Tumor Treating Fields (TTFields): una nuova opzione terapeutica nel trattamento dei tumori solidi?

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Associazione con la radioterapia: evidenze scientifiche e sviluppi futuri

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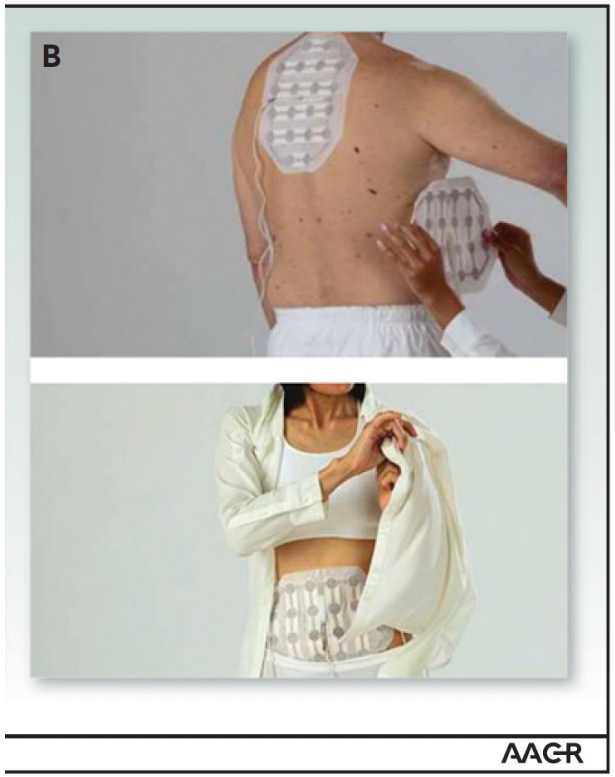
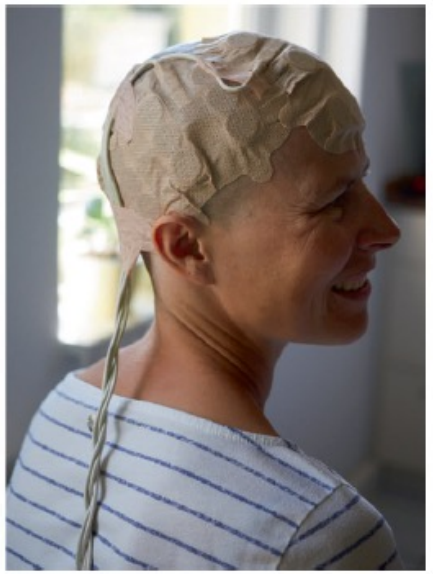
Glioblastoma

The Novocure ® «casco» è un dispositivo che consiste nella serie di sorgenti di onde elettromagnetiche





British Journal of Cancer (2020) 124:697–709; https://doi.org/10.1038/s41416-020-01136-5

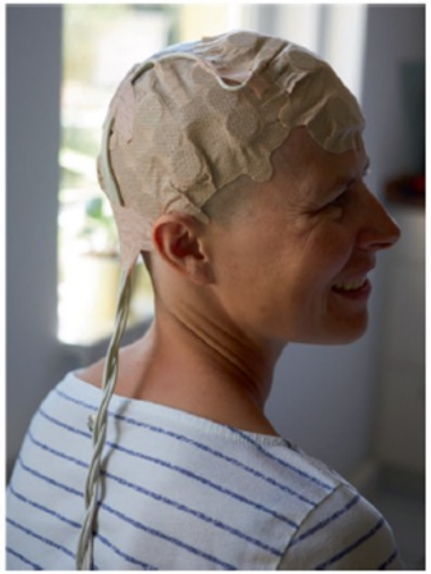
Novocure. Novocure reports fourth quarter and full year 2019 financial results and provides company update. https://www.novocure.com/novocure-reportsfourth-quarter-and-full-year-2019-financial-results-and-provides-companyupdate/ (2020).

TTFields delivery

“il più usato sistema Optune (Novocure™), consiste in un insieme di quattro trasduttori, un generatore di campi elettromagnetici e una batteria. Per GBM, i trasduttori sono applicati in coppie, ortogonalmente allo scalpo del paziente.

La testa deve essere rasata per consentire un contatto ottimale dei trasduttori con il cuoio capelluto, e il posizionamento ottimale degli array viene determinato utilizzando NovoTAL (Novocure Ltd., Haifa, Israele**) software di simulazione basato sulla posizione del tumore e la dimensione e la forma della testa del paziente**.

Ogni serie di trasduttori è composta da nove dischi in ceramica, ciascuno con un rivestimento idrogel superficiale per migliorare la conducibilità con la pelle. Il generatore di campo fornisce al cervello e alla sede del tumore campi elettrici alternati attraverso i trasduttori



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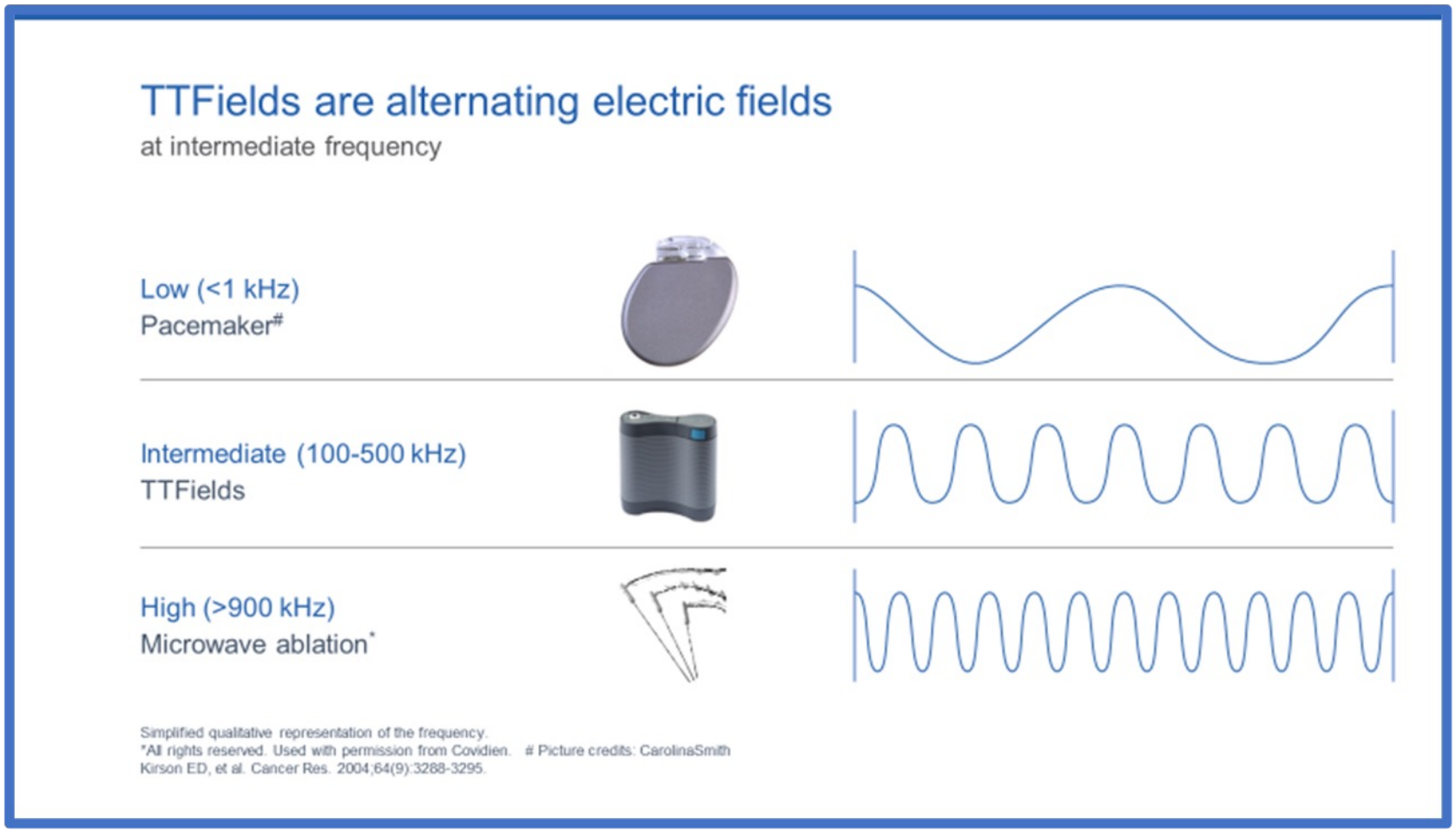
I TTFields consistono nell'emissione transcutanea di campi elettrici a bassa intensità (1-3 V/cm), a frequenza intermedia (100-300 kHz), alternati (l'approccio è noto anche come terapia a campo elettrico alternato) che esercitano forza biofisica su molecole cariche e polarizzabili note come dipoli.
Nel caso delle cellule del glioma, i TTFields sono clinicamente erogati ad una frequenza ottimale di 200 kHz.



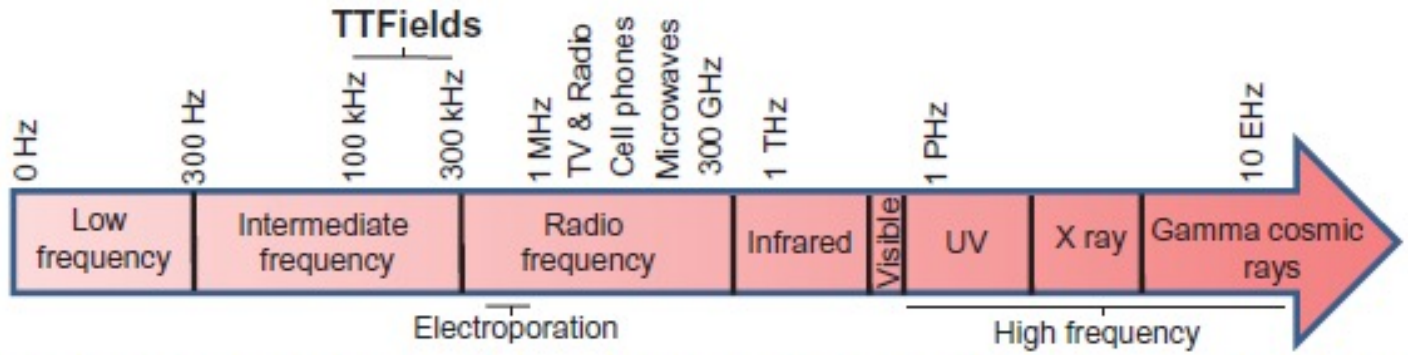


Figure 1. Frequency ranges of different applications across different frequency ranges. TTFields frequency falls in intermediate frequency range as indicated. Electroporation and more popular appliances such as TV, radio, cell phone and microwaves uses radio frequency range waves. Ionizing radiation frequency falls in the higher frequency range.

Tra i parametri più usati per confrontare i risultati in differenti situazione, uno è particolarmente utile:

SAR = specific absorption rate; si misura in watt/kg; a puro titolo di confronto, il corpo umano genera a riposo circa 1W/kg, che può arrivare a 4W/kg durante il lavoro intenso; a potenze elevate (>10W/kg) si ha un aumento di temperatura controllato dai sistemi di termoregolazione; eventuali danni biologici da esposizioni superiori ai 10W/kg si possono avere per esposizioni prolungate nel tempo

Cancer Medicine

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ORIGINAL RESEARCH

Analysis of physical characteristics of Tumor Treating Fields for human glioblastoma

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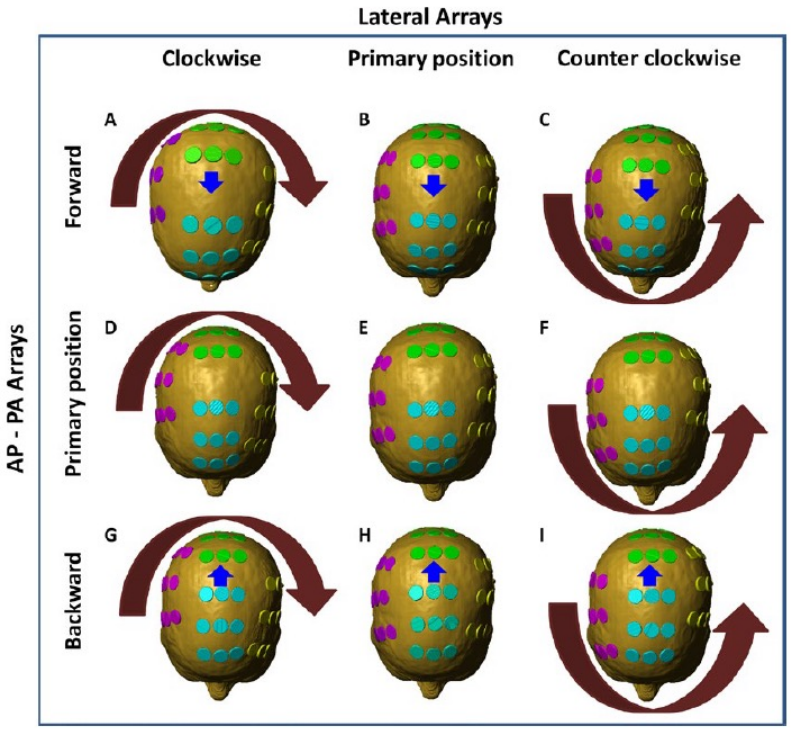
Cancer Medicine **2017; 6(6):1286–1300**

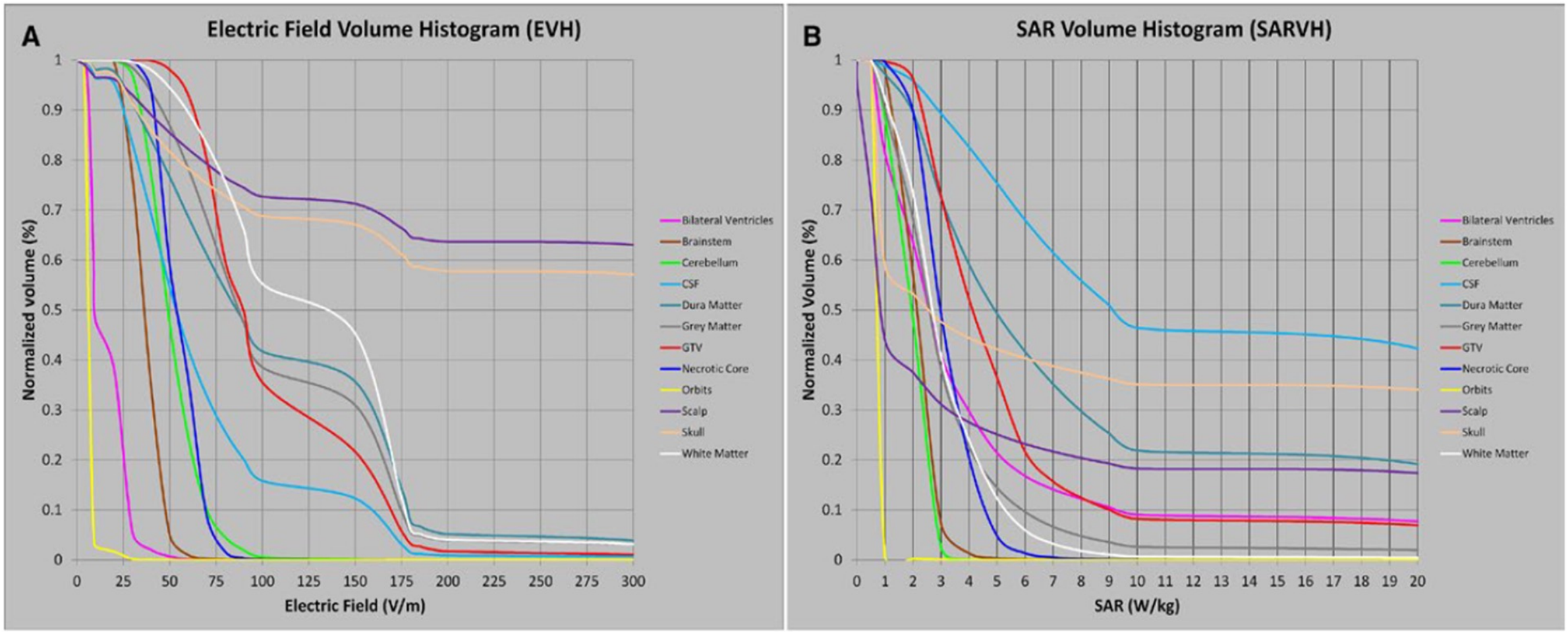


Abstract

Tumor Treating Fields (TTFields) therapy is an approved treatment that has known clinical efficacy against recurrent and newly diagnosed glioblastoma. However, the distribution of the electric fields and the corresponding pattern of energy deposition in the brain are poorly understood. To evaluate the physical parameters that may influence TTFields, postacquisition MP-RAGE, T1 and T2 MRI sequences from a responder with a right parietal glioblastoma were anatomically segmented and then solved using finite-element method to determine the distribution of the electric fields and rate of energy deposition at the gross tumor volume (GTV) and other intracranial structures. Electric field–volume histograms (EVH) and specific absorption rate–volume histograms (SARVH) were constructed to numerically evaluate the relative and/or absolute magnitude volumetric differences between models. The electric field parameters E_{AUC}, V_{E150}, $E_{95\%}$, $E_{50\%}$, and $E_{20\%}$, as well as the SAR parameters SAR_{AUC}, $V_{SAR7.5}$, $SAR_{95\%}$, $SAR_{50\%}$, and $SAR_{20\%}$, facilitated comparisons between models derived from various conditions. Specifically, TTFields at the GTV were influenced by the dielectric characteristics of the adjacent tissues as well as the GTV itself, particularly the presence or absence of a necrotic core. The thickness of the cerebrospinal fluid on the convexity of the brain and the geometry of the tumor were also relevant factors. Finally, the position of the arrays also influenced the electric field distribution and rate of energy deposition in the GTV. Using EVH and SARVH, a personalized approach for TTFields treatment can be developed when various patient-related and tumor-related factors are incorporated into the planning procedure.

In sostanza, è possibile costruire istogrammi SAR/volume per descrivere questa variabilità nella distribuzione della potenza assorbita nelle varie strutture cerebrali

il GTV assorbe molta meno energia rispetto ad altre strutture cerebrali



Il tumore assorbe molta meno energia dei tessuti sani

Table 2. The values for electric field and rate of energy deposition parameters at the GTV and other structures in the head as shown in EVH and SARVH from Figure 2.

Tissue structure	E_{AUC}	$V_{E150\ (\%)}$	$E_{95\%}$	$E_{50\%}$	$E_{20\%}$	SAR_{AUC}	$V_{SAR7.5\ (\%)}$	$SAR_{95\%}$	$SAR_{50\%}$	$SAR_{20\%}$
Bilateral ventricle	14.7	0.0	5.7	9.8	25.2	4.0	13.1	0.7	2.6	5.3
Brainstem	35.7	0.0	23.6	36.3	44.0	1.2	0.0	1.2	2.1	2.6
Cerebellum	50.4	0.1	32.0	49.0	62.6	1.0	0.0	0.8	2	2.5
Cerebrospinal fluid	67.3	12.3	21.0	53.5	90.2	19.0	58.6	2.2	9.2	30
Dura	108.3	35.7	25.4	86.2	169.8	8.2	32.3	1.3	4.9	17.1
Gray matter	108.1	31.0	37.7	87.2	164.7	2.5	5.6	0.8	2.6	4.3
Gross tumor volume (GTV)	104.0	21.7	57.0	89.7	153.5	5.9	13.9	2.1	4.1	6.2
Necrotic core	54.1	0.0	38.8	53.8	65.2	3.5	5.6	2.3	4.1	5.8
Orbits	5.7	0.0	4.2	6.2	7.8	0.0	0.0	0.5	0.8	0.9
Scalp	596.0	71.2	24.8	>1000	>1000	8.7	21.0	0.1	0.9	8.3
Skull	537.8	67.1	24.6	437.2	>1000	31.8	38.1	0.6	2.5	42.8
White matter	126.9	45.3	48.7	137.0	169.8	2.2	2.4	0.9	2.7	4.3

GTV, gross tumor volume; EVH, electric field–volume histogram; SARVH, specific absorption rate–volume histogram; E_{AUC}, electric field area under the curve; V_{E150}, volume covered with electric field intensity of 150 volts per meter; $E_{95\%}$, the electric field intensity encompassing 95% of volume; $E_{50\%}$, the electric field intensity encompassing 50% of volume; $E_{20\%}$, the electric field intensity encompassing 50% of volume; SAR, specific absorption rate; SAR_{AUC}, SAR area under the curve; $V_{SAR7.5}$, volume covered with specific absorption rate of 7.5 watts per kilogram; $SAR_{95\%}$, the magnitude of specific absorption rate encompassing 95% of volume; $SAR_{50\%}$, the magnitude of specific absorption rate encompassing 50% of volume; $SAR_{20\%}$, the magnitude of specific absorption rate encompassing 20% of volume.

La quantità di energia rilasciata dai TTF varia notevolmente a seconda di parametri quali lo spessore della teca cranica, la disposizione e la forma del liquido cefalorachidiano nei ventricoli e negli altri spazi liquorali, la forma e la struttura del Gross Tumor Volume, etc.

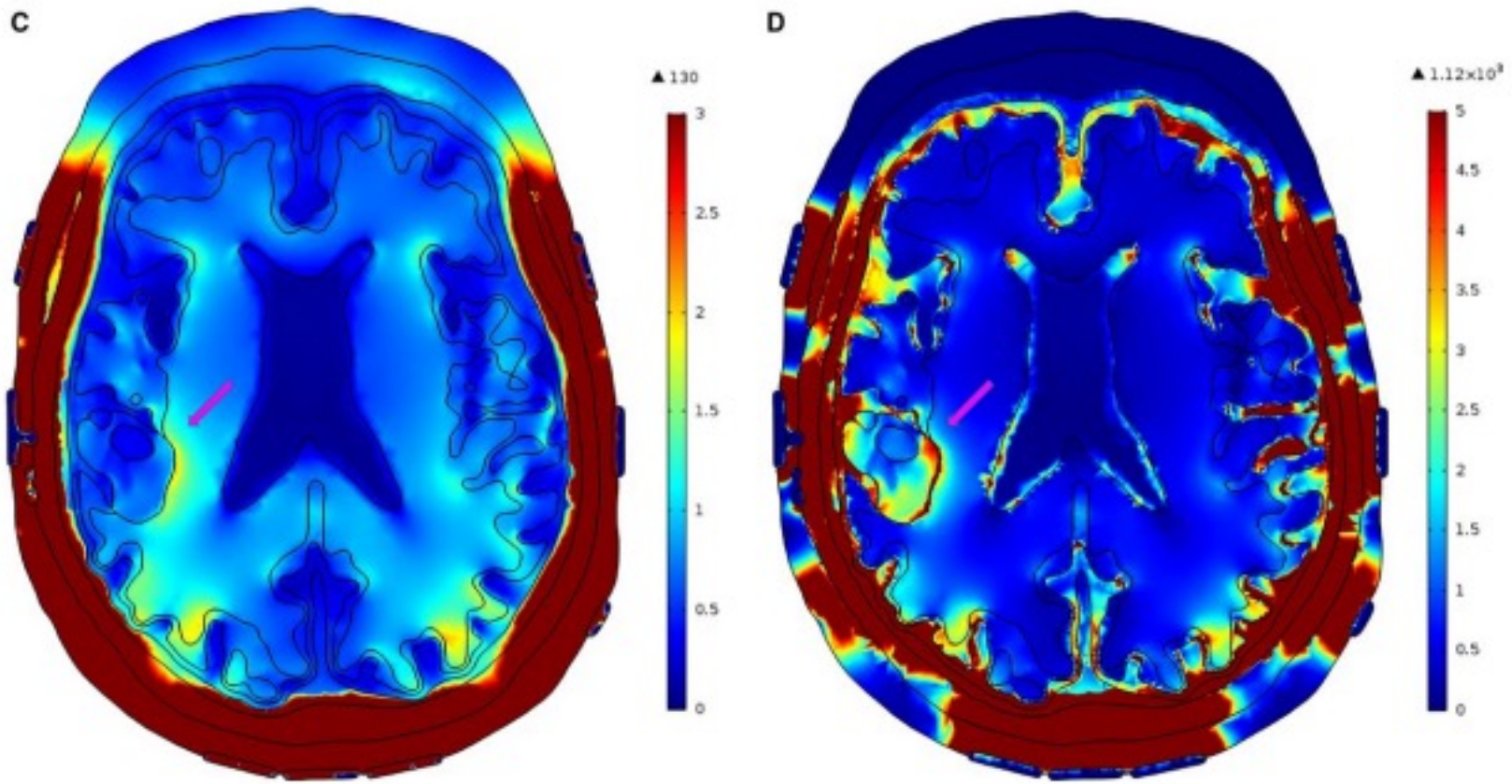


Figure 2. Volume histograms EVH and SARVH. The EVH (A), SARVH (B), electric field map (C), and SAR map (D) were generated using the transducer array placement as outlined in Figure 3E. The highest E_{AUC} was found at the scalp and skull, whereas the lowest was detected at the orbits, bilateral ventricles, and brainstem. The highest SAR_{AUC} was found at the skull, GTV, and the layer of cerebrospinal fluid between cortex and dura, whereas the lowest was found in the orbits, cerebellum, and the orbits. EVH, electric field–volume histogram; SARVH, specific absorption rate–volume histogram; SAR, specific absorption rate.

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Evaluation of Specific Absorption Rate as a Dosimetric Quantity for Electromagnetic Fields Bioeffects

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Abstract

Purpose: To evaluate *SAR* as a dosimetric quantity for EMF bioeffects, and identify ways for increasing the precision in EMF dosimetry and bioactivity assessment.

Methods: We discuss the interaction of man-made electromagnetic waves with biological matter and calculate the energy transferred to a single free ion within a cell. We analyze the physics and biology of *SAR* and evaluate the methods of its estimation. We discuss the experimentally observed non-linearity between electromagnetic exposure and biological effect.

Results: We find that: a) The energy absorbed by living matter during exposure to environmentally accounted EMFs is normally well below the thermal level. b) All existing methods for *SAR* estimation, especially those based upon tissue conductivity and internal electric field, have serious deficiencies. c) The only method to estimate *SAR* without large error is by measuring temperature increases within biological tissue, which normally are negligible for environmental EMF intensities, and thus cannot be measured.

