tumor treating fields clinical evidence appendix

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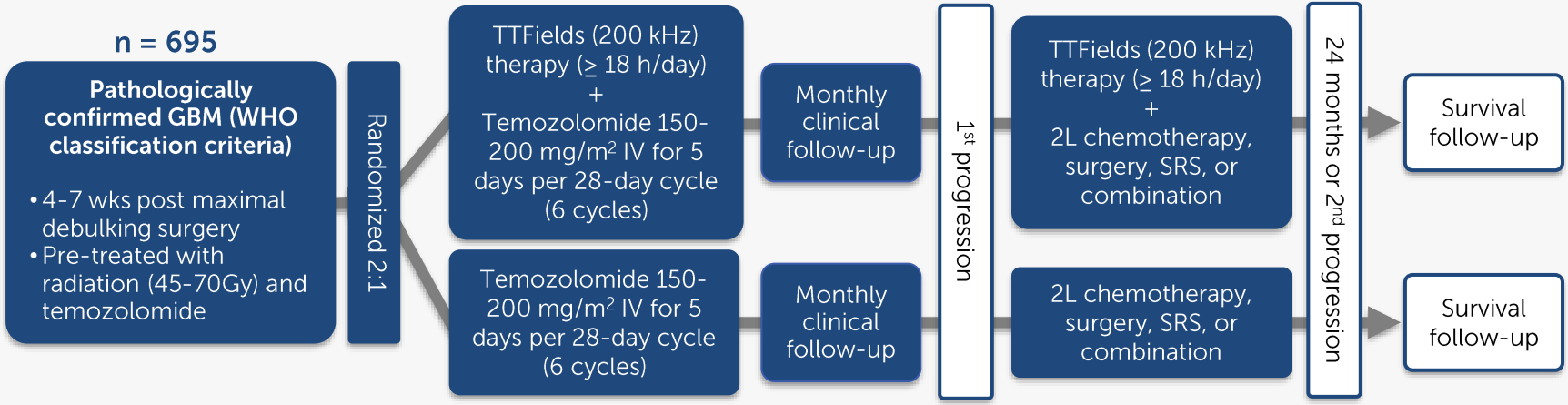
EF-14 phase 3 pivotal trial evaluated Optune + TMZ in 695 patients with ndGBM



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

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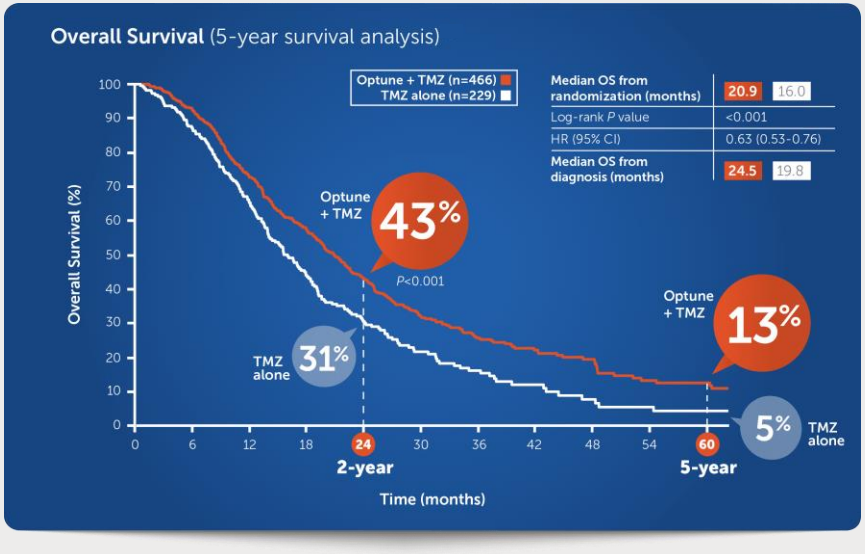
GBM, glioblastoma; ndGBM, newly diagnosed glioblastoma; SRS, stereotactic radiosurgery; TTFields, Tumor Treating Fields; wks, weeks; WHO, World Health Organization
ClinicalTrials.gov. NCT00916409.

in newly diagnosed GBM, Optune + TMZ provided an unprecedented long-term survival benefit

FOR MORE INFORMATION, USE THE QR CODE:




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.

more time on Optune predicted increased significant survival benefit

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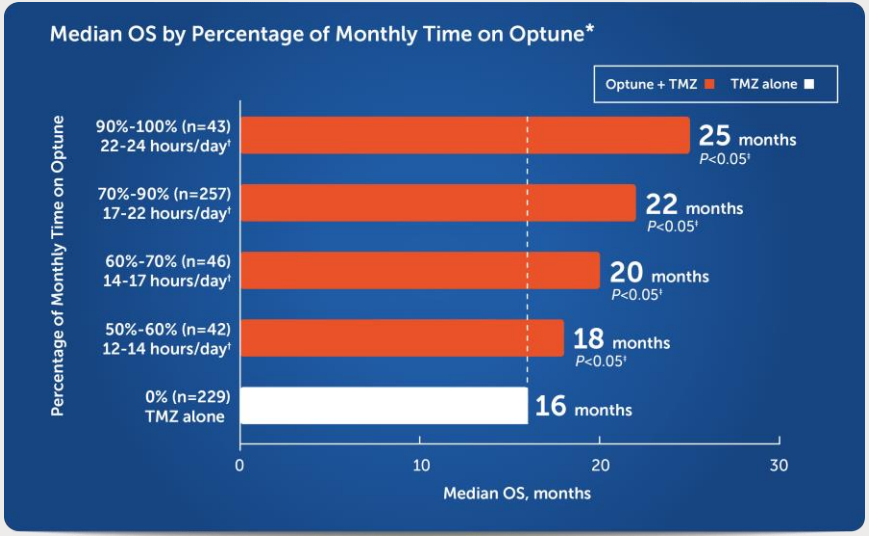
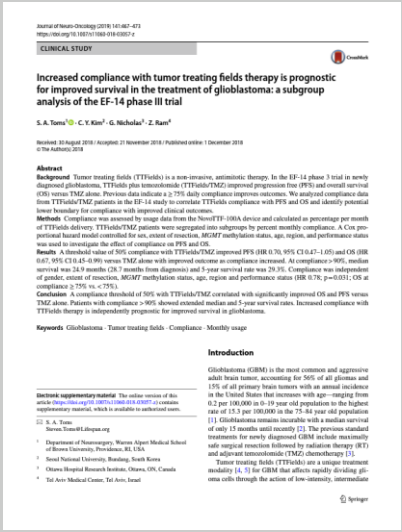


29.3% vs. 4.5%

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

Background Tumor treating fields (TTFields) is a non-invasive, antimitotic therapy. In the EF-14 phase 3 trial in newly diagnosed glioblastoma, TTFields plus temozolomide (TTFields/TMZ) improved progression free (PFS) and overall survival (OS) versus TMZ alone. Previous data indicate a ≥ 75% daily compliance improves outcomes. We analyzed compliance data from TTFields/TMZ patients in the EF-14 study to correlate TTFields compliance with PFS and OS and identify potential lower boundary for compliance with improved clinical outcomes.

Methods Compliance was assessed by usage data from the NovoTTF-100A device and calculated as percentage per month of TTFields delivery. TTFields/TMZ patients were segregated into subgroups by percent monthly compliance. A Cox proportional hazard model controlled for sex, extent of resection, *MGMT* methylation status, age, region, and performance status was used to investigate the effect of compliance on PFS and OS.

Results A threshold value of 50% compliance with TTFields/TMZ improved PFS (HR 0.70, 95% CI 0.47–1.05) and OS (HR 0.67, 95% CI 0.45–0.99) versus TMZ alone with improved outcome as compliance increased. At compliance > 90%, median survival was 24.9 months (28.7 months from diagnosis) and 5-year survival rate was 29.3%. Compliance was independent of gender, extent of resection, *MGMT* methylation status, age, region and performance status (HR 0.78; p = 0.031; OS at compliance ≥ 75% vs. < 75%).

Conclusion A compliance threshold of 50% with TTFields/TMZ correlated with significantly improved OS and PFS versus TMZ alone. Patients with compliance > 90% showed extended median and 5-year survival rates. Increased compliance with TTFields therapy is independently prognostic for improved survival in glioblastoma.

Keywords Glioblastoma · Tumor treating fields · Compliance · Monthly usage

Introduction

Glioblastoma (GBM) is the most common and aggressive adult brain tumor, accounting for 56% of all gliomas and 15% of all primary brain tumors with an annual incidence in the United States that increases with age—ranging from 0.2 per 100,000 in 0–19 year old population to the highest rate of 15.3 per 100,000 in the 75–84 year old population [1]. Glioblastoma remains incurable with a median survival of only 15 months until recently [2]. The previous standard treatments for newly diagnosed GBM include maximally safe surgical resection followed by radiation therapy (RT) and adjuvant temozolomide (TMZ) chemotherapy [3].

Tumor treating fields (TTFields) are a unique treatment modality [4, 5] for GBM that affects rapidly dividing glioma cells through the action of low-intensity, intermediate

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11060-018-03057-z) contains supplementary material, which is available to authorized users.

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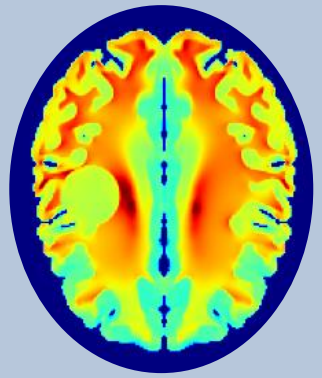
OS, overall survival; TMZ, temozolomide. Toms SA et al. J Neurooncol. 2019; 141(2): 467–473.

higher TTFields therapy dose can lead to increased efficacy

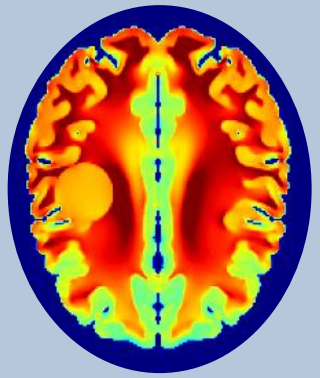
FOR MORE INFORMATION, USE THE QR CODES:

EXISTING ARRAYS
AP channel, 1,364 mAmps



VS.

