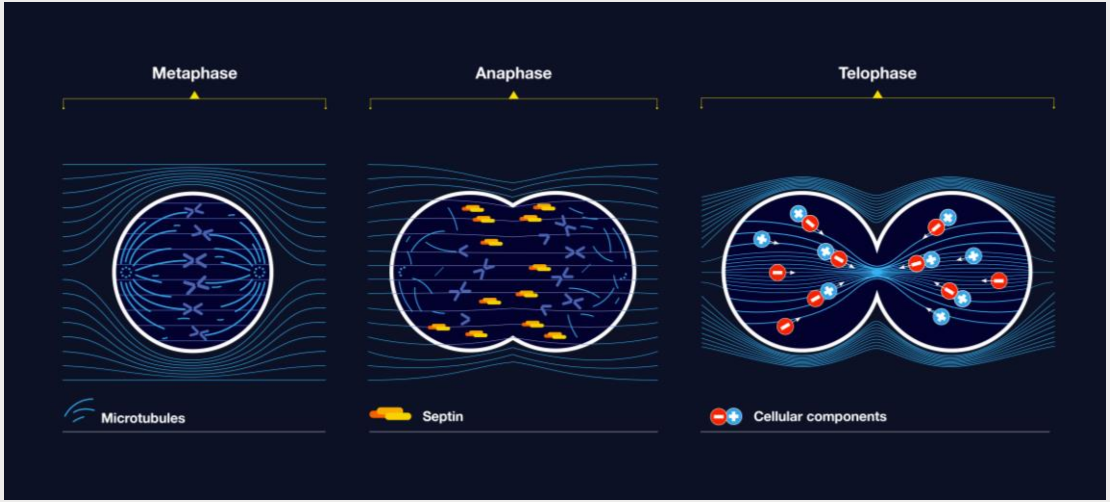
downstream enhancement of antitumor immunity

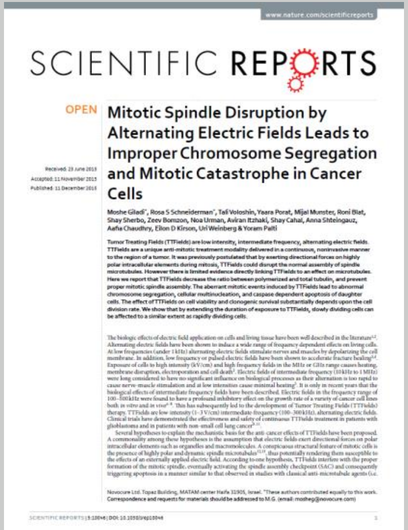


Rominiyi O et al. *Br J Cancer*. 2021;124(4):697-709. 2. Karanam NK, Story MD. *Int J Radiat Biol*. 2021;97(8):1044-1054. 3. Mun EJ et al. *Clin Cancer Res*. 2018;24(2):266-275.

TTFields have been shown to disrupt mitosis in cancer cells by exerting physical forces on their polar components

FOR MORE INFORMATION, USE THE QR CODE:





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Mitotic Spindle Disruption by Alternating Electric Fields Leads to Improper Chromosome Segregation and Mitotic Catastrophe in Cancer Cells

Received: 23 June 2015
Accepted: 11 November 2015
Published: 11 December 2015

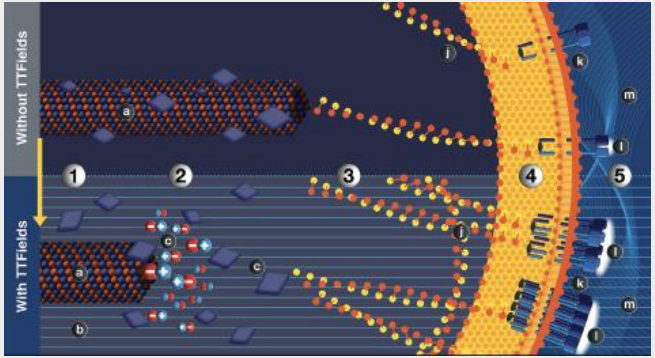
Moshe Giladi*, Rosa S Schneiderman*, Tali Voloshin, Yaara Porat, Mijal Munster, Roni Blat, Shay Sherbo, Zeev Bomzon, Noa Urman, Aviran Itzhaki, Shay Cahal, Anna Shteingauz, Aafia Chaudhry, Eilon D Kirson, Uri Weinberg & Yoram Palti