Conclusions: *SAR* actually refers to thermal effects, while the vast majority of the recorded biological effects from man-made non-ionizing environmental radiation are non-thermal. Even if *SAR* could be accurately estimated for a whole tissue, organ, or body, the biological/health effect is determined by tiny amounts of energy/power absorbed by specific biomolecules, which cannot be calculated. Moreover, it depends upon field parameters not taken into account in *SAR* calculation. Thus, *SAR* should not be used as the primary dosimetric quantity, but used only as a complementary measure, always reporting the estimating method and the corresponding error. Radiation/field intensity along with additional physical parameters (such as frequency, modulation etc) which can be directly and in any case more accurately measured on the surface of biological tissues, should constitute the primary measure for EMF exposures, in spite of similar uncertainty to predict the biological effect due to non-linearity.

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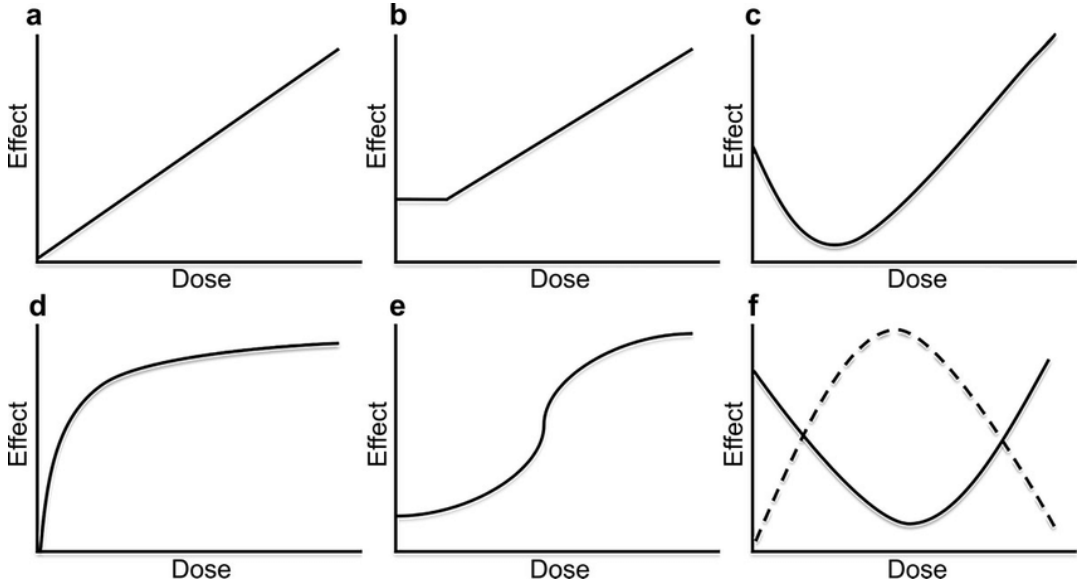
SAR = Solo un indice surrogato per prevedere gli effetti biologici dei campi elettromagnetici (soprattutto di potenza inferiore)

La non linearità tra esposizione ad un campo elettromagnetico e l'effetto biologico.

?

La dosimetria è necessaria per trovare una relazione quantitativa tra causa ed effetto.
Più questa relazione è ben definita, più utile è la dosimetria.
Conoscendo la relazione tra causa ed effetto, possiamo prevedere l'effetto per diversi valori della grandezza della causa per la quale potremmo non avere dati sperimentali.
La previsione più accurata è quando il diagramma causa-effetto è una linea retta, ad esempio, dove raddoppiare la causa raddoppia l'effetto.
In tal caso diciamo che la relazione causa-effetto è lineare.



Gli effetti biologici/sulla salute derivanti da CEM artificiali/radiazioni non ionizzanti non seguono una relazione lineare dose-risposta (o causa-effetto) secondo le prove sperimentali.
Gli esperimenti hanno dimostrato che, l'assorbimento di una maggiore quantità di energia dalla stessa massa di un dato tessuto ed entro lo stesso intervallo di tempo, non necessariamente induce un effetto biologico più grande. In altre parole, un campo più intenso o un SAR più ampio non si riferiscono necessariamente a una risposta biologica più ampia o a un conseguente effetto sulla salute.

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”evidenze sempre maggiori suggeriscono che gli effetti terapeutici dei TTFields possono essere associati con una gamma varia di meccanismi intracellulari.

Questo è forse sorprendente considerando l'abbondanza di molecole cariche e polarizzabili all'interno delle cellule su cui TTFields potrebbe esercitare forze biofisiche.

Anche se lo spettro degli effetti ottenuti rimane non completamente compreso, i dati emergenti suggeriscono che, oltre agli effetti antimitotici di TTFields, una moltitudine di processi biologici [...] sono alterati da TTFields....

.... e possono provocare effetti antitumorali ”

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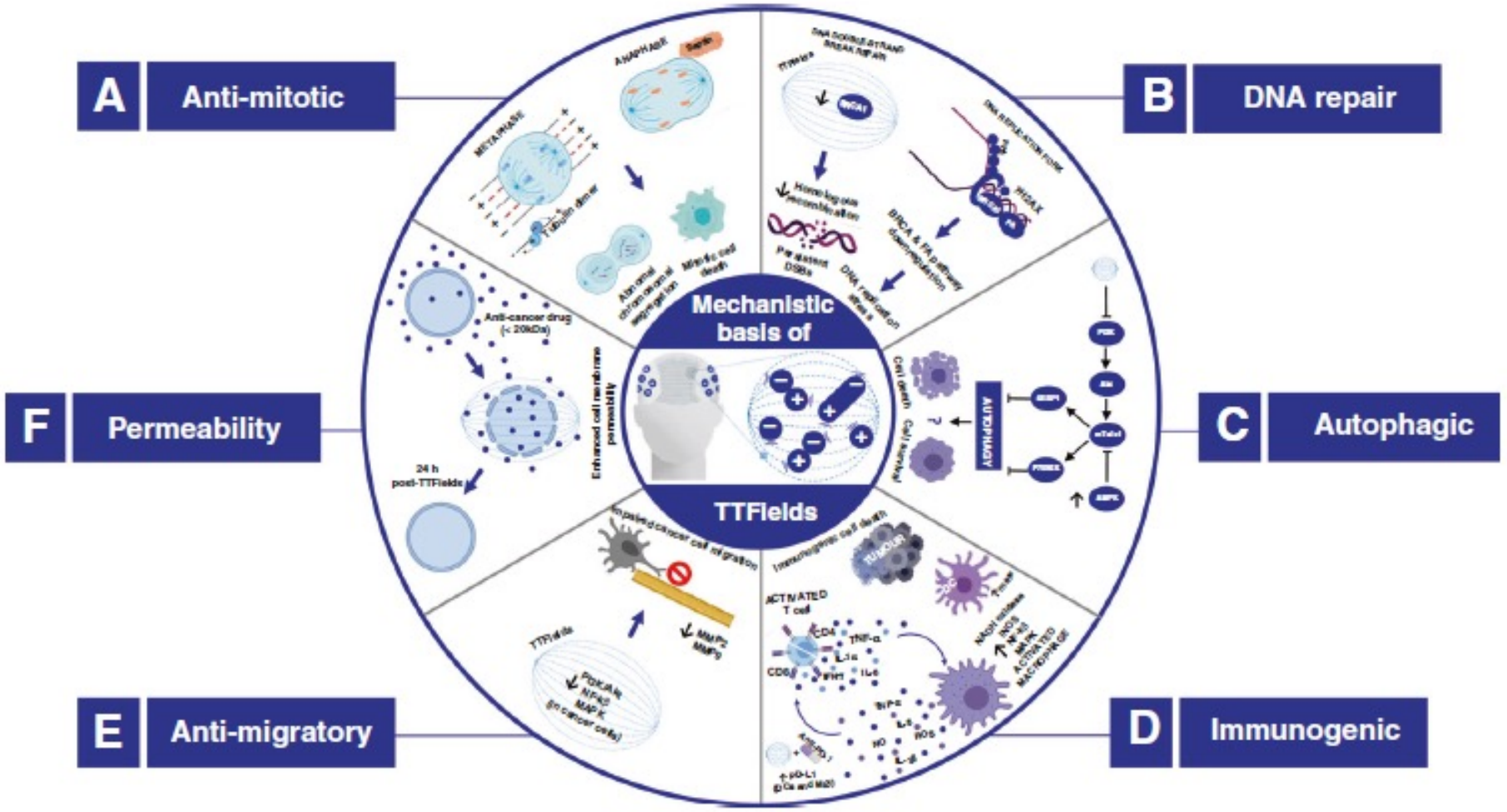
RAZIONALE BIOLOGICO



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PRECLINICAL MODELS

Pre-clinical TTFields generation using the Inovitro system

The Inovitro™ system (NovoCure Ltd, Haifa, Israel) is used to apply TTFields to cultured cells. TTFields are generated using two pairs of electrodes placed perpendicularly on the outer walls of a ceramic Petri dish. Petri dishes containing trays are connected to an electric field generator, which generates low intensity electric fields at the desired frequencies in the medium. The orientation of the TTFields is rotated 90° every second, thus covering the majority of the orientation axes of cell divisions. The plate temperature is maintained at 37° C by placement in a refrigerated 19° C incubator to offset the heat generated by the inovitro system. The temperature is continuously monitored by two thermistors (Omega Engineering, Stamford, CT, USA) attached to the ceramic dish walls. Cells are grown on a cover slip inside the ceramic Petri dish (NovoCure Ltd, Haifa, Israel) and for exposure to TTFields for the times desired.

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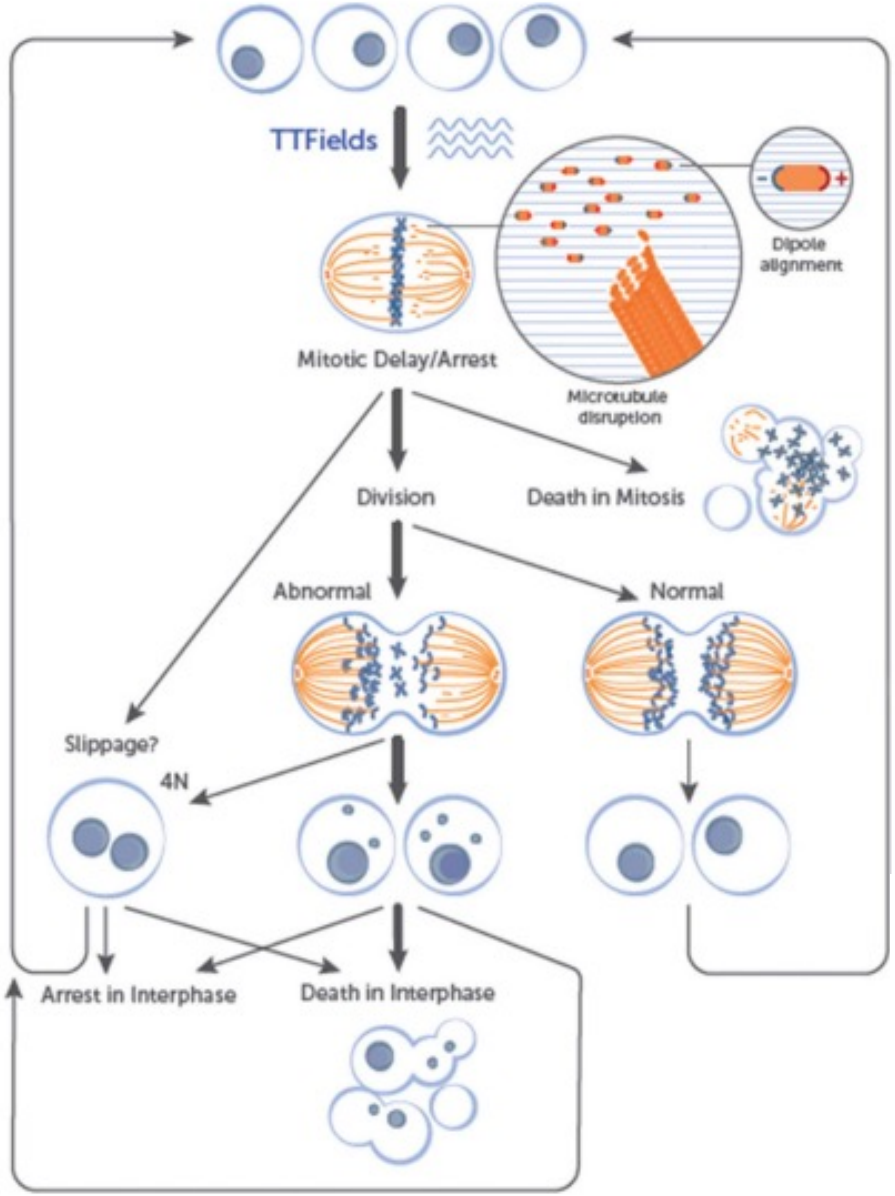


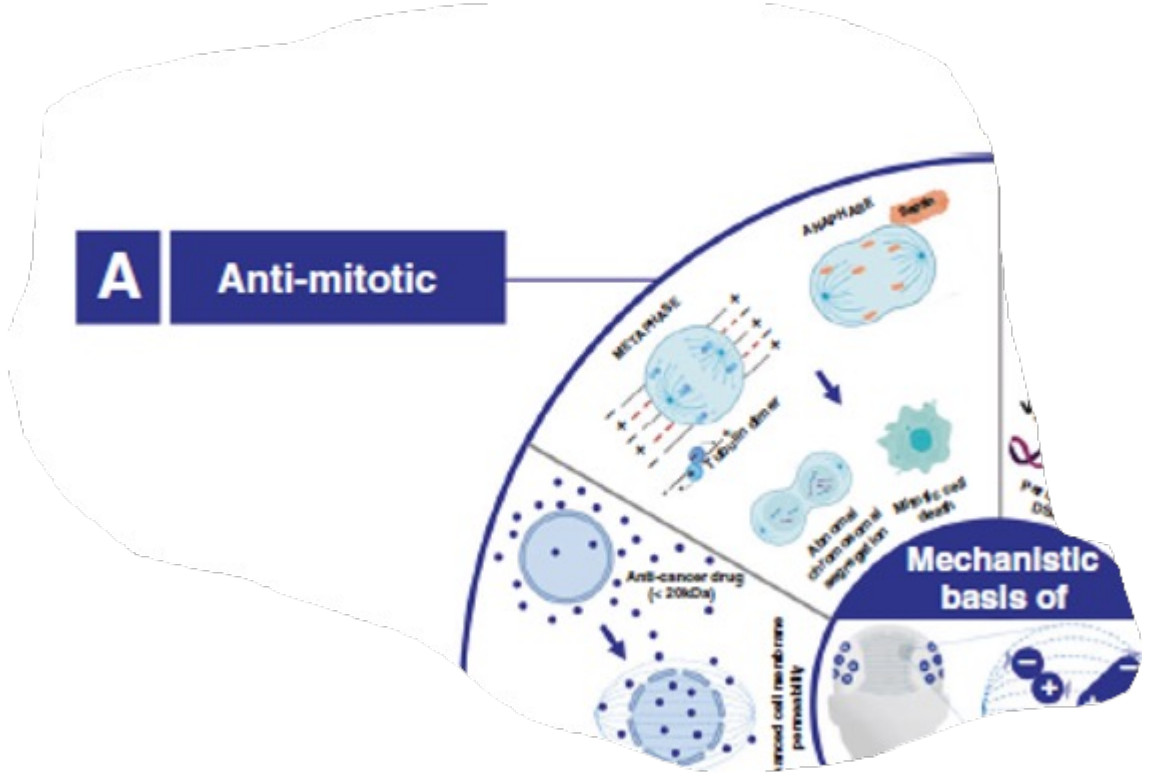


Figure 7. Effects of TTFields on replicating cells. TTFields exert directional forces on polar microtubules and interfere with the assembly of the normal mitotic spindle. Such interference with microtubule dynamics results in abnormal spindle formation and subsequent mitotic arrest or delay, possibly due to improper attachment of chromosomes to the spindle fibers. Cells can die while in mitotic arrest, however, a more common outcome (highlighted by bold arrow) is progression to cell division. This can lead to the formation of either normal or abnormal aneuploid progeny. The formation of the tetraploid cells can occur either due to mitotic exit through slippage or can occur during improper cell division. Abnormal daughter cells can die in the subsequent interphase, can undergo a permanent arrest, or can proliferate through additional mitosis where they will be subjected to further TTFields assault.

Effetto sulla geometria della tubulina …. e sulla mitosi

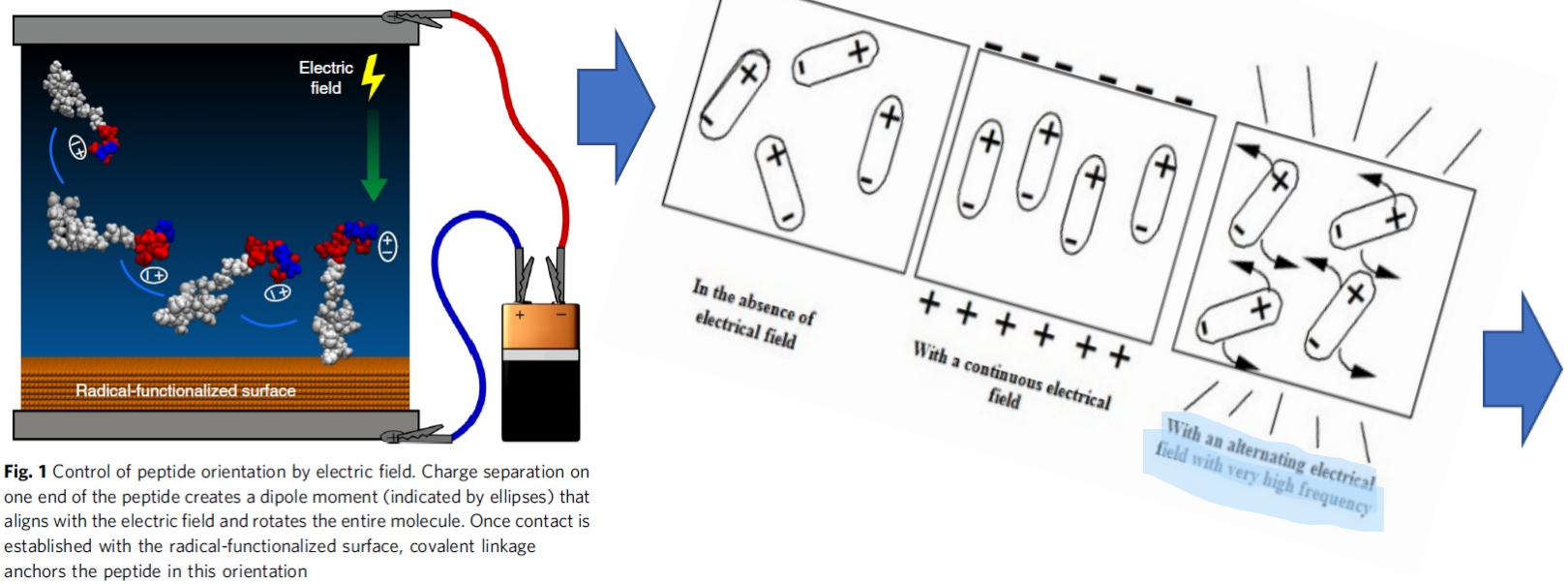


Fig. 1 Control of peptide orientation by electric field. Charge separation on one end of the peptide creates a dipole moment (indicated by ellipses) that aligns with the electric field and rotates the entire molecule. Once contact is established with the radical-functionalized surface, covalent linkage anchors the peptide in this orientation

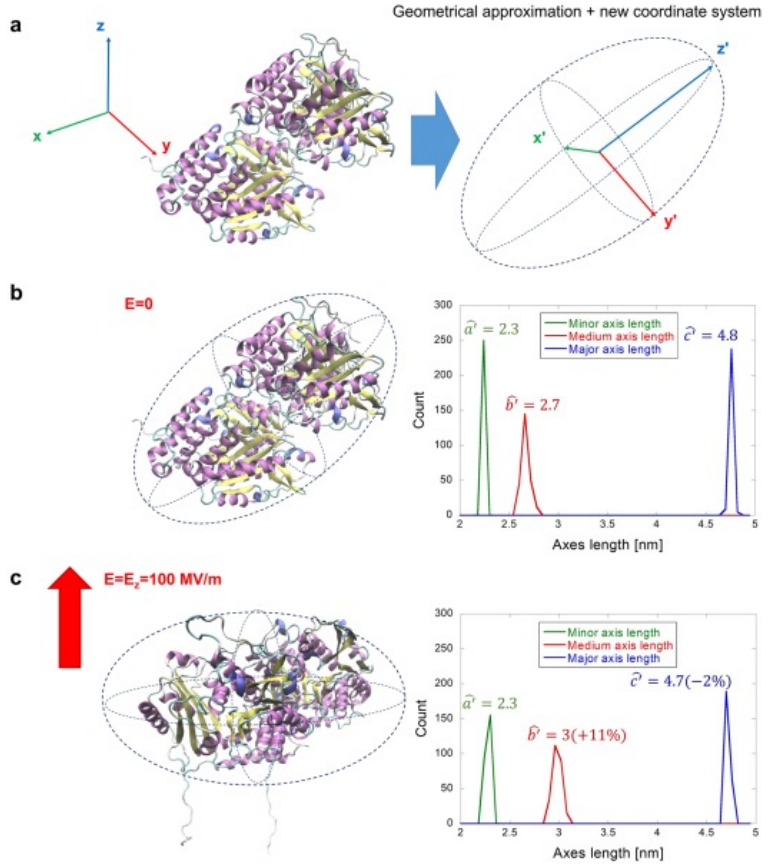


Figure 2. Electric field effects on tubulin geometry represented in the new internal coordinate system. (**a**) New coordinate system and dimensions of the tubulin approximated by an ellipsoid. (**b**) Tubulin shape when no electric field is applied. (**c**) Quantification of the electric field effects on both the orientation of the tubulin dimer and its overall shape. The distributions on the right are from 250 frames from the last 5 ns of the MD simulation (sampling rate 20 ps).

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

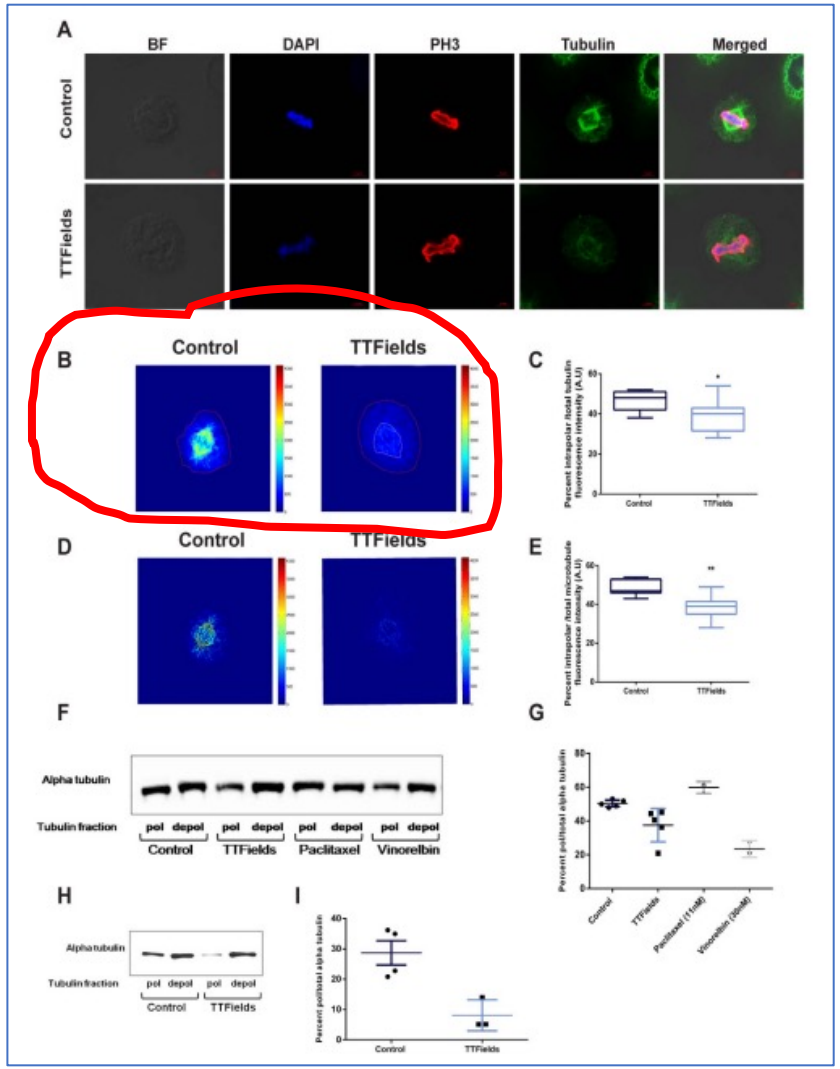
Moshe Giladi*, Rosa S Schneiderman*, Tali Voloshin, Yaara Porat, Mijal Munster, Roni Blat, Shay Sherbo, Zeev Bomzon, Noa Urman, Aviran Itzhaki, Shay Cahal, Anna Shteingauz, Aafia Chaudhry, Eilon D Kirson, Uri Weinberg & Yoram Palti

*A549 (adenoca polmonare) e MDA-MB-231 (adenoca mammario sono state trattate con TTFields (**175V/m RMS) per 24 ore alla loro frequenza di trattamento ottimale (150 kHz)**.*

Le disposizioni del fuso mitotico sono state valutate nelle cellule in replicazione durante la metafase facendo uso di microscopia confocale di fluorescenza.

