TUMOR TREATING FIELDS

MECHANISMS AND CLINICAL TRIALS

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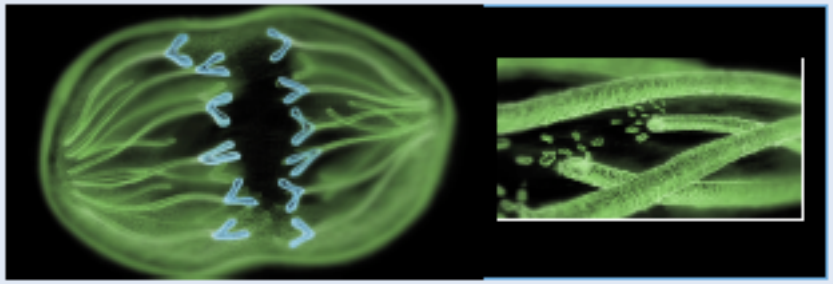
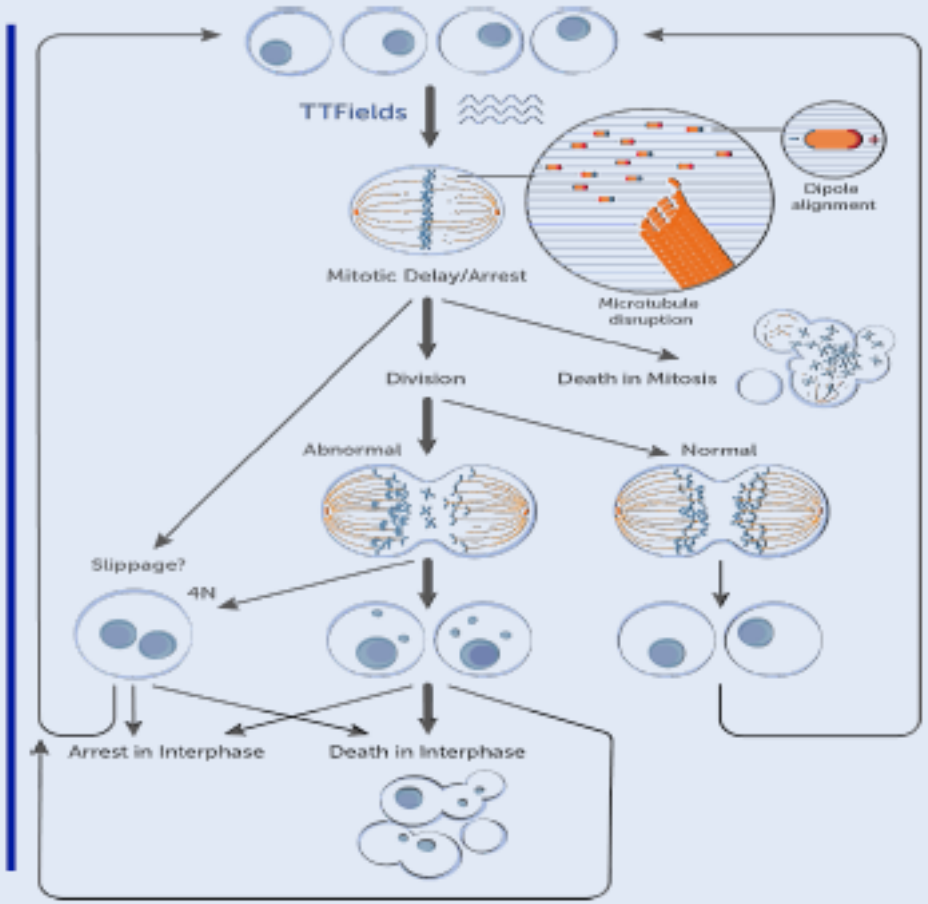
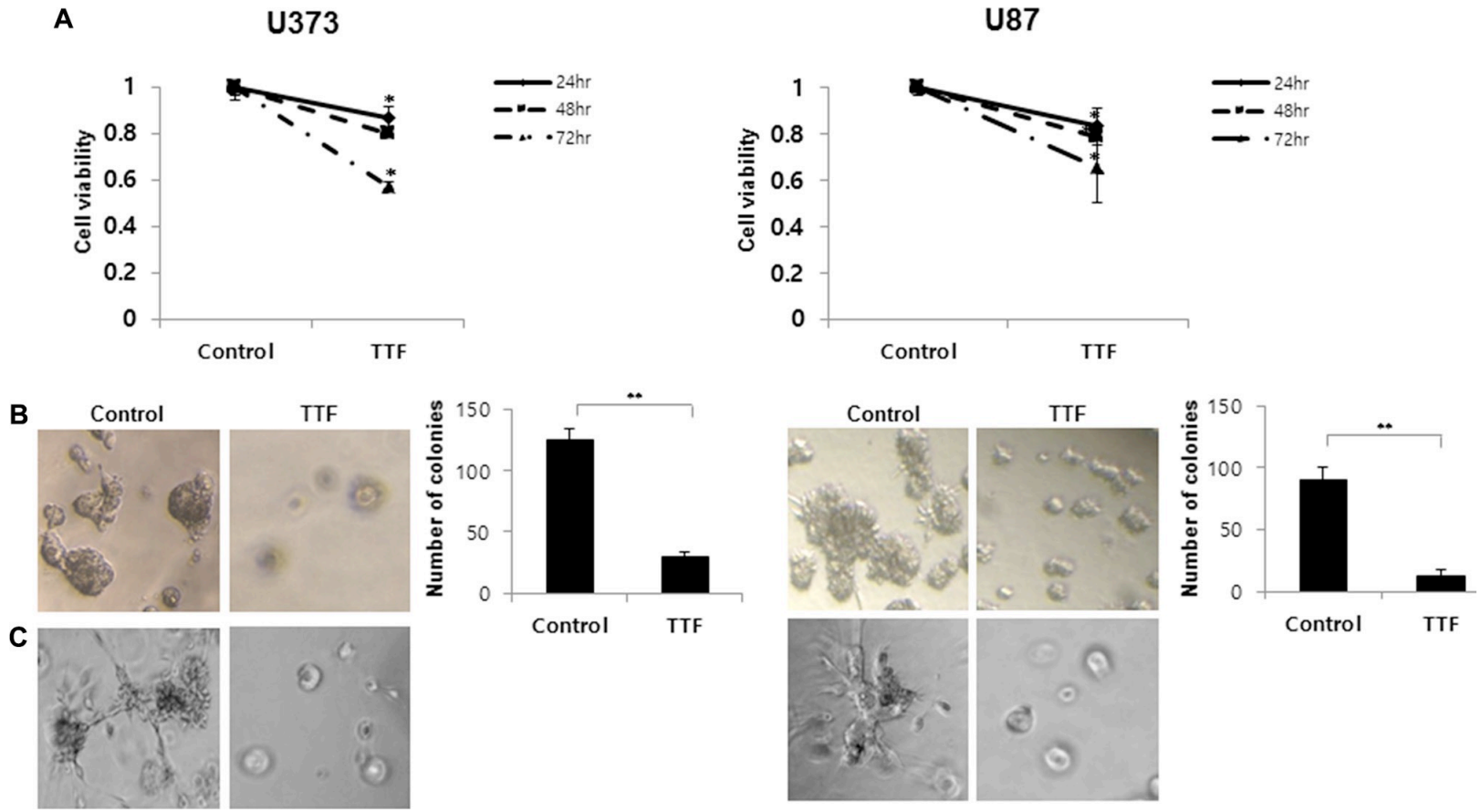
Tumor Treating Fields - Mode of Action