Tumor Treating Fields (TTFields) are low intensity, intermediate frequency, alternating electric fields. TTFields are a unique anti-mitotic treatment modality delivered in a continuous, noninvasive manner to the region of a tumor. It was previously postulated that by exerting directional forces on highly polar intracellular elements during mitosis, TTFields could disrupt the normal assembly of spindle microtubules. However there is limited evidence directly linking TTFields to an effect on microtubules. Here we report that TTFields decrease the ratio between polymerized and total tubulin, and prevent proper mitotic spindle assembly. The aberrant mitotic events induced by TTFields lead to abnormal chromosome segregation, cellular multinucleation, and caspase dependent apoptosis of daughter cells. The effect of TTFields on cell viability and clonogenic survival substantially depends upon the cell division rate. We show that by extending the duration of exposure to TTFields, slowly dividing cells can be affected to a similar extent as rapidly dividing cells.

1. Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD. *PLoS One*. 2015;10(5):1-20. doi:10.1371/journal.pone.0125269 2. Giladi M, Schneiderman RS, Voloshin T, et al. *Sci Rep*. 2015;5:1-16. doi:10.1038/srep18046 3. Voloshin T, Kaynan N, Davidi S, et al. *Cancer Immunol Immunother*. 2020;69(7):1191-1204. doi:10.1007/s00262-020-02534-7 4. Gutin PH, Wong ET. *Am Soc Clin Oncol Educ Book*. 2012:126-131. doi:10.14694/EdBook_AM.2012.32.122 5. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. *Clin Cancer Res*. 2018;24(2):266-275. doi:10.1158/1078-0432.CCR-17-1117

TTFields have been shown to alter the organization and dynamics of the cytoskeleton, disrupting cancer cell motility and migration

FOR MORE INFORMATION, USE THE QR CODE:



a) microtubule; b) TTFields; c) tubulin aligned with field; j) actin fiber; k) integrin; l) focal adhesion; m) extracellular matrix.

A model illustrating the mechanism by which TTFields modulates cancer cell motility.

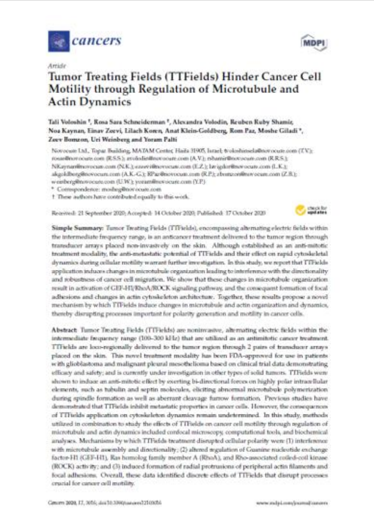
(1) Microtubules are required to specify the direction of cell movement. GEF-H1 catalytic activity is downregulated through microtubule binding.

(2) TTFields exert directional forces on polar tubulins leading to their alignment in the direction of the field. This, in turn, leads to the reorganization of the microtubule network resulting in changes in the abundance of microtubules and initiation of the GEF-H1/RhoA/ROCK signaling pathway

(3) to increase actin bundling

(4) and formation of focal adhesions,

(5) which disrupt cell polarity and migration directionality.


cancers MDPI

Article

Tumor Treating Fields (TTFields) Hinder Cancer Cell Motility through Regulation of Microtubule and Actin Dynamics

Tali Voloshin †, Rosa Sara Schneiderman †, Alexandra Volodin, Reuben Ruby Shamir, Noa Kaynan, Einav Zeevi, Lilach Koren, Anat Klein-Goldberg, Rom Paz, Moshe Giladi *, Zeev Bomzon, Uri Weinberg and Yoram Palti

Received: 21 September 2020; Accepted: 14 October 2020; Published: 17 October 2020