NEW ARRAYS
AP channel, 1,685 mAmps



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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 to TMZ

FOR MORE INFORMATION, USE THE QR CODE:

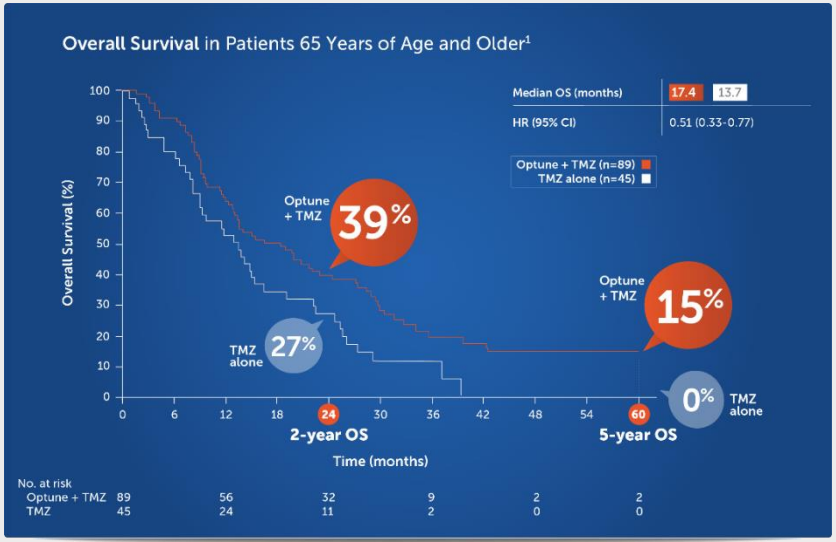
Subgroup		Median survival (months) Optune + TMZ	TMZ	Hazard ratio (95% CI)
MGMT promoter methylation	Unmethylated	16.9	14.7	
	» **Methylated**	31.6	21.2	
Resection	Biopsy	16.5	11.6	
	Partial	21.4	15.1	
	» **Gross total**	22.6	18.5	
Age	» **<65 years**	21.6	17.3	
	≥65 years	17.4	13.7	
KPS	» **90-100**	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**	

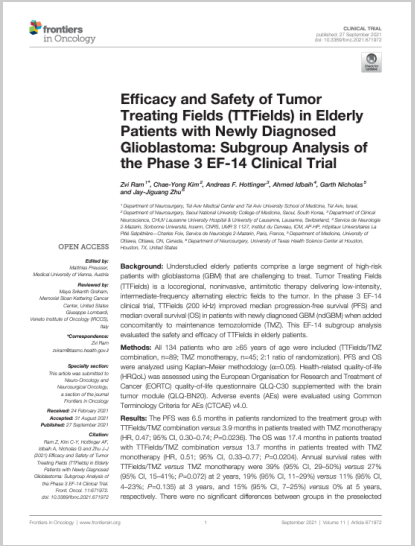
Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma
A Randomized Clinical Trial

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 was associated with increased survival in patients 65 years and older

FOR MORE INFORMATION, USE THE QR CODE:





frontiers in Oncology

CLINICAL TRIAL

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

OPEN ACCESS

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

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

biopsy-only patients using Optune had longer median overall survival

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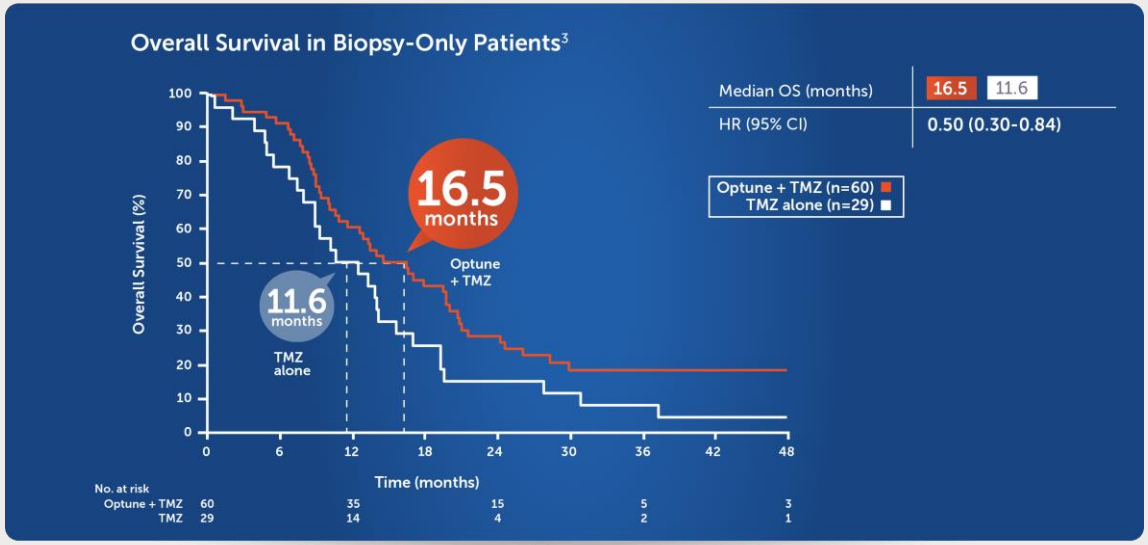


Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma
A Randomized Clinical Trial

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

survival benefit occurred independently of MGMT methylation status

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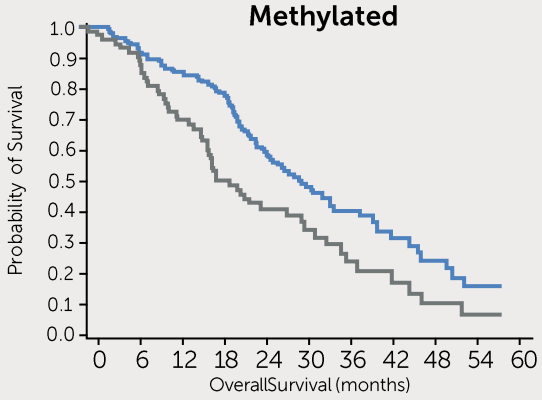

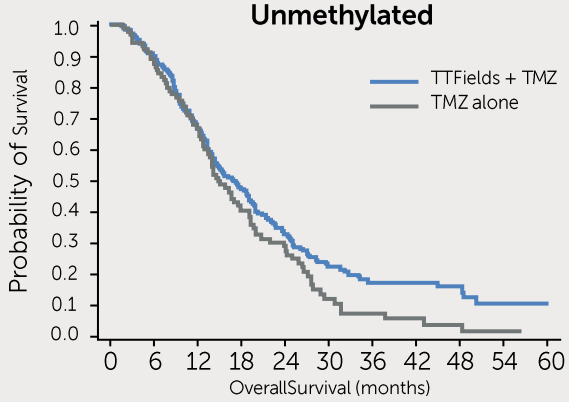

	TTFields + TMZ (n = 137)	TMZ Alone (n = 77)
Median OS, months	31.6	21.2
Range, months	21.1–48.5	12.3–37.9
HR (95% CI)[1]	0.62 (0.43–0.88)	

	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 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

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

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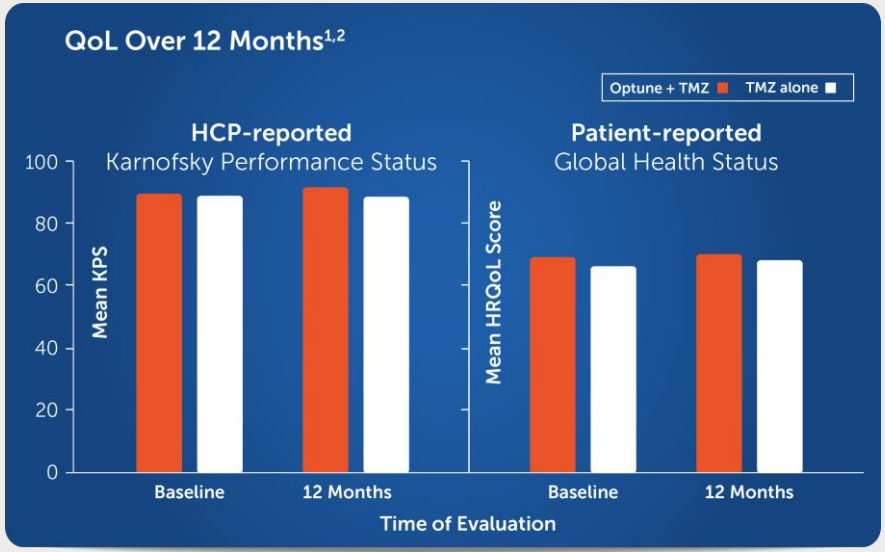
AE, adverse event; TMZ, temozolomide. Stupp R et al. JAMA. 2017;318(23):2306–2316. Shi et al. J Neurooncol. 2020;148:489-500.
Mild to moderate skin irritation was the only device related adverse event

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

FOR MORE INFORMATION, USE THE QR CODES:



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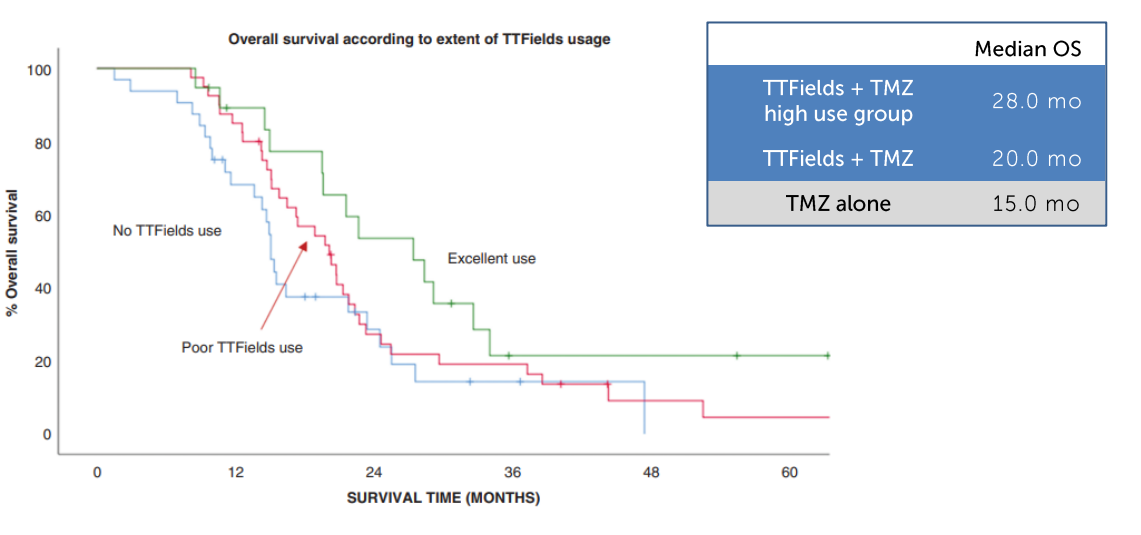
QoL, quality of life; HRQoL, health-related quality of life; TMZ, temozolomide. Taphoorn et al. JAMA Oncol. 2018;4(4):495-504. Palmer et al. Front. Oncol 2021;11:772261.