*I risultati dimostrano che le cellule trattate con TTFields mostrano **una geometria anomala del fuso**, suggerendo che i TTFields **ostacolano la normale organizzazione del fuso**.*

Gli effetti sulla vitalità cellulare dipendono sostanzialmente dalla durata dell'esposizione; il rallentamento della divisione delle cellule può essere modificato solo estendendo la durata dell'esposizione



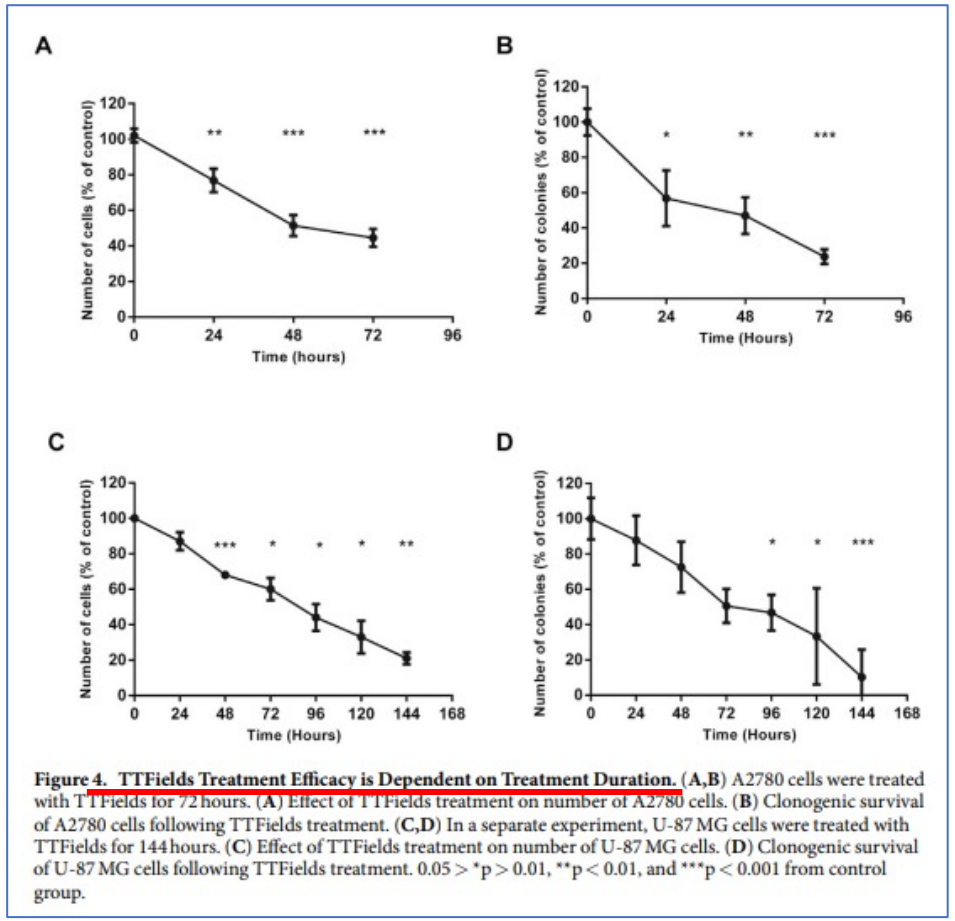


Figure 4. TTFields Treatment Efficacy is Dependent on Treatment Duration. (**A**,**B**) A2780 cells were treated with TTFields for 72 hours. (**A**) Effect of TTFields treatment on number of A2780 cells. (**B**) Clonogenic survival of A2780 cells following TTFields treatment. (**C**,**D**) In a separate experiment, U-87 MG cells were treated with TTFields for 144 hours. (**C**) Effect of TTFields treatment on number of U-87 MG cells. (**D**) Clonogenic survival of U-87 MG cells following TTFields treatment. $0.05 > {}^{*}p > 0.01$, $^{**}p < 0.01$, and $^{***}p < 0.001$ from control group.

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REVIEW

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An overview of potential novel mechanisms of action underlying Tumor Treating Fields-induced cancer cell death and their clinical implications

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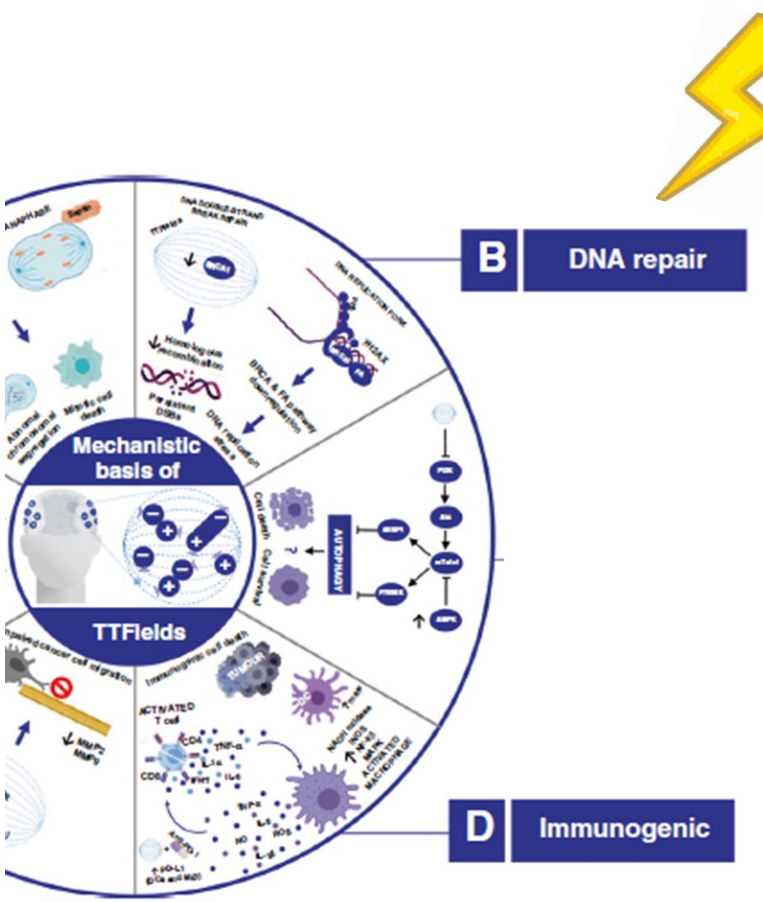
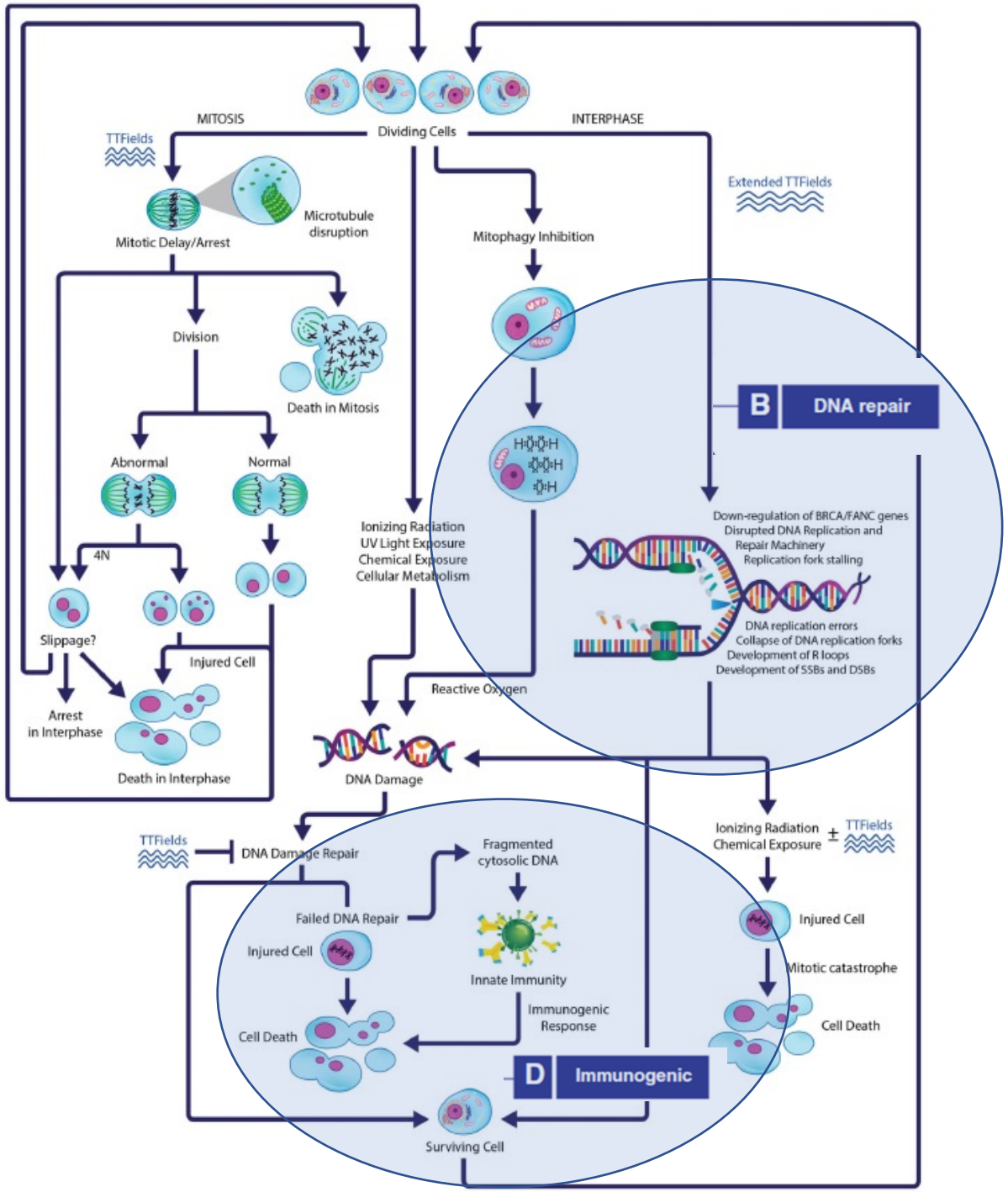
[a]Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX, USA; [b]Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA





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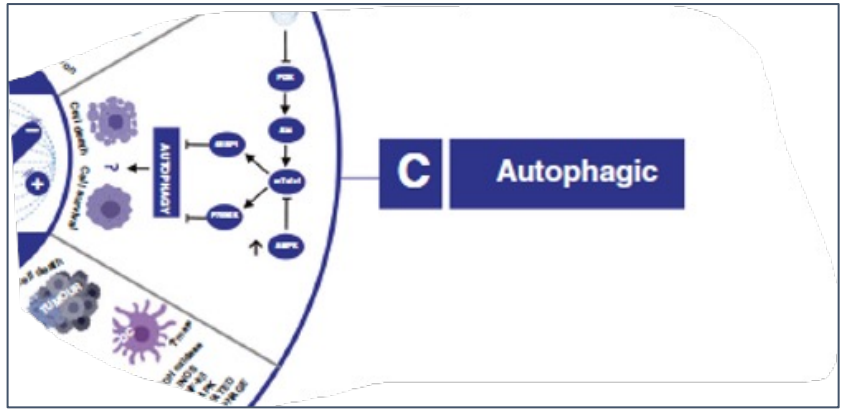
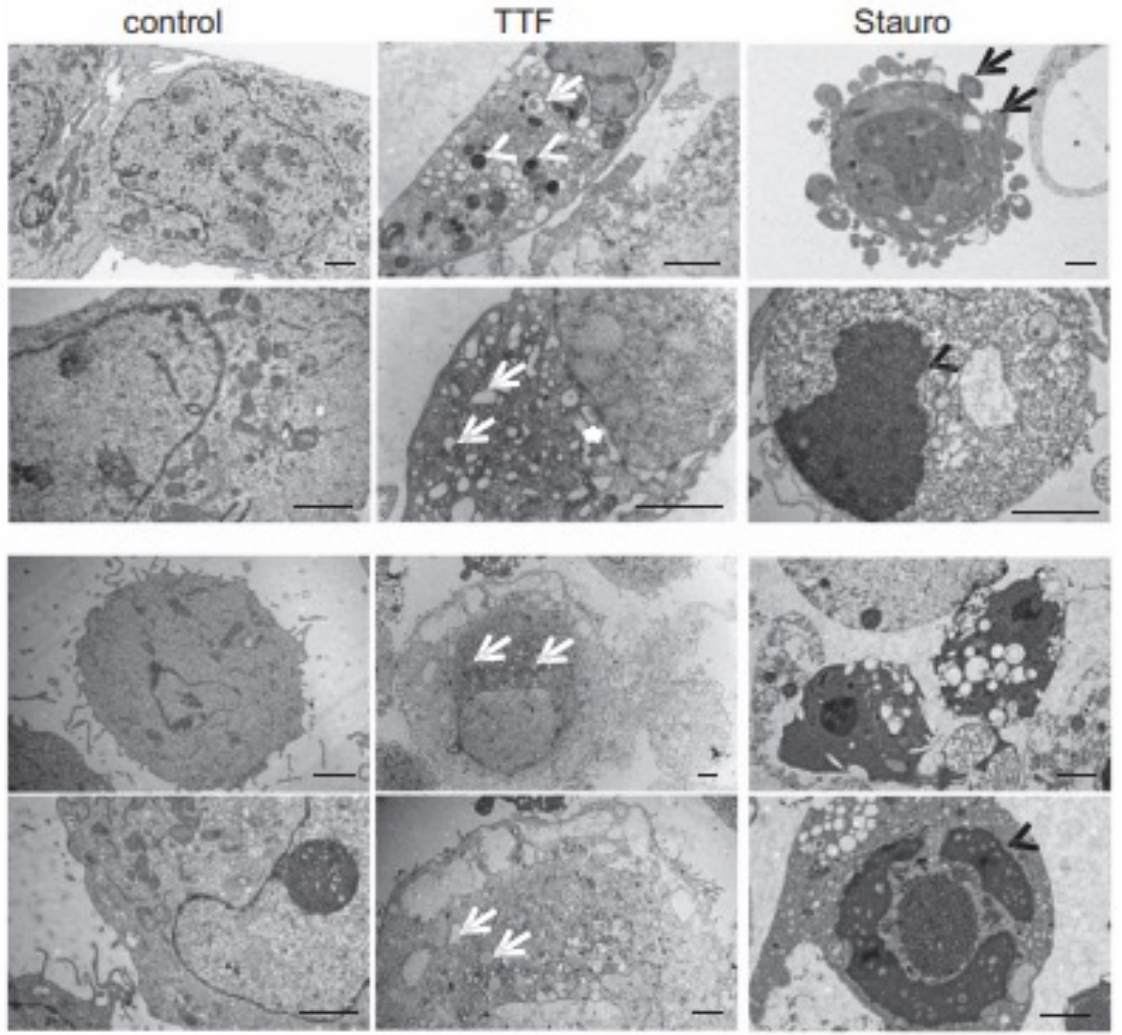
Biological activity of tumor-treating fields in preclinical glioma models

Manuela Silginer[1], Michael Weller[1], Roger Stupp[2] and Patrick Roth*[,1]

"Abbiamo quindi esaminato la morfologia della morte cellulare indotta da TTField utilizzando la microscopia elettronica a trasmissione. Le cellule LN-18 o ZH-161 esposte a TTField hanno mostrato segni tipici di autofagia come un marcato aumento della frequenza degli autofagosomi, mitocondri con matrici gonfie o un reticolo endoplasmatico dilatato.
Al contrario, la staurosporina, come induttore classico di apoptosi, ha portato al «blebbing» della membrana o alla condensazione del DNA lungo il nucleo e il citoplasma scuro (Figura 2c)"





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Research Paper

Tumor treating fields inhibit glioblastoma cell migration, invasion and angiogenesis

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Keywords: *tumor treating fields, glioblastoma multiforme, NF-kB, metastasis, angiogenesis*

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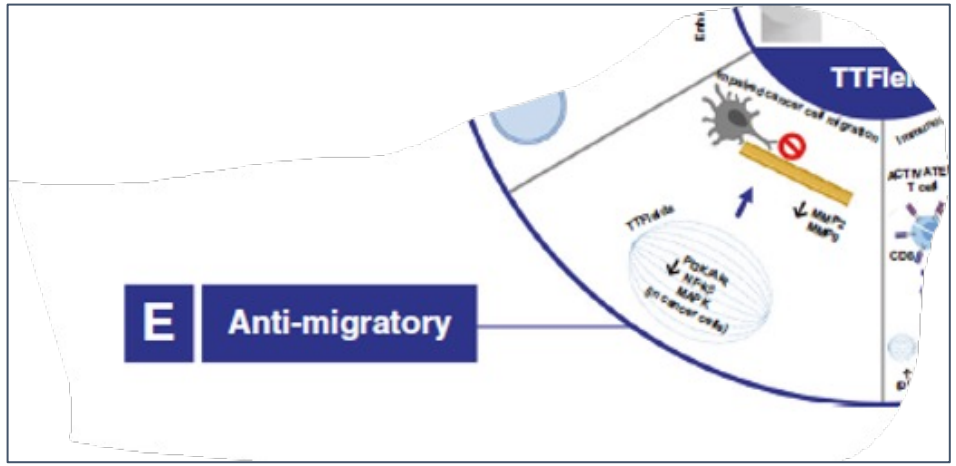


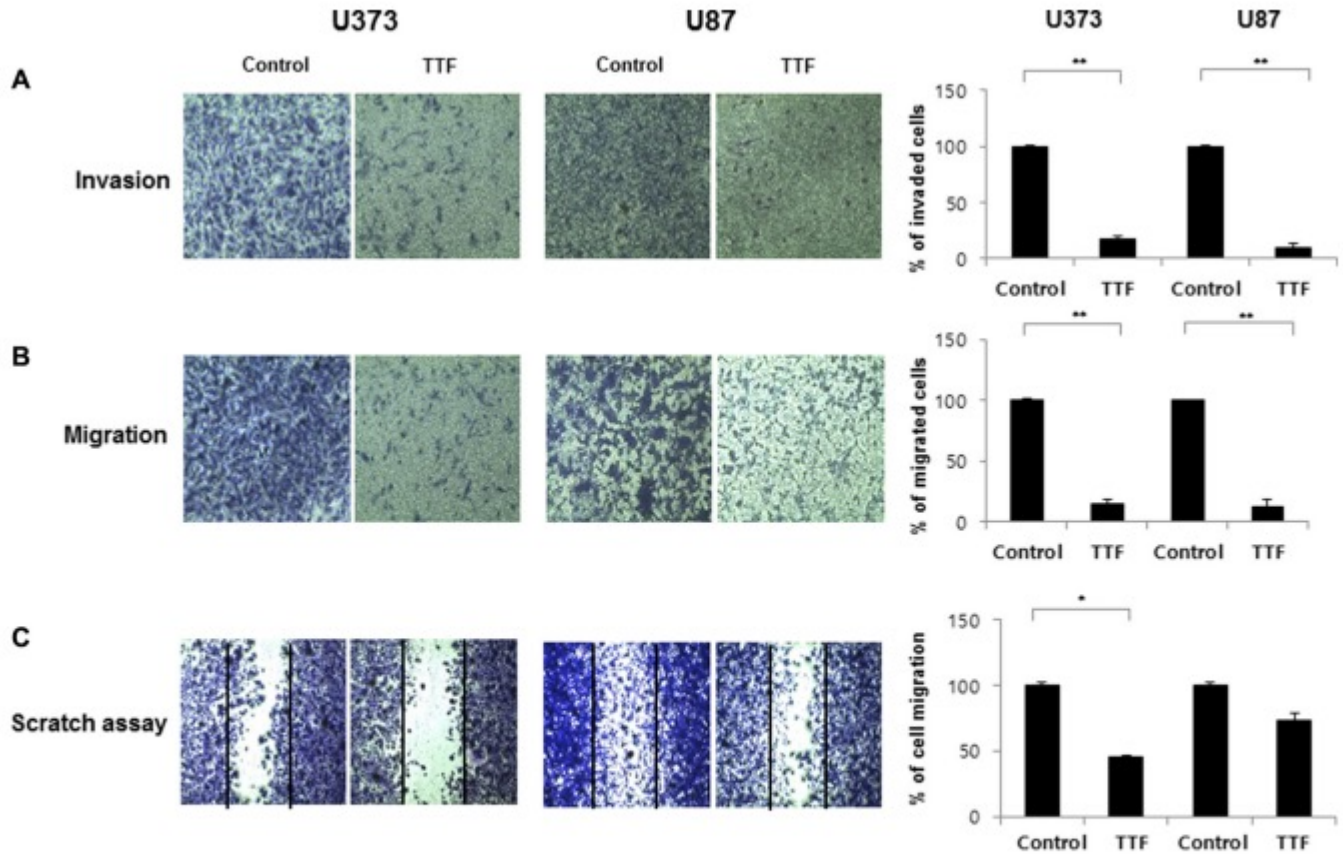


Figure 2: TTF inhibits migration and invasion of GBM cells. (**A**, **B**) Tumor cell invasion and migration after 24 hr TTF treatment were examined by transwell chamber assays. The number of invading tumor cells that penetrated through the Matrigel and gelatin was counted using 5 high-intensity fields. Values represent the means of 3 experiments ± SD; $*p < 0.05$, $**p < 0.001$. (**C**) GBM cells were treated with TTF for 24 hr TTF treatment and then incubated for 24 h. Then, the cells were scraped with yellow pipette tips for the scratch assay. Values represent the means of 3 experiments ± SD; $*p < 0.05$, $**p < 0.001$.

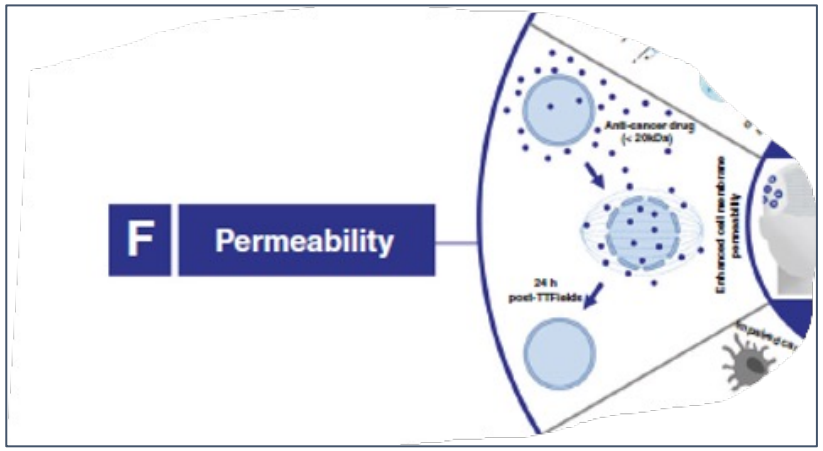
Chang et al. *Cell Death Discovery* (2018)4:113
https://doi.org/10.1038/s41420-018-0130-x

Cell Death Discovery

ARTICLE Open Access

Tumor treating fields increases membrane permeability in glioblastoma cells

Edwin Chang[1], Chirag B. Patel[1,2], Christoph Pohling[1], Caroline Young[1], Jonathan Song[1], Thomas Anthony Flores[3], Yitian Zeng[4], Lydia-Marie Joubert[5], Hamed Arami[1], Arutselvan Natarajan[1], Robert Sinclair[4] and Sanjiv S. Gambhir[1,4,6]