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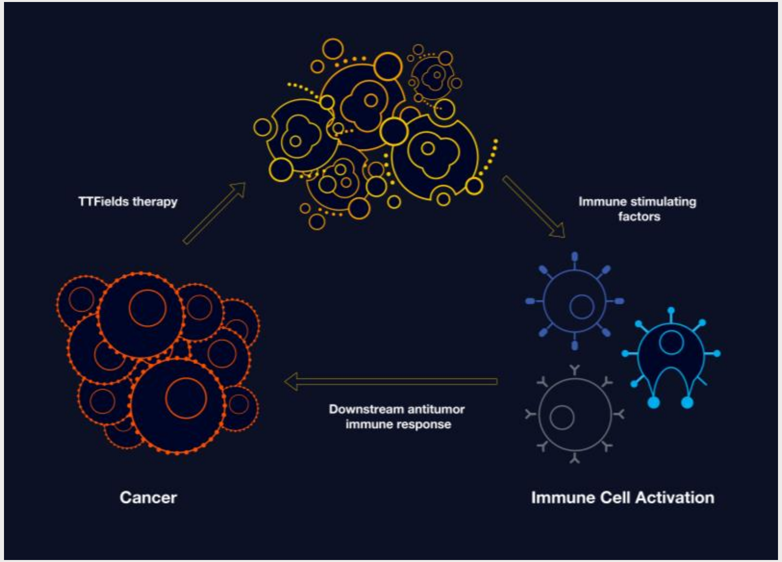
Adapted from Voloshin et al. 2020.
GEF-H1=a microtubule-associated protein that couples microtubule dynamics to cell contractility.
RhoA/ROCK=a pathway that regulates cell morphology, polarity, and cytoskeletal remodeling by regulating actin and cell migration.

Voloshin T, Schneiderman RS, Volodin A, et al. *Cancers (Basel)*. 2020;12(10):1-18. doi:10.3390/cancers12103016

TTFields-mediated cell disruption activates the immune system and triggers a downstream antitumor cell response

FOR MORE INFORMATION, USE THE QR CODE:



TTFields induces downstream immunogenic cell death, including release of DAMPs (damage-associated molecular patterns)


Cancer Immunology, Immunotherapy (2020) 69:1191–1204
https://doi.org/10.1007/s00262-020-02534-7

ORIGINAL ARTICLE

Tumor-treating fields (TTFields) induce immunogenic cell death resulting in enhanced antitumor efficacy when combined with anti-PD-1 therapy

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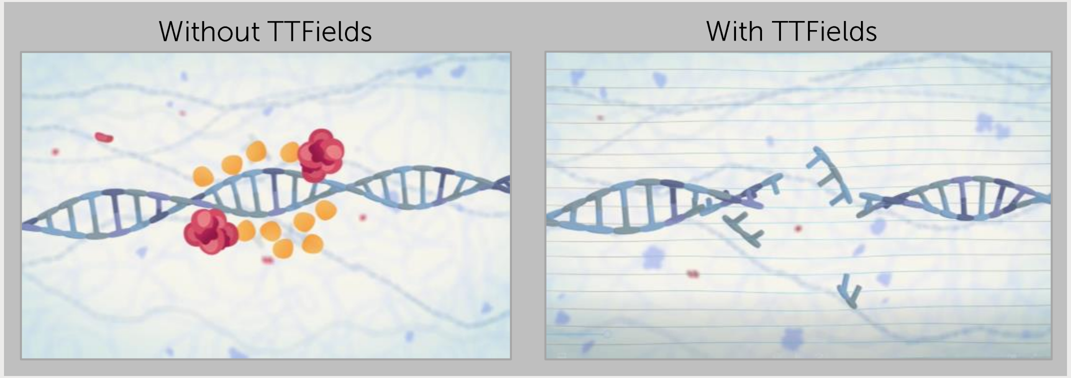
Abstract
Tumor-treating fields (TTFields) are alternating electric fields in a specific frequency range (100–300 kHz) delivered to the human body through transducer arrays. In this study, we evaluated whether TTFields-mediated cell death can elicit antitumoral immunity and hence would be effectively combined with anti-PD-1 therapy. We demonstrate that in TTFields-treated cancer cells, damage-associated molecular patterns including high-mobility group B1 and adenosine triphosphate are released and calreticulin is exposed on the cell surface. Moreover, we show that TTFields treatment promotes the engulfment of cancer cells by dendritic cells (DCs) and DCs maturation in vitro, as well as recruitment of immune cells in vivo. Additionally, our study demonstrates that the combination of TTFields with anti-PD-1 therapy results in a significant decline

Voloshin T, Kaynan N, Davidi S, et al. *Cancer Immunol Immunother.* 2020;69(7):1191-1204.