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	28.0 mo
TTFields + TMZ	20.0 mo
TMZ alone	15.0 mo

Neuro-Oncology Advances

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

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]

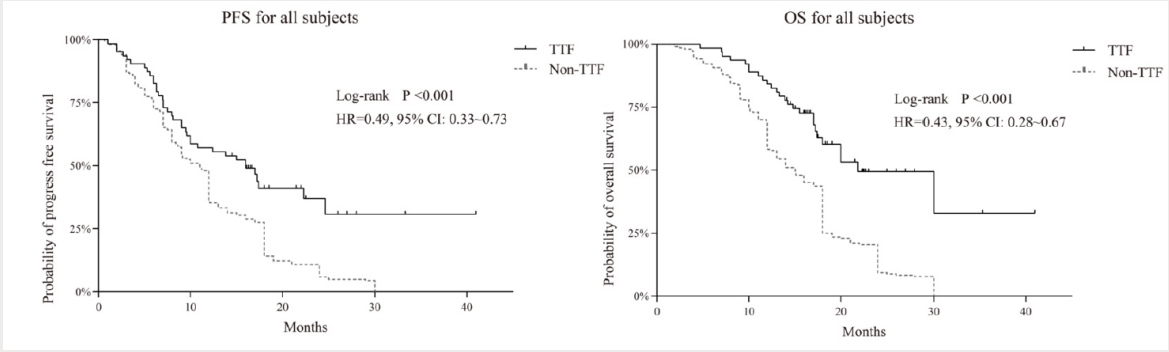
Tumor treating fields (TTFields) represent a novel therapy in the treatment of glioblastoma. TTFields deliver low-intensity, intermediate-frequency (200 kHz) alternating electric fields

High use group (n=19): >2 months use and ≥75% usage. Low use group (n=40): <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

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

FOR MORE INFORMATION, USE THE QR CODE:



	Median OS	Median PFS
TTFields + TMZ	21.8 mo	16.0 mo
TMZ alone	15.0 mo	11.0 mo

Journal of Clinical Medicine

MDPI

Article

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

Chunjui Chen, Hao Xu, Kun Song, Yi Zhang, Junyan Zhang, Yang Wang, Xiaofang Sheng, Lingchao Chen and Zhiyong Qin

Abstract: Introduction: TTFields plus Temozolomide (TTFields/TMZ) extended survival versus TMZ alone in newly diagnosed glioblastoma (GBM) patients in the EF-14 trial. We have reported a retrospective analysis of newly diagnosed Chinese GBM patients who received TTFields/TMZ treatment and TMZ treatment from August 2018 to May 2021 in Huashan hospital in Shanghai. Methods: Overall survival (OS) and progression-free survival (PFS) curves were constructed using the Kaplan-Meier method. A Cox proportional hazards regression model, propensity score matched data, and inverse probability of treatment weighting (IPTW) based on propensity score were used to assess the effect of TTFields and account for confounding factors. Results: In the preliminary analysis, the median PFS in TTFields/TMZ group was 16 months (95% CI, 9.6–24.4) versus 11 months (95% CI, 9–12) in TMZ group ($p < 0.05$). Median overall survival was 21.8 months (95% CI, 17.4-NA) with TTFields/TMZ versus 15 months (HR = 0.43; 95% CI, 13–18) with TMZ alone. The multivariate analysis identified surgery type, MTAP scheme, IDH status, and TTFields use as favorable prognostic factors. After PSM adjustment, the variate among the groups was similar, except that the methylation rate of MGMT promoter remained high in the TMZ group (12 v 32 months; $p < 0.01$). Upon IPTW Survival analysis, TTFields was associated with a significantly lower risk of death (HR = 0.39 in OS; 95% CI, 0.09–0.41) and progression (HR = 0.35; 95% CI 0.14–0.9) compared with TMZ group. Conclusions: In the final analysis of our single-center Chinese patients with glioblastoma, adding TTFields to temozolomide chemotherapy resulted in statistically significant improvement in PFS and OS.

Keywords: glioblastoma; tumor treating fields; chemotherapy; retrospective cohort

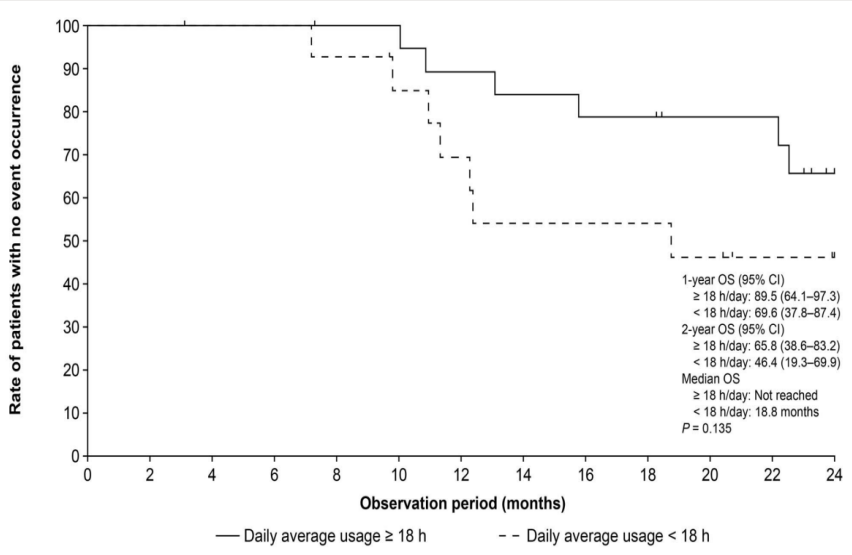
1. Introduction

Adult glioblastoma is one of the most fatal and challenging diseases and is associated with repeated recurrence and inferior prognosis [1–3]. Multimodal therapy of glioblastoma includes surgery, radiotherapy, systemic chemotherapy, and target therapy, which have been proven to result in limited improvement [4]. Most clinical trials revealed that the overall survival was around 15 months [5–7], and 5-year survival rate was only 5.8% [8–10].

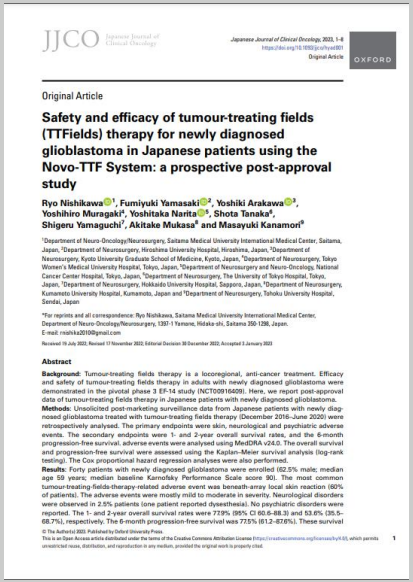
Chen et al. J. Clin. Med. Volume 11, 5855. https://doi.org/10.3390/jcm11195855

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

FOR MORE INFORMATION, USE THE QR CODE:



	1-year survival	2-year survival
TMZ alone	65%	31%
TTFields + TMZ	77.9%	53.6%
TTFields + TMZ high use group	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]

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E-mail: nishika2010@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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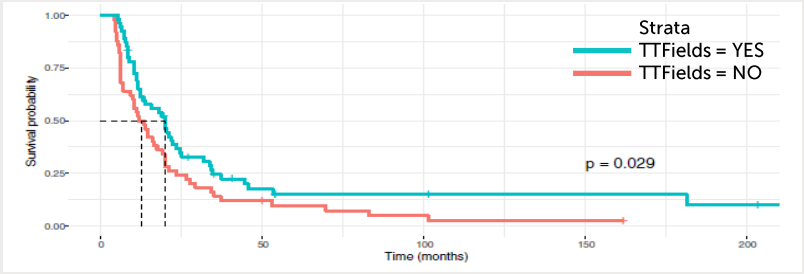
High use group (n=21): daily average usage ≥18 hours. Low use group (n=14): daily average usage <18 hours.
Nishikawa et al. Japanese Journal of Clinical Oncology, 2023; https://doi.org/10.1093/jjco/hyad001

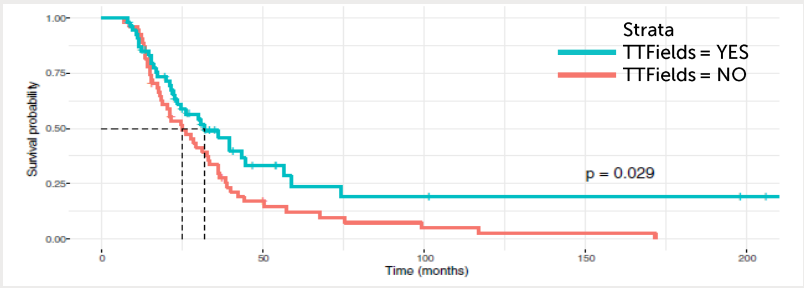
the most extensive study of ndGBM patients covering 18 year period confirms TTFields' positive effect on PFS and OS

FOR MORE INFORMATION, USE THE QR CODE:

Progression Free Survival



Overall Survival



	median PFS	median OS
TTFields + TMZ	19.75 mo	31.67 mo
TMZ alone (EF-14)	12.45 mo	24.80 mo

frontiers | Frontiers in Oncology

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

Josef Vymazal[1*], Tomas Kazda[2], Tomas Novak[3], Petr Slanina[1], Jan Sroubek[4], Jan Klener[4], Tomas Hrbac[5], Martin Syrucek[6] and Aaron M. Rulseh[7*]

Introduction: The prognosis of glioblastoma remains unfavorable. TTFields utilize low intensity electric fields (frequency 150–300 kHz) that disrupt cellular processes critical for cancer cell viability and tumor progression. TTFields are delivered via transducer arrays placed on the patients' scalp. Methods: Between the years 2004 and 2022, 55 patients (20 female), aged 21.9–77.8 years (mean age 47.3 ± 11.8 years; median 47.6 years) were treated with TTFields for newly diagnosed GBM, and compared to 54 control patients (20 female), aged 27.0–76.7 years (mean age 51.4 ± 12.2 years; median 51.7 years) (p=0.08). All patients underwent gross total or partial resection of GBM. One patient had biopsy only. When available, MGMT promoter methylation status and IDH mutation was detected.

Results: Patients on TTFields therapy demonstrated improvements in PFS and OS relative to controls (hazard ratio: 0.64, p=0.031; and 0.61, p=0.028 respectively). TTFields average time on therapy was 74.8% (median 82%); median PFS of these patients was 19.75 months. Seven patients with TTFields usage >60% (25–60%, mean 46.3%, median 53%) had a median PFS of 7.95 months (p=0.0356). Control patients with no TTFields exposure had a median PFS of 12.45 months. Median OS of TTF patients was 31.67 months compared to 24.80 months for controls.

Discussion: This is the most extensive study on newly-diagnosed GBM patients treated with TTFields, covering a period of 18 years at a single center and presenting not only data from clinical trials but also a group of 36 patients treated with TTFields as a part of routine clinical practice.

glioblastoma, magnetic resonance imaging, survival, treatment, tumor treating field (TTF) therapy

Frontiers in Oncology 01

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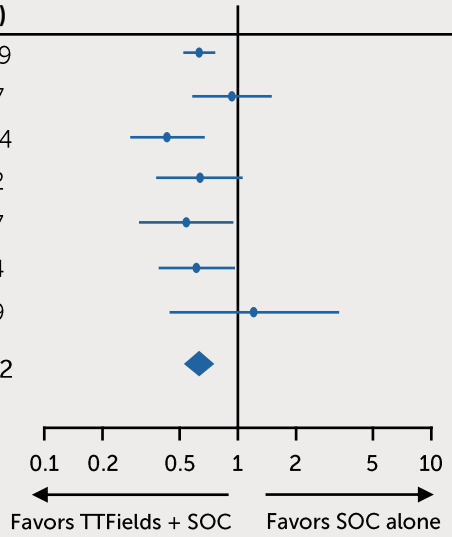
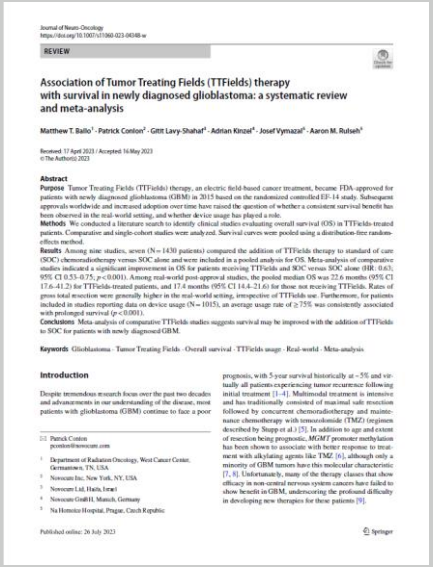
OS, median overall survival; PFS, median progression-free survival.
Vymazal J, et al. Front. Oncol. 12:1014455. doi: 10.3389/fonc.2022.1014455