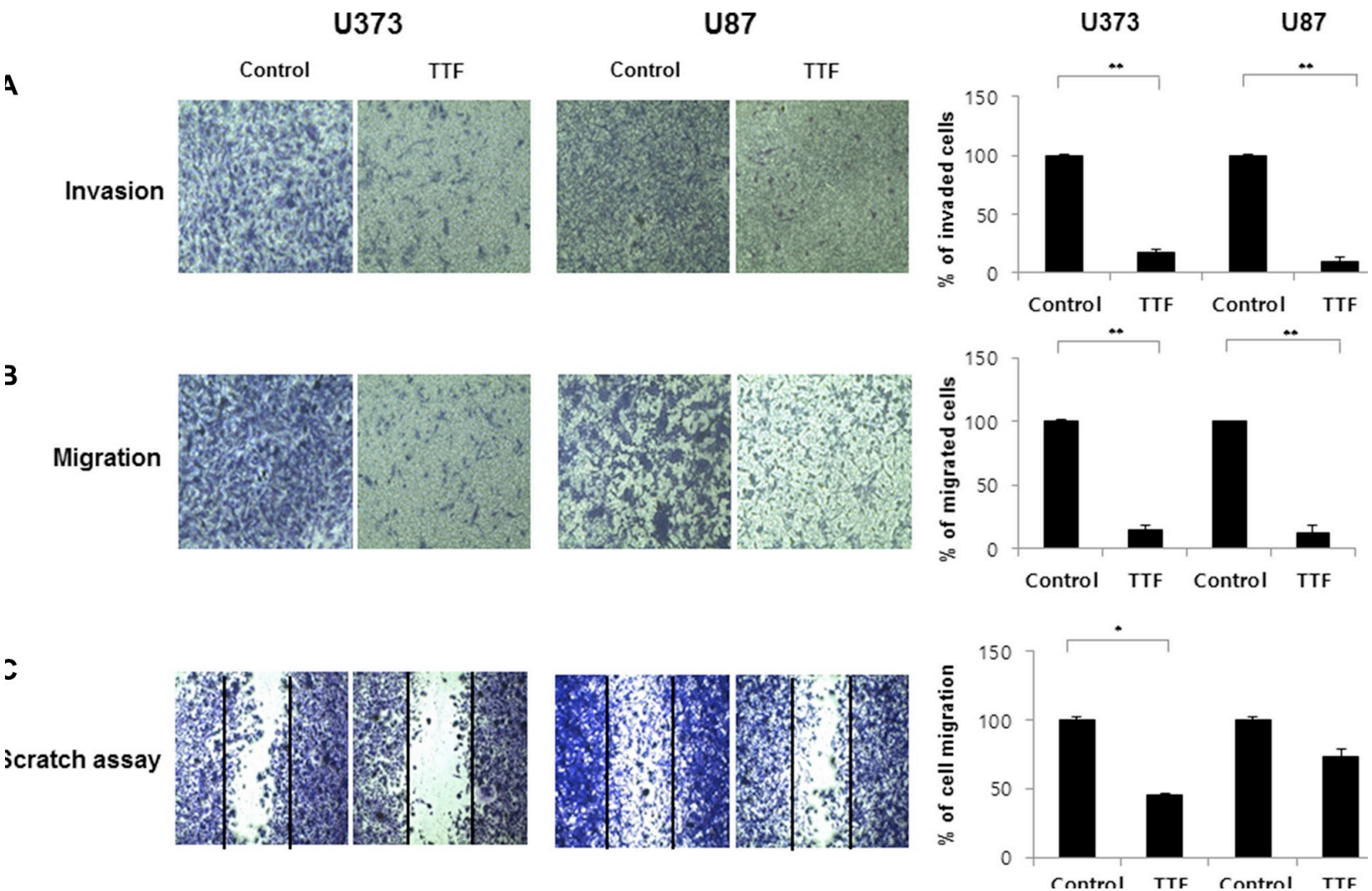


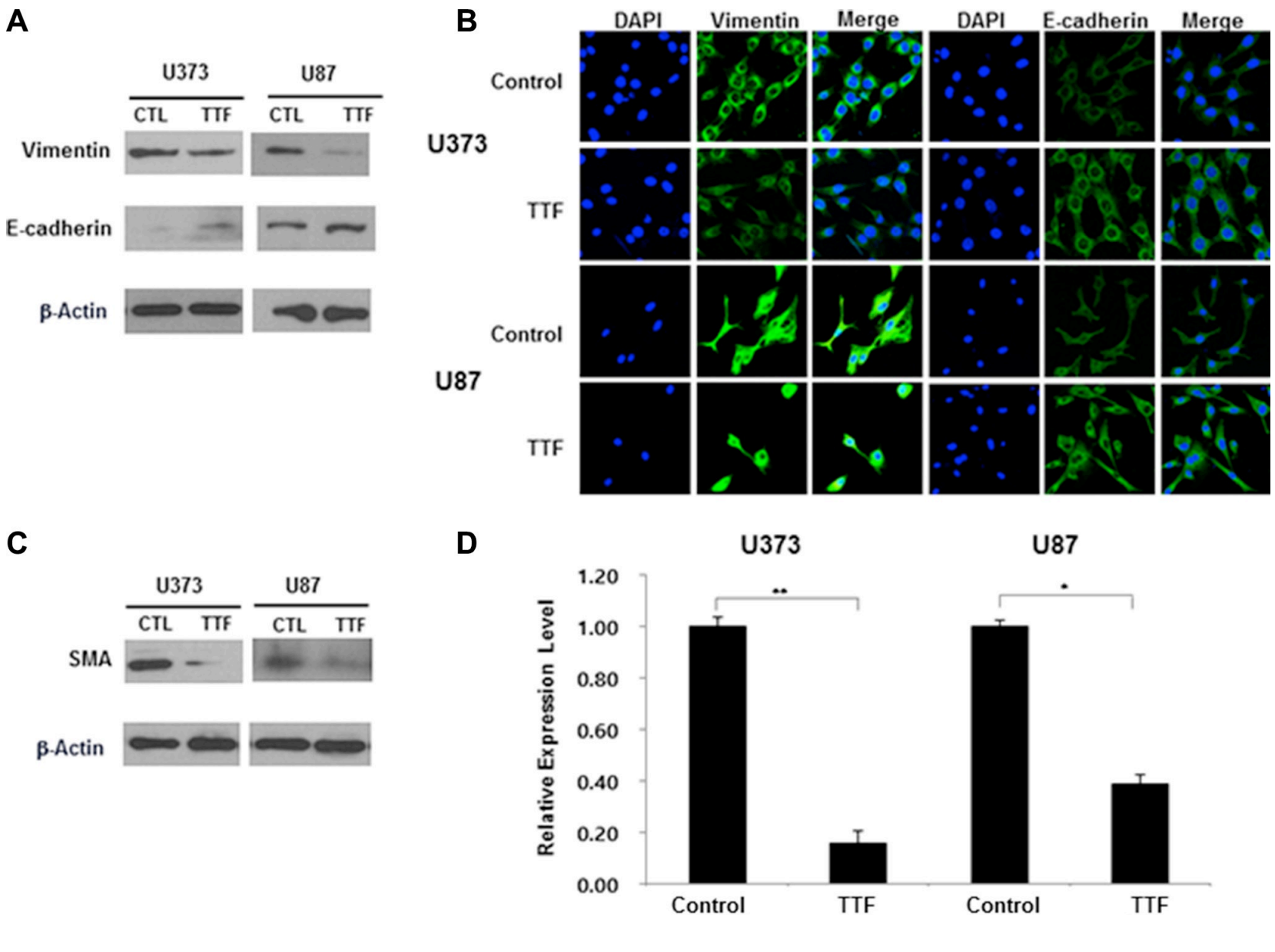
- Action on dividing cells
  - Effect on spindle apparatus
- Alternating fields effect on polar tubulin→
  - Disruption of microtubule assembly
  - Cell cycle arrest
    - → prolongation of mitosis
  - Aneuploidy