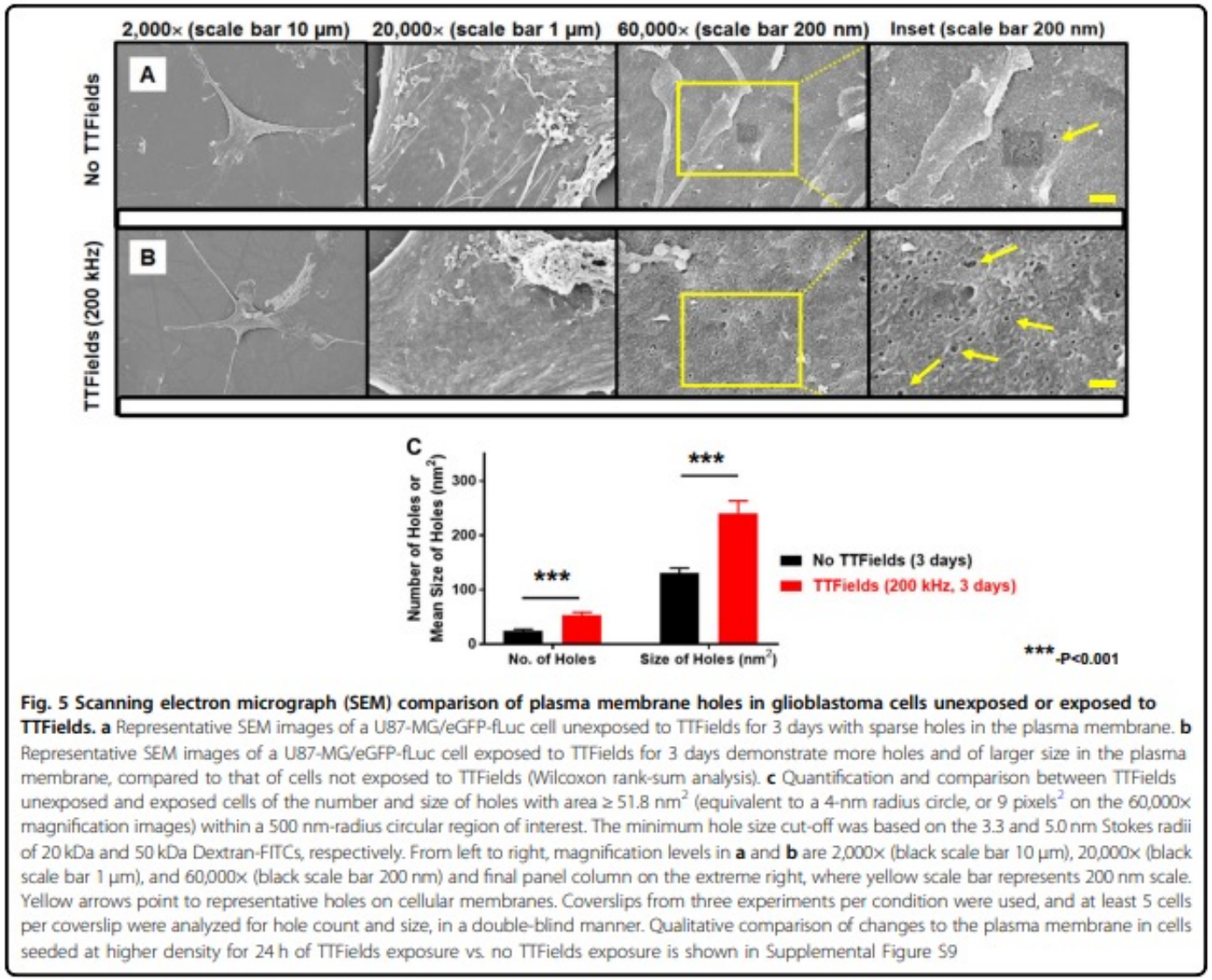
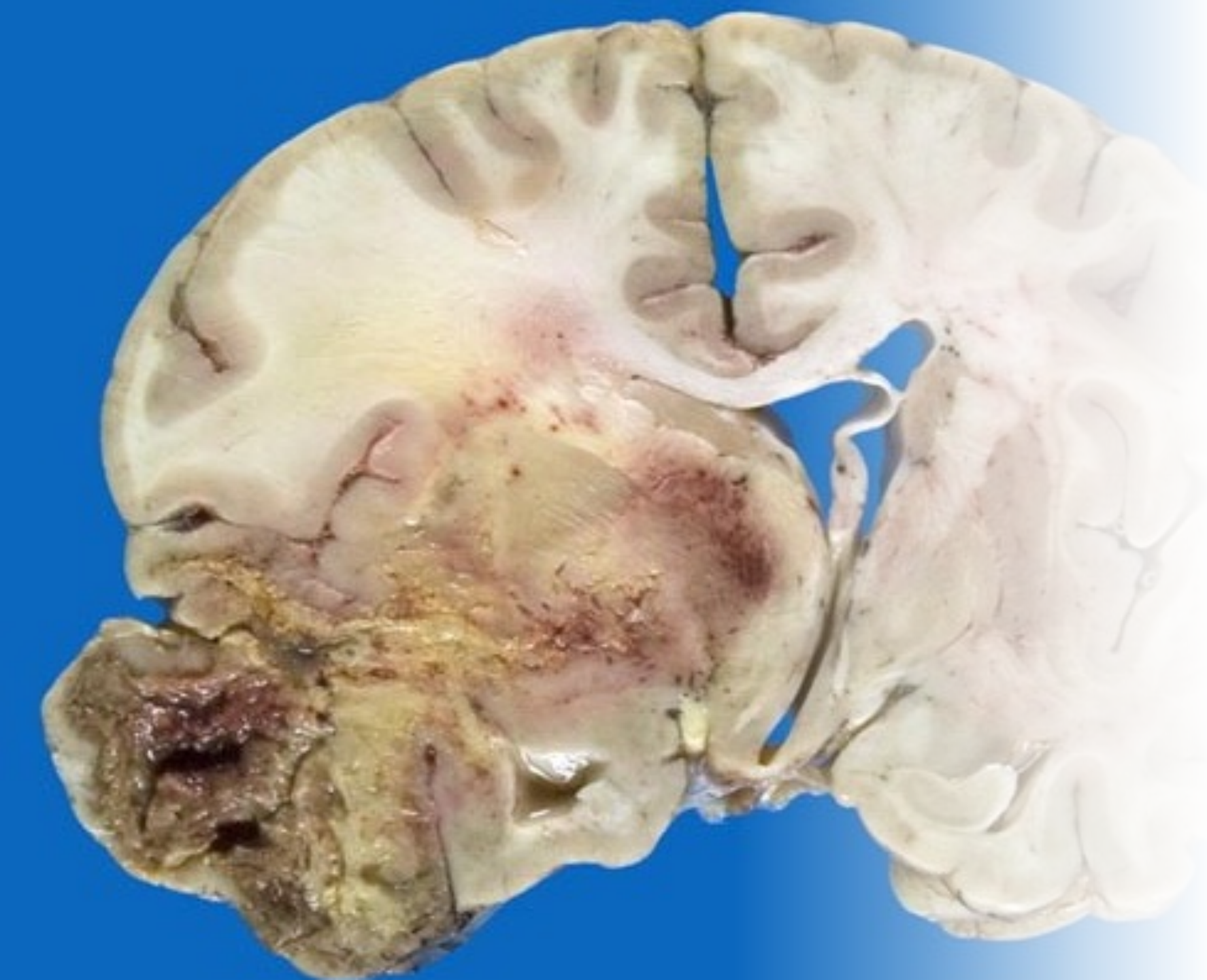


Fig. 5 Scanning electron micrograph (SEM) comparison of plasma membrane holes in glioblastoma cells unexposed or exposed to TTFields. a Representative SEM images of a U87-MG/eGFP-fLuc cell unexposed to TTFields for 3 days with sparse holes in the plasma membrane. **b** Representative SEM images of a U87-MG/eGFP-fLuc cell exposed to TTFields for 3 days demonstrate more holes and of larger size in the plasma membrane, compared to that of cells not exposed to TTFields (Wilcoxon rank-sum analysis). **c** Quantification and comparison between TTFields unexposed and exposed cells of the number and size of holes with area ≥ 51.8 nm^2 (equivalent to a 4-nm radius circle, or 9 $pixels^2$ on the 60,000× magnification images) within a 500 nm-radius circular region of interest. The minimum hole size cut-off was based on the 3.3 and 5.0 nm Stokes radii of 20 kDa and 50 kDa Dextran-FITCs, respectively. From left to right, magnification levels in **a** and **b** are 2,000× (black scale bar 10 μm), 20,000× (black scale bar 1 μm), and 60,000× (black scale bar 200 nm) and final panel column on the extreme right, where yellow scale bar represents 200 nm scale. Yellow arrows point to representative holes on cellular membranes. Coverslips from three experiments per condition were used, and at least 5 cells per coverslip were analyzed for hole count and size, in a double-blind manner. Qualitative comparison of changes to the plasma membrane in cells seeded at higher density for 24 h of TTFields exposure vs. no TTFields exposure is shown in Supplemental Figure S9



Questi dati sperimentali, *preclinici* sono stati giudicati sufficienti, anche se non conclusivi, per iniziare una attività di ricerca clinica, data la peculiarità della neoplasia studiata per prima (gliomi ad alto grado): relativa rarità, prognosi molto severa.

Quali le sperimentazioni concluse ad oggi ed i loro risultati?

Dati Clinici in glioblastoma recidivati e di nuova diagnosi

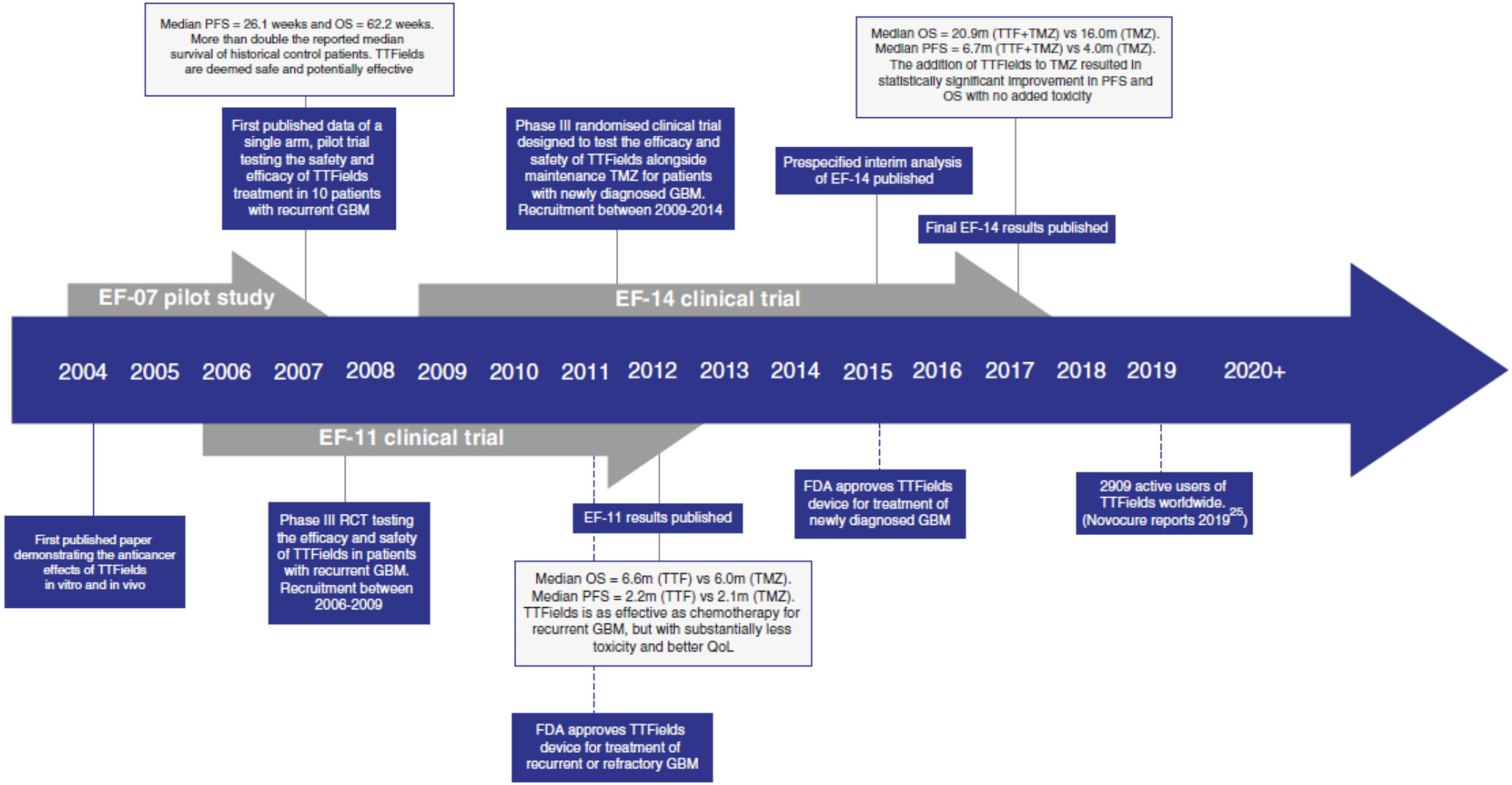


Fig. 1 Historical timeline of the emergence of TTFields as novel therapy for GBM patients. In 2004, the first paper demonstrating the anticancer effects of TTFields in vitro and in vivo was published.[9] Following these promising preclinical data, a number of clinical trials investigating the safety and efficacy of TTFields for the treatment of GBM were completed (details described at each relevant date), leading to the approval in 2011 and 2015 of TTFields for the treatment of recurrent and newly diagnosed GBM, respectively.

EF 11 – Relapsed Glio

European Journal of Cancer (2012) 48, 2192–2202

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journal homepage: www.ejconline.com

NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

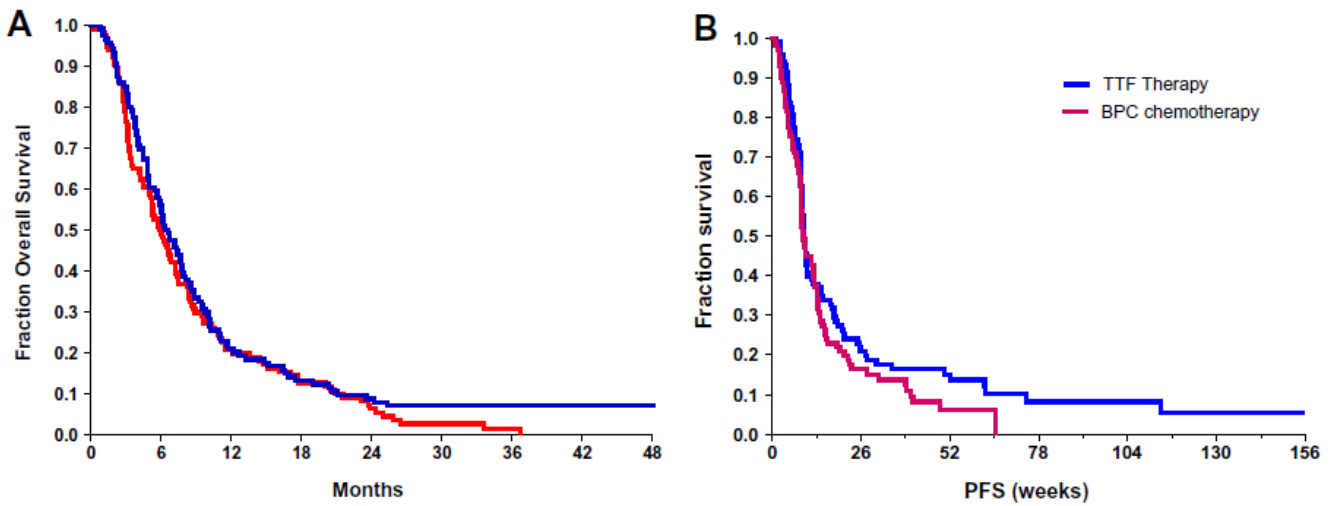
Roger Stupp [a,*], Eric T. Wong [b], Andrew A. Kanner [c], David Steinberg [d], Herbert Engelhard [e], Volkmar Heidecke [f], Eilon D. Kirson [g], Sophie Taillibert [h], Frank Liebermann [i], Vladimir Dbalý [j], Zvi Ram [c], J. Lee Villano [e], Nikolai Rainov [f], Uri Weinberg [g], David Schiff [k], Lara Kunschner [l], Jeffrey Raizer [m], Jerome Honnorat [n], Andrew Sloan [o], Mark Malkin [p], Joseph C. Landolfi [q], Franz Payer [r], Maximilian Mehdorn [s], Robert J. Weil [t], Susan C. Pannullo [u], Manfred Westphal [v], Martin Smrcka [w], Lawrence Chin [x], Herwig Kostron [y], Silvia Hofer [z], Jeffrey Bruce [aa], Rees Cosgrove [ab], Nina Paleologous [ac], Yoram Palti [g], Philip H. Gutin [ad]

Obiettivi dello studio e disegno statistico

2.4. Statistical analysis

The primary end-point was OS. Secondary end-points were progression free survival (PFS), the percentage of patients alive and progression-free at 6 months (PFS6), 1-year survival rate, radiological response rate (RR), QoL and safety. OS and PFS were computed from the day of randomisation until event or censored at last follow-up according to the Kaplan–Meier method, with 2-sided logrank statistics for comparison. The study had an 80 per cent power at a significance level of 0.05 to detect a 60 per cent increase in median OS (hazard ratio for death, 0.63). All analyses were per-

«Although **the trial did not reach its primary end-point of improved survival compared to active chemotherapy**, this new minimally invasive and chemotherapy-free local treatment modality demonstrated **a statistically non-significant increased response rate** (14 versus 9.6%, **p = 0.19**), an improved **PFS6 rate** (21% versus 15%, **p = 0.13**), and a trend towards reduction of the risk of death (hazard ratio 0.86, 95% CI 0.66–1.12, p = 0.27), as well as sustained improvement in QoL.»



At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m	42 m	48 m
TTF	120	63	24	15	9	7	4	2	1
BPC	117	56	22	14	6	2	1	0	0

0 m	13 w	26w	39w	52w	65 w	78 w	91 w
120	38	19	14	11	6	4	3
117	34	14	10	3	1	0	0

Fig. 2. Overall survival (A) and progression free survival (B) Kaplan–Meier curves.

Post Hoc Analyses of Intention-to-Treat Population in Phase III Comparison of NovoTTF-100A™ System Versus Best Physician's Choice Chemotherapy

Andrew A. Kanner,[a] Eric T. Wong,[b] John L. Villano,[c] Zvi Ram[a], on behalf of EF-11 Investigators

Semin Oncol 41:S25-S34 © 2014 Elsevier Inc.

NovoTTF-100A System in an analysis of the phase III data that focused on the "as-treated" or modified intention-to-treat (mITT) population rather than on the ITT population examined in the original report.

EF 11 Relapsed

Only patients receiving
At least 1 cycle of CHT
Or 1 cycle of TTF

Advantage is greater for patients with previous low grade disease, TTF compliance, IK>80, previously on bevacizumab

Post Hoc Analyses of Intention-to-Treat Population in Phase III Comparison of NovoTTF-100A™ System Versus B

Andrew A. Kanne

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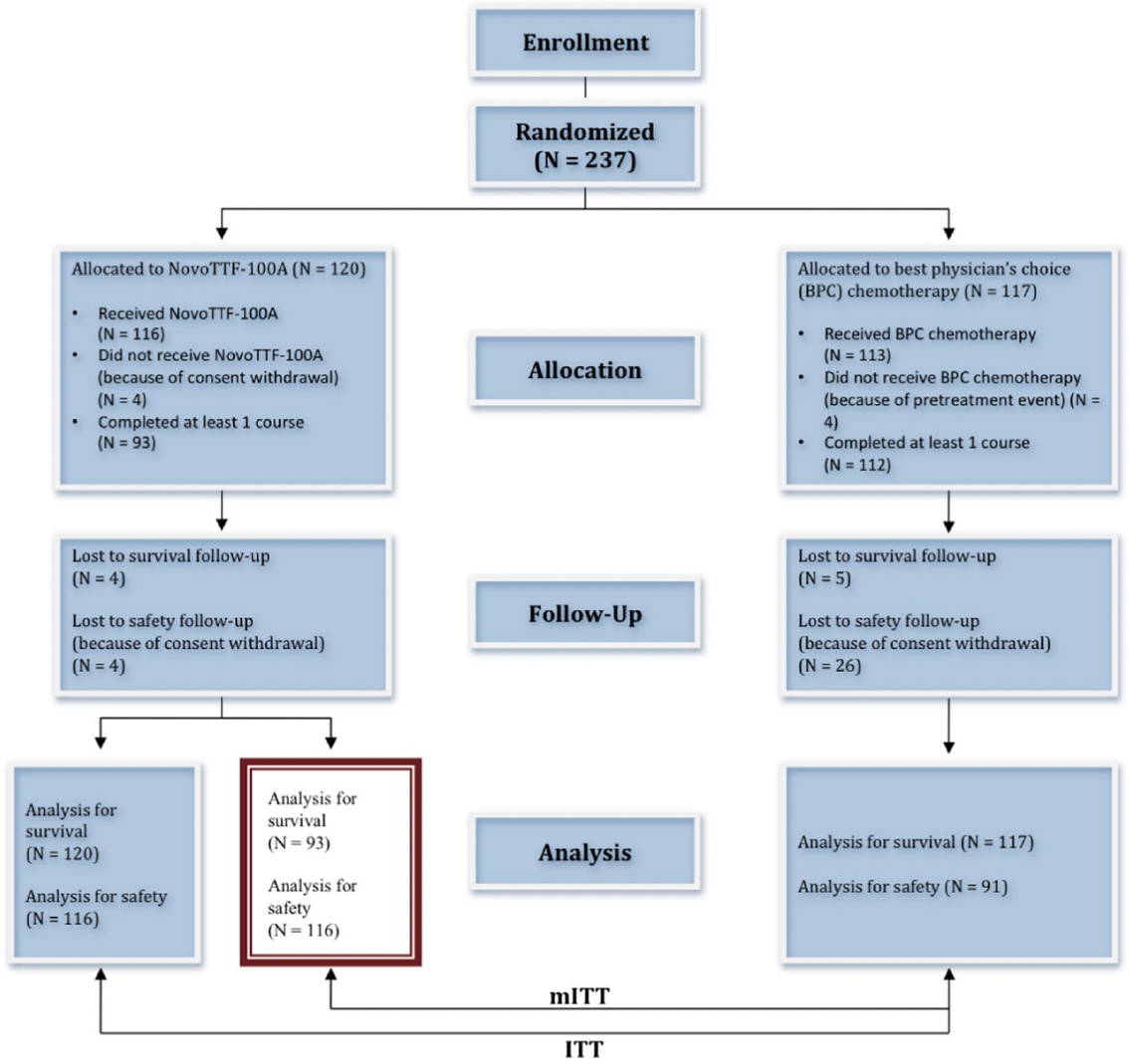

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram and modified intention-to-treat (mITT) and ITT populations.

EF 11 Relapsed

Only patients receiving
At least 1 cycle of CHT
Or 1 cycle of TTF

Advantage is greater for patients with previous low grade disease, TTF compliance, IK>80, previously on bevacizumab

Post Hoc Analyses of Intention-to-Treat Population in Phase III Comparison of NovoTTF-100A™ System Versus Best Physician's Choice Chemotherapy

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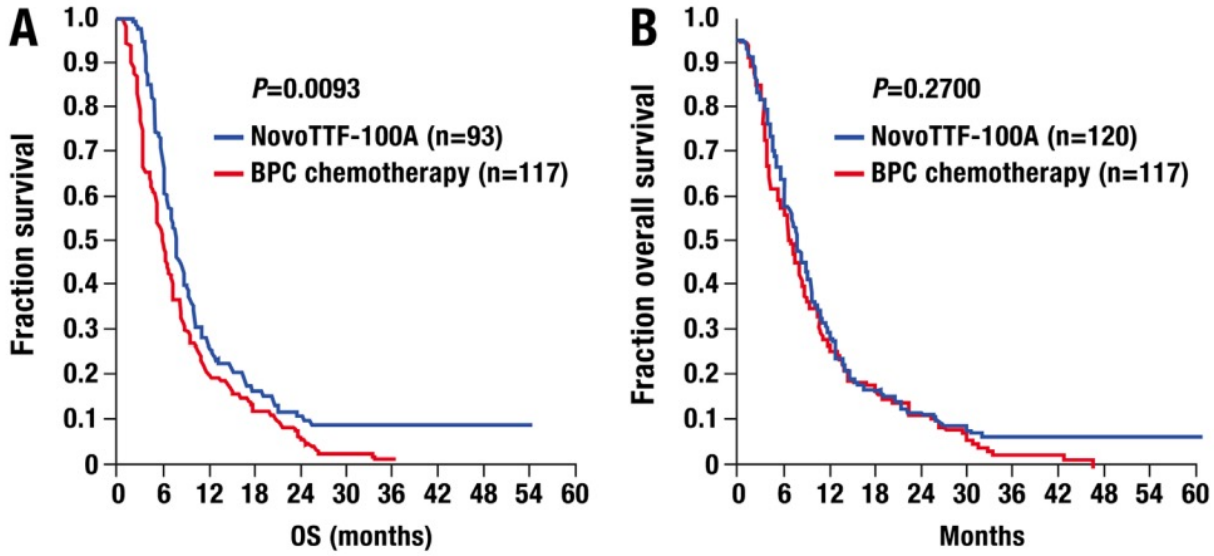


Figure 2. Kaplan-Meier overall survival for modified intention-to-treat (mITT) (A) and intention-to-treat (ITT) (B) populations with recurrent glioblastoma multiforme treated with NovoTTF Therapy or BPC (best physician's choice) chemotherapy in the phase III trial.

EF 11 Relapsed

Only patients receiving
At least 1 cycle of CHT
Or 1 cycle of TTF

Advantage is greater for patients with previous low grade disease, TTF compliance, IK>80, previously on bevacizumab

EF-14
Glioblastoma

Primo report 2015

Pubblicazione definitiva 2017

Research

JAMA | Original Investigation

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

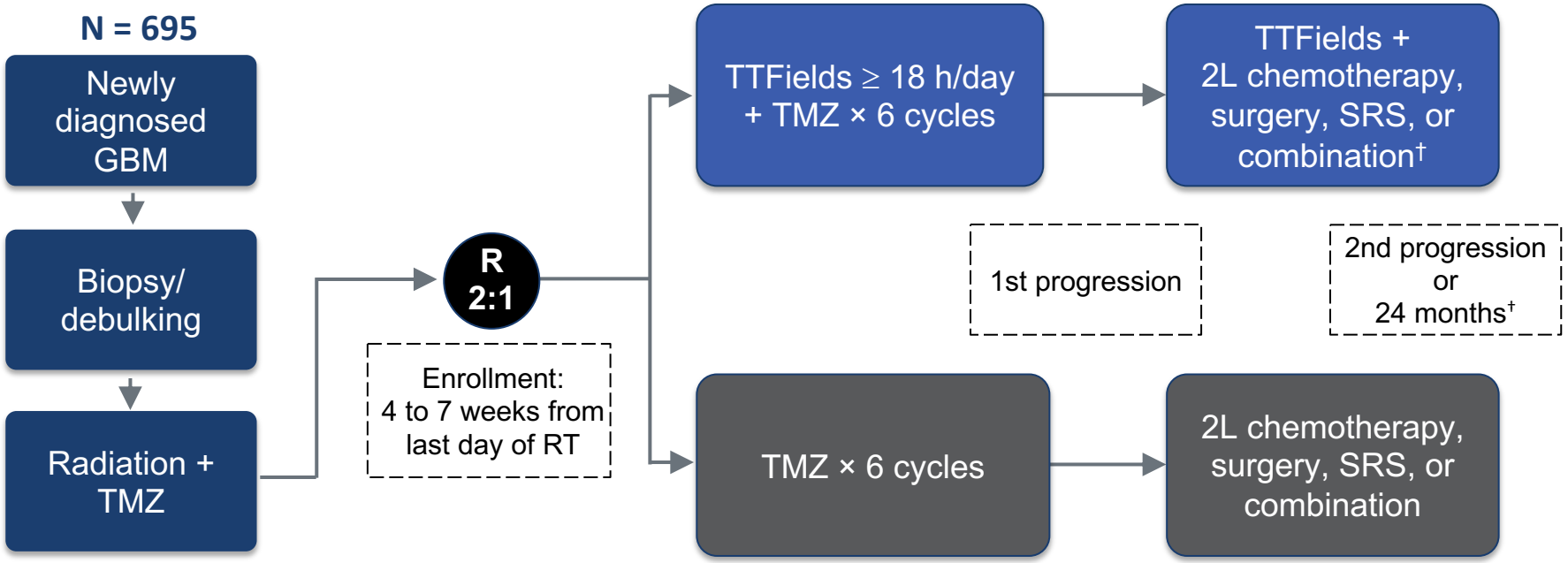
A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew Kanner, MD; William Read, MD; David M. Steinberg, PhD; Benoit Lhermitte, MD; Steven Toms, MD; Ahmed Idbaih, MD; Manmeet S. Ahluwalia, MD; Karen Fink, MD, PhD; Francesco Di Meco, MD; Frank Lieberman, MD; Jay-Jiguang Zhu, MD, PhD; Giuseppe Stragliotto, MD, PhD; David D. Tran, MD, PhD; Steven Brem, MD; Andreas F. Hottinger, MD, PhD; Eilon D. Kirson, MD, PhD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Chae-Yong Kim, MD, PhD; Sun-Ha Paek, MD, PhD; Garth Nicholas, MD; Jordi Bruna, MD; Hal Hirte, MD; Michael Weller, MD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718

EF-14: fase III - Pivotal Trial Design[1-4]

TTFields + maintenance TMZ vs maintenance TMZ in newly diagnosed GBM



Start date: June 2009
Primary completion: Dec 2016
Study completion: March 2017
Study sites: 83 (North America, Europe, Republic of Korea, Israel)