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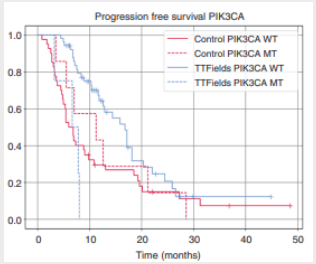
Ballo et al. J Neurooncol (2023). Published 26 July 2023. https://doi.org/10.1007/s11060-023-04348-w

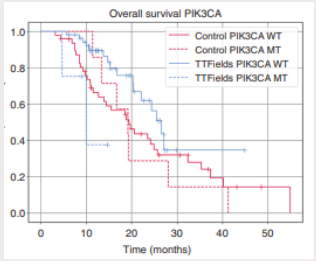
TTFields therapy provide consistent activity for patients with GBM irrespective of molecular alterations

FOR MORE INFORMATION, USE THE QR CODE:

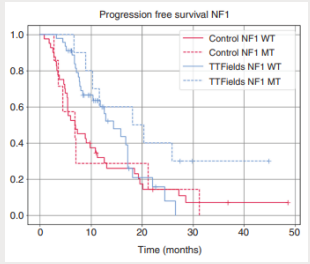
SURVIVAL PROBABILITY

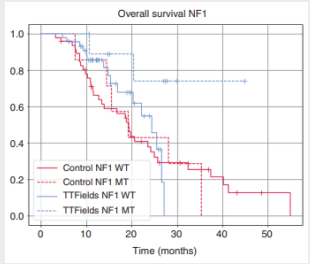
PIK3CA



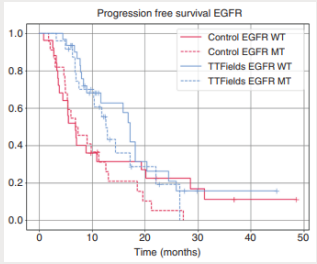


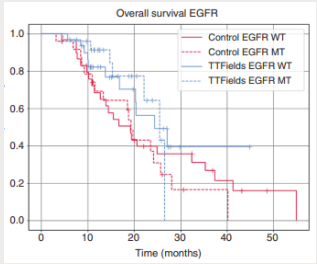
NF1





EGFR





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

Abstract

Background. The genomic and overall biologic landscape of glioblastoma (GB) has become clearer over the past 2 decades, as predictive and prognostic biomarkers of both de novo and transformed forms of GB have been identified. The oral chemotherapeutic agent temozolomide (TMZ) has been integral to standard-of-care treatment for nearly 2 decades. More recently, the use of non-pharmacologic interventions, such as application of alternating electric fields, called Tumor-Treating Fields (TTFields), has emerged as a complementary treatment option that increases overall survival (OS) in patients with newly diagnosed GB. The genomic factors associated with improved or lack of response to TTFields are unknown.

Methods. We performed comprehensive genomic analysis of GB tumors resected from 55 patients who went on to receive treatment using TTFields, and compared results to 57 patients who received standard treatment without TTFields.

Results. We found that molecular driver alterations in NF1, and wild-type PIK3CA and epidermal growth factor receptor (EGFR), were associated with increased benefit from TTFields as measured by progression-free survival (PFS) and OS. There were no differences when stratified by TP53 status. When NF1, PIK3CA, and EGFR status were combined as a Molecular Survival Score, the combination of the 3 factors significantly correlated with improved OS and PFS in TTFields treated patients compared to patients not treated with TTFields.

Conclusions. These results shed light on potential driver and passenger mutations in GB that can be validated as predictive biomarkers of response to TTFields treatment, and provide an objective and testable genomic-based approach to assessing response.

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

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:

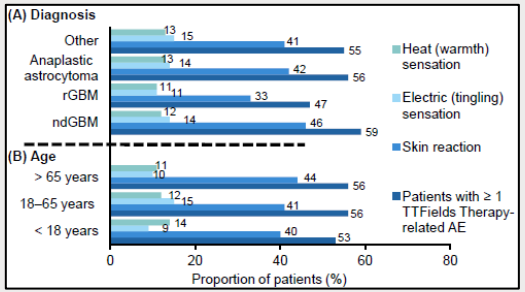
Neff et al.

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)

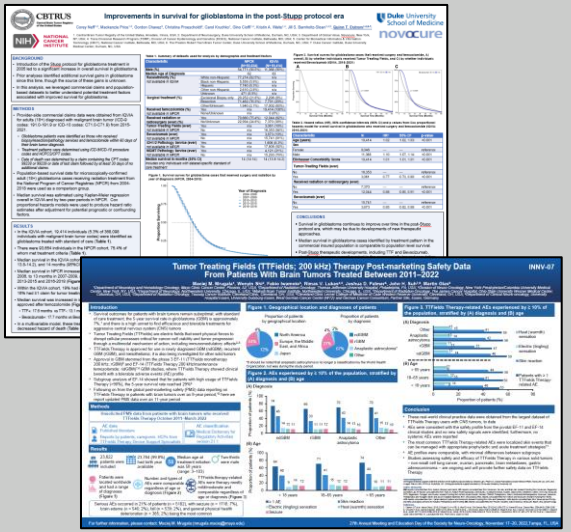
TTFields subset n=3,061 over 6 years

Mrugala et al.



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

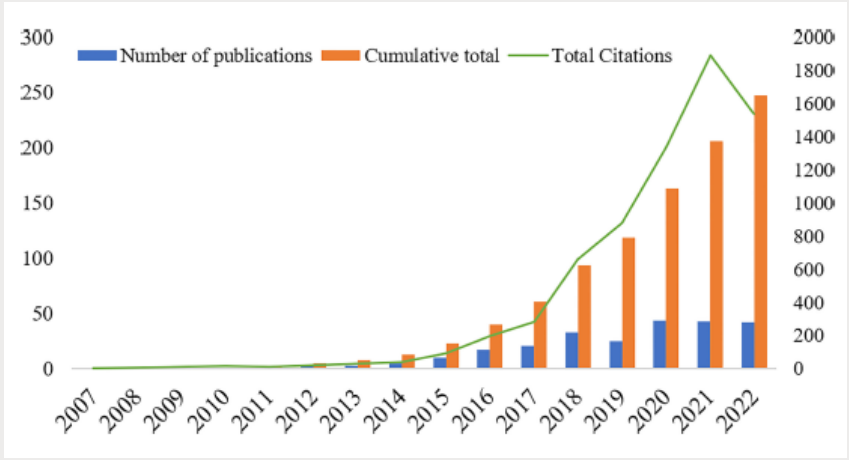
n=23,822 over 11 years



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

the therapeutic potential of TTFields becoming a research "hotspot"

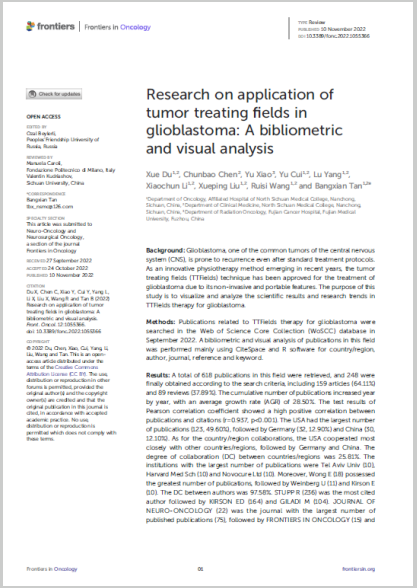
FOR MORE INFORMATION, USE THE QR CODE:



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[3], Yu Xiao[2], 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]*

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=0.957, 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 (101), Harvard Med Sch (110) and Novocure Ltd (110). Moreover, Wong E (88) possessed the greatest number of publications, followed by Weinberg U (111) and Kinzon E (101). The DC between authors was 97.58%. STUPP R (256) 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

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 glioblastoma

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,[1] 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.

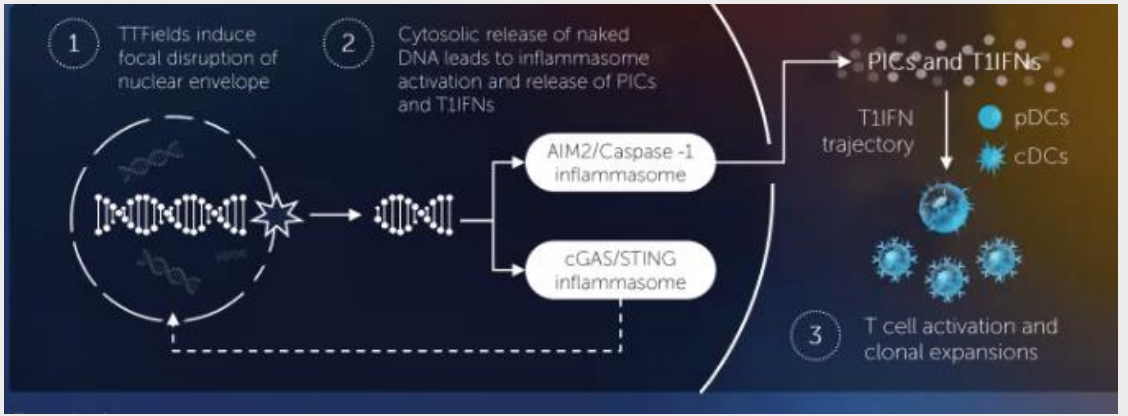
Introduction

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 proteins light chain 3 α/β (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. 63313862 and 63055393) based on the data. All rights were transferred to Novocure. DDT has received research funding in the last 10 months from Merck, Sumitra, 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.



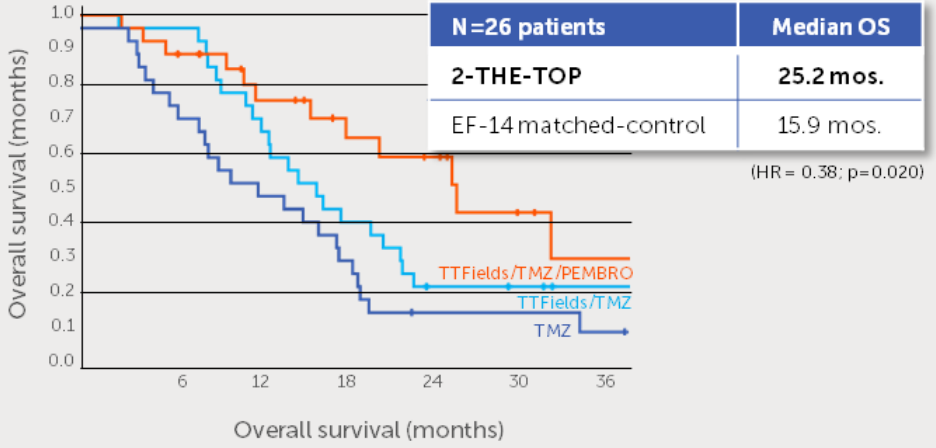
Chen et al. J Clin Invest. 2022;132(8):e149258. https://doi.org/10.1172/JCI149258.

