Tumor Treating Fields for Glioblastoma

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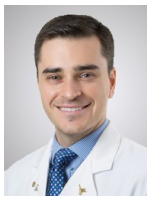
N.C. CANCER HOSPITAL

Disclosures

- Consulting: RTI International (clinical advisor), Novocure (uncompensated)

What I used to look like…



…professional, right?

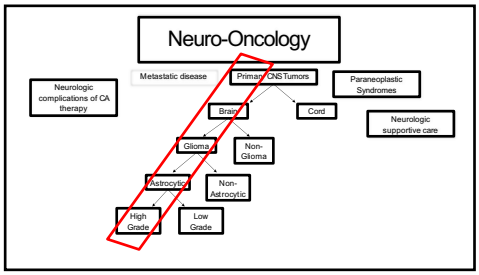

Head for the Cure
Foundation
Photo: K.Pietrosimone

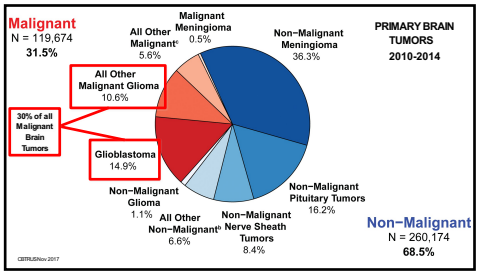

Head for the Cure
Foundation
Beverly's
Hillbillies
Beating Brain Cancer
Photo: K.Pietrosimone

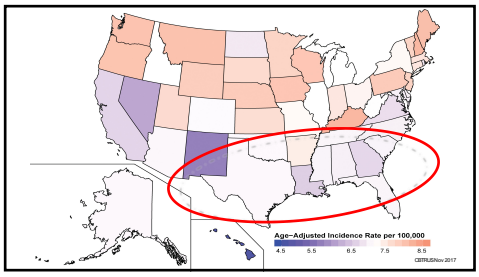

Head for the Cure
Foundation
So, this happened today…
HEAD FOR THE CURE
Photo: K.Pietrosimone

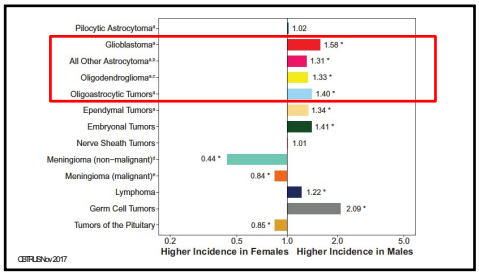
Key Takeaways

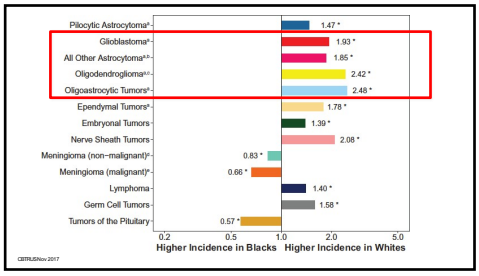
- Glioma management is an extensive field with significant room for improvement
- Glioblastoma remains a difficult cancer to manage
- The one-size-fits-all "Stupp protocol" for high grade glioma is being challenged
- Distinct mechanisms of action are unique to TTFields and complementary to current SOC
- TTFields (Optune®) should be considered SOC for newly diagnosed glioblastoma






Age-Adjusted Incidence Rate per 100,000
4.5
5.5
6.5
7.5
8.5
CBTRUSNov 2017


Pilocytic Astrocytoma[a]
Glioblastoma[a]
All Other Astrocytoma[a,b]
Oligodendroglioma[a,c]
Oligoastrocytic Tumors[a]
Ependymal Tumors[a]
Embryonal Tumors
Nerve Sheath Tumors
Meningioma (non-malignant)[d]
Meningioma (malignant)[a]
Lymphoma
Germ Cell Tumors
Tumors of the Pituitary
1.02
1.58 *
1.31 *
1.33 *
1.40 *
1.34 *
1.41 *
1.01
0.44 *
0.84 *
1.22 *
2.09 *
0.85 *
0.2
0.5
1.0
2.0
5.0
Higher Incidence in Females
Higher Incidence in Males
CBTRUSNov 2017