TTFields downregulate genes important for DNA damage repair

FOR MORE INFORMATION, USE THE QR CODE:

- TTFields disrupt DNA damage repair in cancer cells by downregulating genes that are part of the well-known FA-BRCA pathway[1,2]



OPEN

Citation: Cell Death and Disease (2017) 8, e2711; doi:10.1038/cddis.2017.136

Tumor-treating fields elicit a conditional vulnerability to ionizing radiation via the downregulation of BRCA1 signaling and reduced DNA double-strand break repair capacity in non-small cell lung cancer cell lines

Narasimha Kumar Karanam[1], Kalayarasan Srinivasan[1], Lianghao Ding[1], Brock Sishc[1], Debabrata Saha[1] and Michael D Story*[1,2]

The use of tumor-treating fields (TTFields) has revolutionized the treatment of recurrent and newly diagnosed glioblastoma (GBM). TTFields are low-intensity, intermediate frequency, alternating electric fields that are applied to tumor regions and cells using non-invasive arrays. The predominant mechanism by which TTFields are thought to kill tumor cells is the disruption of mitosis. Using five non-small cell lung cancer (NSCLC) cell lines we found that there is a variable response in cell proliferation and cell killing between these NSCLC cell lines that was independent of p53 status. TTFields treatment increased the G2M population, with a concomitant reduction in S-phase cells followed by the appearance of a sub-G1 population indicative of apoptosis. Temporal changes in gene expression during TTFields exposure was evaluated to identify molecular signaling changes underlying the differential TTFields response. The most differentially expressed genes were associated with the cell cycle and cell proliferation pathways. However, the expression of genes found within the BRCA1 DNA-damage response were significantly downregulated ($P < 0.05$) during TTFields treatment. DNA double-strand break (DSB) repair foci increased when cells were exposed to TTFields as did the appearance of chromatid-type aberrations, suggesting an interphase mechanism responsible for cell death involving DNA repair. Exposing cells to TTFields immediately following ionizing radiation resulted in increased chromatid aberrations and a reduced capacity to repair DNA DSBs, which were likely responsible for at least a portion of the enhanced cell killing seen with the combination. These findings suggest that TTFields induce a state of 'BRCAness' leading to a conditional susceptibility resulting in enhanced sensitivity to ionizing radiation and provides a strong rationale for the use of TTFields as a combined modality therapy with radiation or other DNA-damaging agents.

Cell Death and Disease (2017) 8, e2711; doi:10.1038/cddis.2017.136; published online 30 March 2017

Lung cancer is the second most prevalent cancer and the leading cause of cancer-related death in the United States.[1] Non-small cell lung cancer (NSCLC) is the most prevalent type, accounting for ~80% of new cases.[2,3] A plethora of …

molecules toward the region of higher field intensity, effectively preventing polymerization and other critical biochemical functions.[11] As such, TTFields preferentially target cancer cells through the exploitation of cell proliferation, effectively …

1. Karanam NK, Srinivasan K, Ding L, Sishc B, Saha D, Story MD. *Cell Death Dis*. 2017;8(3):1-10. doi:10.1038/cddis.2017.136 **2.** Karanam NK, Ding L, Aroumougame A, Story MD. *Transl Res*. 2020;217:33-46. doi:10.1016/j.trsl.2019.10.003 **3.** Giladi M, Munster M, Schneiderman RS, et al. *Radiat Oncol*. 2017;12(1):1-13. doi:10.1186/s13014-017-0941-6 **4.** Kim EH, Kim YJ, Song HS, et al. *Oncotarget*. 2016;7(38):62267-62279. doi:10.18632/oncotarget.11407.