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:

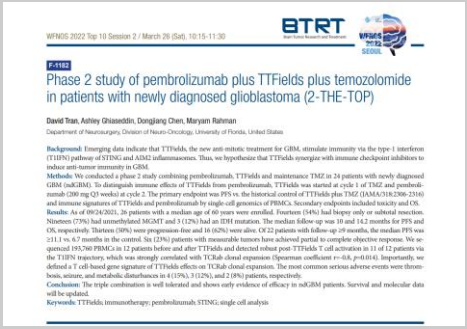
Overall Survival

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

BTRT

F-1102

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.

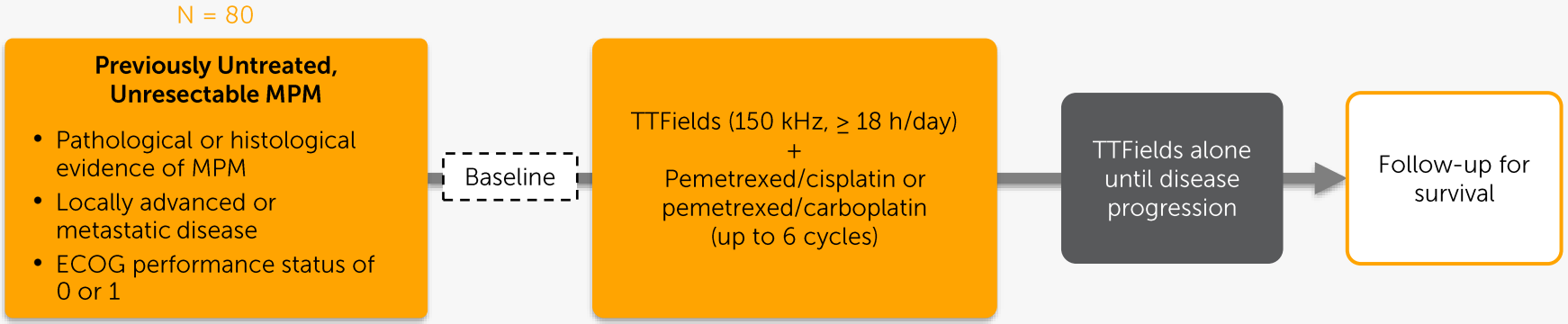
Results: As of 09/24/2021, 26 patients with a median age of 60 years were enrolled. Fourteen (54%) had biopsy only or subtotal resection. Nineteen (73%) had unmethylated MGMT and 3 (12%) had an IDH mutation. The median follow-up was 10 and 14.2 months for PFS and OS, respectively. Thirteen (50%) were 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



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

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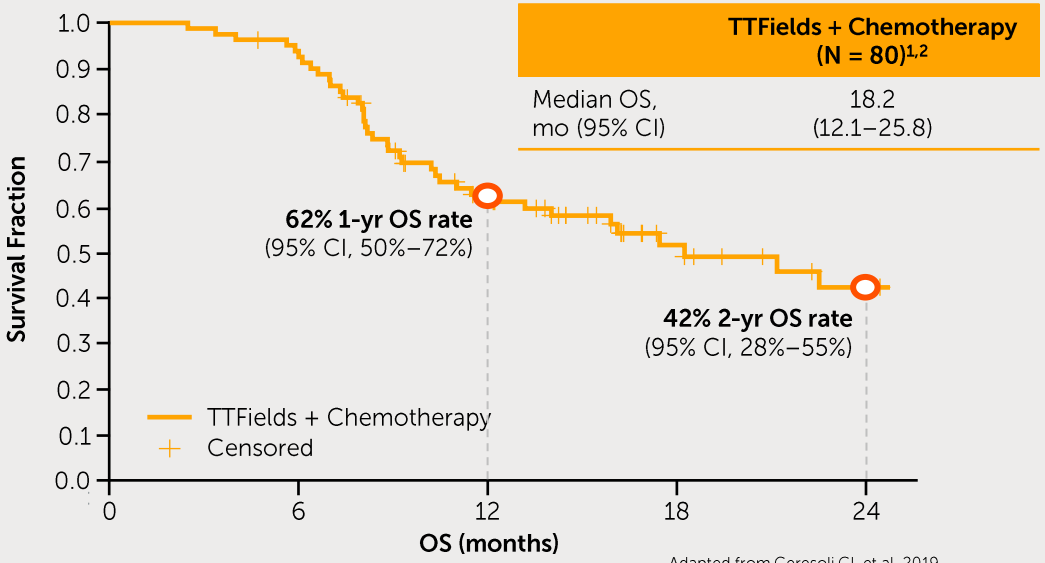
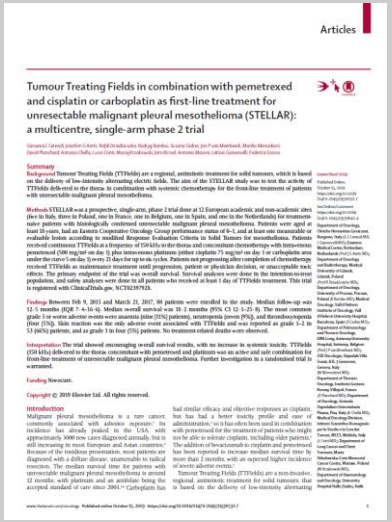
ECOG, Eastern Cooperative Oncology Group; MPM, malignant pleural mesothelioma; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TTFields, Tumor Treating Fields.
ClinicalTrials.gov. NCT02397928. Accessed June 15,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

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

FOR MORE INFORMATION, USE THE QR CODE:



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

Summary

Background Tumour Treating Fields (TTFields) are a regional, antimitotic treatment for solid tumours, which is based on the delivery of low-intensity alternating electric fields. The aim of the STELLAR study was to test the activity of TTFields delivered to the thorax in combination with systemic chemotherapy for the front-line treatment of patients with unresectable malignant pleural mesothelioma.

Methods STELLAR was a prospective, single-arm, phase 2 trial done at 12 European academic and non-academic sites (five in Italy, three in Poland, one in France, one in Belgium, one in Spain, and one in the Netherlands) for treatment-naive patients with histologically confirmed unresectable malignant pleural mesothelioma. Patients were aged at least 18 years, had an Eastern Cooperative Oncology Group performance status of 0–1, and at least one measurable or evaluable lesion according to modified Response Evaluation Criteria in Solid Tumors for mesothelioma. Patients received continuous TTFields at a frequency of 150 kHz to the thorax and concomitant chemotherapy with histotype-specific pemetrexed (500 mg/m² on day 1) plus intravenous platinum (either cisplatin 75 mg/m² on day 1 or carboplatin area under the curve 5 on day 1) every 21 days for up to six cycles. Patients not progressing after completion of chemotherapy received TTFields as maintenance treatment until progression, patient or physician decision, or unacceptable toxic effects. The primary endpoint of the trial was 1-year overall survival. Survival analyses were done in the intention-to-treat population, and safety analyses were done in all patients who received at least 1 day of TTFields treatment. This trial is registered with ClinicalTrials.gov, NCT02397928.

Findings Between Feb 9, 2015 and March 21, 2017, 80 patients were enrolled in the study. Median follow-up was 12·5 months (IQR 7·4–16·4). Median overall survival was 18·2 months (95% CI 12·1–25·8). The most common grade 3 or worse adverse events were anaemia (nine [11%] patients), neutropenia (seven [9%]), and thrombocytopenia (four [5%]). Skin reaction was the only adverse event associated with TTFields and was reported as grade 1–2 in 53 (66%) patients, and as grade 3 in four (5%) patients. No treatment-related deaths were observed.

Interpretation The trial showed encouraging overall survival results, with no increase in systemic toxicity. TTFields (150 kHz) delivered to the thorax concomitant with pemetrexed and platinum was an active and safe combination for front-line treatment of unresectable malignant pleural mesothelioma. Further investigation in a randomised trial is warranted.

Funding Novocure.

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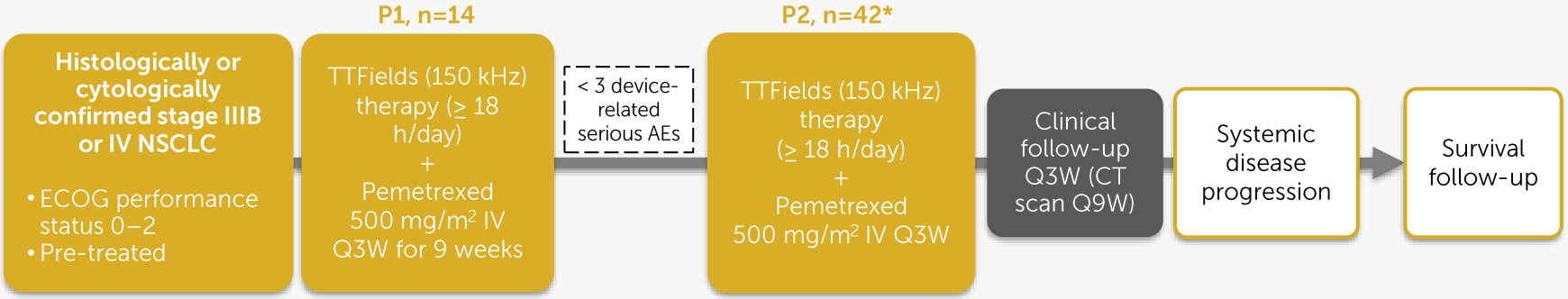
Introduction

Malignant pleural mesothelioma is a rare cancer, commonly associated with asbestos exposure.[1] Its incidence has already peaked in the USA, with approximately 3000 new cases diagnosed annually, but is still increasing in most European and Asian countries.[2] Because of the insidious presentation, most patients are diagnosed with a diffuse disease, unamenable to radical resection. The median survival time for patients with unresectable malignant pleural mesothelioma is around 12 months, with platinum and an antifolate being the accepted standard of care since 2003.[3–5] Carboplatin has had similar efficacy and objective responses as cisplatin but has had a better toxicity profile and ease of administration,[3] so it has often been used in combination with pemetrexed for the treatment of patients who might not be able to tolerate cisplatin, including older patients.[6] The addition of bevacizumab to cisplatin and pemetrexed has been reported to increase median survival time by more than 2 months, with an expected higher incidence of severe adverse events.[7]

Tumour Treating Fields (TTFields) are a non-invasive, regional, antimitotic treatment for solid tumours, that is based on the delivery of low-intensity alternating