Pilocytic Astrocytoma[a]
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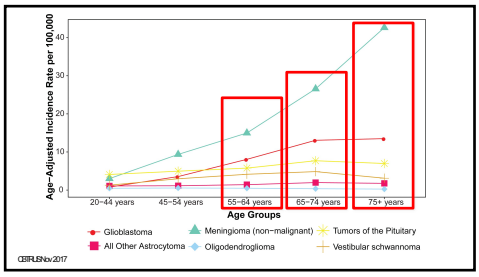
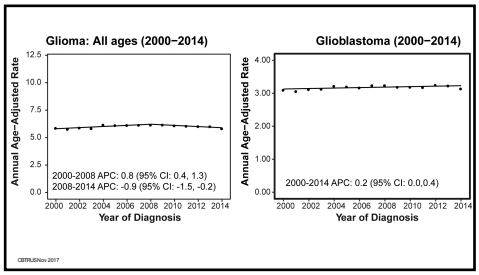
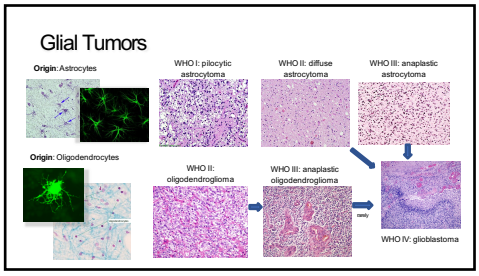
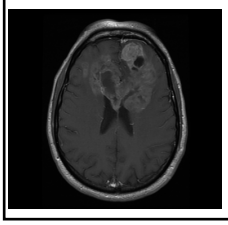
Embryonal Tumors
Nerve Sheath Tumors
Meningioma (non-malignant)[d]
Meningioma (malignant)[a]
Lymphoma
Germ Cell Tumors
Tumors of the Pituitary
1.47 *
1.93 *
1.85 *
2.42 *
2.48 *
1.78 *
1.39 *
2.08 *
0.83 *
0.66 *
1.40 *
1.58 *
0.57 *
0.2
0.5
1.0
2.0
5.0
Higher Incidence in Blacks
Higher Incidence in Whites
CBTRUSNov 2017

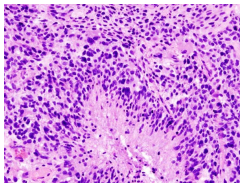

Age-Adjusted Incidence Rate per 100,000
0
10
20
30
40
20–44 years
45–54 years
55–64 years
65–74 years
75+ years
Age Groups
Glioblastoma
All Other Astrocytoma
Meningioma (non-malignant)
Oligodendroglioma
Tumors of the Pituitary
Vestibular schwannoma
CBTRUSNov 2017


Glioma: All ages (2000–2014)
Glioblastoma (2000–2014)
Annual Age-Adjusted Rate
2000-2008 APC: 0.8 (95% CI: 0.4, 1.3)
2008-2014 APC: -0.9 (95% CI: -1.5, -0.2)
2000-2014 APC: 0.2 (95% CI: 0.0,0.4)
Year of Diagnosis
CBTRUSNov 2017


Glial Tumors
Origin: Astrocytes
WHO I: pilocytic astrocytoma
WHO II: diffuse astrocytoma
WHO III: anaplastic astrocytoma
Origin: Oligodendrocytes
WHO II: oligodendroglioma
WHO III: anaplastic oligodendroglioma
rarely
WHO IV: glioblastoma

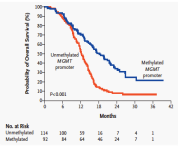
"Characteristic Appearance" of HGG

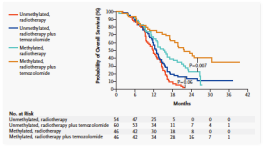




Courtesy of Dr. Kelly Peters (Duke)