Stratification:
- Resection extent
- *MGMT* promoter methylation status*

Primary endpoint:
- PFS (ITT population)

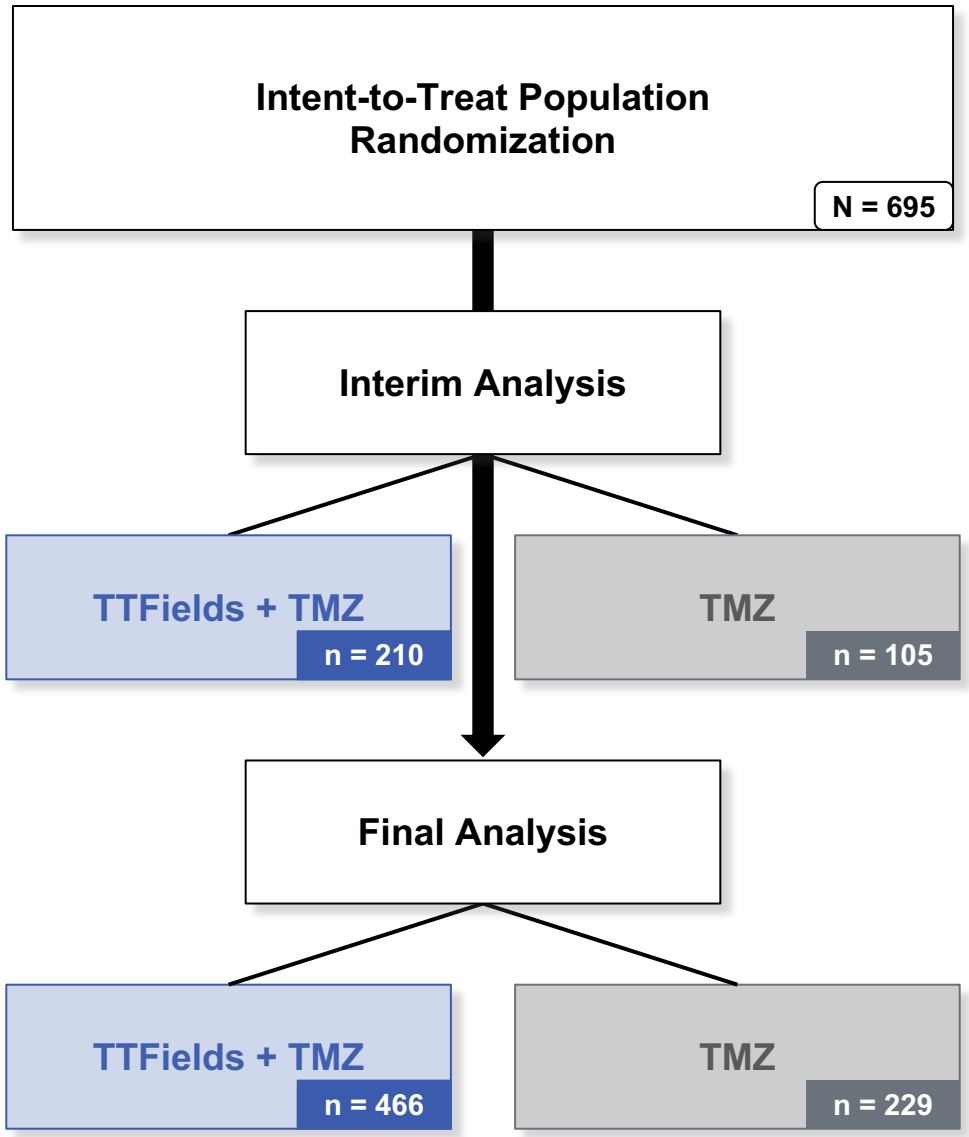
Secondary endpoint:
- OS* (ITT population)

Additional secondary endpoints:
- PFS6, 1-y/2-y survival, ORR, safety, QoL

*Overall survival was a powered secondary endpoint for efficacy.
†Treatment with TTFields was continued for 24 months or until second progression, whichever occurred first unless prohibited by the patient's clinical condition.[1,2]
2L, second-line; GBM, glioblastoma multiforme; ITT, intent-to-treat; KPS, Karnofsky performance score; MGMT, O6-methylguanine-DNA methyltransferase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS6, progression-free survival at 6 months; QoL, quality of life; R, randomized; RT, radiation therapy; SRS, stereotactic radiosurgery; TMZ, temozolomide; TTFields, Tumor Treating Fields.

1. Optune. Instructions for Use. Novocure; January 2019. **2.** Stupp R et al. *JAMA*. 2017;318(23):2306-2316. **3**. Stupp R et al. *JAMA*. 318(23):2306-2316 [supplement 1]. **4.** ClinicalTrials.gov. [NCT00916409]. Accessed June 10, 2020.

EF-14: arruolamento e trattamento[1-3]



TMZ, temozolomide; TTFields, Tumor Treating Fields.

1. Optune. Instructions for Use. Novocure; January 2019. **2.** Stupp R et al. *JAMA*. 2015;314(23):2535-2543. **3.** Stupp R et al. *JAMA*. 2017;318(23):2306-2316.

EF-14: Baseline and Treatment Characteristics (Final Analysis)

ITT Population

Characteristics	TTFields + TMZ (n = 466)	TMZ Alone (n = 229)
Median age, years (range)	56 (19–83)	57 (19–80)
Female sex, %	32	31
Median KPS (range)	90 (60–100)	90 (70–100)
Extent of resection, %		
Gross total resection	53	54
Partial resection	34	33
Biopsy	13	13
Median time from diagnosis to randomization, months (range)	3.8 (1.7–6.2)	3.7 (1.4–6.3)
Median TMZ cycles, months (range)	6 (0–51)	5 (0–33)
Median TTFields therapy duration, months (range)	8.2 (0–82)	0 (0–0)

Baseline characteristics were well balanced between the two treatment arms

ITT, intent-to-treat; KPS, Karnofsky Performance Score; SD, standard deviation; TMZ, temozolomide; TTFields, Tumor Treating Fields.
Stupp R et al. *JAMA*. 2017;318(23):2306-2316.

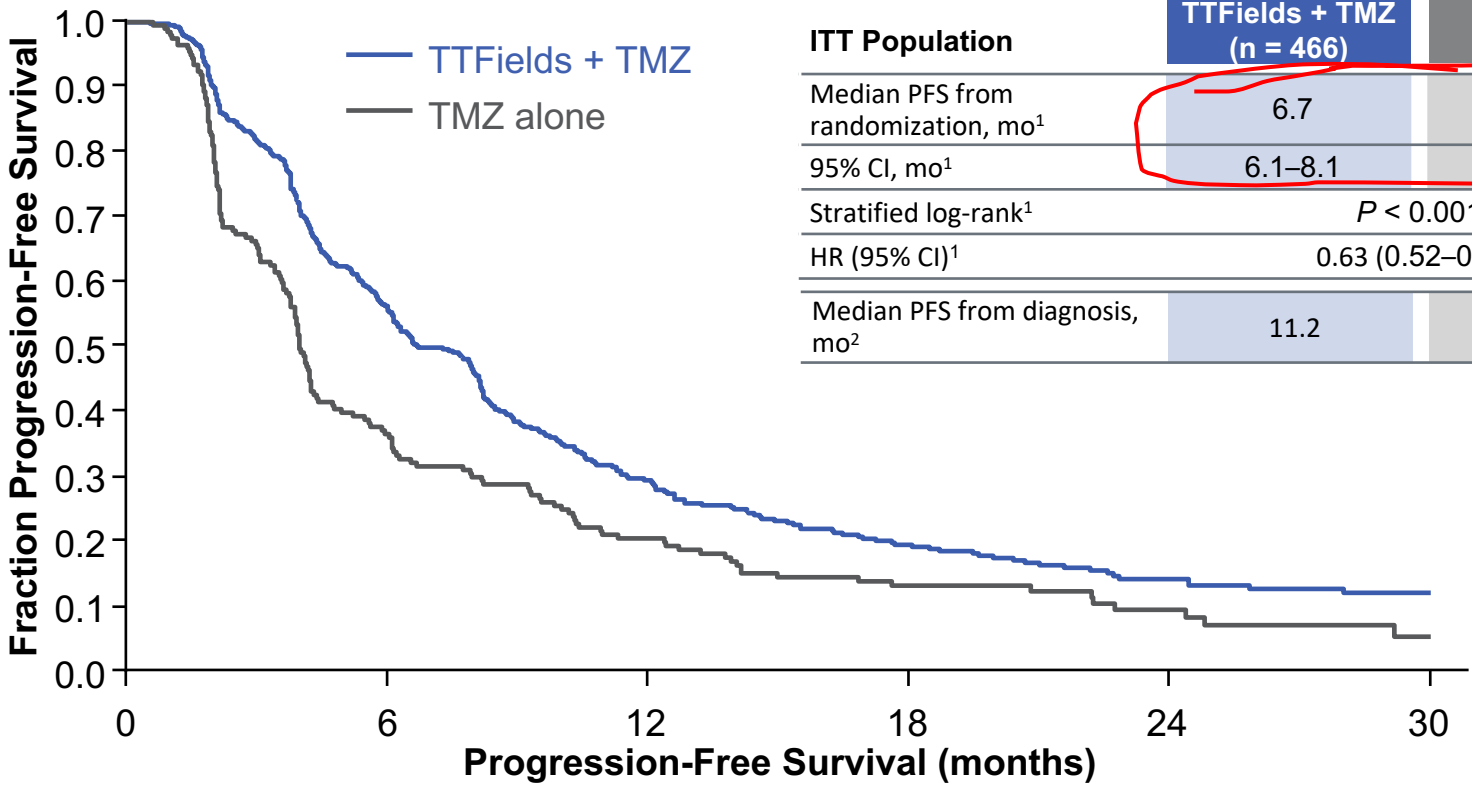
EF-14: Baseline and Treatment Characteristics (Final Analysis)

ITT Population **Molecular Profiles, %**	**TTFields + TMZ (n = 466)**	**TMZ Alone (n = 229)**
MGMT status		
Tissue available and tested	83	81
Methylated	36	42
Unmethylated	54	51
Insufficient for testing	10	7
IDH1 R132H mutation status		
Tissue available and tested	56	52
Positive	7	5
Medications, %		
Antiepileptics	44	41
Corticosteroids	29	28
Adherence to TTFields*, %	75	-

Baseline characteristics were well balanced between the two treatment arms

*Defined as use of TTFields ≥ 75% of the time, or ≥18 hours per day, in the first 3 months of treatment.
IDH1, isocitrate dehydrogenase 1; ITT, intent-to-treat; MGMT, O6-methylguanine-DNA methyltransferase; TMZ, temozolomide; TTFields, Tumor Treating Fields.
Stupp R et al. *JAMA*. 2017;318(23):2306-2316.

EF-14: Progression-Free Survival (Final Analysis)[1]



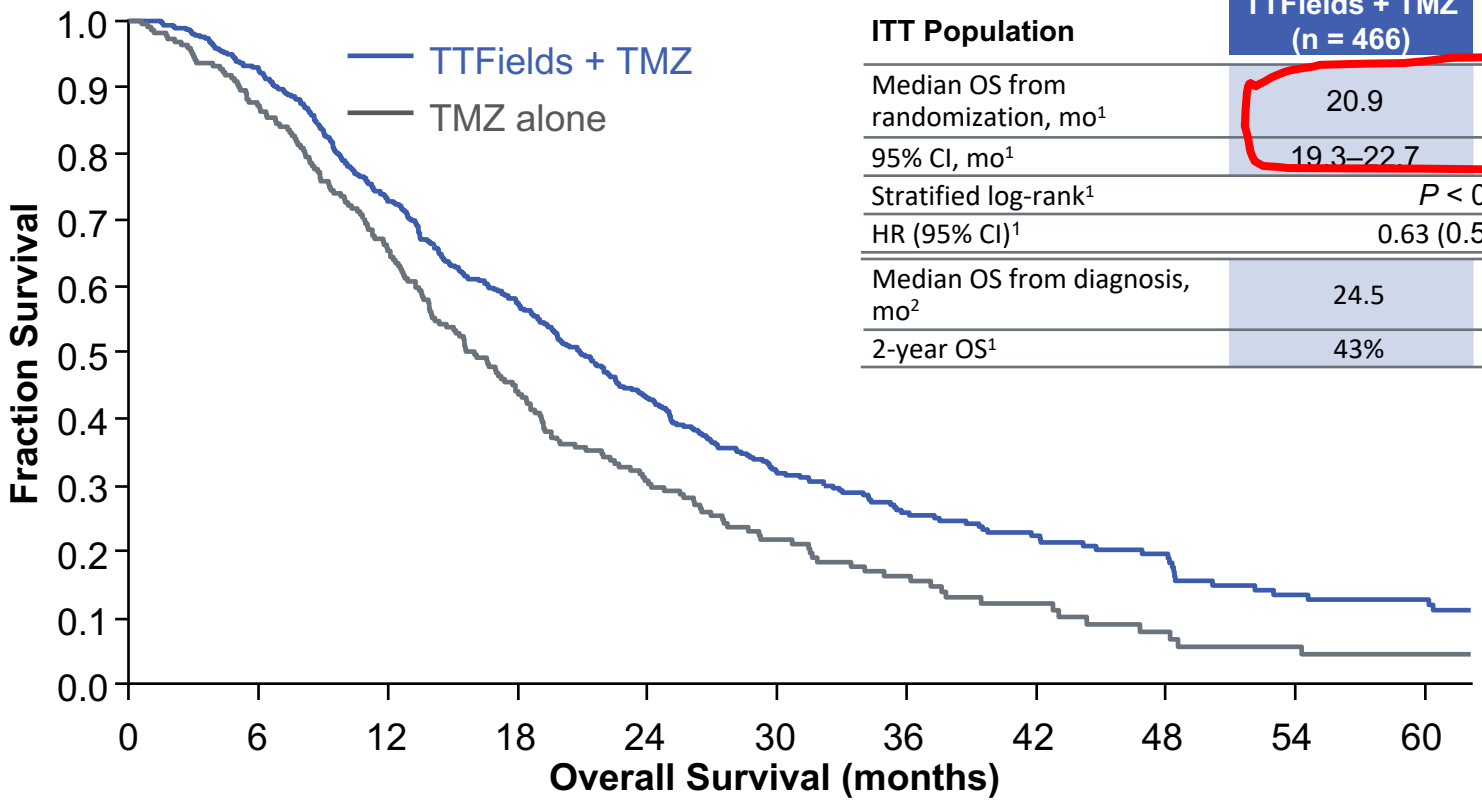
ITT Population	TTFields + TMZ (n = 466)	TMZ Alone (n = 229)
Median PFS from randomization, mo[1]	6.7	4.0
95% CI, mo[1]	6.1–8.1	3.8–4.4
Stratified log-rank[1]	$P < 0.001$	
HR (95% CI)[1]	0.63 (0.52–0.76)	
Median PFS from diagnosis, mo[2]	11.2	7.8

This final analysis (n = 695) confirms the results from the interim analysis (n = 315) where TTFields + TMZ improved PFS by more than 3 months[3]

CI, confidence interval; HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival; TMZ, temozolomide; TTFields, Tumor Treating Fields.

1. Stupp R et al. *JAMA*. 2017;318(23):2306-2316. **2.** Stupp R et al. *Cancer Res*. 2017;77(13 suppl): Abstract CT007. As presented at the American Association for Cancer Research (AACR); April 1–5, 2017; Washington DC. **3.** Optune. Instructions for Use. Novocure; January 2019.

EF-14: Overall Survival (Final Analysis)[1]



ITT Population	TTFields + TMZ (n = 466)	TMZ Alone (n = 229)
Median OS from randomization, mo[1]	20.9	16.0
95% CI, mo[1]	19.3–22.7	14.0–18.4
Stratified log-rank[1]	$P < 0.001$	
HR (95% CI)[1]	0.63 (0.53–0.76)	
Median OS from diagnosis, mo[2]	24.5	19.8
2-year OS[1]	43%	31%

This 5-year survival analysis (n = 695) confirms the results from the interim analysis in the per protocol population (n = 280) where TTFields + TMZ extended OS by almost 5 months[3,4]

Overall survival was a powered secondary endpoint for efficacy.
CI, confidence interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide; TTFields, Tumor Treating Fields.
1. Stupp R et al. *JAMA*. 2017;318(23):2306-2316. **2.** Stupp R et al. *Cancer Res.* 2017;77(13 suppl): Abstract CT007. As presented at the American Association for Cancer Research (AACR); April 1–5, 2017; Washington DC. **3.** Stupp R et al. *JAMA*. 2015;314(23):2535-2543. **4.** Optune. Instructions for Use. Novocure; January 2019.

EF-14 Safety Summary: Incidence of Grade 3/4 Adverse Events in ≥ 5% of Patients (Final Analysis)[1,2]

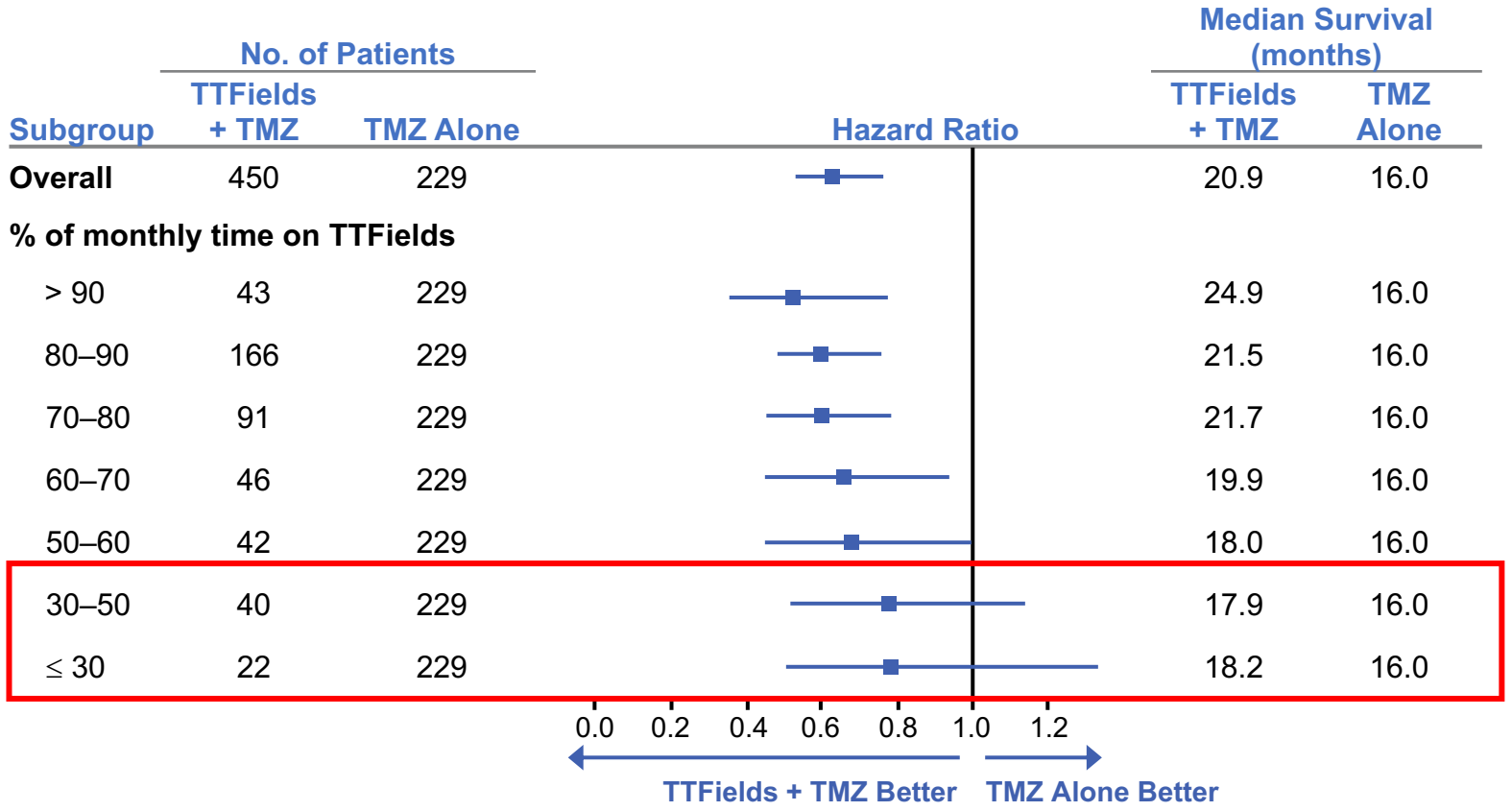
Safety Population	TTFields + TMZ (n = 456) %	TMZ Alone (n = 216) %
≥1 Adverse event	48	44
Blood and lymphatic system disorder*	13	11
Thrombocytopenia	9	5
Gastrointestinal disorders	5	4
Asthenia, fatigue, and gait disturbance	9	6
Infections	7	5
Injury, poisoning, and procedural complications (falls and 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

- The most common (≥10%) adverse events involving TTFields in combination with TMZ were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression[3]
- The only common device-related AE was a skin irritation seen beneath the arrays in 53% percent of patients. The majority (52%) of these events were mild to moderate (2% severe)[1]

*The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group.
TMZ, temozolomide; TTFields, Tumor Treating Fields.

1. Optune. Instructions for Use. Novocure; January 2019. **2.** Stupp R et al. *JAMA*. 2017;318(23):2306-2316. **3.** Novocure Data on File OPT-103.

EF-14: Monthly Time on TTFields Impacts Overall Survival (*Post Hoc* Analysis)



Vantaggio NS per TTF

There is a survival trend in favor of TTFields plus TMZ with progressively higher levels of monthly device usage

GBM, glioblastoma; OS, overall survival; TMZ, temozolomide; TTFields, Tumor Treating Fields.
Toms SA et al. *J Neurooncol*. 2019;141(2):467-473.

EF-14: Patients Completing Quality of Life Questionnaire

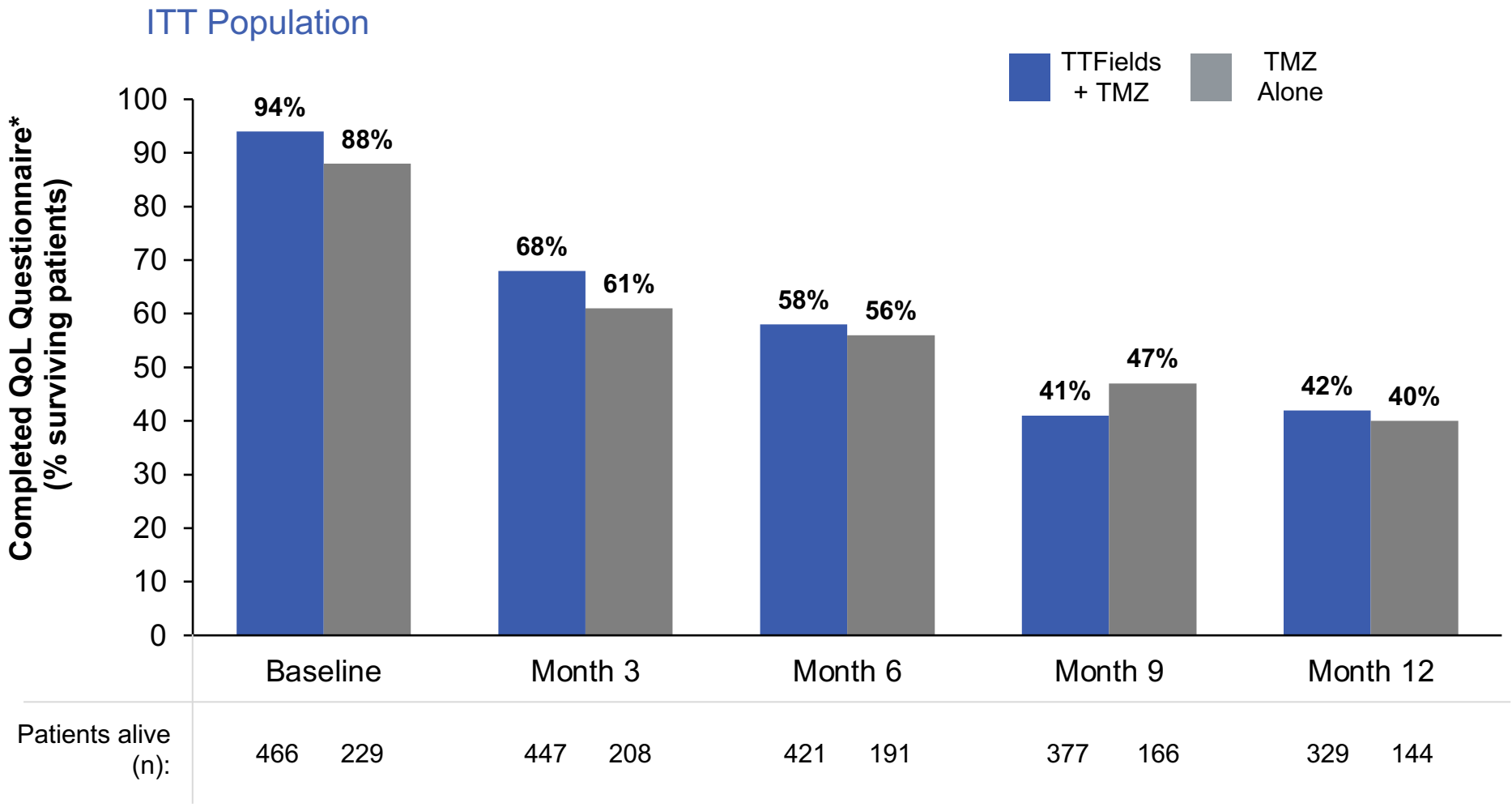
This secondary analysis of a randomized clinical trial examines the association between therapy with tumor-treating fields plus temozolomide and survival and health-related quality of life in patients with glioblastoma after completion of chemoradiotherapy.