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

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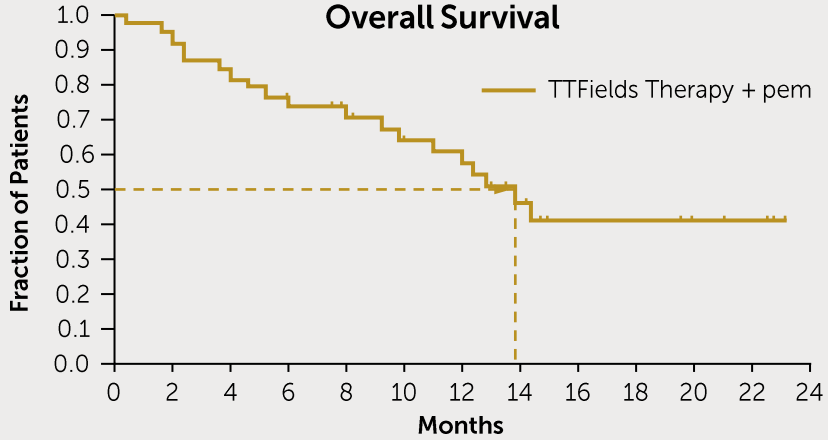
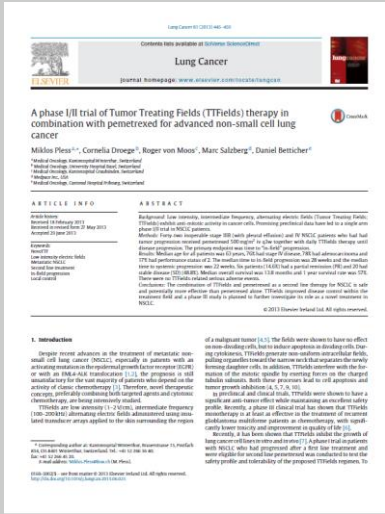
*One out of the 42 patients enrolled was excluded from the analysis due to brain metastasis on screening.
AE, adverse event; CT, computerized tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, 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

FOR MORE INFORMATION, USE THE QR CODE:



	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%


Lung Cancer

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

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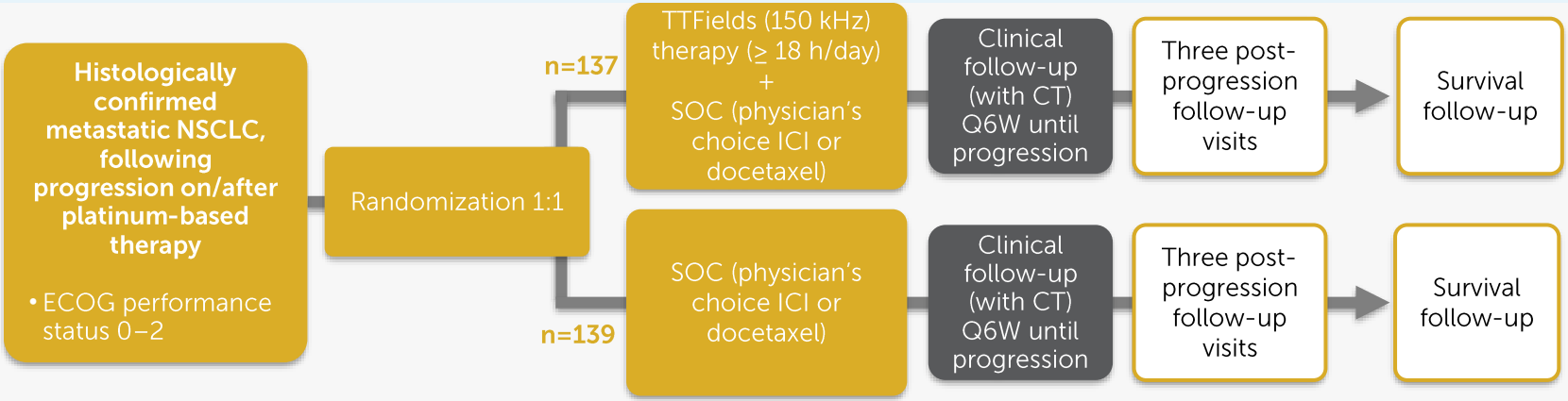
Pem, pemetrexed; TTFields, Tumor Treating Fields; PFS, progression-free survival; OS overall survival.
Pless M et al. *Lung Cancer.* 2013;81(3):445-450.

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

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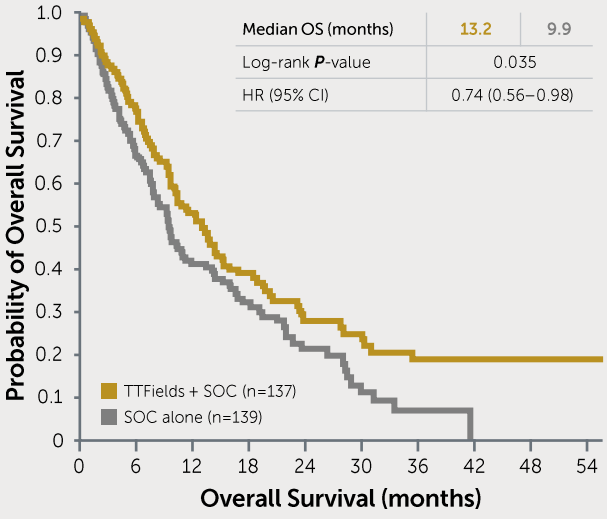
CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; TTFields, Tumor Treating Fields.
ClinicalTrials.gov. NCT02973789.

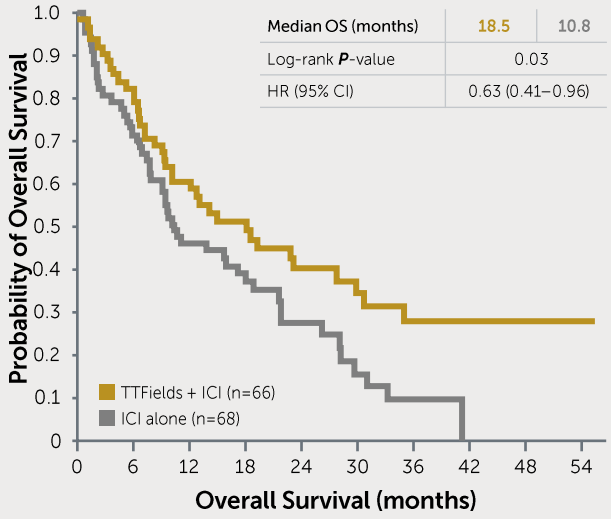
TTFields therapy together with either standard of care therapies or immune checkpoint inhibitor improved overall survival in second-line NSCLC

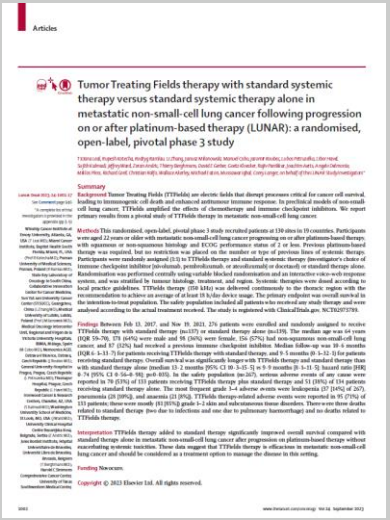
FOR MORE INFORMATION, USE THE QR CODE:

Overall survival (ITT population)



Overall survival (ICI-treated patients)





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

Summary

Background Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical for cancer cell survival, leading to immunogenic cell death and enhanced antitumour immune response. In preclinical models of non-small-cell lung cancer, TTFields amplified the effects of chemotherapy and immune checkpoint inhibitors. We report primary results from a pivotal study of TTFields therapy in metastatic non-small-cell lung cancer.

Methods This randomised, open-label, pivotal phase 3 study recruited patients at 130 sites in 19 countries. Participants were aged 22 years or older with metastatic non-small-cell lung cancer progressing on or after platinum-based therapy, with squamous or non-squamous histology and ECOG performance status of 2 or less. Previous platinum-based therapy was required, but no restriction was placed on the number or type of previous lines of systemic therapy. Participants were randomly assigned (2:1) to TTFields therapy and standard systemic therapy (investigator's choice of immune checkpoint inhibitor [nivolumab, pembrolizumab, or atezolizumab] or docetaxel) or standard therapy alone. Randomisation was performed centrally using variable blocked randomisation and an interactive voice–web response system, and was stratified by tumour histology, treatment, and region. Systemic therapies were dosed according to local practice guidelines. TTFields therapy (150 kHz) was delivered continuously to the thoracic region with the recommendation to achieve an average of at least 18 h/day device usage. The primary endpoint was overall survival in the intention-to-treat population. The safety population included all patients who received any study therapy and were analysed according to the actual treatment received. The study is registered with ClinicalTrials.gov, NCT02973789.

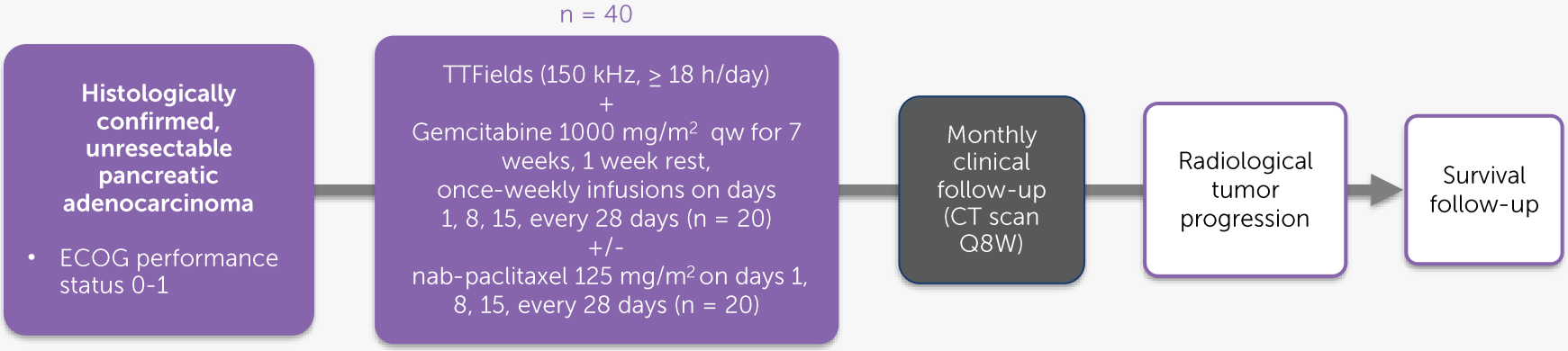
Findings Between Feb 13, 2017, and Nov 19, 2021, 276 patients were enrolled and randomly assigned to receive TTFields therapy with standard therapy (n=137) or standard therapy alone (n=139). The median age was 64 years (IQR 59–70), 178 (64%) were male and 98 (36%) were female; 156 (57%) had non-squamous non-small-cell lung cancer, and 87 (32%) had received a previous immune checkpoint inhibitor. Median follow-up was 10·6 months (IQR 6·1–11·7) for patients receiving TTFields therapy with standard therapy, and 9·5 months (6·1–12·1) for patients receiving standard therapy. Overall survival was significantly longer with TTFields therapy and standard therapy than with standard therapy alone (median 13·2 months [95% CI 10·3–15·1] vs 9·9 months [8·1–11·7]; hazard ratio [HR] 0·74 [95% CI 0·56–0·98]; p=0·035). In the safety population (n=267), serious adverse events of any cause were reported in 76 (55%) of 137 patients receiving TTFields therapy plus standard therapy and 51 (38%) of 134 patients receiving standard therapy alone. The most frequent grade 3–4 adverse events were leukopenia (17 [14%] of 267), pneumonia (16 [10%]), and anaemia (15 [8%]). TTFields therapy-related adverse events were reported in 95 (71%) of 133 patients; three were mostly (61 [65%]) grade 1–2 skin and subcutaneous tissue disorders. There were three deaths related to standard therapy (two due to infections and one due to pulmonary haemorrhage) and no deaths related to TTFields therapy.