MGMT promotor methylation sensitizes glioma cells to alkylating agents

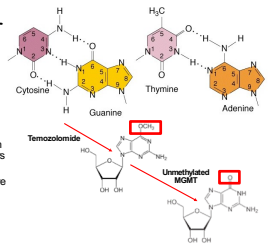


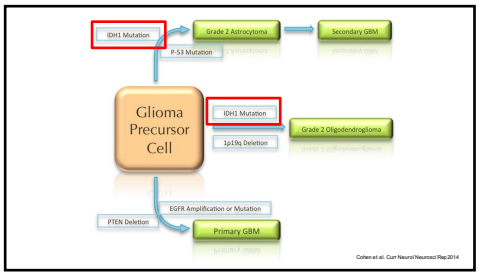


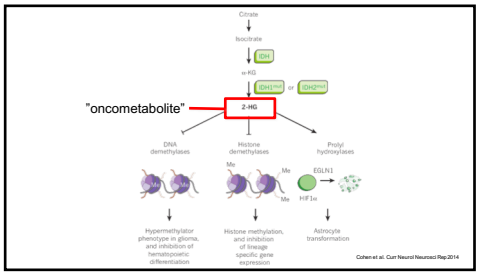
Hegi NEJM 2005

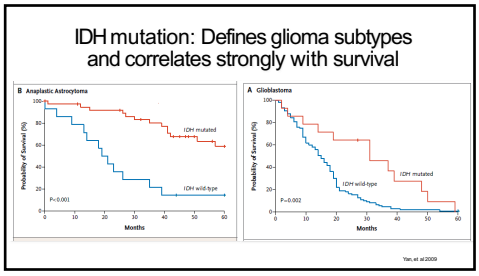
MGMT promotor

- Gene product: O-6-methylguanine-DNA methyltransferase
- Participates in maintaining genome stability
- Functions to repair mutagenic DNA methylation at the N7 & O6 position of guanine; prevents mismatch errors
- Cells defective of MGMT are sensitive to alkylating agents

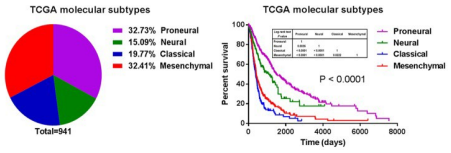


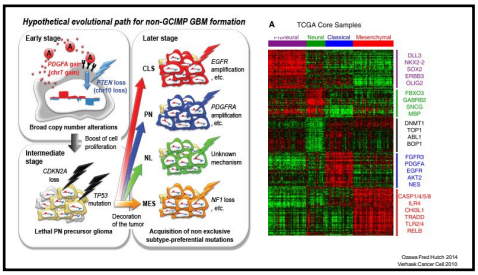

IDH1 Mutation
Grade 2 Astrocytoma
Secondary GBM
P-53 Mutation
Glioma Precursor Cell
IDH1 Mutation
Grade 2 Oligodendroglioma
1p19q Deletion
EGFR Amplification or Mutation
PTEN Deletion
Primary GBM
Cohen et al. Curr Neurol Neurosci Rep 2014


Citrate
Isocitrate
IDH
α-KG
"oncometabolite"
2-HG
DNA demethylases
Histone demethylases
Prolyl hydroxylases
EGLN1
HIF1α
Hypermethylator phenotype in glioma, and inhibition of hematopoietic differentiation
Histone methylation, and inhibition of lineage specific gene expression
Astrocyte transformation
Cohen et al. Curr Neurol Neurosci Rep 2014

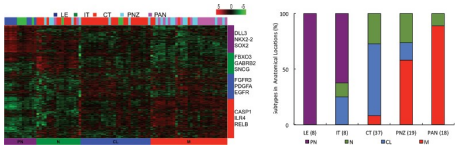

IDH mutation: Defines glioma subtypes and correlates strongly with survival
B Anaplastic Astrocytoma
IDH mutated
IDH wild-type
P<0.001
Probability of Survival (%)
Months
A Glioblastoma
IDH mutated
IDH wild-type
P=0.002
Probability of Survival (%)
Months
Yan, et al 2009

The Trouble with GBM:
Intra- and Inter- tumor heterogeneity contributes to glioblastoma resistance



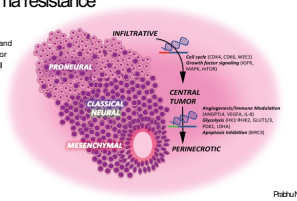


The Trouble with GBM:
Intra- and Inter- tumor heterogeneity contributes to glioblastoma resistance



The Trouble with GBM: Intra- and Inter- tumor heterogeneity contributes to glioblastoma resistance

- Evolutionary biology and environmental stressor driver **INTRA-tumoral heterogeneity** in a predictable manner.
- A single molecular subtype does not predominate!