Giladi M et al., Sci Rep. 2015 Dec 11;5:18046


A
U373
U87
Cell viability
1
0.8
0.6
0.4
0.2
0
Control
TTF
24hr
48hr
72hr
B
C
Control
TTF
Number of colonies
150
100
50
0
**


U373
U87
U373
U87
Control
TTF
Control
TTF
A
Invasion
% of invaded cells
150
100
50
0
**
**
Control
TTF
Control
TTF
B
Migration
% of migrated cells
150
100
50
0
**
**
Control
TTF
Control
TTF
C
Scratch assay
% of cell migration
150
100
50
0
*
Control
TTF
Control
TTF


A
U373
U87
CTL
TTF
CTL
TTF
Vimentin
E-cadherin
β-Actin
B
DAPI
Vimentin
Merge
DAPI
E-cadherin
Merge
Control
U373
TTF
Control
U87
TTF
C
U373
U87
CTL
TTF
CTL
TTF
SMA
β-Actin
D
U373
U87
Relative Expression Level
1.20
1.00
0.80
0.60
0.40
0.20
0.00
**
*
Control
TTF
Control
TTF

EFFECTS ON SIGNALLING PATHWAYS GBM CELL LINES

- DOWN REGULATES
  - NFKb, MMP2, MMP9
  - PI3K, MAPK
  - HIF1a, VEGF

- Kim EH, 2016 Oncotarget 7:40: 65125

TTF AND IONIZING RADIATION IN VITRO MODELS

- SYNERGISTIC EFFECTS
  - INDUCING APOPTOSIS
  - DOUBLE STRAND BREAKS / PROLONGED H2AXgamma
  - INDUCTION OF MULTINUCLEATION AND MITOTIC ABNORMALITIES
  - INHIBITION OF MIGRATION IN TRANSWELL CHAMBER ASSAYS
  - RADIOSENSITIZATION EFFECT

- Kim EH, 2016 Oncotarget 7:38: 62267

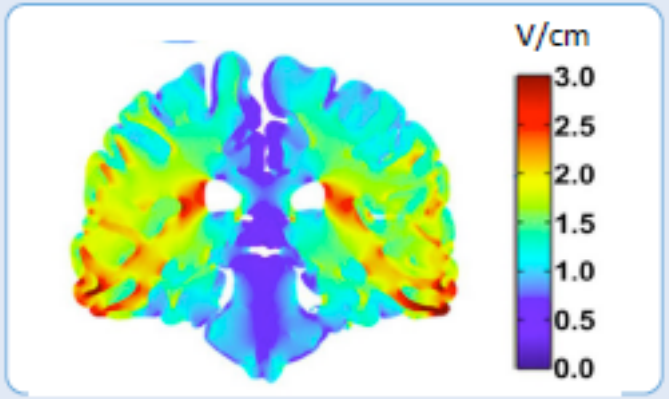
BIOPHYSICAL MECHANISMS COMPUTATIONAL MODELLING

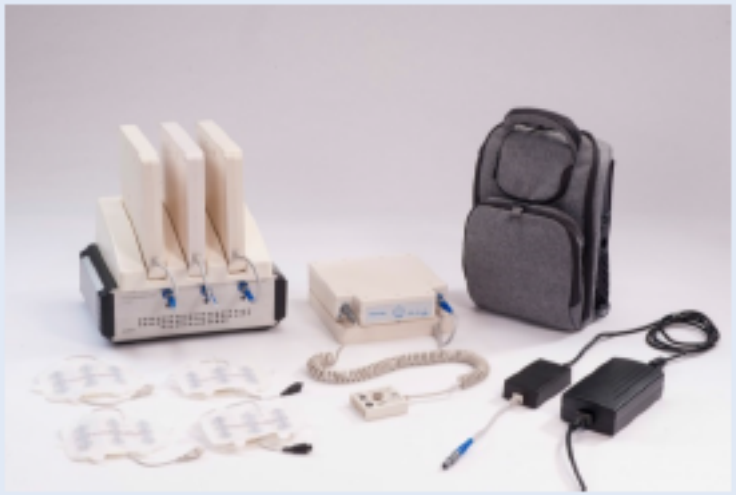
- POTENTIALLY COMPATIBLE WITH COMPUTATIONAL MODELS
  - ELECTROSTATIC EFFECTS ON TUBULIN DIPOLES EFFECT CONFORMATION
    - C-TERMINAL DYNAMICS
  - ION CONDUCTIVITY THROUGH MICROTUBULAR CORES OR SURFACE
- INCOMPATIBLE WITH MODELS
  - MEMBRANE DEPOLARIZATION EFFECTS
  - ION CHANNEL CONDUCTION EFFECTS

  - Tuzsynski et al; 2016

Delivery System and Field Distribution

- TTFields are delivered to the supratentorial brain using a portable medical device
- The device includes:
  - a field generator
  - batteries and power supply
  - four transducer arrays at a time
- Following EF-14 termination a second generation device is available
  - half size and weight of gen 1
  - device with battery weigh 2.7 lbs





Miranda PC et al., Phys Med Biol.; 2014; 59(15): 4137–4147

CLINICAL TRIAL ENDPOINTS DEFINITIONS

- OVERALL SURVIVAL
- TIME TO PROGRESSION/PROGRESSION FREE SURVIVAL
- IN FIELD VRS SYSTEMIC PROGRESSION
- RESPONSE RATES
  - COMPLETE
  - PARTIAL
  - STABLE DISEASE
  - CLINICAL BENEFIT RATE: CR+PR+SD

TUMOR TREATING FIELDS RECURRENT GLIOBLASTOMA EF-11

- RECURRENT GLIOBLASTOMA: 237 PATIENTS
- TTF VRS CLINICIAN CHOICE CHEMOTHERAPY
- EQUIVALENT OS TO CHEMOTHERAPY
- MINIMAL TOXICITY
- APPROVED IN US FOR RECURRENT GBM
- 6M OS 6.6 VRS 3.3M IN BEVACIZUMAB FAILURES

Tumor Treating Fields (TTFields) in Recurrent GBM. An Updated Subgroup Analysis of the Phase III Data

Andrew A. Kanner (1), Eric T. Wong (2), John L. Villano (3), Zvi Ram (1) on behalf of the EF-11 investigators

(1) Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, (2) Beth Israel Deaconess Medical Center, Boston, MA, USA, (3) UK HealthCare, Lexington, KY, USA

ABSTRACT

•NovoTTF-100A (Novocure Ltd.) is an anti-mitotic therapeutic device which delivers low intensity, alternating electric fields (Tumor treating fields - TTFields) to the brain. These fields interfere with cell division during metaphase and anaphase. This portable device was investigated in a prospective, randomized clinical phase III trial (n=237) and showed that NovoTTF-100A was equivalent in efficacy with better quality of life and lower toxicity compared to active chemotherapy (including bevacizumab) in patients with recurrent glioblastoma. The device has been approved by the FDA for the treatment of recurrent GBM based this data.