Studio non a doppio cieco

Results

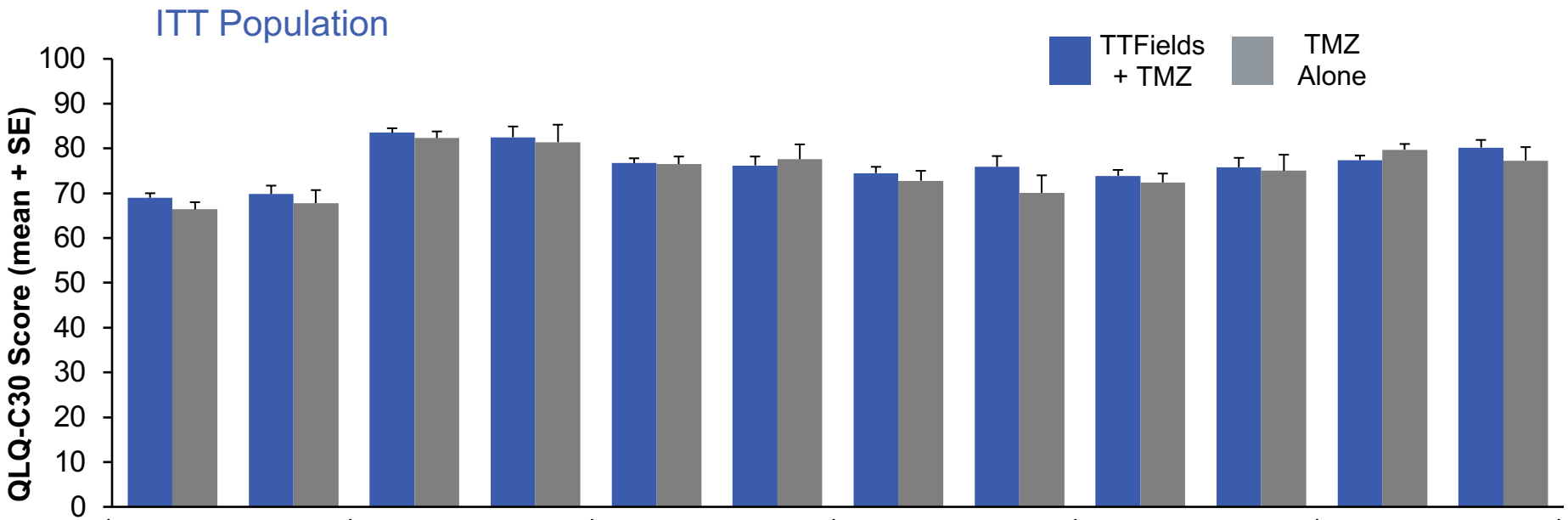
Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months; $P < .01$); physical (5.1 vs 3.7 months; $P < .01$) and emotional functioning (5.3 vs 3.9 months; $P < .01$); pain (5.6 vs 3.6 months; $P < .01$); and leg weakness (5.6 vs 3.9 months; $P < .01$), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months; $P < .001$) and pain (TTFields improved; 13.4 vs 12.1 months; $P < .01$). Role, social, and physical functioning were not affected by TTFields.

EF-14: Patients Completing Quality of Life Questionnaire



*Data are the percentage of patients alive who completed the HRQoL questionnaire
HRQoL, health related quality of life; ITT, intent to treat; TMZ, temozolomide; TTFields, Tumor Treating Fields.
Taphoorn MJB et al. *JAMA Oncol*. 2018;4(4):495-504.

EF-14: Function Scales[1,2]



	Global Health Status		Physical Functioning		Cognitive Functioning		Role Functioning		Social Functioning		Emotional Functioning	
	Baseline	12 Month	Baseline	12 Month	Baseline	12 Month	Baseline	12 Month	Baseline	12 Month	Baseline	12 Month
TTFields+ TMZ (n)	435	137	437	139	435	138	437	139	435	138	435	138
TMZ alone (n)	199	58	202	58	202	58	202	58	202	58	202	58

- Data collected by EORTC QLQ-C30 and QLQ-BN20 questionnaire
- For the domains shown on this slide, a higher score represents a higher level of functioning

QoL was not different with TTFields + TMZ

EORTC, European Organisation for Research and Treatment of Cancer; ITT, intent to treat; QLQ-C30, Quality of Life Core Questionnaire-C30; QLQ-BN20, Quality of Life Questionnaire for Brain Neoplasms; QoL, quality of life; SE, standard error; TMZ, temozolomide; TTFields, Tumor Treating Fields.

1. Taphoorn MJB et al. *JAMA Oncol*. 2018;4(4):495-504; **2.** Taphoorn MJB et al. *JAMA Oncol.* 2018;4(4 suppl 1):S1-S14.

EF-14: No Change in Global Health Status Over Time

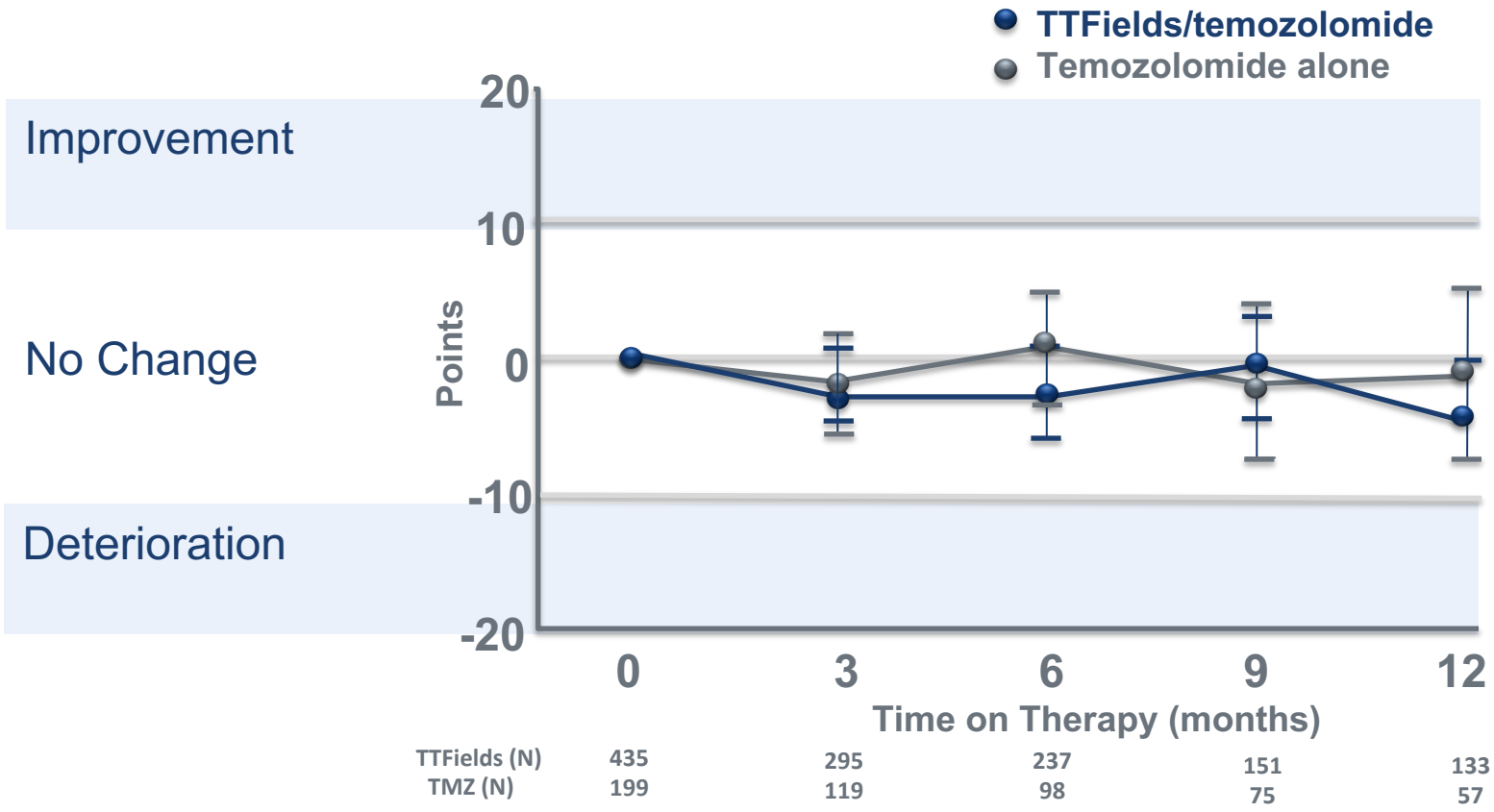


Figure Legend:

Mean changes in points on health-related quality of life scales from baseline in global health status with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. No change, between 0 and 10 points; improvement and deterioration, changes of 10 points or more. Error bars indicate SD.

SD, Standard deviation; TMZ, temozolomide; TTFields, Tumor Treating Fields.

Taphoorn MJB et al. *JAMA Oncol.* 2018;4(4)(suppl 1):S1-S14.

EF-14: Mean Change in Symptom Scale: Itchy Skin Over Time

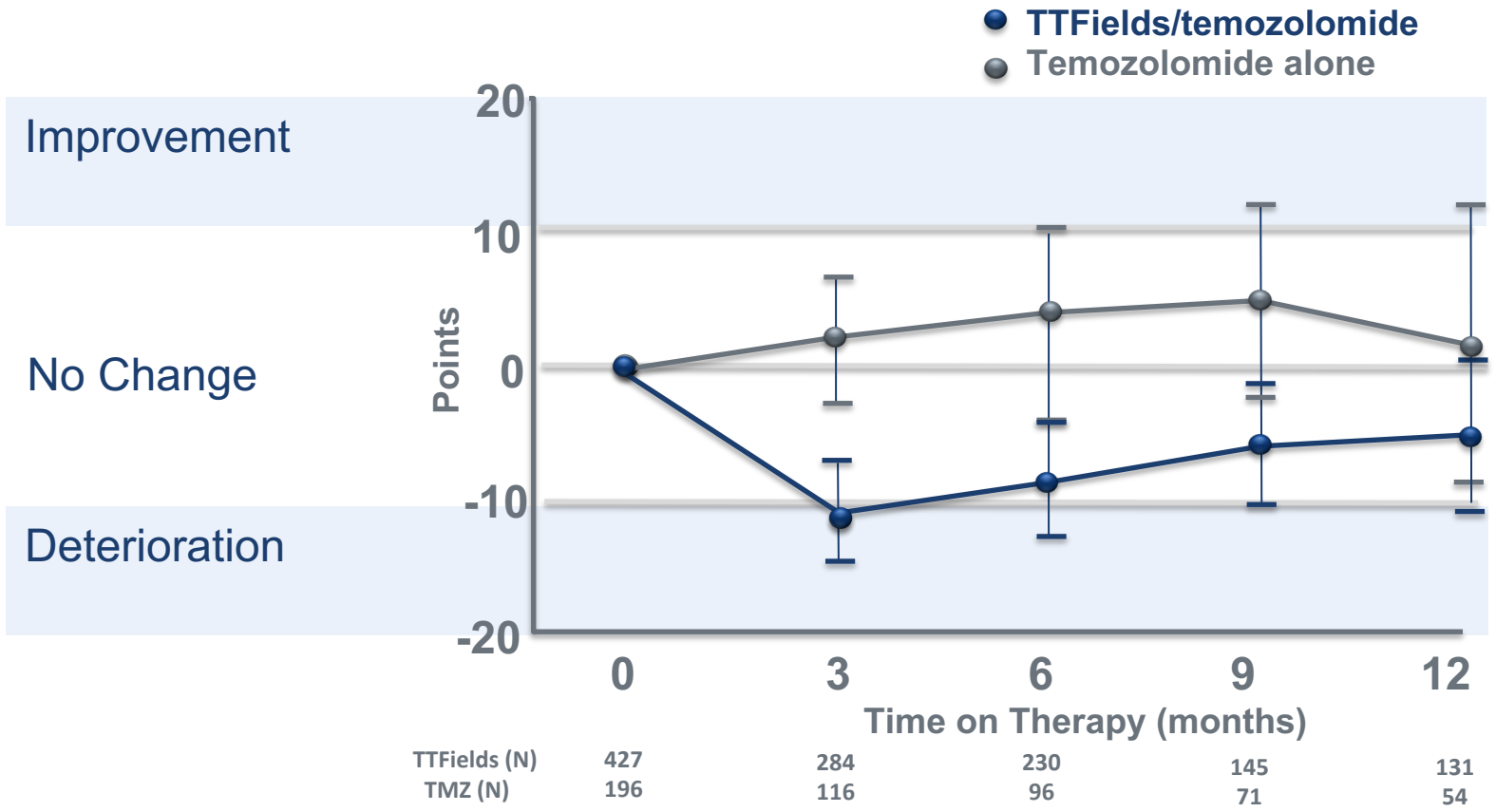


Figure Legend:
Mean changes in points on health-related quality of life scales from baseline in itchy skin with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. No change, between 0 and 10 points; improvement and deterioration, changes of 10 points or more. Error bars indicate SD.

SD, Standard deviation; TMZ, temozolomide; TTFields, Tumor Treating Fields.
Taphoorn MJB et al. *JAMA Oncol.* 2018;4(4)(suppl 1):S1-S14.

EF-14: Summary of Outcomes for TTFields + TMZ Compared With TMZ Alone

Significantly improved PFS and OS[1]

- Median PFS: 6.7 months vs 4.0 months ($P < 0.001$)
- Median OS: 20.9 months vs 16.0 months ($P < 0.001$); survival rate at 5 y 13% vs 5%

Survival benefit that increased with more time on TTFields[1,2]

- Increased monthly usage with TTFields therapy is independently prognostic for improved survival in glioblastoma
- Survival rate at 5 y 29%

Maintained QoL over time and across predefined daily-functioning domains[3]

- The addition of TTFields to standard treatment with TMZ resulted in improved survival without a negative impact on patient HRQoL

TTFields + TMZ combined safely[1]

- The most common device-related side effect with TTFields was mild-to-moderate skin irritation
- No late-emerging serious AEs or increase in systemic side effects were seen in the final analysis

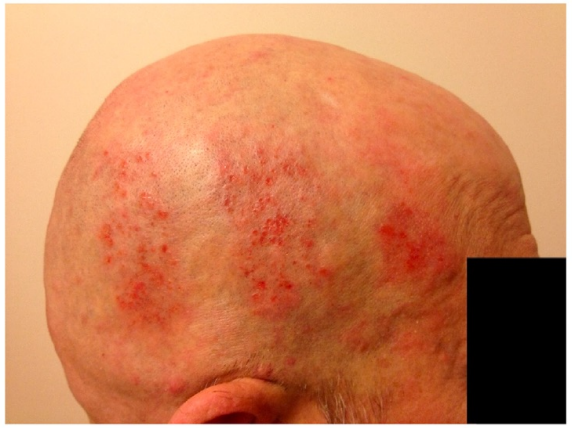
AE, adverse event; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TMZ, temozolomide, TTFields, Tumor Treating Fields.

1. Optune. Instructions for Use. Novocure; January 2019. **2**. Toms SA et al. *J Neurooncol*. 2019;141(2):467-473. **3.** Taphoorn MJB et al. *JAMA Oncol*. 2018;4(4):495-504.

Tossicità cutanea

Characterization and Management of Dermatologic Adverse Events With the NovoTTF-100A System, a Novel Anti-mitotic Electric Field Device for the Treatment of Recurrent Glioblastoma

A



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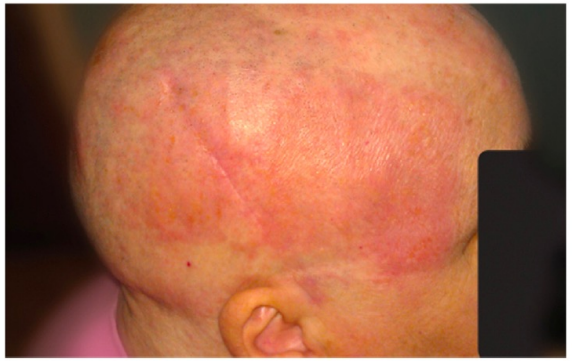

Figure 4. Contact dermatitis (may or may not be symp-

Table 1. Types and Potential Causes of Dermatologic Adverse Events

Adverse Event	Potential Cause
Irritant contact dermatitis	Chemical irritation from hydrogel, moisture, and/or alcohol
Allergic contact dermatitis	Allergy to tape and/or hydrogel
Erosion	Mechanical trauma from shaving and/or array pressure/removal
Ulcer	Decreased perfusion from array pressure (especially in areas overlying scars/ hardware/prior radiation)
Skin infection/ pustules	Secondary bacterial infection

Seminars in Oncology, Vol 41, No 3, Suppl 4, June 2014, pp S1-S14

Tossicità cutanea

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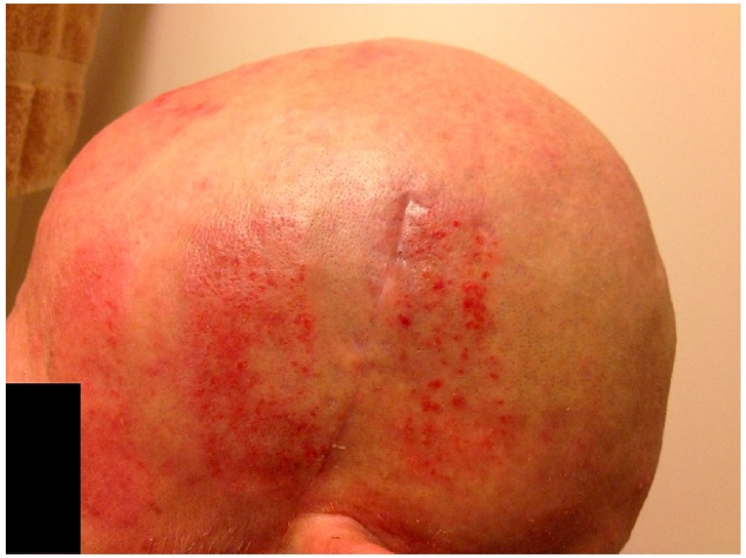

Figure 5. Dermatologic erosions and skin infection

Table 1. Types and Potential Causes of Dermatologic Adverse Events

Adverse Event	Potential Cause
Irritant contact dermatitis	Chemical irritation from hydrogel, moisture, and/or alcohol
Allergic contact dermatitis	Allergy to tape and/or hydrogel
Erosion	Mechanical trauma from shaving and/or array pressure/removal
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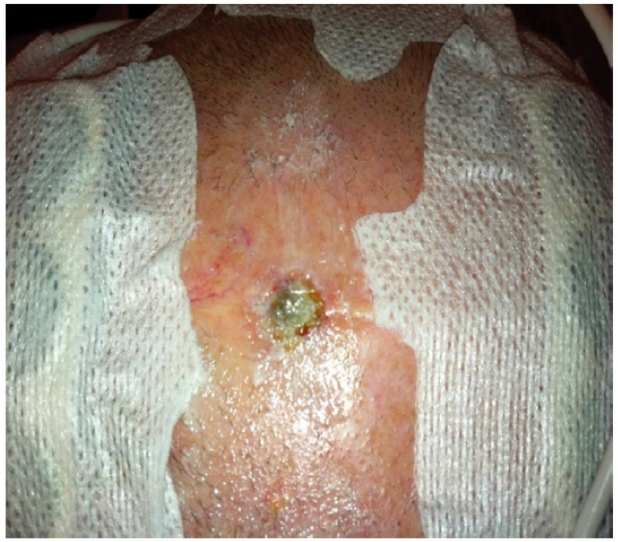

Figure 7. Skin ulceration. Note how the arrays are arranged around the site of the ulcer (61-year-old man after receiving NovoTTF Therapy for 2 weeks).

Table 1. Types and Potential Causes of Dermatologic Adverse Events

Adverse Event	Potential Cause
Irritant contact dermatitis	Chemical irritation from hydrogel, moisture, and/or alcohol
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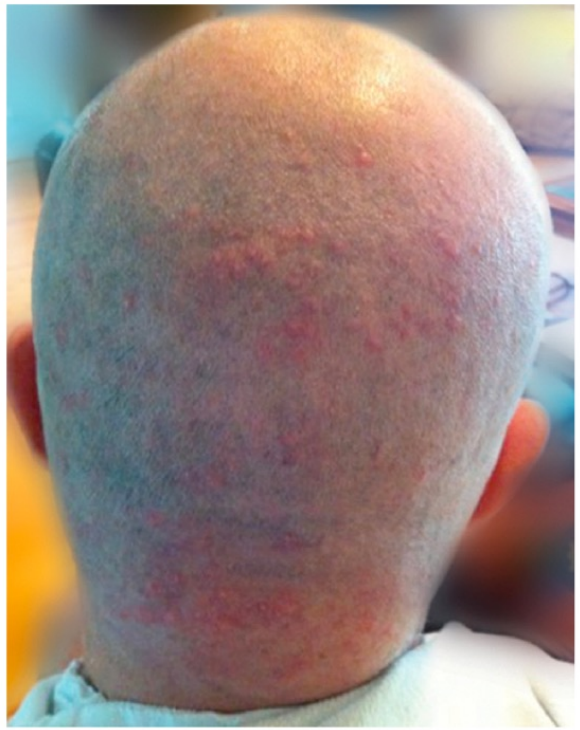
A



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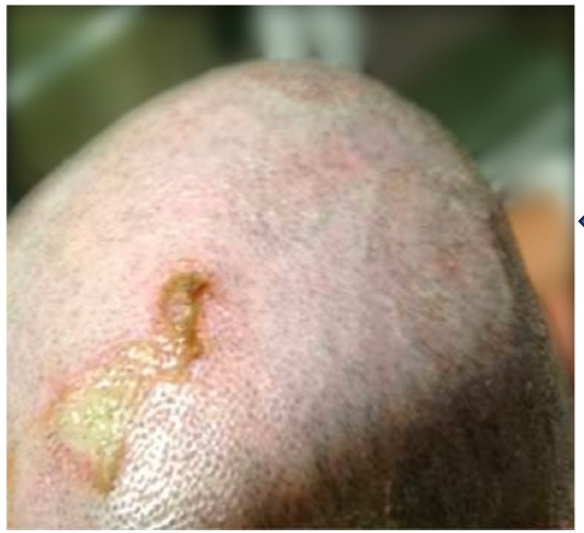

Figure 6. Skin infection/folliculitis. (A) Folliculitis (62-year-old man after receiving NovoTTF Therapy for 4 weeks). (B) Skin infection (41-year-old woman after

Table 1. Types and Potential Causes of Dermatologic Adverse Events

Adverse Event	Potential Cause
Irritant contact dermatitis	Chemical irritation from hydrogel, moisture, and/or alcohol
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o 3, Suppl 4, June 2014, pp S1-S14

Characterization and Management of Dermatologic Adverse Events With the NovoTTF-100A System, a Novel Anti-mitotic Electric Field Device for the Treatment of Recurrent Glioblastoma

Table 2. Preventive Strategies for Dermatologic Adverse Events

Category	Guideline for Patient/Caregiver
Shaving and preparation of the scalp	• Proper hand washing prior to preparing the scalp for array application • Take time shaving the scalp using gentle but firm circular motions • Ensure a close shave prior to applying the arrays • Cleaning the electric razor *after* every shave is important to lessen the risk of skin infection • Wash scalp with fragrance-free, mild shampoo (eg, baby shampoo); seborrheic dermatitis shampoo can also be used as it has antibacterial properties (eg, pyrithione zinc 2%, ciclopirox 1%, ketoconazole 2%). • Ensure scalp is completely dry before applying a new set of arrays
Use of isopropyl (70%) alcohol	• Use of first aid antiseptic rubbing alcohol (70% isopropyl alcohol) prior to array application is a necessary step to remove naturally occurring scalp oils, resulting in better adherence of the arrays to the scalp • After shaving and before placing the arrays, wipe the scalp with a gauze or cotton ball soaked in first aid antiseptic rubbing alcohol (70% isopropyl alcohol) • Avoid areas of skin irritation, as the first aid antiseptic rubbing alcohol (70% isopropyl alcohol) may further irritate the skin
Transducer array exchanges	• Change arrays on a regular basis (at least every 3-4 days) • When removing the arrays, avoid "pulling" on the skin and take approximately 60 seconds to remove each array • Using mineral (baby) oil on the edges of the array may make the removal of the adhesive tape easier and less irritating to the skin • To remove leftover array adhesive, use gauze or cotton ball soaked in mineral (baby) oil or pour into hands and gently rub scalp in areas of remaining adhesive • Pay close attention to the scalp at each array exchange and notify the doctor/nurse if there are signs of skin irritation or open areas, in order to receive information on how to treat the affected area(s). Taking a picture of the affected area(s) on the scalp and sharing with doctor/nurse is advised

Figure 8. Preventive measures. Illustration of shifting transducer arrays at each array exchange.

Seminars in Oncology, Vol 41, No 3, Suppl 4, June 2014, pp S1-S14

PubMed®

ttfields and cancer

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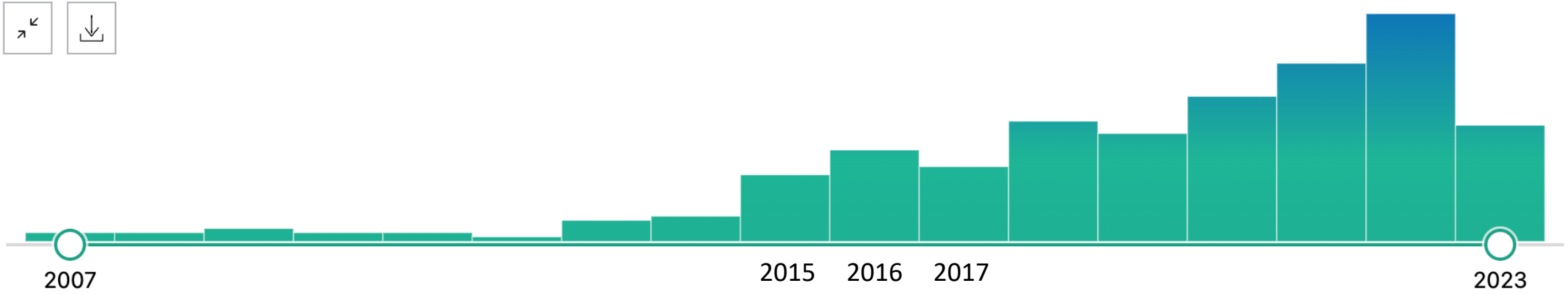
RESULTS BY YEAR

248 results

Page 1 of 25



Neuro-Oncology Practice

8(4), 426–440, 2021 | doi:10.1093/nop/npab026 | Advance Access date 20 April 2021

Tumor-Treating Fields for the treatment of glioblastoma: a systematic review and meta-analysis

Ohad Regev, Vladimir Merkin, Deborah T. Blumenthal, Israel Melamed, and Tehila Kaisman-Elbaz

Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Be'er-Sheva, Israel (O.R.); Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er-Sheva, Israel (O.R., V.M., I.M., T.K.E); Department of Neurosurgery, Soroka University Medical Center, Be'er-Sheva, Israel (V.M., I.M., T.K.E); Neuro-Oncology Service, Tel Aviv Medical Center, Tel Aviv University, Tel Aviv, Israel (D.T.B.).