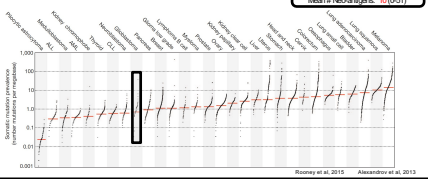


Prabhu Neuro Oncol 2017

The Trouble with GBM: Glioblastoma is an immunologically "cold" malignancy

The Neo-epitope Landscape in Human Glioblastoma

In analysis of 144 TCGA GBM tumors:
Mean # mutations: 65.2 (2-258)
Mean # Neo-antigens: 10 (0-51)

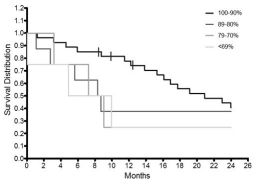


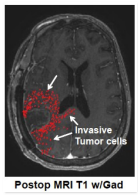
Rooney et al, 2015 Alexandrov et al, 2013

First Thing's First: Surgery

When neurosurgeons semi-retire

First Thing's First: Surgery

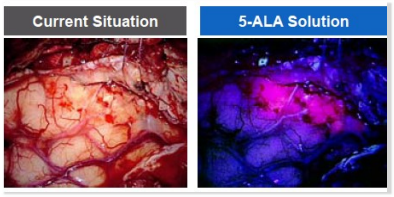




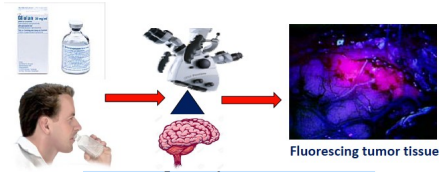
Postop MRI T1 w/Gad

Ortinger, et al. 2012

5-aminolevulinic acid hydrochloride (5-ALA)



Stummer et al. FDAAdvisory Committee 2017



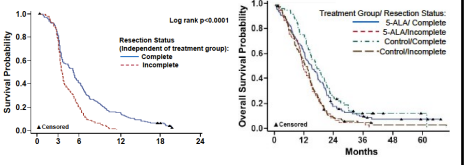
Fluorescing tumor tissue

5-ALA → Enzymes of heme biosynthesis → Protoporphyrin IX (PpIX)

Malignant glioma intracellular synthesis

Stummer et al. FDAAdvisory Committee 2017

Progression Free Survival by Completeness of Resection

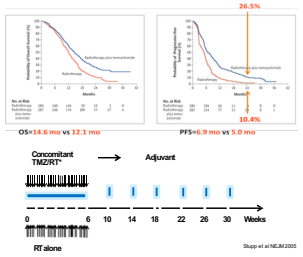


Overall Survival by Treatment Group

Stummer et al. FDAAdvisory Committee 2017

Stupp Protocol

- "RT + TMZ à TMZ" vs. RT alone
  - RT (60Gy)+TMZ (75 mg/m2) + TMZ (150-200 mg/m2, 5/28d) X6 mo.
- PFS= **6.9** mo. vs. **5** mo.
- OS= **14.6** mo. vs. **12.1** mo.
- Increased 2-yr. survival from **~10% to ~27%**
- FDA approved in 2005

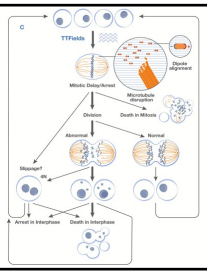


Stupp et al NEJM 2005

Alternating Electric Tumor Treating Fields (Optune ®)

Proposed Mechanism of Action of TTFields

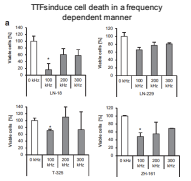
- Microtubule polymerization impaired due to dipole alignment
- Abnormal segregation of chromosomes
- Abnormal segregation of organelles