•We performed a subgroup analysis using a Cox Proportional Hazards model on the latest update of the trial database. As expected, older age, biopsy only, larger tumor size, prior bevacizumab failure and lower KPS were associated with shorter survival. Interestingly, in certain subgroups the effect of NovoTTF-100A appeared superior to that of cytotoxic chemotherapy and bevacizumab. These included bevacizumab failures (n=44; median OS = 6 vs. 3.3 months respectively, p=0.01), prior low grade gliomas (n=21; median OS = 25.3 vs. 7.7 months respectively, p=0.049) and KPS=>80 (n=161; median OS = 7.9 vs. 6.1 months, respectively, p=0.045). In addition, higher compliance with NovoTTF-100A use was associated with a statistically significant increase in survival (log rank test for trends p = 0.039). Patients aged <=60 years used the device more than those >60 years of age (80% vs. 74% compliance, respectively, p=0.043). Accordingly, patient aged <=60 years showed a survival trend in favor of NovoTTF-100A compared to chemotherapy (n=168; median OS = 7.4 vs. 6.2 months, respectively, p=0.063).

•In conclusion, this post hoc, subgroup analysis suggests certain patient and tumor characteristics which may be associated with better response to NovoTTF-100A treatment. These results should be viewed as hypothesis generating analyses to guide future testing of this novel treatment modality.

METHODS AND MATERIALS

NovoTTF-100A (Novocure Ltd.) is a portable device delivering low intensity, anti-mitotic electric fields (NovoTTF Therapy) via disposable transducer arrays. The device has recently been approved by the FDA for the treatment of recurrent GBM based on data from a phase III study in recurrent GBM. Bevacizumab (BEV) is FDA approved based on non-controlled data for the treatment of the same indication. This presentation will describe a post-hoc sub-analysis of the phase III data of NovoTTF-100A monotherapy and will try to uncover which patient populations may benefit most from the device. In addition, the device patients will be compared to the patients in the control group who received BEV containing regimens.

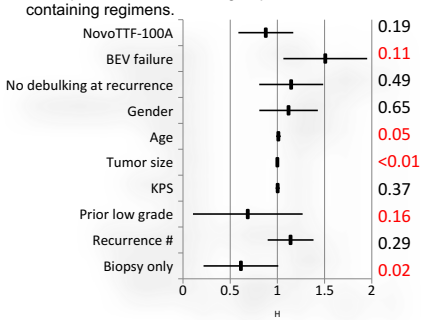


Fig. 1: Cox Proportional Hazards Model of baseline prognostic factors. *p-values (red = significant)*

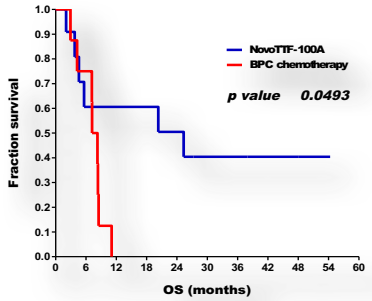


Fig. 2: Overall survival of secondary recurrent GBM patients (prior low grade glioma). NovoTTF treated n=12, BPC chemotherapy treated n=9. Median = 25.3 mo vs. 7.7 mo, respectively. HR = 0.31.

RESULTS

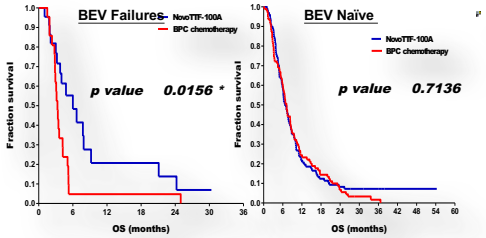


Fig. 3: Overall survival comparison between NovoTTF treatment and BPC chemotherapy in BEV naïve and BEV failure patients. In BEV failures median overall survival was 6.0 mo vs. 3.3 mo, respectively. HR = 0.43.

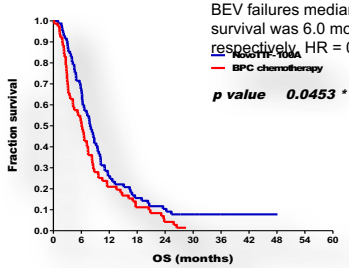


Fig. 4: Overall survival in patients with KPS ≥ 80. NovoTTF treated n=83, BPC chemotherapy treated n=77. Median survival = 7.9 mo vs. 6.1 mo, respectively. HR = 0.71.

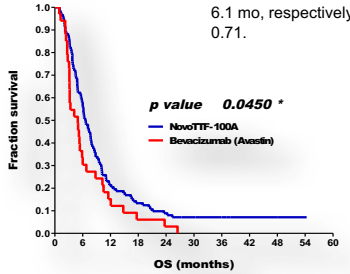


Fig. 5: Overall survival of NovoTTF patients (n=120) compared to patients on BEV containing regimens (n=36). Median overall survival was 6.6 mo vs. 4.9 mon, respectively. HR = 0.64.

RESULTS

In addition, higher compliance with NovoTTF-100A use was associated with a statistically significant increase in survival (log rank test for trends p = 0.039). Patients aged ≤60 years used the device more than those >60 years of age (80% vs. 74% compliance, respectively, p=0.043). Patients > 60 years of age has a trend towards longer survival on NovoTTF (HR=0.74; p=0.0631).

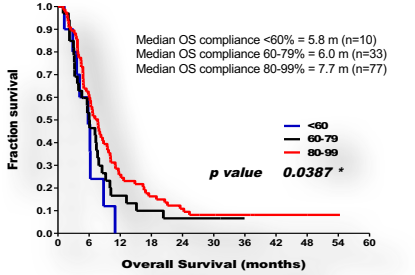


Fig.: 6: Trend in overall survival K-M curves by compliance with NovoTTF treatment. Increased compliance was significantly correlated with improvement in overall survival.

CONCLUSIONS

- This post-hoc subgroup analysis suggests certain patient and tumor characteristics which may be associated with better response to NovoTTF-100A treatment.
- These characteristics include younger age, prior diagnosis of low grade glioma, better performance status and better compliance with NovoTTF-100A treatment.
- In addition, patients who failed BEV appeared to benefit more from NovoTTF-100A than from chemotherapy.
- Finally, patients randomized to receive BEV on the control arm of the study had shorter survival times than those who received NovoTTF-100A.
- These results should be viewed as hypothesis generating analyses to guide future testing of this novel treatment modality.

Reference: Stupp R, Wong ET, Kanner AA et al., **NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality.** Eur J Cancer. 2012 Sep;48(14):2192-202.