Interpretation TTFields therapy added to standard therapy significantly improved overall survival compared with standard therapy alone in metastatic non-small-cell lung cancer after progression on platinum-based therapy without exacerbating systemic toxicities. These data suggest that TTFields therapy is efficacious in metastatic non-small-cell lung cancer and should be considered as a treatment option to manage the disease in this setting.

Funding Novocure.

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.

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



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

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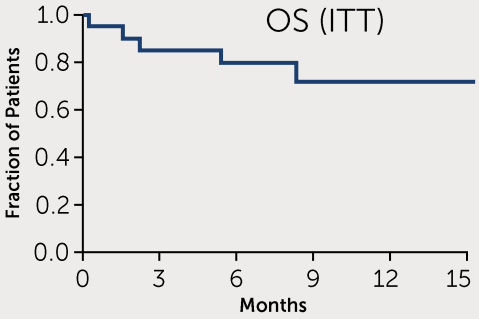
CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS6, progression-free survival rate 6 months; qw, every week; Q8W, every 8 weeks; SR, survival rate.
ClinicalTrials.gov. [NCT01971281].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

Pancreatology

Tumor treating fields in combination with gemcitabine or gemcitabine plus nab-paclitaxel in pancreatic cancer: Results of the PANOVA phase 2 study

Fernando Rivera, Manuel Benavides, Javier Gallego, Carmen Guillen-Ponce, José Lopez-Martin, Marc Ring

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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*

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)

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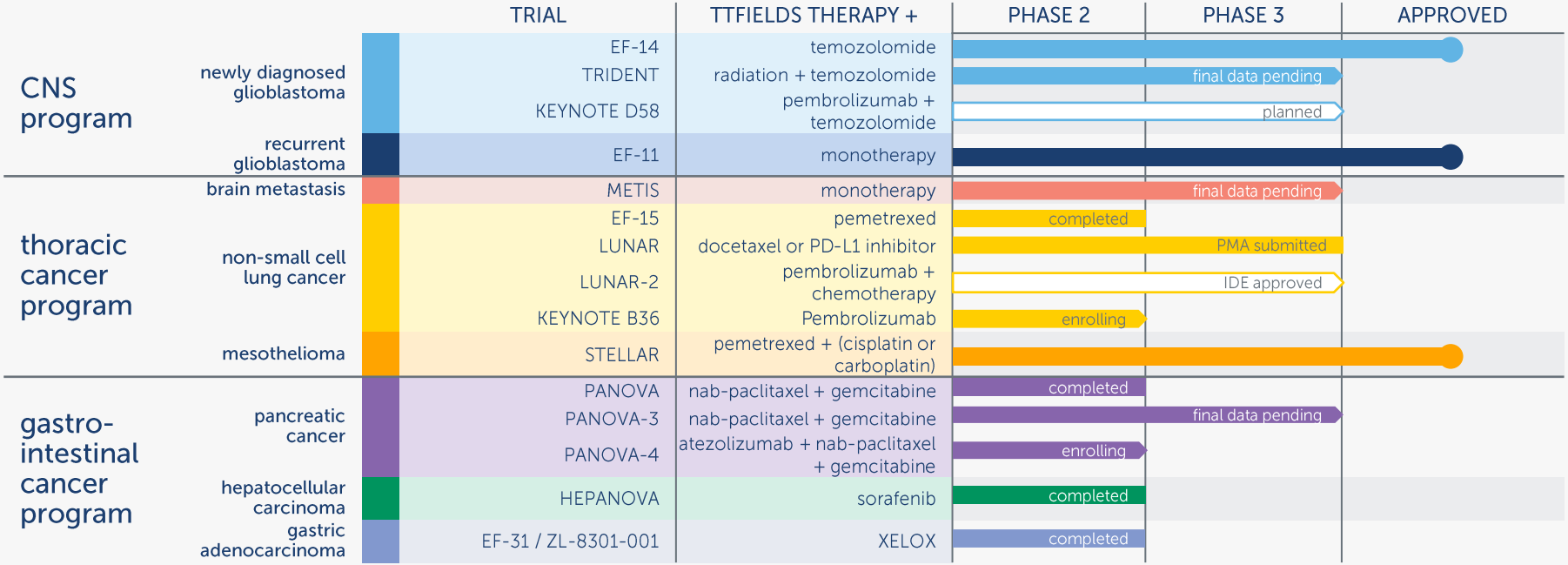
1. Gkika E et al. Cancers Cancers (Basel). 2022 Mar 18;14(6):1568. doi: 10.3390/cancers14061568.
2. Novocure, Ltd. Effect of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Sorafenib For Advanced Hepatocellular Carcinoma (HCC) (HEPANOVA) In: ClinicalTrials.gov [Internet]. Bethesda (MD): National 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.

platform technology driving robust clinical pipeline



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tumor treating fields mechanism of action overview

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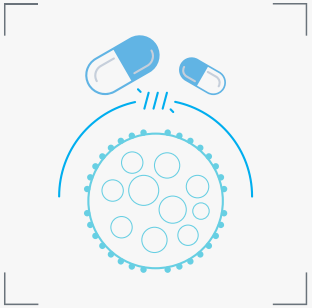
patients with aggressive solid tumors often face suboptimal survival outcomes, despite advancements in treatment modalities

These outcomes are due to diverse treatment challenges, including:



Therapeutic tumor resistance

Drug-to-drug interactions

Additive systemic toxicities

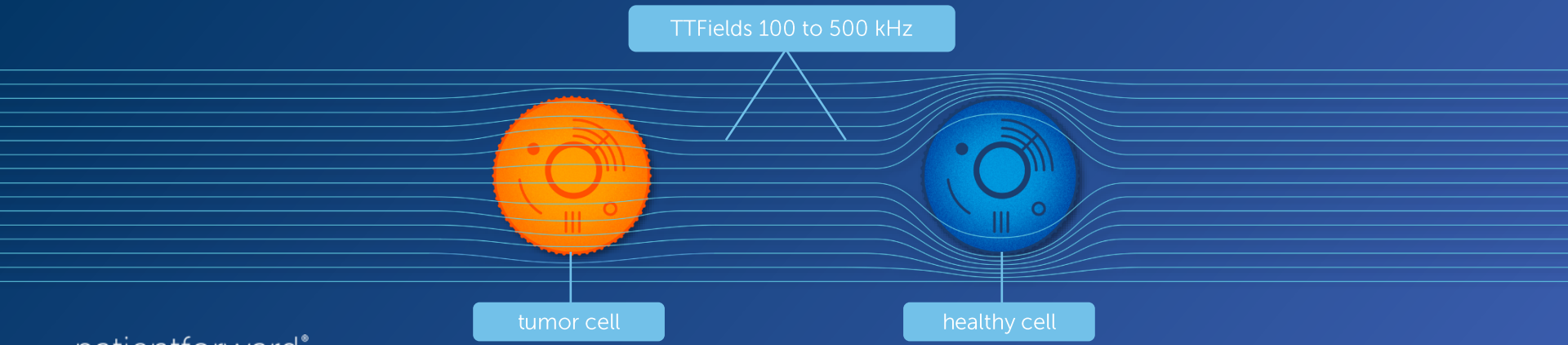
With a poor survival outlook, physicians and patients need additional treatment strategies

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



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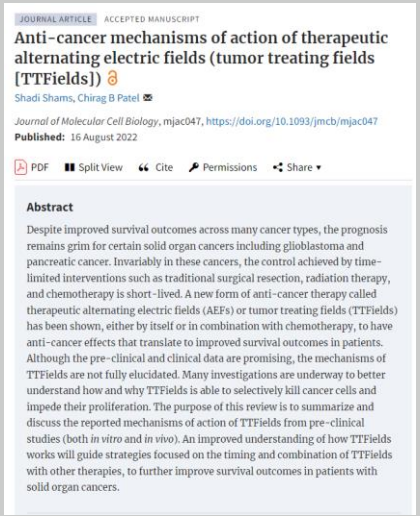
1. Karanam NK, Story MD. *Int J Radiat Biol.* 2021;97(8):1044-1054. 2. Cooper GM. The Cell: A Molecular Approach. 2nd ed. Sinauer Associates; 2000:chap 15. https://www.ncbi.nlm.nih.gov/books/NBK9963/. 3. Baba AI, Câtoi C. Comparative Oncology. The Publishing House of the Romanian Academy; 2007:chap 3. 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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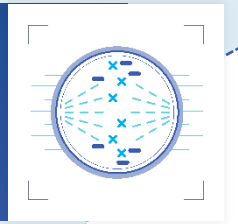
Abstract

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.

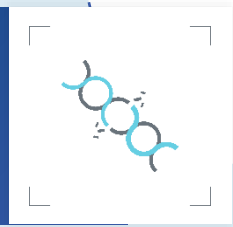
Chirag B. Patel, et al. Journal of Molecular Cell Biology. *Anti-cancer mechanisms of action of therapeutic alternating electric fields (tumor treating fields [TTFields]).* https://academic.oup.com/jmcb/advance-article/doi/10.1093/jmcb/mjac047/6668799

Tumor Treating Fields have multiple, distinct mechanisms of action

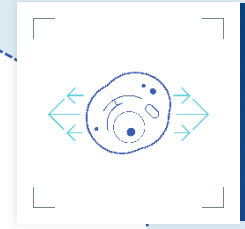
disruption of mitosis



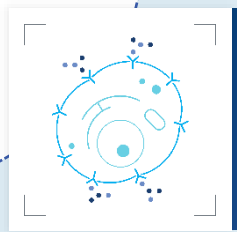
downregulation of DNA damage response



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



interference of cell movement and migration

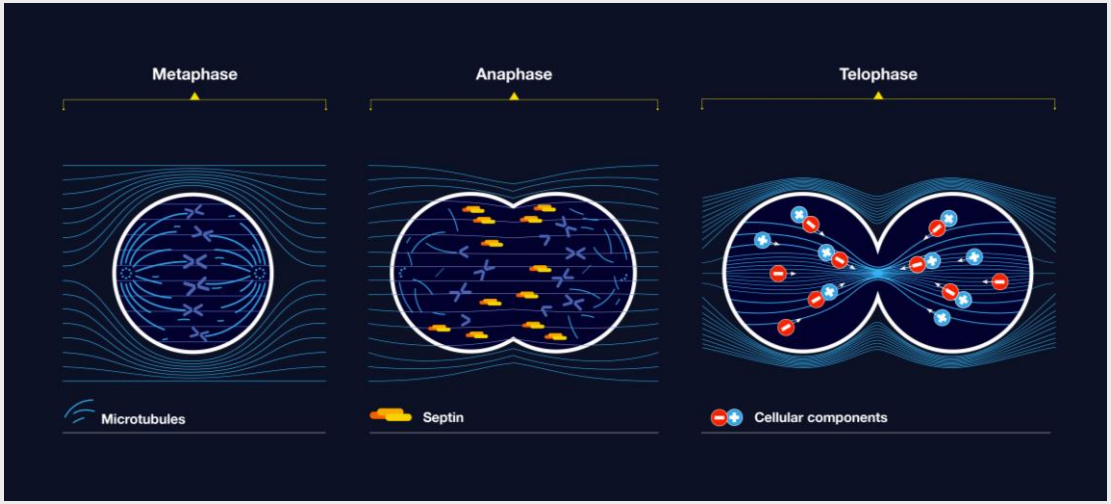


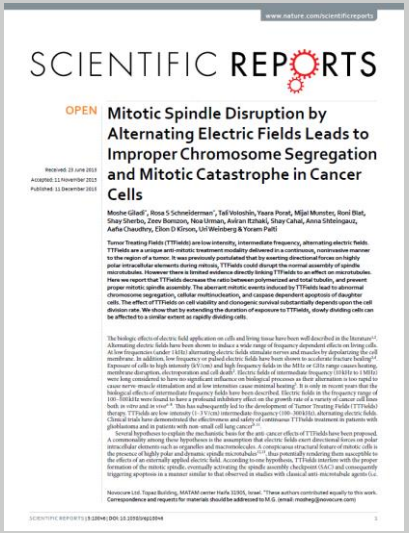
downstream enhancement of antitumor immunity