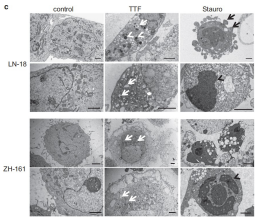


Hottinger Neuro Oncol 2016

Pre-Clinical Rationale for TTFields in Glioma

TTFsinduce cell death in a frequency dependent manner

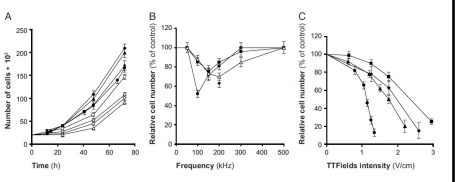




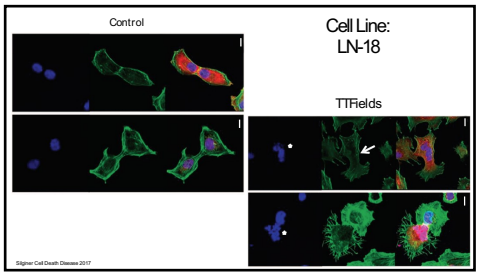
TTFields induce formation of autophagosomes and mitochondria swelling

Stupp Cell Death Disease 2017

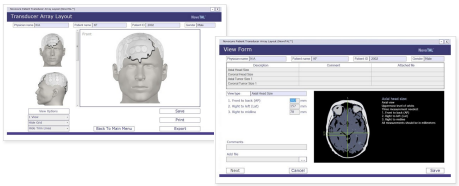
Pre-Clinical Rationale for TTFields in Glioma



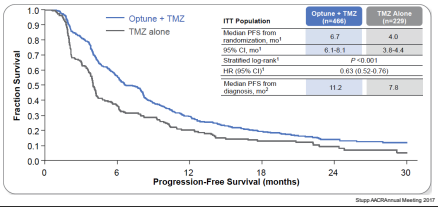
Kirson PNAS 2007



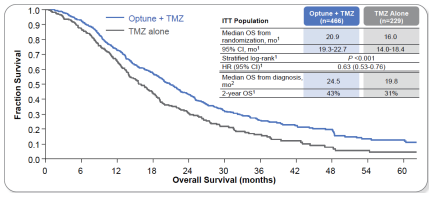
Optune® is worn by patients on the scalp and can be mapped using the NovoTAL® system



EF-14: Progression-Free Survival (5-year survival analysis)

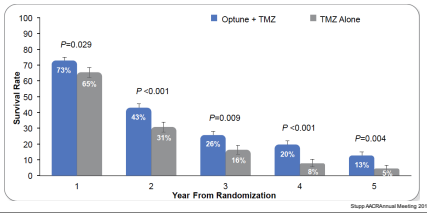


EF-14: Overall Survival (5-year survival analysis)



Stupp AACRAnnual Meeting 2017

EF-14: Long-term survival rates



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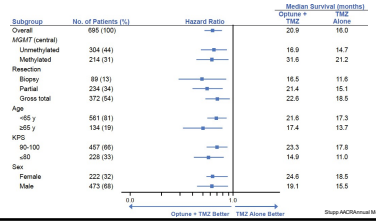
EF-14: Subgroup Analysis for OS@5 years



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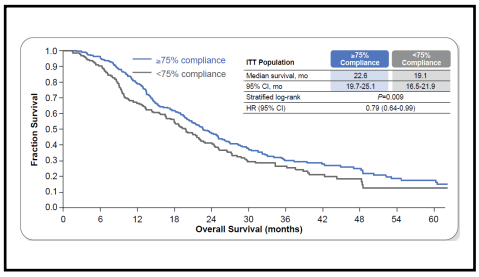
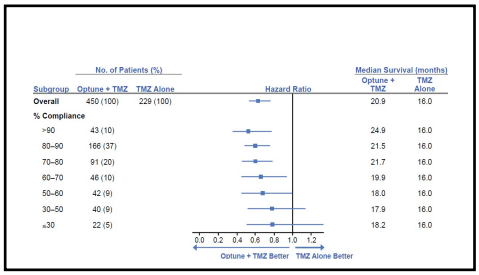
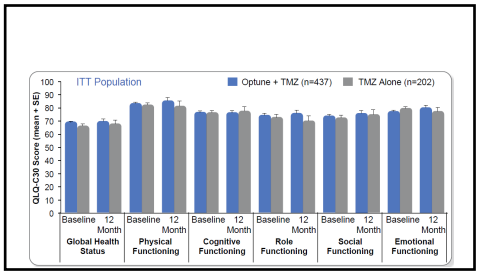
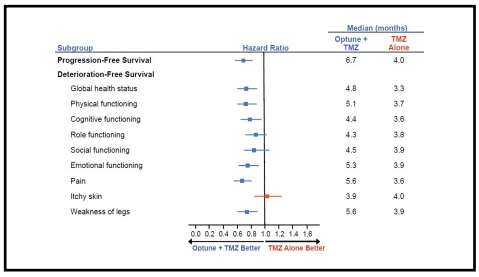
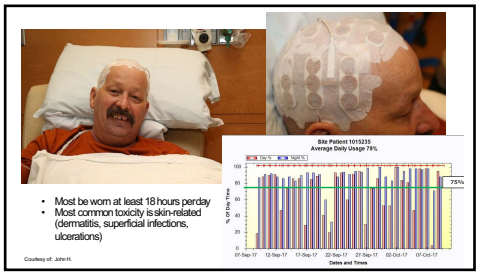
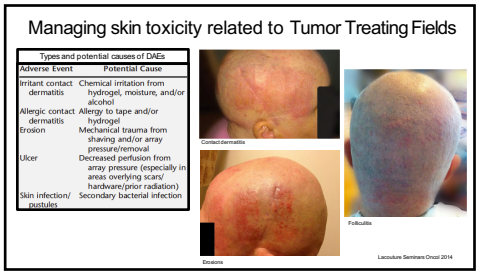