Corresponding Author: Tehila Kaisman-Elbaz, MD/PhD, BPT, Department of Neurosurgery, Soroka University Medical Center, 151 Rager Blvd, Be'er-Sheva, Israel (kaisman@bgu.ac.il).

Abstract

Background. Tumor-Treating Fields (TTFields) is an emerging treatment modality for glioblastoma (GBM). Studies have shown a good safety profile alongside improved efficacy in newly diagnosed GBM (ndGBM), while a less clear effect was shown for recurrent GBM (rGBM). Despite regulatory support, sectors of the neuro-oncology community have been reluctant to accept it as part of the standard treatment protocol. To establish an objective understanding of TTFields' mechanism of action, safety, efficacy, and economical implications, we conducted a systematic literature review and meta-analysis.

Methods. A systematic search was conducted in PubMed, Scopus, and Cochrane databases. Twenty studies met the pre-defined inclusion criteria, incorporating 1636 patients (542 ndGBM and 1094 rGBM), and 11 558 patients (6403 ndGBM and 5155 rGBM) analyzed for the clinical outcomes and safety endpoints, respectively.

Results. This study demonstrated improved clinical efficacy and a good safety profile of TTFields. For ndGBM, pooled median overall survival (OS) and progression-free survival (PFS) were 21.7 (95%CI = 19.6-23.8) and 7.2 (95%CI = 6.1-8.2) months, respectively. For rGBM, pooled median OS and PFS were 10.3 (95%CI = 8.3-12.8) and 5.7 (95%CI = 2.8-10) months, respectively. Compliance of ≥75% was associated with an improved OS and the predominant adverse events were dermatologic, with a pooled prevalence of 38.4% (95%CI = 32.3-44.9). Preclinical studies demonstrated TTFields' diverse molecular mechanism of action, its potential synergistic efficacy, and suggest possible benefits for certain populations.

Conclusions. This study supports the use of TTFields for GBM, alongside the standard-of-care treatment protocol, and provides a practical summary, discussing the current clinical and preclinical aspects of the treatment and their implication on the disease course.

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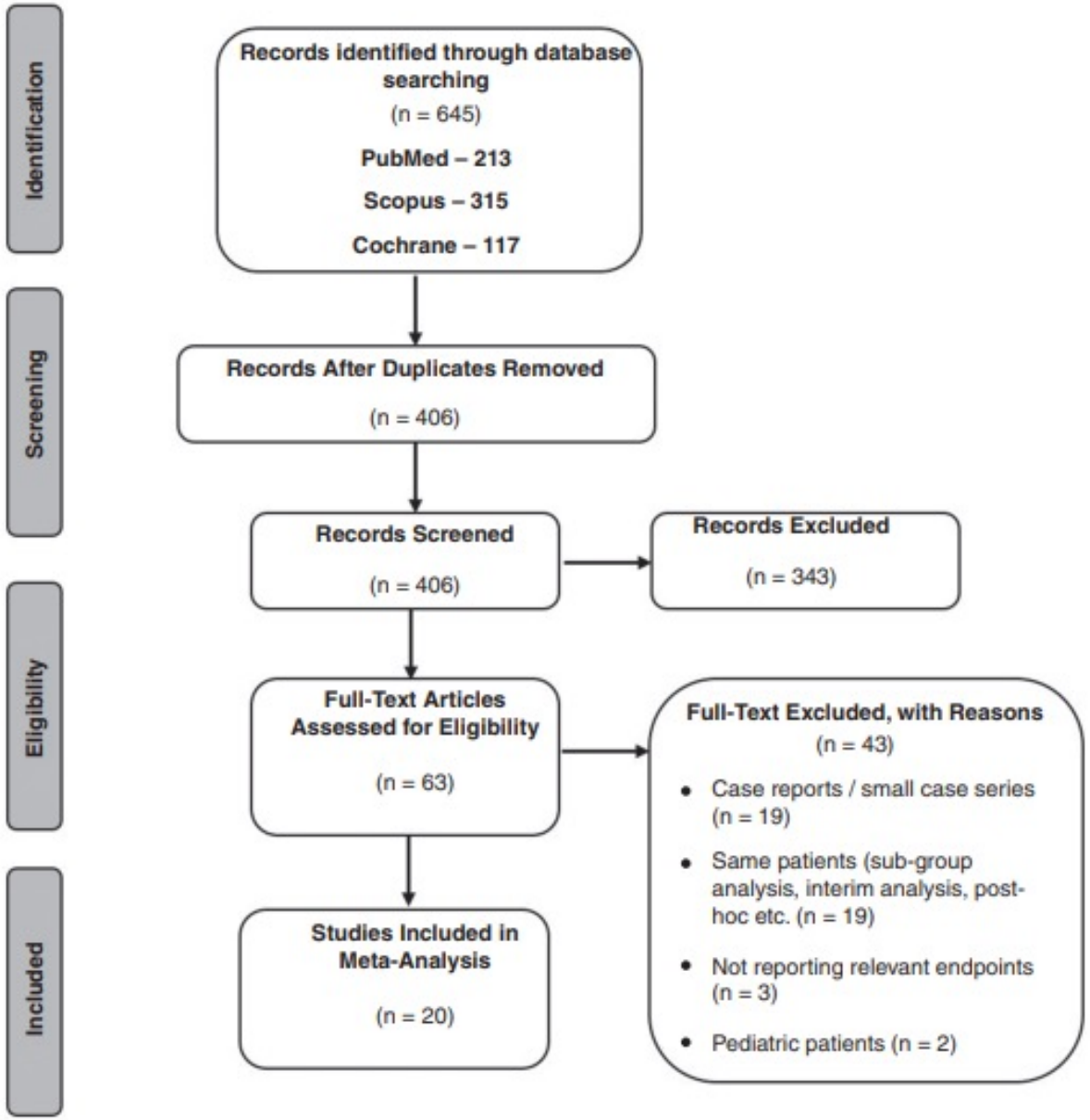

Figure 1. Flowchart of studies included in this study.

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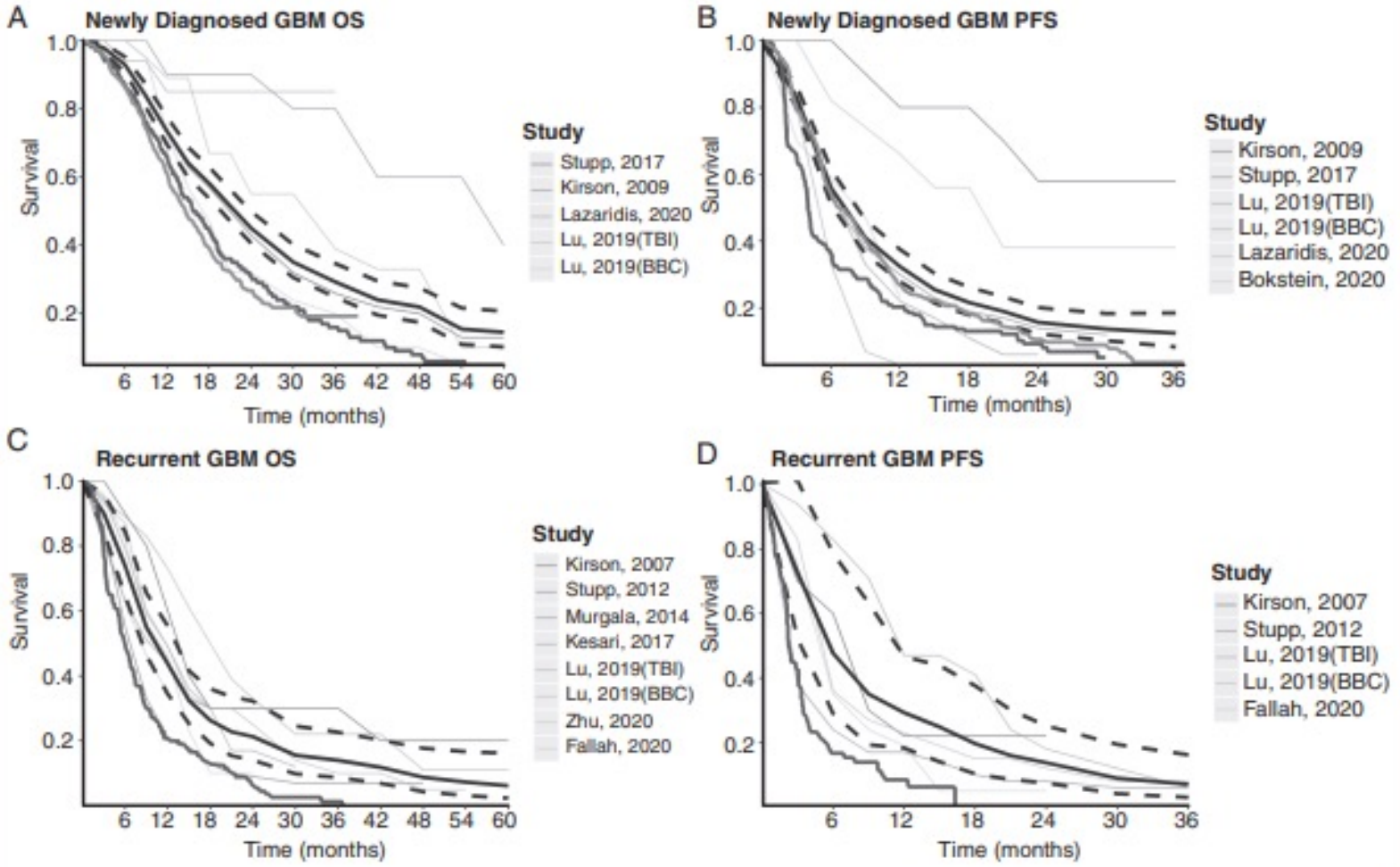


Figure 2. Pooled Kaplan-Meier (KM) survival curves of patients treated with TTFields for GBM. Pooled KM survival curves of OS (A and C) and PFS (B and D). The gray-scale thin lines represent the survival in each individual study. The thick black line represents the summarized survival curve with the 95%CI (dashed black lines). The thick dark gray line represents the original survival curve of controls according to EF11 (rGBM: best standard-of-care treatment) and EF14 (ndGBM: RT + TMZ). The thick bright gray line represents the original survival curve of ndGBM patients treated with RT + TMZ in the historic study by Stupp et al.[3] which established the current standard of care for ndGBM (EORTC protocol). (A) OS survival curve for ndGBM (512 patients), (B) PFS survival curve for ndGBM (522 patients), (C) OS survival curve for rGBM (984 patients), (D) PFS survival curve for rGBM (201 patients). Abbreviations: GBM, glioblastoma; ndGBM, newly diagnosed GBM; OS, overall survival; PFS, progression-free survival; rGBM, recurrent GBM; RT + TMZ, radiotherapy + temozolomide; TTFields, Tumor-Treating Fields.

Una recente meta-analisi sembra confermare il vantaggio nell'uso dei TTF per i pazienti con glioblastoma sia alla diagnosi che alla recidiva; sia in termini di OS che PFS

Annals of Oncology

Tumor-treating fields: time for demystification

Qualche preoccupazione?

In this Editorial in Annals of Oncology, Prof. Weller (who was among the authors of the EF-14 study along with others) raised some concerns about the study…

M. Weller
Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland
(E-mail: michael.weller@usz.ch)

doi:10.1093/annonc/mdy220
Published online 14 June 2018

The EF-14 trial represents the first positive trial of any therapeutic intervention in newly diagnosed glioblastoma since 2005. Yet, neither the trial results nor the treatment itself have been broadly embraced, neither by neuro-oncology health care professionals nor by patients and caregivers, at least in most European countries. Why is that so? The reasons are manifold and arise at multiple levels.

There are scientific questions that have produced uncertainty.

Alcuni dubbi relativi allo studio…

1. “Why would a treatment in an incurable, steadily progressive disease fail to work at first recurrence after radiotherapy as defined largely by magnetic resonance imaging, but work quite impressively when given in the setting of maintenance temozolomide chemotherapy after completion of radiotherapy with concomitant temozolomide?

2. Do we believe that the biology of glioblastoma changes within a few months? Should we postulate that radiotherapy preceding TTF only shortly provided sensitization? Why have no specific imaging changes been observed and reported in patients treated with TTF?

3. We await careful characterization of tissues from patients undergoing surgery at failure after TTF, but no systematic studies are available although many patients must have been operated since.

4. No subgroup of patients defined by any known prognostic factor or biomarker has been identified to preferentially derive benefit from TTF.

5. A substantial increase in long-term survival was not achieved.”

Annals of Oncology

Tumor-treating fields: time for demystification

"Still, patients in the experimental arm of the EF-14 trial received **major support and coaching …** which continues to raise concerns because **the study design could have controlled for that but did not.**

Importantly, placebo effects should not be equaled with survival benefit afforded by measures other than tumor-specific therapy since **early palliative care has been reported to prolong survival in patients with non-small-cell lung cancer"**

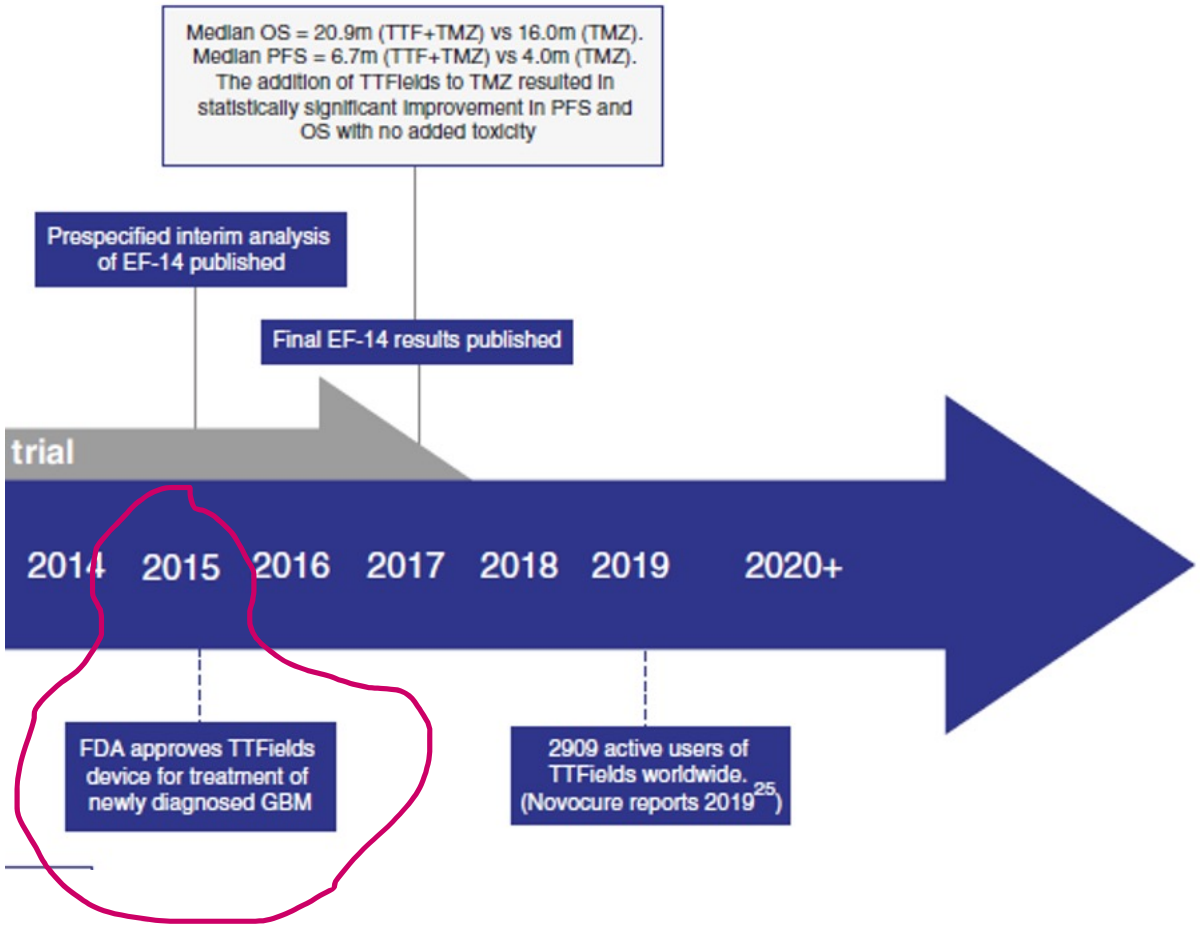
"Could we truly ask for a second clinical trial with a placebo control?

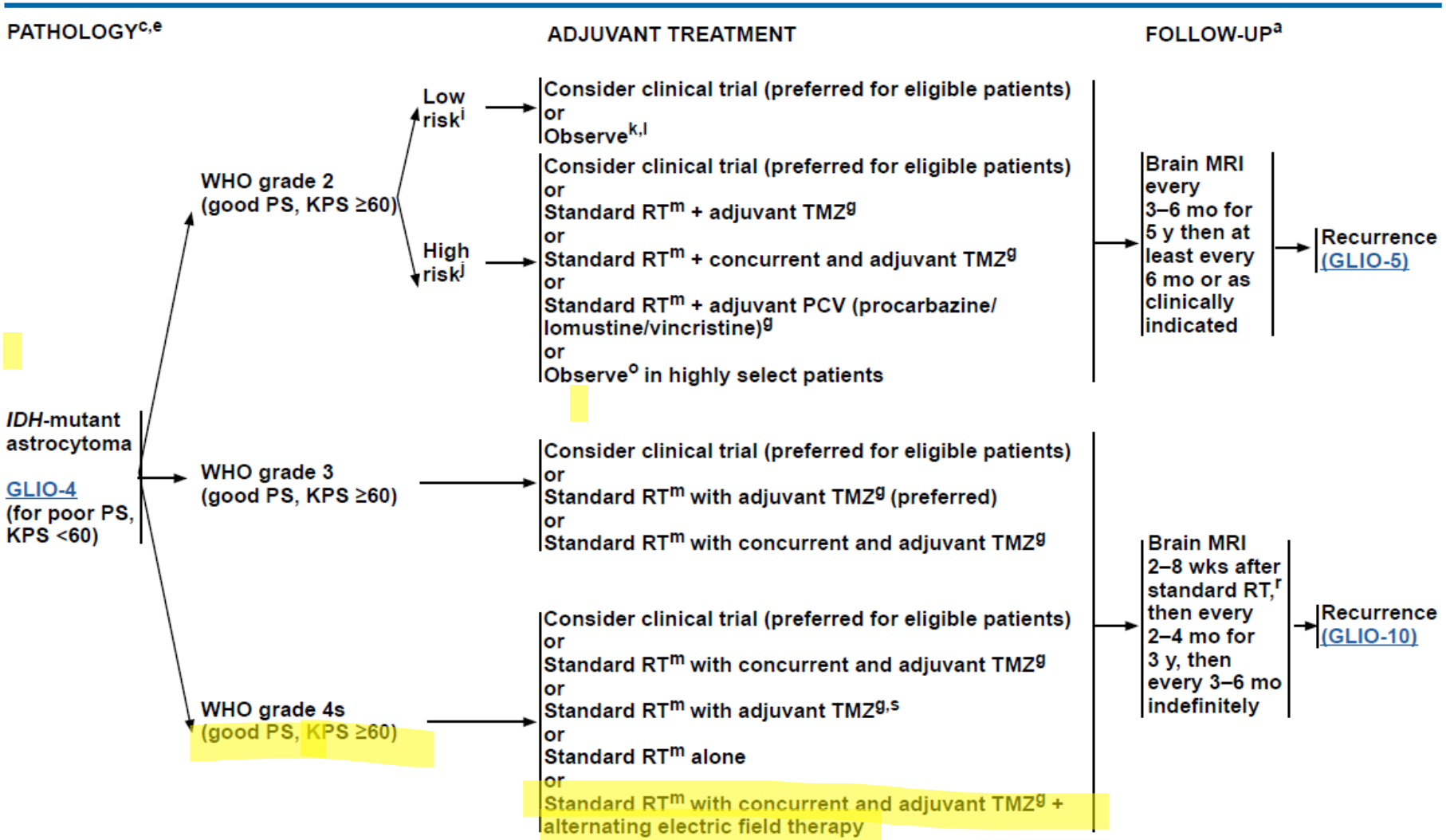
In the setting of one positive trial, **I do not think that it is reasonable to request from patients to have their heads shaved and to spend 85% of their life including sleep with a heavy device to help altruistically solving a controversy over a still moderate survival difference.**

Conversely**, an alternative path forward for the neuro-oncology community would be to try to conduct clinical trials of intensive supportive care early in the disease course which may help to estimate the potential survival benefit that can be derived from such interventions"**

Annals of Oncology

Tumor-treating fields: time for demystification

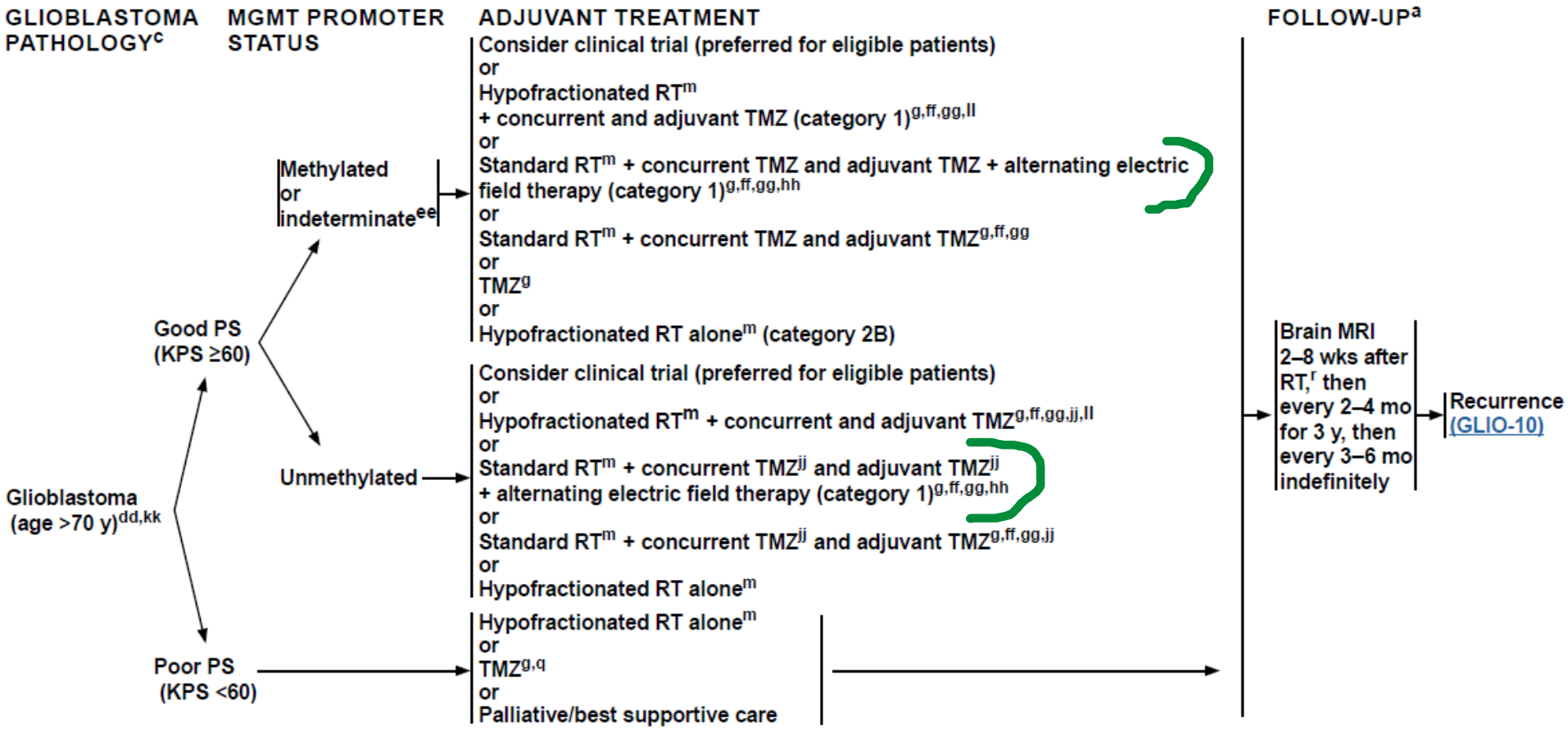

Median OS = 20.9m (TTF+TMZ) vs 16.0m (TMZ).
Median PFS = 6.7m (TTF+TMZ) vs 4.0m (TMZ).
The addition of TTFields to TMZ resulted in statistically significant improvement in PFS and OS with no added toxicity
Prespecified interim analysis of EF-14 published
Final EF-14 results published
trial
2014
2015
2016
2017
2018
2019
2020+
FDA approves TTFields device for treatment of newly diagnosed GBM
2909 active users of TTFields worldwide. (Novocure reports 2019[25])



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
Footnotes (GLIO-4)

NCCN Guidelines Version 1.2023
Adult Glioma: Glioblastoma



[a] Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[c] Principles of Brain Tumor Pathology (BRAIN-E).
[g] Systemic Therapy Options (GLIO-A).
[m] Principles of Radiation Therapy for Brain and Spinal Cord (BRAIN-C 1 of 9).
[q] Consider TMZ if tumor is MGMT promoter methylated.
[r] Within the first 3 months after completion of RT and concomitant TMZ, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[dd] This pathway also includes gliosarcoma.
[ee] Consider pyrosequencing if not done (Mansouri A, et al. Neuro Oncol 2019;21:167-178).
[ff] Combination of modalities may lead to increased toxicity or radiographic changes.
[gg] There are no clear data that treatment with TMZ beyond 6 months is beneficial, even in patients with MGMT-methylated disease.
[hh] Alternating electric field therapy is only an option for patients with supratentorial disease.
[jj] Clinical benefit from TMZ is likely to be lower in patients whose tumors lack MGMT promoter methylation.
[kk] NCCN Guidelines for Older Adult Oncology.
[ll] Hypofractionated RT and TMZ have not been formally compared with standard RT and TMZ in patients aged >70 y.