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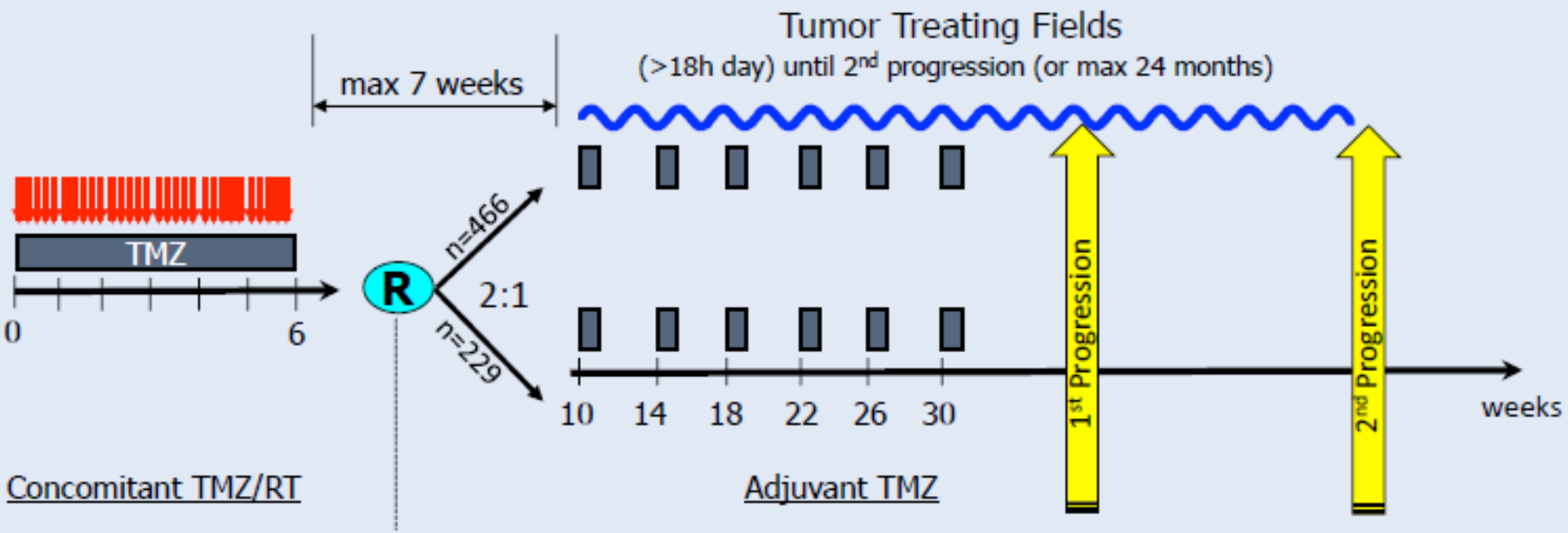
PROSPECTIVE, MULTI-CENTER PHASE III TRIAL OF TUMOR TREATING FIELDS TOGETHER WITH TEMOZOLOMIDE COMPARED TO TEMOZOLOMIDE ALONE IN NEWLY DIAGNOSED GLIOBLASTOMA

Roger Stupp, Ahmed Idbaih, David M. Steinberg, William Read, Steven Toms, Gene Barnett, Garth Nicholas, Chae-Yong Kim, Karen Fink, Andrea Salmaggi, Frank Lieberman, Jay Zhu, Lynne Taylor, Giuseppe Stragliotto, Andreas F. Hottinger, Eilon D. Kirson, Uri Weinberg, Yoram Palti, Monika E. Hegi, and Zvi Ram on behalf of the EF-14 Trial investigators

Late Breaking Abstract

18. November 2016

EF14: Treatment Scheme & Study Design



Stratification:
Resection: complete *vs* parital *vs* biopsy
MGMT methylation status

Stupp R et al., JAMA; 2015; 314:2535-43

Endpoints & Statistical Considerations

Primary:

- Progression-free survival
  - blinded central radiology review
  - 80% power; p=0.05; HR = 0.78

Secondary:

- Overall survival
  - Only if PFS positive
  - 80% power; p=0.05; HR=0.76
- PFS6
- Landmark survival rates every 12 months
- Quality of life

- Randomization 2 : 1
- 700 patients / 4 yrs
  - (630 pts + 10% for lost to follow-up)
- Planned interim analysis
  - *Stupp et al. JAMA Dec 2015*
- Final analysis
  - PFS - stratified Log Rank test
    - $P < 0.04574$ (*at final analysis)
  - OS – stratified log Rank test
    - $P < 0.0481$ (*at final analysis)
- All results presented as ITT (intent-to-treat)

*Based on the Lan-DeMets - O'brien Flemming method

Patient Characteristics

	TTFields/TMZ (n=466)	TMZ alone (n=229)
Age, median (range)	56.0 (19-83)	57.0 (19-80)
Male	68%	69%
KPS, median (range)	90 (60-100)	90 (70-100)
Impaired MMSE (< 27)	20%	23%
Antiepileptic therapy at baseline	44%	41%
Steroids at baseline	29%	28%

Tumor Characteristics

	TTFields/TMZ (n=466)	TMZ alone (n=229)
Extent of resection		
Biopsy only	13%	13%
Partial / complete resection	34% / 53%	34% / 53%
MGMT : tissue avail. + tested	82%	81%
methylated / unmethylated / invalid	**35%** / 54% / 10%	**42%** / 51% / 7%
IDH1 Mutation (R132H), assessable	56%	52%
positive	7%	5%

Safety (Grade 3-4 AEs) in ≥ 2% of Patients

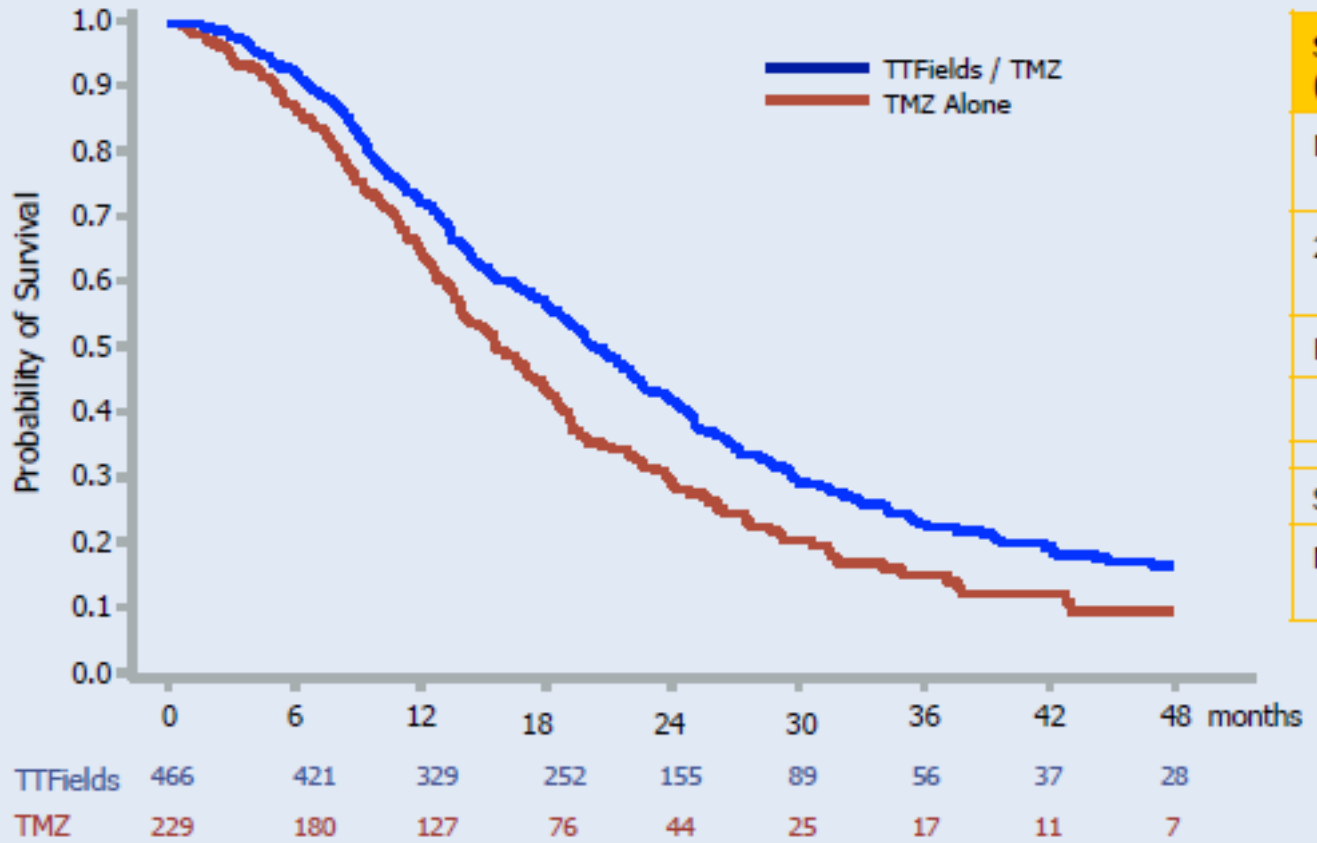
	TTFields / TMZ (N=456)		TMZ Alone (N=216)	
System Organ Class \ Preferred Term	Grade 3	Grade 4	Grade 3	Grade 4
Number of Patients with >=1 AE	37%	14%	36%	12%
Blood and lymphatic system disorders	9%	4%	9%	2%
Leukopenia	2%	0	<1%	0
Lymphopenia	3%	1%	3%	0
Neutropenia	2%	1%	1%	<1%
Thrombocytopenia	6%	3%	4%	1%
Gastrointestinal disorders	5%	<1%	3%	<1%
General disorders + administration site conditions	9%	<1%	6%	0
Asthenia	3%	0	1%	0
Fatigue	4%	0	3%	0
Gait disturbance	2%	0	1%	0
Infections and infestations	7%	<1%	4%	1%
Injury, poisoning and procedural complications	5%	0	3%	0
Fall	2%	0	1%	0
Medical device site reaction	2%†	0	0	0