≥75% compliance
<75% compliance
Fraction Survival
Overall Survival (months)
ITT Population
≥75% Compliance
<75% Compliance
Median survival, mo 22.6 19.1
95% CI, mo 19.7-25.1 16.5-21.9
Stratified log-rank P=0.009
HR (95% CI) 0.79 (0.64-0.99)


No. of Patients (%)
Median Survival (months)
Subgroup Optune + TMZ TMZ Alone Hazard Ratio Optune + TMZ TMZ Alone
Overall 450 (100) 229 (100) 20.9 16.0
% Compliance
>90 43 (10) 24.9 16.0
80–90 166 (37) 21.5 16.0
70–80 91 (20) 21.7 16.0
60–70 46 (10) 19.9 16.0
50–60 42 (9) 18.0 16.0
30–50 40 (9) 17.9 16.0
≤30 22 (5) 18.2 16.0
Optune + TMZ Better
TMZ Alone Better


ITT Population
Optune + TMZ (n=437)
TMZ Alone (n=202)
QLQ-C30 Score (mean ± SE)
Baseline
12 Month
Global Health Status
Physical Functioning
Cognitive Functioning
Role Functioning
Social Functioning
Emotional Functioning


Median (months)
Subgroup
Hazard Ratio
Optune + TMZ
TMZ Alone
Progression-Free Survival 6.7 4.0
Deterioration-Free Survival
Global health status 4.8 3.3
Physical functioning 5.1 3.7
Cognitive functioning 4.4 3.6
Role functioning 4.3 3.8
Social functioning 4.5 3.9
Emotional functioning 5.3 3.9
Pain 5.6 3.6
Itchy skin 3.9 4.0
Weakness of legs 5.6 3.9
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6
Optune + TMZ Better
TMZ Alone Better


Site Patient 1015235
Average Daily Usage 79%
75%
% Of the Time
Dates and Times
Most be worn at least 18 hours perday
Most common toxicity is skin-related (dermatitis, superficial infections, ulcerations)
Courtesy of: John H.


Managing skin toxicity related to Tumor Treating Fields
Types and potential causes of DAEs
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
Contact dermatitis
Folliculitis
Erosions
Lacouture Seminars Oncol 2014

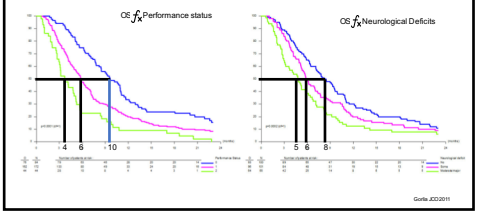
Managing skin toxicity related to Tumor Treating Fields