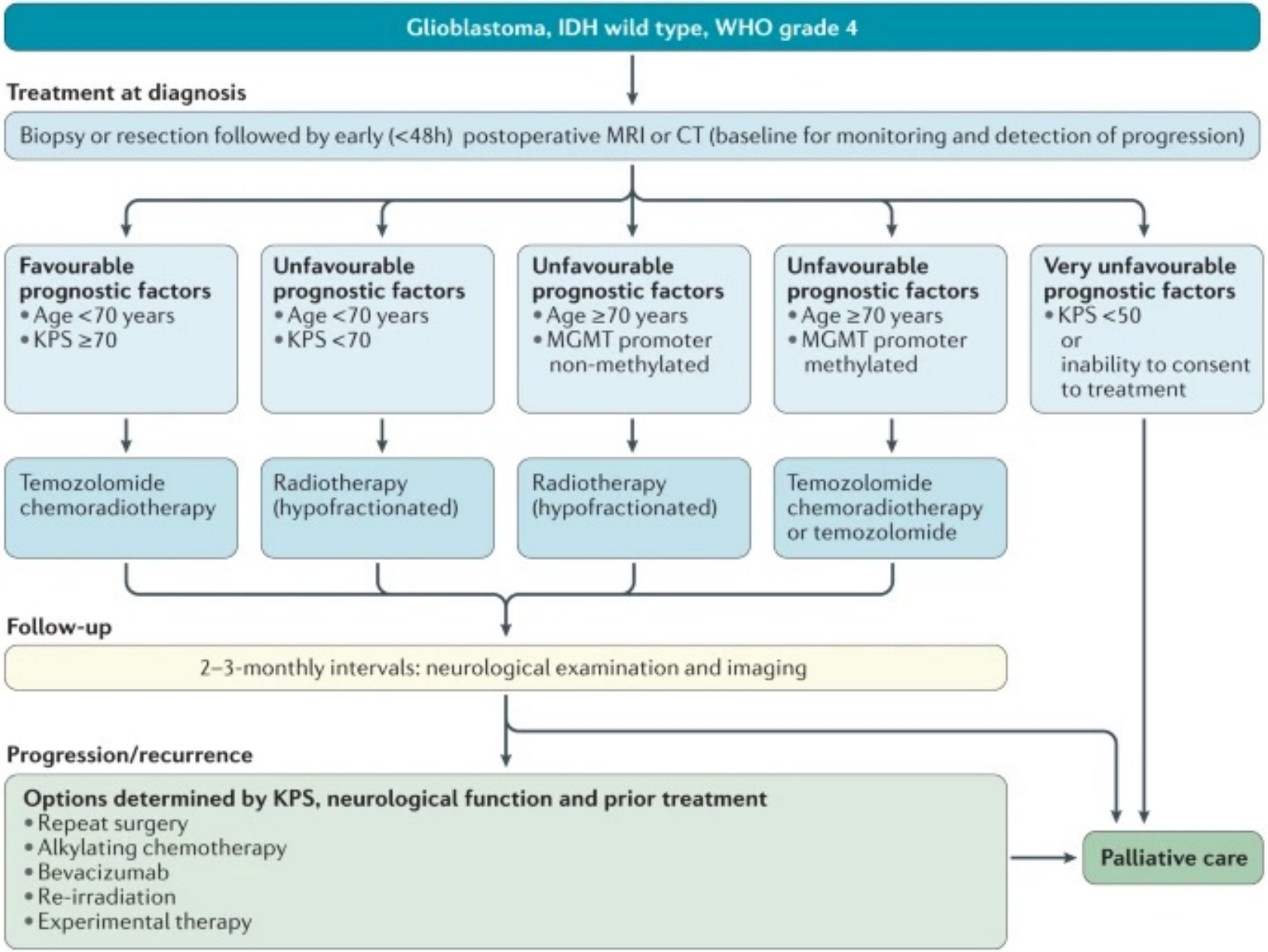
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EANO EUROPEAN ASSOCIATION OF NEURO-ONCOLOGY

Pertanto, per il momento, lo schema più ampiamente accettato per il trattamento del glioblastoma appena diagnosticato rimane quello suggerito dall'Associazione europea di neuro-oncologia (EANO) nel 2021.

OPEN

EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood



Linee guida

NEOPLASIE CEREBRALI

Edizione 2021

In collaborazione con

AINR Associazione Italiana di Neuroradiologia Diagnostica e Interventistica

Associazione Italiana Radioterapia e Oncologia clinica

SIAPEC - IAP Società Italiana di Anatomia Patologica e Citologia Diagnostica - Divisione Italiana della International Academy of Pathology

Sin Società Italiana di Neurologia

SINch Società Italiana Neurochirurgia

SIRM Società Italiana di Radiologia Medica e Interventistica

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

In corso di rinnovamento …– July 2023

GRADE Quesito 4: Nei pazienti con glioblastoma di nuova diagnosi l'utilizzo del device novo TTF potrebbe essere applicato nella pratica clinica?
RACCOMANDAZIONE: L'utilizzo del novoTTF nei pazienti con glioblastoma di nuova diagnosi non deve essere preso in considerazione come opzione terapeutica di prima intenzione
Forza della raccomandazione: FORTE A SFAVORE
…uova diagnosi dopo il trattamento chemio …concomitante e in aggiunta a temozolomide di mantenimento è stato valutato in uno studio randomizzato, in aperto di fase III. Lo studio era stato disegnato per valutare l'efficacia e la safety del device novo TTF in combinazione con temozolomide per il trattamento del glioblastoma dopo il trattamento chemioradioterapico. Alla fine del trattamento con temozolomide e radioterapia, i pazienti venivano randomizzati (rapporto 2:1) a ricevere la terapia di mantenimento standard con temozolomide da sola o in aggiunta al device. Sono stati riportati i risultati della interim analisi dopo i primi 315 dei previsti 695 pazienti (210 del braccio NovoTTF e temozolomide, e 105 pazienti del braccio sola temozolomide) con un follow up mediano di 18 mesi. La PFS mediana nella popolazione intention-to-treat population è stata di 7.1 mesi (95% CI, 5.9-8.2 mesi) nel braccio sperimentale e 4.0 mesi (95% CI, 3.3-5.2 mesi) nel braccio standard (HR, 0.62 [98.7% CI, 0.43-0.89]; P = .001) (27).
Implicazioni per le ricerche future: Ulteriori studi potranno fornire dati di migliore qualità relativi a questo approccio terapeutico.
Qualità delle Prove La qualità delle evidenze è stata giudicata **MOLTO BASSA** per i seguenti motivi: Lo studio presentava una serie di limiti metodologici. In primo luogo si tratta di risultati provenienti da un'analisi ad interim, dunque imprecisi. Inoltre, nonostante fosse stata pianificata una intention-to-treat analysis, i risultati si riferivano alla per-protocol population. Si è deciso inoltre di abbassare la qualità delle evidenze per performance e detection bias visto il disegno dello studio non in cieco e per attrition bias a causa del gran numero di pazienti persi al follow-up (attrition bias)
Qualità globale delle prove: MOLTO BASSA
COI: nessun conflitto dichiarato

Un problema da considerare

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CLINICAL STUDY

Cost-effectiveness of tumor-treating fields added to maintenance temozolomide in patients with glioblastoma: an updated evaluation using a partitioned survival model

Martin Connock[1] · Peter Auguste[1] · Claude Dussart[2] · Jacques Guyotat[3] · Xavier Armoiry[1,4,5]

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Abstract

Purpose A first cost-effectiveness analysis has raised a strong concern regarding the cost of tumor treatment fields (TTF) added to maintenance temozolomide for patients with glioblastoma. This evaluation was based on effectiveness outcomes from an interim analysis of the pivotal trial, moreover it used a "standard" Markov model. Our objective was to update the cost-effectiveness evaluation using the more flexible potential of the "partitioned survival" model design and using the latest effectiveness data.

Methods We developed the model with three mutually exclusive health states: stable disease, progressive disease, and dead. Good fit parametric models were developed for overall survival and progression free survival and these generated clinically plausible extrapolations beyond the observed data. We adopted the perspective of the French national health insurance and used a 20-year time horizon. Results were expressed as cost/life-years (LY) gained (LYG).

Results The base case model generated incremental benefit of 0.604 LY at a cost of €453,848 which, after 4% annual discounting of benefits and costs, yielded an incremental cost effectiveness ratio (ICER) of €510,273/LYG. Using sensitivity analyses and bootstrapping methods results were found to be relatively robust and were only sensitive to TTF device costs and the modelling of overall survival. To achieve an ICER below €100,000/LYG would require a reduction in TTF device cost of approximately 85%.

Conclusions Using a different type of model and updated survival outcomes, our results show TTF remains an intervention that is not cost-effective, which greatly restrains its diffusion to potentially eligible patients.

"There has also been a **lot of debate on the financial toxicity imposed by TTF. This is a relevant issue as of today, but probably not in the long term.** History tells us that prizes come down and both oncology and the neurosciences have seen other treatments that incurred or incur high cost with moderate efficacy at best."

Regione Toscana

Commissione per la valutazione delle tecnologie e degli investimenti sanitari

Centro operativo

RAPID HTA REVIEW

N° richiesta	Data richiesta	Richiedente
260	14/09/2022	Dipartimento del farmaco USL Nord-Ovest, G. Taurino

Tipo di scheda	
Nuova scheda	Si
Aggiornamento di una scheda precedente	No
Se aggiornamento, indicare il motivo:	

Dati generali della tecnologia in valutazione

Nome commerciale

UNE (NOVOTTF-200A)

e generico

(tumour treating field)

e fabbricante

ocure GmbH

e fornitore

ocure GmbH

	REF		
9063	TFH9100EU		
	Marchio CE (data)	Classe di rischio	Approvazione FDA
	27/01/2020	IIB	Si

040299

po di applicazione

ologico

ente target

enti con glioblastoma multiforme di recente diagnosi dopo chirurgia e radioterapia con temozolomide vante in combinazione con temozolomide di mantenimento.

cazione d'uso da scheda tecnica

è destinato a pazienti con glioblastoma multiforme di recente diagnosi o recidivante.

cipali competitor

ci sono competitor

Dati riassuntivi

Numero richiesta	Data richiesta	Richiedente
260	Settembre 2022	ASLNO

Tecnologia in valutazione

Dispositivo che emette un campo elettrico tramite applicazione sulla cute della testa

Eventuali esperti esterni coinvolti

Nessuno

Conclusioni e parere del Centro Operativo (CO)

Il fattore di gran lunga più importante ai fini della decisione su Optune è costituito dal prezzo a cui Optune viene offerto e dal conseguente rapporto costo-efficacia (RCE). Come sopra evidenziato, Optune (in riferimento al prezzo

Annals of Oncology

Tumor-treating fields: time for demystification

Quindi cosa fare?

- Dati biologici → presenti; non ancora del tutto esaustivi soprattutto per quel che riguarda le correlazioni con altri fattori biologici in vivo

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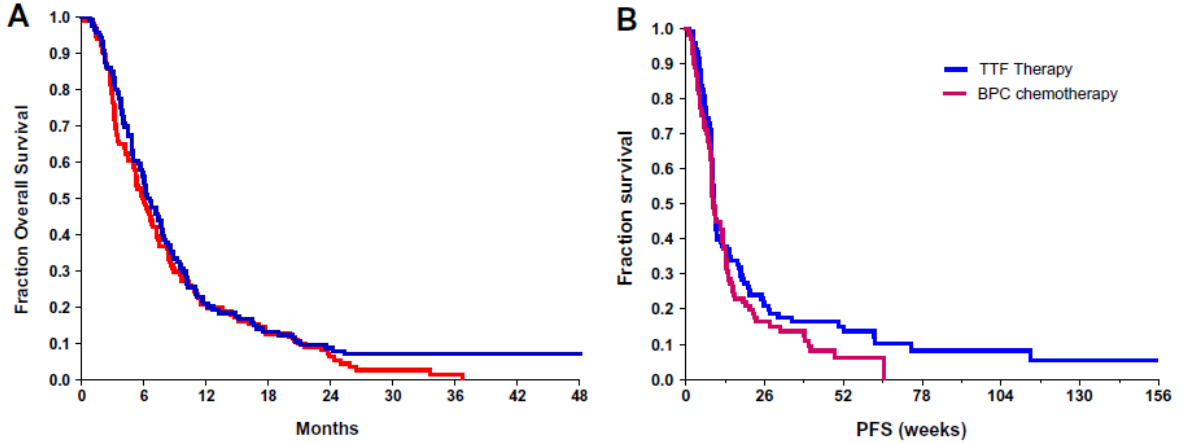
  - Dati clinici → nel paziente recidivato → no chiaro vantaggio



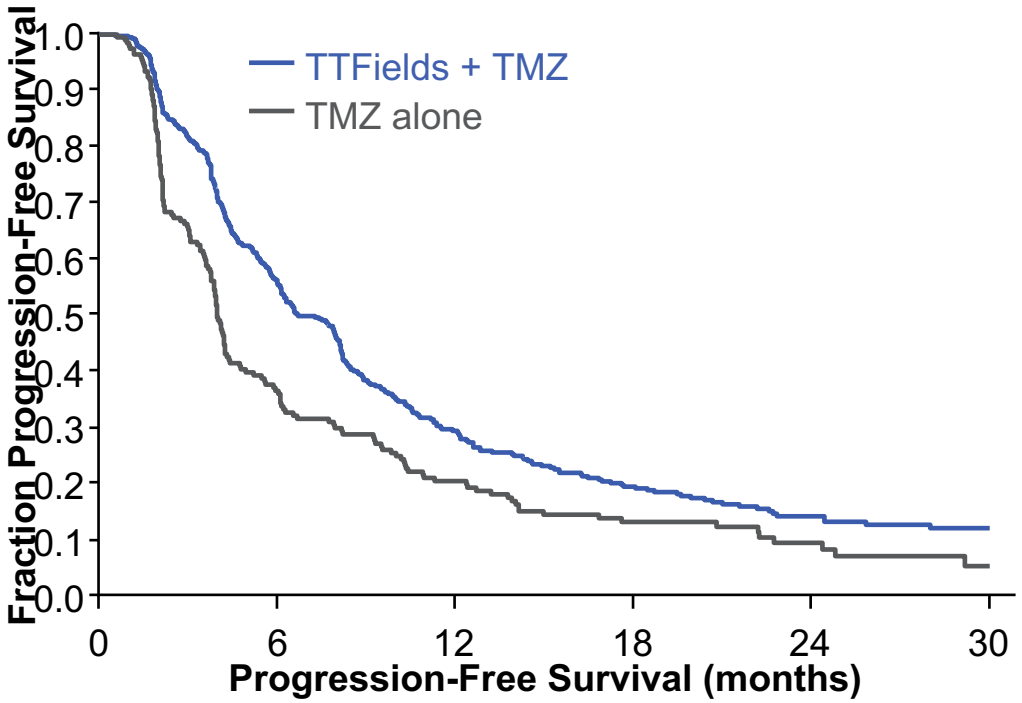
At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m	42 m	48 m
TTF	120	63	24	15	9	7	4	2	1
BPC	117	56	22	14	6	2	1	0	0

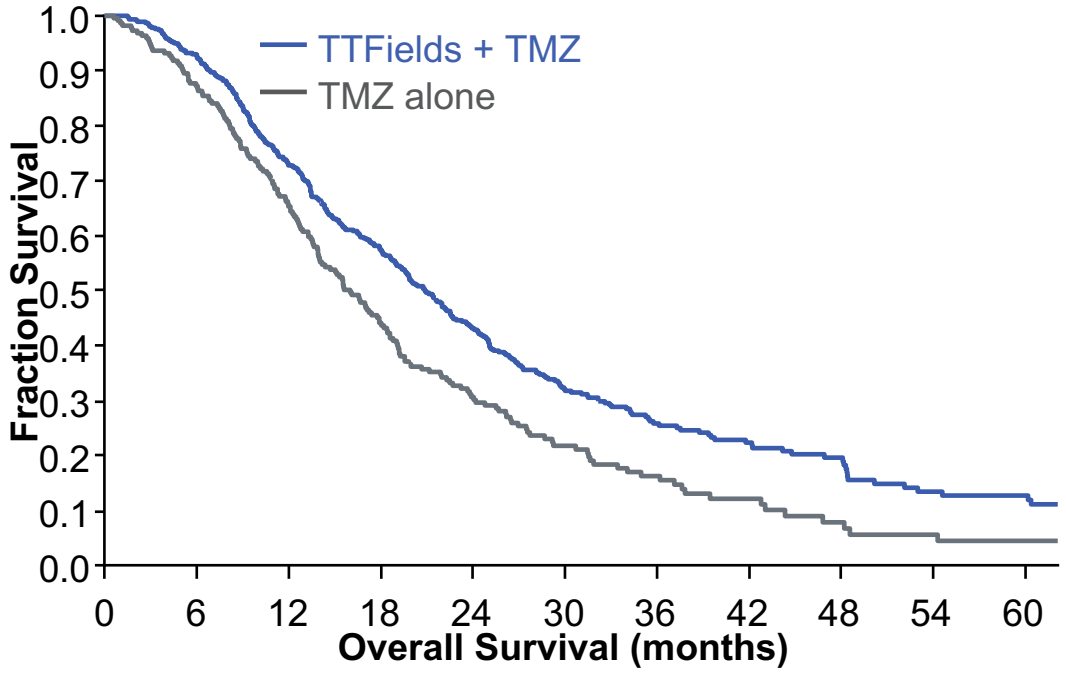
0 m	13 w	26w	39w	52w	65 w	78 w	91 w
120	38	19	14	11	6	4	3
117	34	14	10	3	1	0	0

Fig. 2. Overall survival (A) and progression free survival (B) Kaplan–Meier curves.

Quindi cosa fare?

- Dati biologici → presenti; non ancora del tutto esaustivi soprattutto per quel che riguarda le correlazioni con altri fattori biologici in vivo
- Dati clinici → nel paziente recidivato
  → nel mantenimento post Stupp E14 → vantaggio di massimo 5 mesi in OS





Quindi cosa fare?

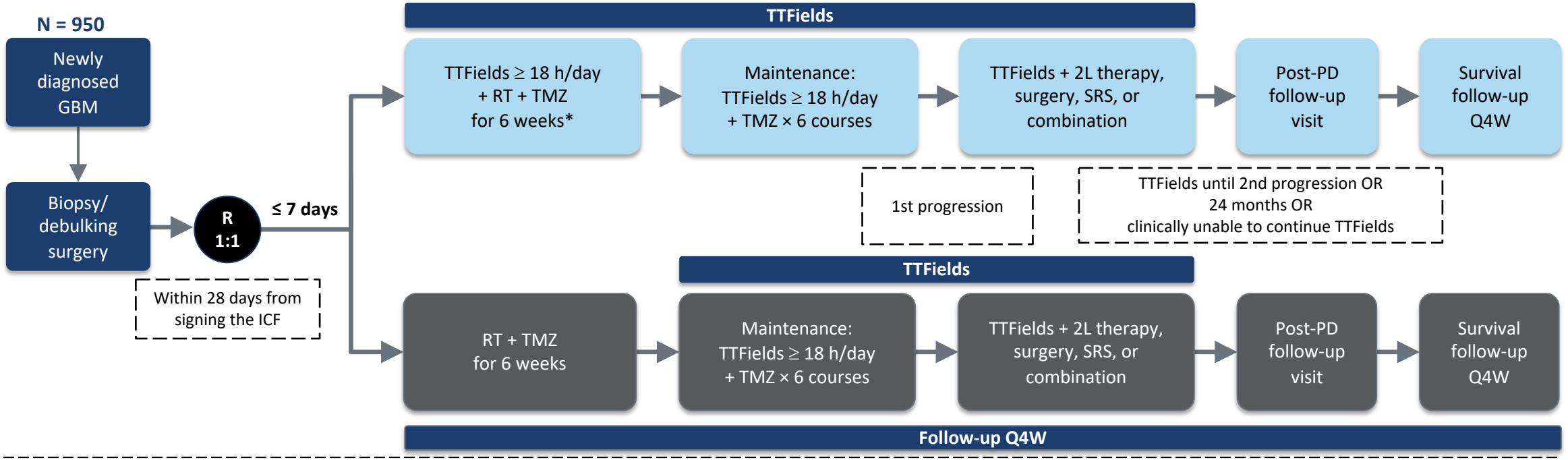
- Dati biologici → presenti; non ancora del tutto esaustivi soprattutto per quell che riguarda le correlazioni con altri fattori biologici in vivo
- Dati clinici → nel paziente recidivato
  → nel mantenimento post Stupp E14 → vantaggio di massimo 5 mesi in OS (cross over)
- Dati economici → contrastanti
- Dubbi sui bias di valutazione → es. QoL (non doppio cieco; interim analysis; ITT)
- Linee Guida Europee → non completamente supportato quando è applicate la metodologia di definizione dell'evidenza.

tutti

EF-32: Pivotal, Randomized, Open-Label Study of Optune® (Tumor Treating Fields Therapy [TTFields], 200 kHz) Concomitant With Radiation Therapy and Temozolomide for the Treatment of Newly Diagnosed Glioblastoma

(Trident)

Phase 3 Pivotal Trial Design[1,2]
TTFields therapy with concomitant chemoradiotherapy in newly diagnosed GBM



Start date: December 2020
Primary completion date: August 2024
Study completion date: August 2026
Study sites: 119 (North America, Europe, Israel)

Stratification
- Resection extent
- *MGMT* promoter methylation status

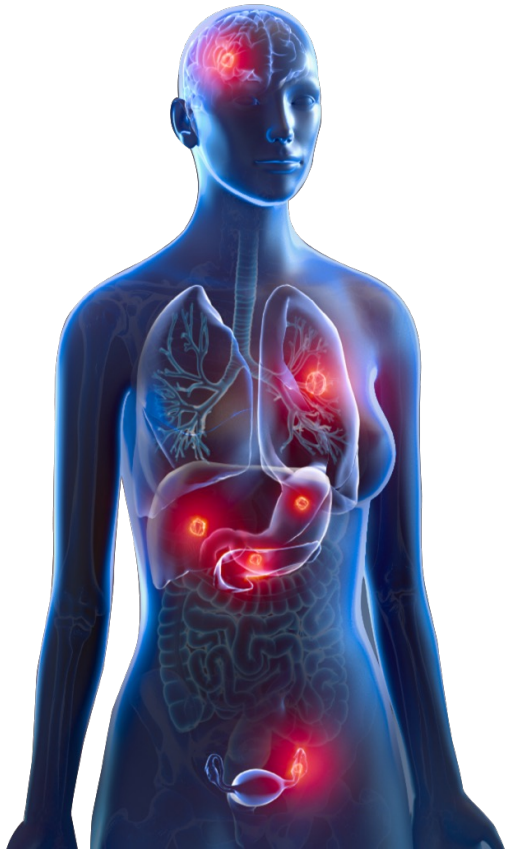
Primary endpoint
- OS

Secondary endpoints
- PFS, PFS6/12, 1Y/2Y SR, ORR, 2nd PFS, EORTC QLQ-C30/BN20, AEs (severity and frequency), dependence of OS on TTFields dose, pathological changes in resected GBM tumors, NANO scale

- *RT delivered through the arrays (INE transducer arrays).
- 1Y, 1-year; 2L, second-line; 2Y, 2-year; AE, adverse event; EORTC, European Organization for Research and Treatment of Cancer; GBM, glioblastoma; ICF, informed consent form; MGMT, O6-methylguanine-DNA methyltransferase; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS6/12, progression-free survival at 6/12 months; Q4W, every 4 weeks; QLQ, quality of life questionnaire; R, randomized; RT, radiation therapy; SR, survival rate; SRS, stereotactic radiosurgery; TMZ, temozolomide; TTFields, Tumor Treating Fields.
- **References: 1.** Novocure Data on File OPT-160.1. **2.** ClinicalTrials.gov. [NCT04471844]. Accessed June 12, 2023.

Clinical Pipeline

Overview of Novocure's Clinical Pipeline



		Phase 2 / Pilot	Phase 3 / Pivotal	Approved
Primary Brain Cancer Program	Newly Diagnosed Glioblastoma	EF-07	EF-14	
		TRIDENT		
		EF-41/KEYNOTE-D58*		
	Recurrent Glioblastoma	EF-07	EF-11	
		EF-33		
Thoracic Cancer Program	Brain Metastasis from NSCLC	METIS		
	Non-Small Cell Lung Cancer	EF-15	LUNAR	
		KEYNOTE B36*		
	Mesothelioma	STELLAR		
Abdominal/ Pelvic Cancer Program	Pancreatic Cancer	PANOVA	PANOVA-3	
		PANOVA-4†		
	Hepatocellular Carcinoma	HEPANOVA		
	Gastric Adenocarcinoma	EF-31/ZL-8301-001‡		
	Ovarian Cancer	INNOVATE	ENGOT-ov50/INNOVATE-3	

*In collaboration with MSD, a tradename of Merck & Co., Inc. †In collaboration with Roche. ‡In collaboration with Zai Lab.

Tumor Treating Fields (TTFields) are not approved in the United States or CE marked in Europe for the treatment of brain metastasis, pancreatic cancer, hepatocellular carcinoma, gastric adenocarcinoma, or ovarian cancer. The safety and effectiveness of TTFields therapy for these uses has not been established. TTFields therapy (200 kHz) is approved in the United States for the treatment of adult patients (22 years of age or older) with histologically confirmed supratentorial GBM by the US FDA through the PMA pathway. TTFields therapy has received a CE mark for marketing authorization in Europe for the treatment of GBM in adult patients (18 years of age or older). TTFields therapy (150 kHz) has been approved in the United States by the FDA under the HDE pathway for the treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma to be used concurrently with pemetrexed and platinum-based chemotherapy. TTFields therapy (150 kHz) is also CE marked in Europe for the treatment of adult patients with unresectable, advanced or metastatic mesothelioma to be used concurrently with pemetrexed and platinum-based chemotherapy, as well as for adult patients for the treatment of stage IV non-squamous non-small cell lung cancer in combination with pemetrexed, after failure of first line treatments. TTFields are not approved in the United States for the treatment of lung cancer.

For further information, visit novocuretrials.com or scan the following QR code: