TUMOR TREATING FIELDS CLINICAL TRIALS AND MECHANISMS

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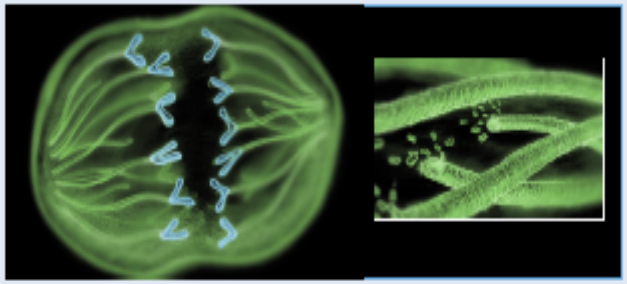
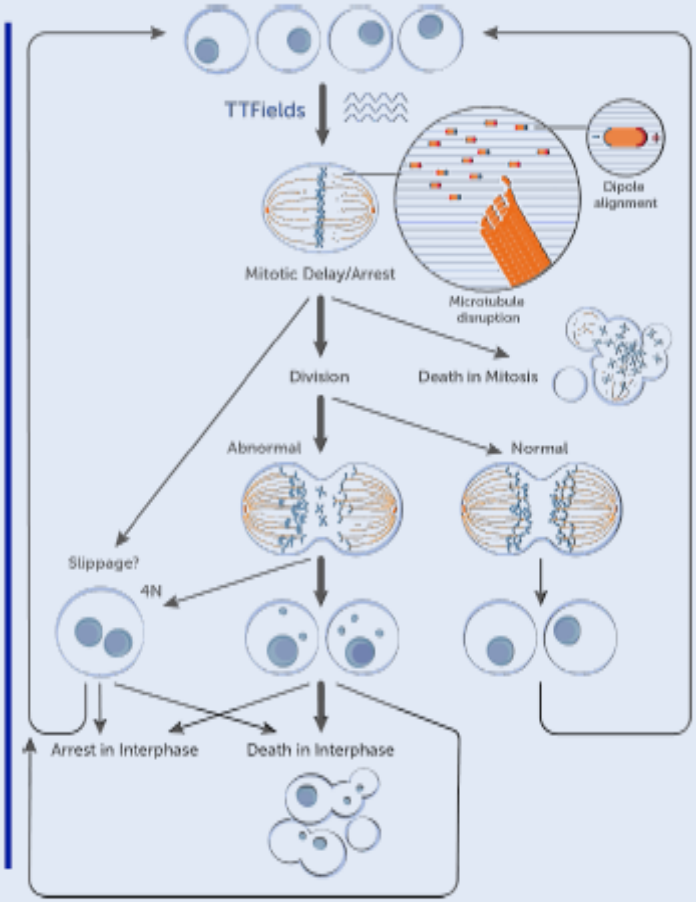
Tumor Treating Fields - Mode of Action



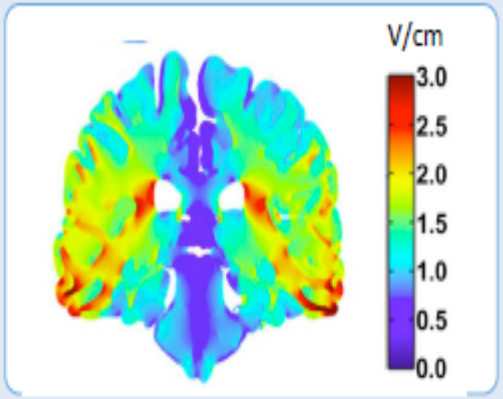
- Action on dividing cells
  - Effect on spindle apparatus
- Alternating fields effect on polar tubulin→
  - Disruption of microtubule assembly
  - Cell cycle arrest
    - → prolongation of mitosis
  - Aneuploidy