TTFields is a highly versatile first-in-class treatment modality

FOR MORE INFORMATION, USE THE QR CODE:

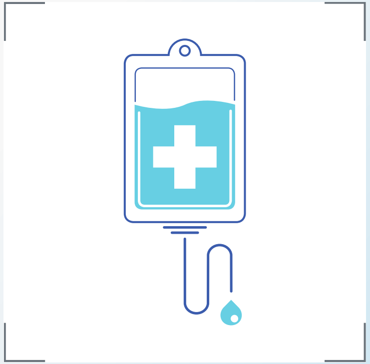
- TTFields therapy has significant potential for broad applicability across solid tumor types and lines of therapy
  - Investigation of TTFields therapy is ongoing across clinical trials in multiple tumor types
  - In approved indications, TTFields therapy is well tolerated, suggesting a low risk of additive systemic toxicity when used with other cancer treatment modalities

1. Karanam NK, Story MD. *Int J Radiat Biol.* 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984. **2**. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. *Clin Cancer Res*. 2018;24(2):266-275. doi:10.1158/1078-0432.CCR-17-1117 **3**. Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, Al-Tamimi Y, Collis SJ. *Br J Cancer*. 2021;124(4):697-709. doi:10.1038/s41416-020-01136-5. **4**. Pless M, Droege C, von Moos R, Salzberg M, Betticher D. *Lung Cancer*. 2013;81(3):445-450. doi:10.1016/j.lungcan.2013.06.025 **5**. Novocure. Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT02831959 **6**. Rivera F, Benavides M, Gallego J, Guillen-Ponce C, Lopez-Martin J, Küng M. *Pancreatology*. 2019;19(1):64-72. doi:10.1016/j.pan.2018.10.004 **7**. Novocure. Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03377491 **8**. Vergote I, von Moos R, Manso L, Van Nieuwenhuysen E, Concin N, Sessa C. *Gynecol Oncol.* 2018;150(3):471-477. doi:10.1016/j.ygyno.2018.07.018 **9**. Novocure. Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03940196 **10**. Stupp R, Taillibert S, Kanner A, et al. JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718.

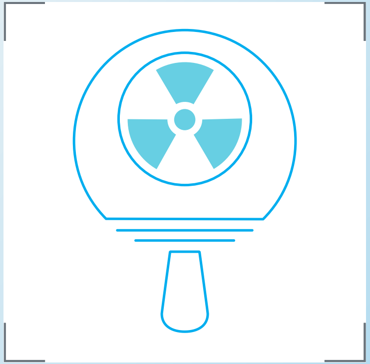
novocure

TTFields therapy can be added to cancer treatment modalities in approved indications

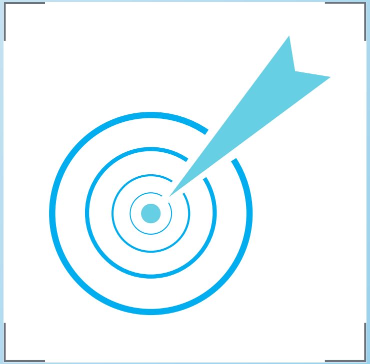
TTFields **demonstrate enhanced effects** across multiple solid tumor types, when used concomitantly with each of the following:



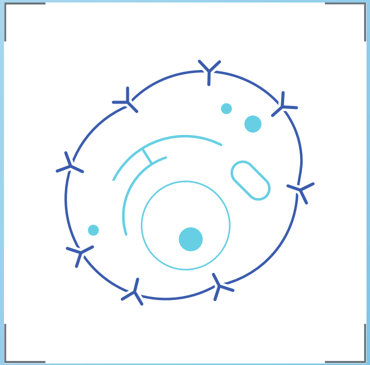
Chemotherapy



Radiation therapy (RT)



Targeted therapies



Immuno-oncologic (IO) agents

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1. Pless M, et al. *Lung Cancer*. 2013;81(3):445-450. 2. clinicaltrials.gov. [NCT02831959] 3. Rivera F, et al. *Pancreatology*. 2019;19(1):64-72. 4. clinicaltrials.gov. [NCT03377491] 5. Vergote I, et al. *Gynecol Oncol*. 2018;150(3):471-477. 6. clinicaltrials.gov. [NCT03940196]