†: Grade 1+2 skin irritations in 52% of patients

Safety (Grade 3-4 AEs) in ≥ 2% of Patients

	TTFields / TMZ		TMZ Alone	
	(N=456)		(N=216)	
System Organ Class \ Preferred Term	Grade 3	Grade 4	Grade 3	Grade 4
Metabolism and nutrition disorders	2%	1%	5%	0
Hyperglycemia	<1%	1%	2%	0
Musculoskeletal and connective tissue disorders	4%	<1%	4%	0
Nervous system disorders	21%	3%	18%	2%
Aphasia	2%	0	1%	0
Brain edema	2%	<1%	2%	<1%
Convulsion	5%	1%	6%	<1%
Headache	3%	0	2%	0
Hemiparesis	4%	0	2%	0
Neurological decompensation	2%	0	1%	0
Psychiatric disorders	3%	1%	3%	0
Renal and urinary disorders	1%	0	2%	0
Respiratory, thoracic and mediastinal disorders	2%	4%	3%	2%
Pulmonary embolism	<1%	3%	<1%	2%
Vascular disorders	4%	0	2%	0
Hypertension	2%	0	<1%	0

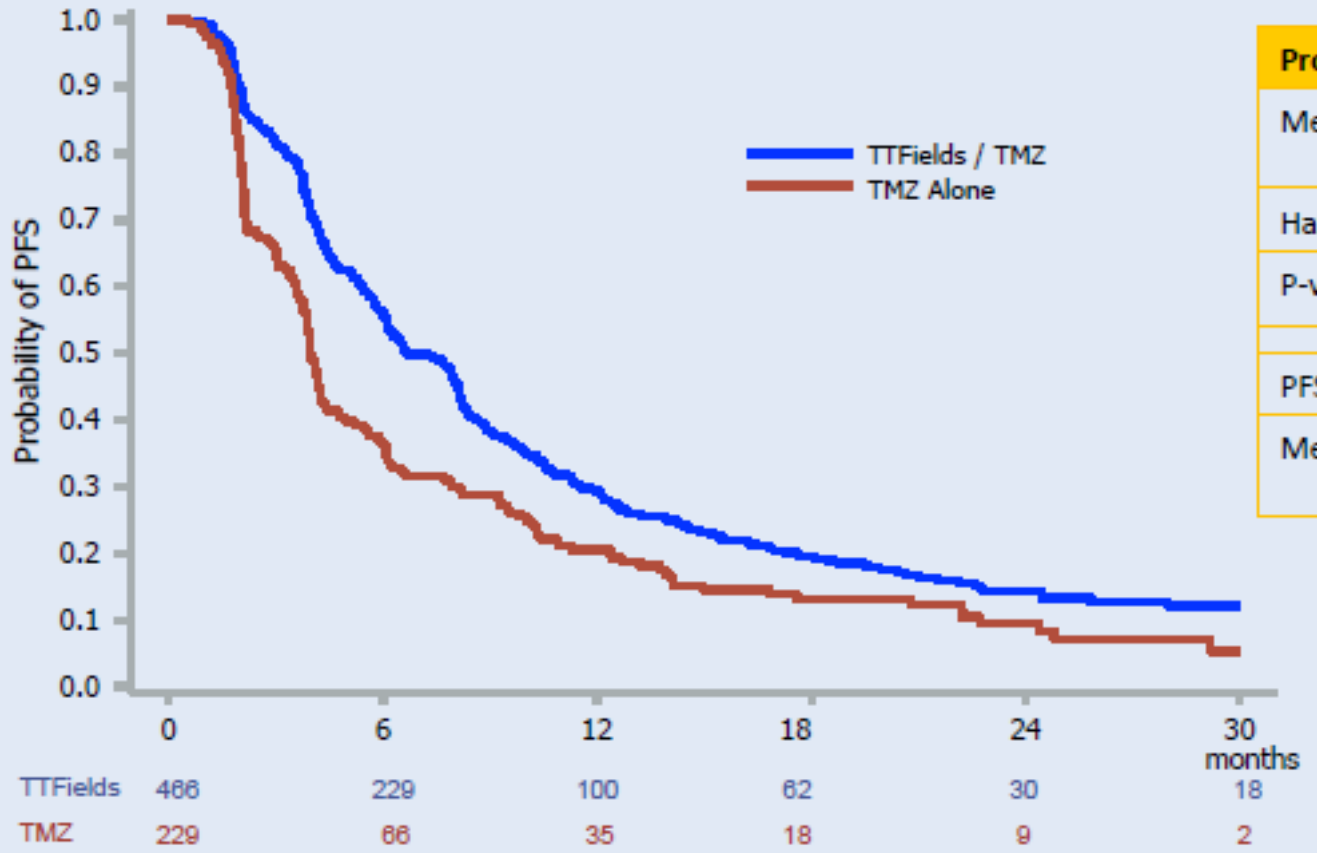
Overall Survival - ITT



Survival (from random)	TTFields/TMZ	TMZ
Median 95% CI	20.8 mo 19 .0 – 22.6	16.0 mo 13.9 – 18.2
2-year 95% CI	42.5 % (38.0 – 47.4)	30.0 % (24.4 – 37.0)
Hazard ratio	0.65 (CI 0.54 – 0.79)	
P-value	0.0006	
Survival from diagnosis (!):		
Median 95% CI	24.5 mo 22.8 – 26.3	19.8 mo 17.6 22.1