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

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

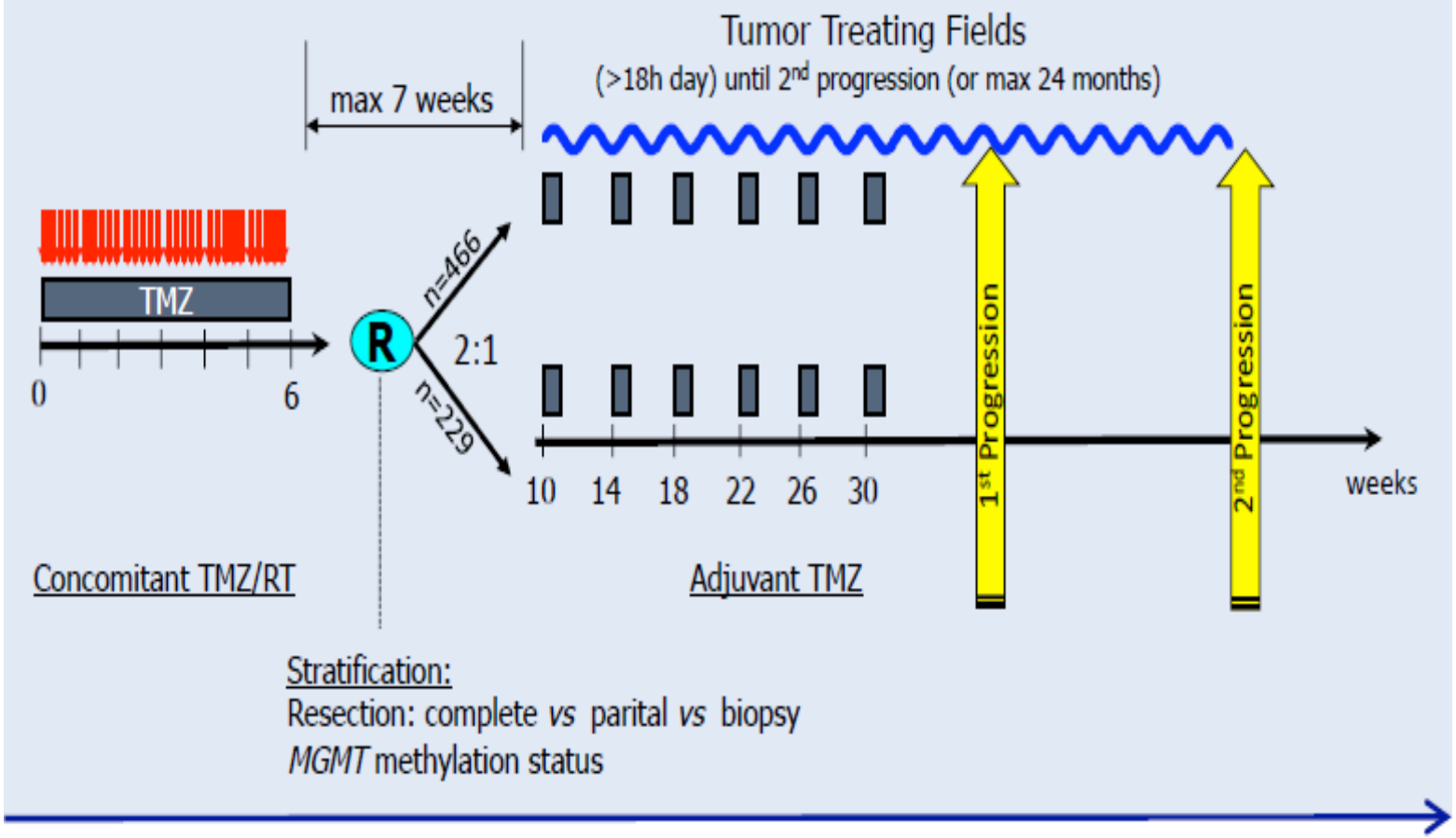
PROSPECTIVE, MULTI-CENTER PHASE III TRIAL OF TUMOR TREATING FIELDS TOGETHER WITH TEMOZOLOMIDE COMPARED TO TEMOZOLOMIDE ALONE IN NEWLY DIAGNOSED GLIOBLASTOMA

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

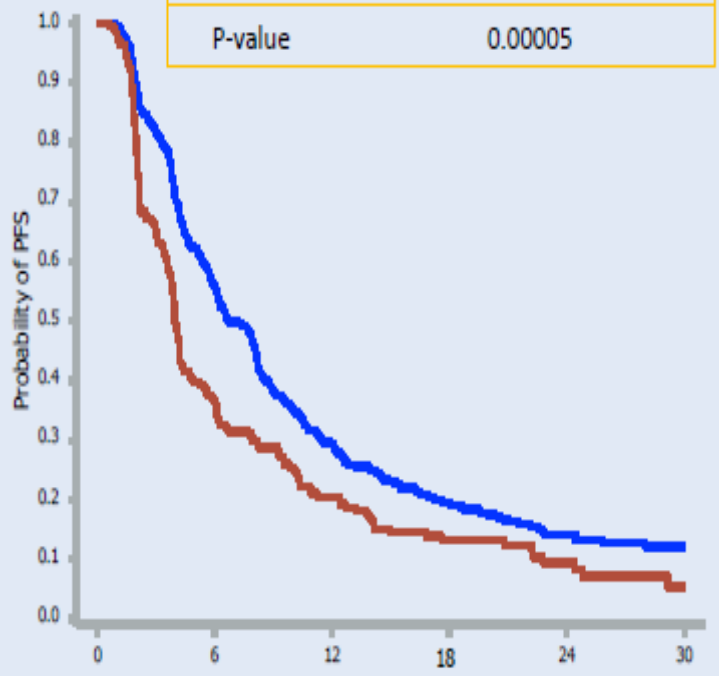


Stupp R et al., JAMA; 2015; 314:2535-43

Summary: Consistency of Results: Prolongation of

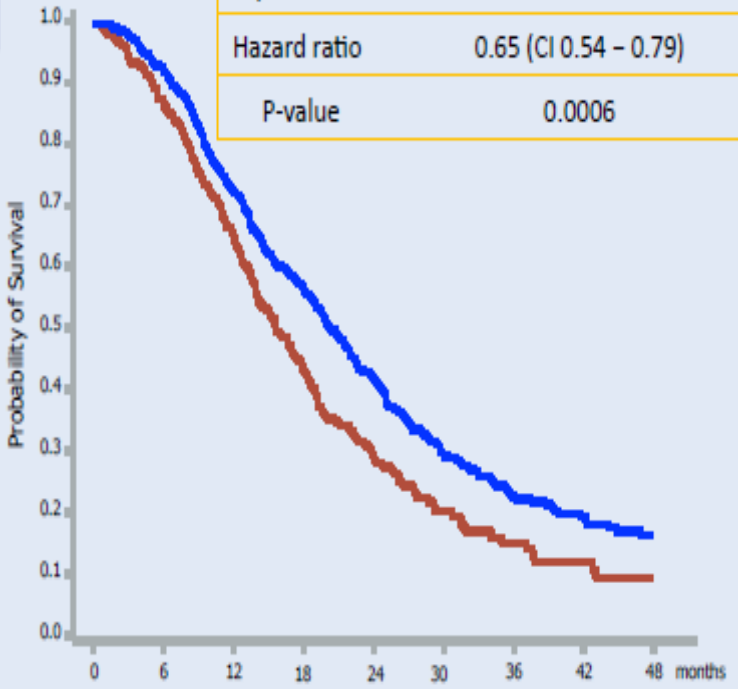
Progr.-Free Survival

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	



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

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

AVASTIN FAILURES

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

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%