Clinical issue	Risk reduction	Treatment
Contact dermatitis	Slight shift in arrays avoiding ceramic disc placement immediately over scars or surgical screws Use of electric razor to remove hair Keeping scalp dry Using 70% alcohol on scalp prior to array placement	Temporary removal of arrays (treatment break) Topical steroids—consider high potency ointment such as clobetasol 0.5% (twice daily for ≤2 weeks)
Skin infection	Slight shift in arrays avoiding ceramic disc placement immediately over scars or surgical screws Use of electric razor to remove hair Keeping scalp dry Using 70% alcohol on scalp prior to array placement	Temporary removal of arrays (treatment break) Culture if possible Topical antibiotics, such as mupirocin (2%, three times a day, for up to 10 days) and polymyxin B/Bacitracin (polysporin, two to three times a day) Consideration of dermatology consultation based on severity
Wound dehiscence	Avoid array pressure on incision sites and underlying hardware Caution in considering patients with prior surgical delayed wound healing and risk of wound dehiscence or concurrent antiangiogenic treatment	Wound infection—systemic antibiotics such as beta-lactam (e.g., penicillin derivatives, cephalosporins) or macro-lides or fluoroquinolones Recommendation of neurosurgical evaluation
Burn secondary to power supply	Avoid scenarios where prolonged contact to the power supply can occur This is of particular importance for patients with sensory deficits or neglect	Removal of contact with power source

Lukas JNeurooncol 2017

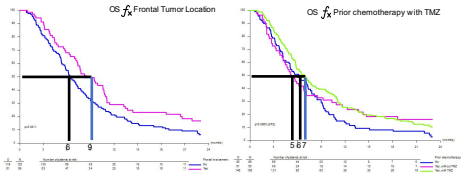
Disease Recurrence

Disease Recurrence



Gorlia JCO 2011

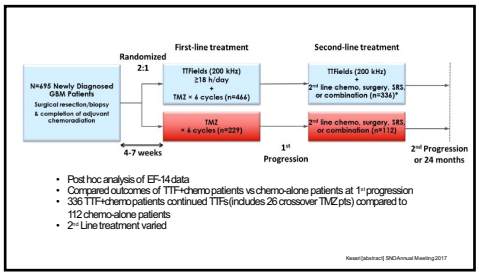
Disease Recurrence



Disease recurrence remains a vexing problem

- There are no standard treatments for recurrent disease
  - Metronomic (daily) temozolomide
  - Bevacizumab
  - Lomustine
  - Irinotecan
  - Carboplatin
  - Etoposide
  - Carmustine wafers (Gliadel®)
  - Tumor treating fields (Optune®)
  - Combination of the above?
- Preferred: **CLINICAL TRIALS**

Is there benefit to continuing Tumor Treating Fields beyond 1st Progression



- Post hoc analysis of EF-14 data
- Compared outcomes of TTF+chemo patients vs chemo-alone patients at 1st progression
- 336 TTF+chemo patients continued TTFs (includes 26 crossover TMZ pts) compared to 112 chemo-alone patients
- 2nd Line treatment varied

Kesari [abstract] SNO Annual Meeting 2017

Second line treatments following 1st disease progression

Treatment	Treatment group		
	TMZ alone (n=112)	TTFields/TMZ (n=336)	Chi-square test
	n (%)	n (%)	P-value
Bevacizumab	55 (49)	110 (33)	0.986
Chemotherapy	94 (84)	185 (55)	0.884
Operation	32 (29)	75 (22)	0.401
Operation with gliadel wafers	4 (4)	9 (3)	0.840
Stereotactic radiosurgery	9 (8)	18 (5)	0.995
Fractionated radiotherapy	12 (11)	14 (4)	0.158
TTFields monotherapy		93 (28)	

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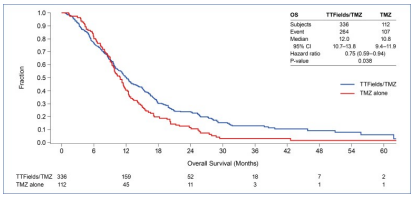
Overall survival in patients receiving second line therapy



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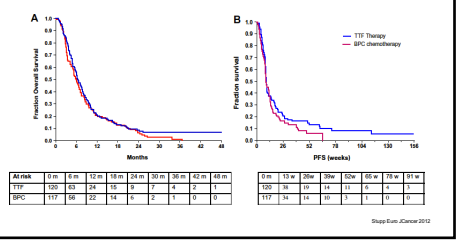
Is there a role for Tumor Treating Fields in Recurrent Glioblastoma?



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	58	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	7	1	0	0

Thank you for your attention!

Questions?