Stupp on behalf of EF-14 investigators. Society of Neuro-Oncology, 18. Nov. 2016

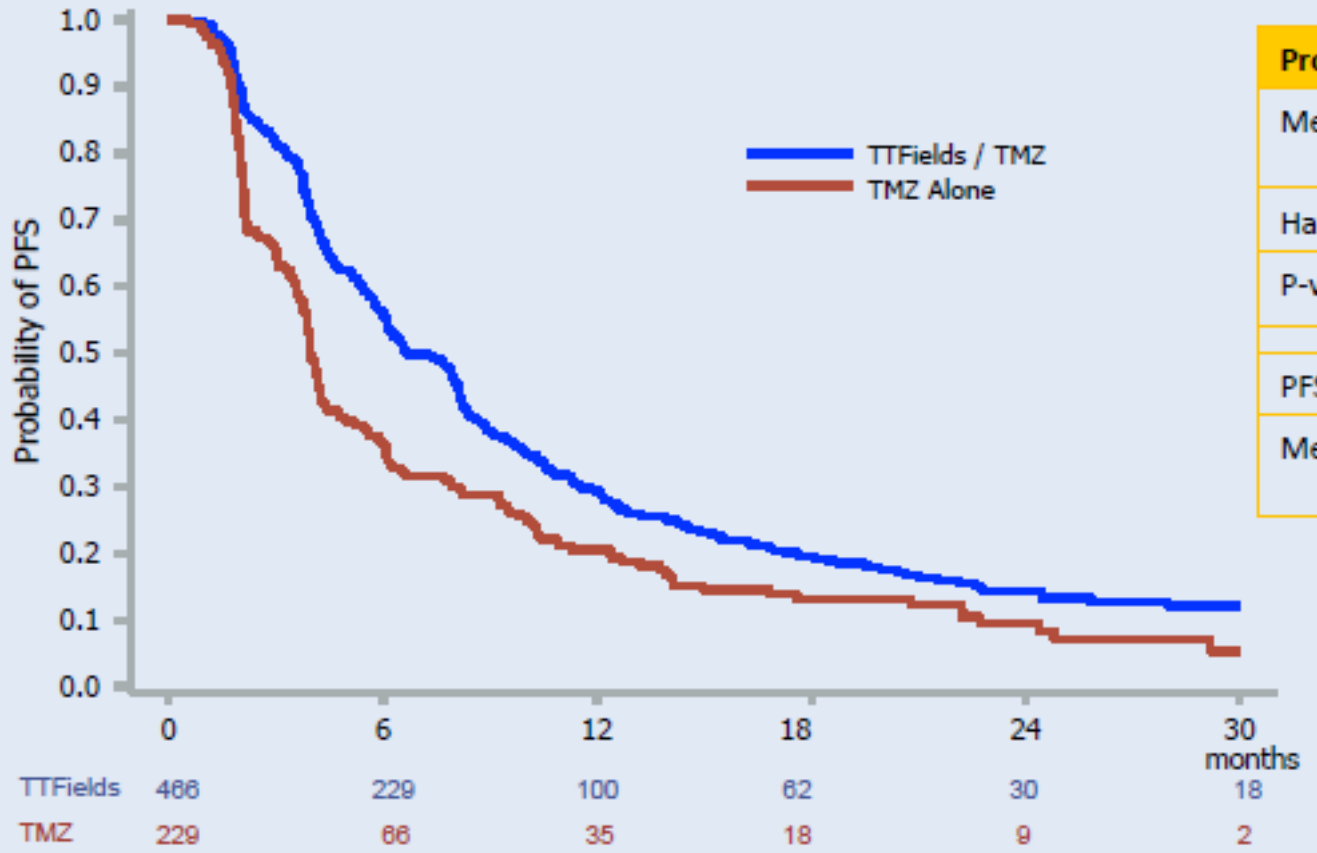
Progression Free Survival - ITT



Progr.-free	TTFields/TMZ	TMZ
Median	6.7 mo 6.1 – 8.1	4.0mo 3.8 – 4.3
Hazard ratio	0.63 (CI 0.52 – 0.76)	
P-value	0.00005	
PFS from diagnosis:		
Median	11.2 mo 10.0 – 11.8	7.8mo 7.3 – 8.2

Stupp on behalf of EF-14 investigators. Society of Neuro-Oncology, 18. Nov. 2016

Progression Free Survival - ITT



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PFS from diagnosis:		
Median	11.2 mo 10.0 – 11.8	7.8mo 7.3 – 8.2

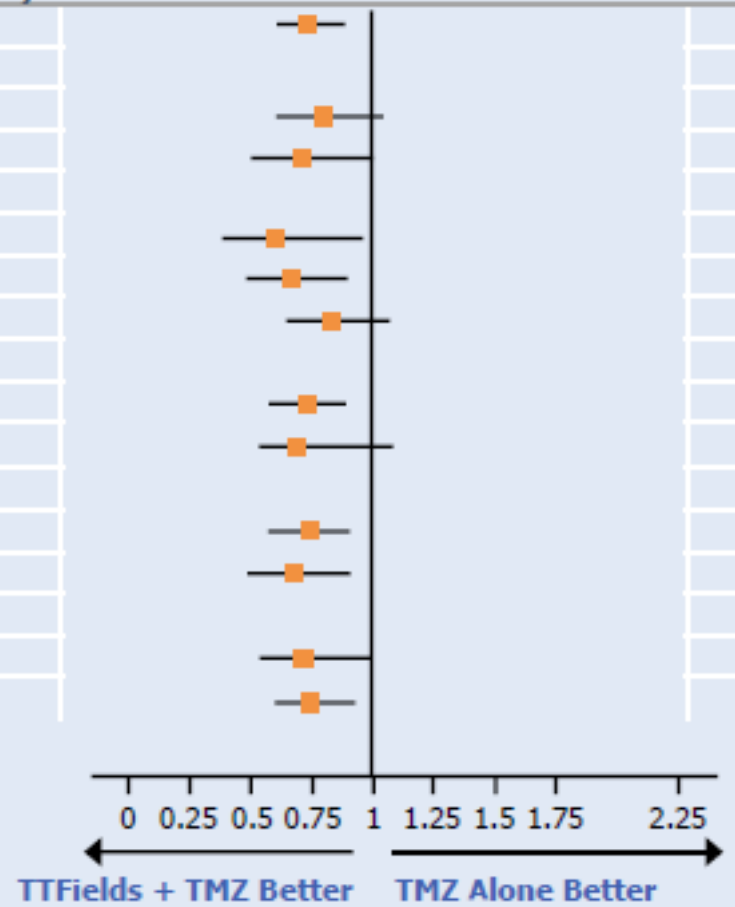
Stupp on behalf of EF-14 investigators. Society of Neuro-Oncology, 18. Nov. 2016

Cox Proportional Hazards Model for OS

Parameter	Parameter Value	Hazard Ratio	Two-sided p-value
Treatment	TTFields + TMZ	0.692	<.001
Gender	FEMALE	0.717	<.001
MGMT	METHYLATED	0.512	<.001
Age	<50 (Ref ≥50)	0.698	<.001
KPS	90-100 (Ref ≤80)	0.633	<.001
Tumor location	Frontal lobe	0.803	0.019
Region	USA (Ref Rest of Word)	0.860	0.094