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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SCIENTIFIC REPORTS

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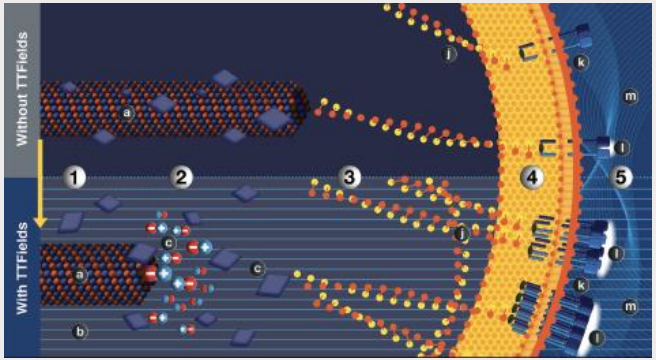
Mitotic Spindle Disruption by Alternating Electric Fields Leads to Improper Chromosome Segregation and Mitotic Catastrophe in Cancer Cells

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

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Article

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

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Simple Summary: Tumor Treating Fields (TTFields), encompassing alternating electric fields within the intermediate frequency range, is an anticancer treatment delivered to the tumor region through transducer arrays placed non-invasively on the skin. Although established as an anti-mitotic treatment modality, the anti-metastatic potential of TTFields and their effect on rapid cytoskeletal dynamics during cellular motility warrant further investigation. In this study, we report that TTFields application induces changes in microtubule organization leading to interference with the directionality and robustness of cancer cell migration. We show that these changes in microtubule organization result in activation of GEF-H1/RhoA/ROCK-signaling pathway, and the consequent formation of focal adhesions and changes in actin cytoskeleton architecture. Together, these results propose a novel mechanism by which TTFields induce changes in microtubule and actin organization and dynamics, thereby disrupting processes important for polarity generation and motility in cancer cells.

Abstract: Tumor Treating Fields (TTFields) are noninvasive, alternating electric fields within the intermediate frequency range (100–300 kHz) that are utilized as an antimitotic cancer treatment. TTFields are loco-regionally delivered to the tumor region through 2 pairs of transducer arrays placed on the skin. This novel treatment modality has been FDA-approved for use in patients with glioblastoma and malignant pleural mesothelioma based on clinical trial data demonstrating efficacy and safety, and is currently under investigation in other types of solid tumors. TTFields were shown to induce an anti-mitotic effect by exerting bi-directional forces on highly polar intracellular elements, such as tubulin and septin molecules, eliciting abnormal microtubule polymerization during spindle formation as well as aberrant cleavage furrow formation. Previous studies have demonstrated that TTFields inhibit metastatic properties in cancer cells. However, the consequences of TTFields application on cytoskeleton dynamics remain undetermined. In this study, methods utilized in combination to study the effects of TTFields on cancer cell motility through regulation of microtubule and actin dynamics included confocal microscopy, computational tools, and biochemical analyses. Mechanisms by which TTFields treatment disrupted cellular polarity were (1) interference with microtubule assembly and directionality; (2) altered regulation of Guanine nucleotide exchange factor-H1 (GEF-H1), Ras homolog family member A (RhoA), and Rho-associated coiled-coil kinase (ROCK) activity; and (3) induced formation of radial protrusions of peripheral actin filaments and focal adhesions. Overall, these data identified discrete effects of TTFields that disrupt processes crucial for cancer cell motility.

Cancers 2020, 12, 3016; doi:10.3390/cancers12103016 www.mdpi.com/journal/cancers

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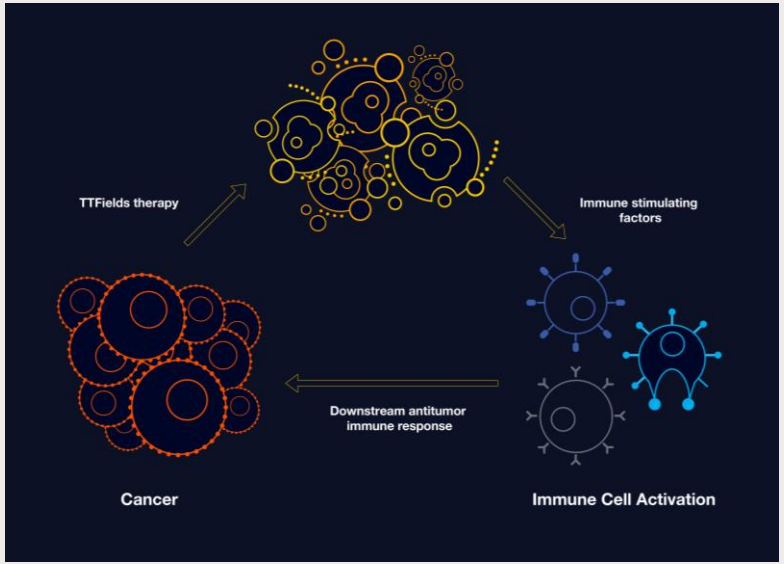
Adapted from Voloshin et al. 2020.
GEF-H1=a microtubule-associated protein that couples microtubule dynamics to cell contractility.
RhoA/ROCK=a pathway that regulates cell morphology, polarity, and cytoskeletal remodeling by regulating actin and cell migration.
Voloshin T, Schneiderman RS, Volodin A,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

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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

Tali Voloshin[1] · Noa Kaynan[1] · Shiri Davidi[2] · Yaara Porat[1] · Anna Shteingauz[1] · Rosa S. Schneiderman[1] · Einav Zeevi[1] · Mirjal Munster[1] · Roni Blat[1] · Catherine Tempel Brami[1] · Shay Cahal[1] · Aviran Itzhaki[1] · Moshe Giladi[2] · Eilon D. Kirson[1] · Uri Weinberg[1] · Adrian Kinzel[2] · Yoram Palti[1]

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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

This work was presented as a poster at the annual meeting of the American Association of Immunologists (AAI), May 15–17, 2016, Seattle, WA, USA (#P7279); the annual meeting of the American Association for Cancer Research (AACR), April 1–5, 2017, Washington, DC, USA (#5591); the annual meeting of the Society for NeuroOncology (SNO), November 16–19, 2017, San Francisco, USA (IMMU-40); the annual meeting of the Society for NeuroOncology (SNO), November 15–18, 2018, New Orleans, LA, USA (IMMU-52); the European Association of Neuro-Oncology (EANO) Meeting, October 10–12, 2018, Stockholm, Sweden (P02.04); the annual meeting of the American Association for Cancer Research (AACR), March 29–April 3, 2019, Atlanta, GA, USA (3961); the International Cancer Immunotherapy Conference, CICI19, September 25–28, 2019, Paris, France (B036); the annual meeting of the Society for Immunotherapy of Cancer (SITC), November 6–10, 2019, National Harbor, MD, USA (poster P 189); the annual meeting of the American Society for Radiation Oncology (ASTRO), September 15–18, 2019, Chicago, IL, USA (351-0); the Brain Tumor Meeting, May 23–24, 2019, Berlin, Germany; the European Lung Cancer Congress (ELCC), April 10–13, 2019, Geneva, Switzerland (75); the Multidisciplinary Thoracic Cancers Symposium, March 14–16, 2019, San Diego, CA, USA (102).

Tali Voloshin and Noa Kaynan have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00262-020-02534-7) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

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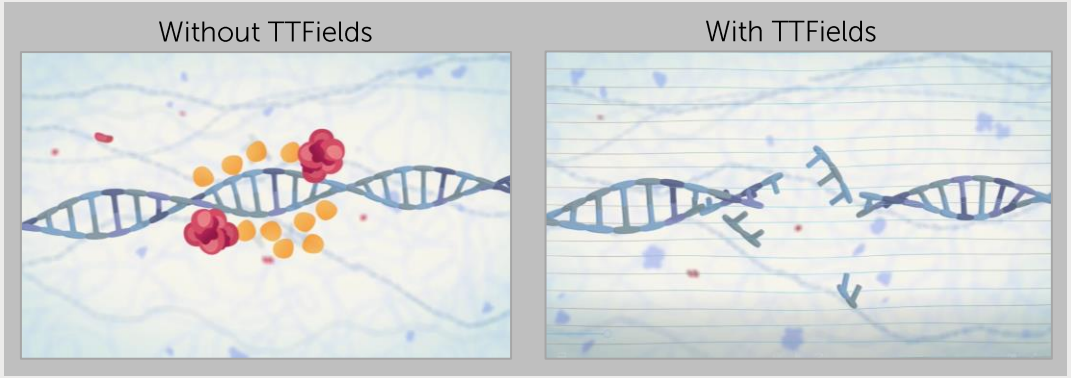
Voloshin T, Kaynan N, Davidi S, et al. *Cancer Immunol Immunother*. 2020;69(7):1191-1204.

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]



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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

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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

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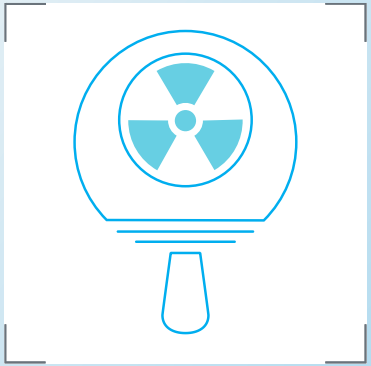
1. Karanam NK, Story MD. *Int J Radiat Biol*. 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984. **2**. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. *Clin Cancer Res*. 2018;24(2):266-275. doi:10.1158/1078-0432.CCR-17-1117 **3**. Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, 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.

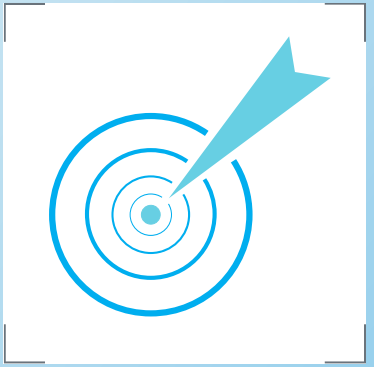
TTFields therapy can be added to cancer treatment modalities in approved indications

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

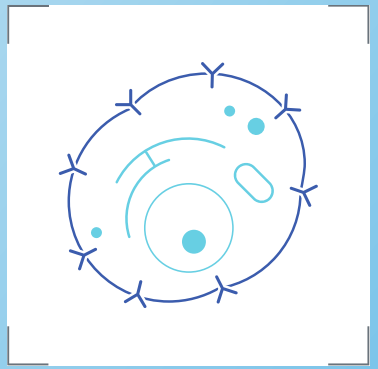
Chemotherapy



Radiation therapy (RT)



Targeted therapies



Immuno-oncologic (IO) agents

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]