Subgroup Analysis for OS

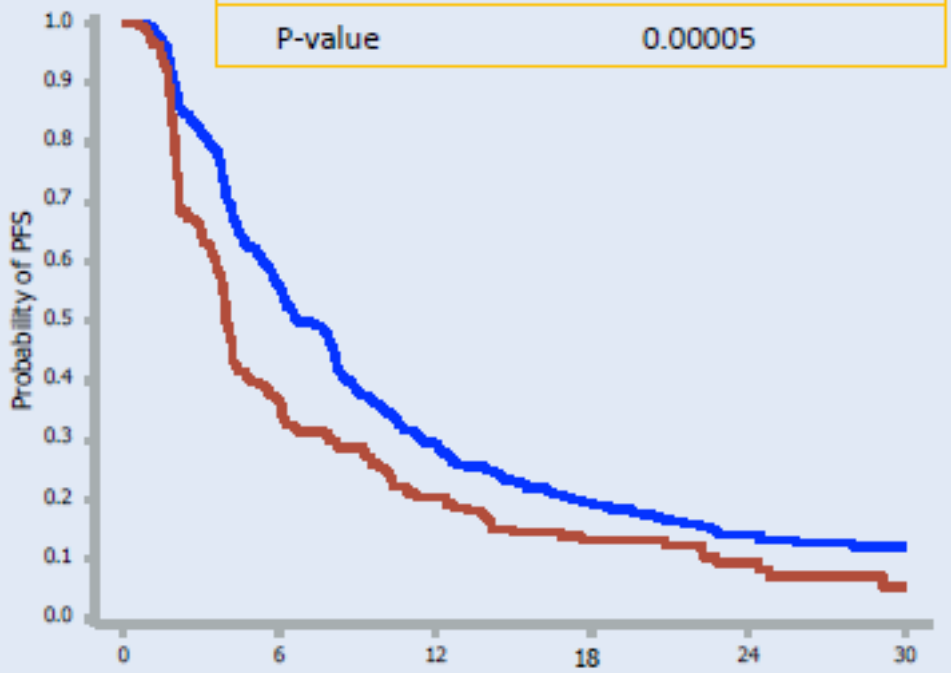
Subgroup	No. of Patients (%)	Median Survival (months)	
		TTFields/TMZ	TMZ Alone
Overall	695 (100)	20.8	16
MGMT			
Unmethylated	303 (44)	17.3	13.9
Methylated	213 (31)	29.7	21.2
Resection			
Biopsy	89 (13)	14.7	11.6
Partial	234 (34)	21.4	15.1
Gross total	372 (53)	22.6	18.5
Age			
<50 y	194 (28)	24.4	19.9
50+ y	501 (72)	19.8	15.3
KPS			
90-100	457 (67)	22.7	17.8
≤80	228 (33)	14.7	11
Gender			
Female	222 (32)	24.4	18.5
Male	473 (68)	19	15.5



Summary: Consistency of Results: Prolongation of

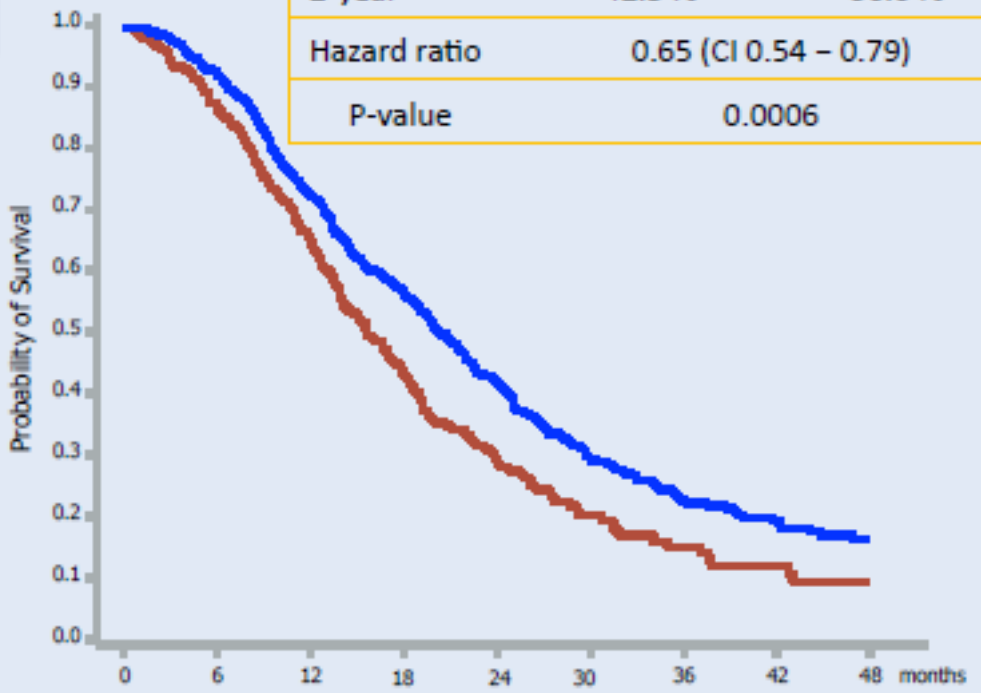
Progr.-Free Survival

Progr.-free	TTFields/TMZ	TMZ
Median	6.7 mo	4.0 mo
Hazard ratio	0.63 (CI 0.52 – 0.76)	
P-value	0.00005	



Overall Survival

Survival	TTFields/TMZ	TMZ
Median	20.8 mo	16.0 mo
2-year	42.5 %	30.0 %
Hazard ratio	0.65 (CI 0.54 – 0.79)	
P-value	0.0006	



Comparable performance of control arms of EF-14 and RTOG0525

Overall Survival		EF-14[a]	RTOG0525[b]
		Control (n=695)	Control (n=411)
from random.	median	**16.0**	**16.6**
	95%CI	13.9 – 18.2	
2 yr. – survival	median	**30%**	**34.2%**
	95%CI	21 - 39	
from registr.	median	**19.8**	**18.9**
	95%CI	17.6 – 22.1	

Summary: Magnitude of Benefit comparable to TMZ

	TMZ/RT vs TMZ *(Stupp/EORTC, NEJM 2005)*	**TTFields/TMZ vs TMZ** *Stupp/EF-14, SNO 2016*
HR	0.63	0.65
Median survival	12.1 mo → 14.5 mo Δ 2.4 mo	16.0 mo → 20.8 mo Δ 4.8 mo
2-yr surv. rate	10% → 27% Δ 17%	30% → 43% Δ 13%

TMZ; temozolomide

Stupp for EORTC/NCIC. NEJM 2005;352:987-96

Stupp for EF-14. JAMA 314:2535-2543
Society of Neuro-Oncology 2016

Conclusions

- EF-14 full dataset analysis confirms the conclusions of the interim analysis
- TTFields are safe and can be combined with TMZ chemotherapy.
  - Toxicity is limited to local skin irriation and cutaneuous reactions
  - The perceived burden of carrying the TTFields device will be assessed in the ongoing quality of life analyses
- Adjuvant therapy with TTFields significantly prolongs progression-free and overall survival in patients with newly diagnosed GBM
- TTFields should be considered part of the standard of care for patients with newly diagnosed glioblastoma
- EF-14 proves the concept of Tumor Treating Fields as a novel cancer treatment modality

AVASTIN FAILURES

- POST HOC ANALYSIS OF EF-11
- 44 PATIENTS: 23 TTF AND 21 CHEMO
- MOS 6M VRS 3.3

PANOVA

- UPFRONT UNRESECTABLE LOCALLY ADVANCED PANCREATIC CANCER
- TTF PLUS GEMCITABINE VRS GEMCITOBINE ALONE
- 20 PATIENTS
- PFS: 8.3 VRS 3.7m
- OS: 14.9 VRS 6.7M
- SURVIVAL 1 YEAR: 55% VRS 22%
- PR: 30% VRS 7%

PANOVA
COHORT 2

- UPFRONT NAVALBINE/PACLITAXEL + TTF
- WELL TOLERATED
- PFS AND SURVIVAL 1 YEAR DOUBLE PHASE 3 HISTORICAL CONTROLS

INNOVATE

- OPEN LABEL SINGLE ARM PILOT STUDY IN RECURRENT OVARIAN CA
- TTF PLUS WEEKLY PACLITAXEL
- SAFE AND TOLERABLE
- PFS DOUBLE THAT OF RECENT PHASE 3 HISTORICAL CONTROL

NSCLC

- 43 STAGE 3B AND 4
- PREMETRXED 500MG/M2 Q3W
- TTF
- ENDPOINTS: IN FIELD PROGRESSION, PFS
- IFP 28 W, PFS 22 W
- PR: 14.6% SD: 48.8%
- MOS 13.8M (5M OVER HISTORICAL CONTORLS) 1YS 57%