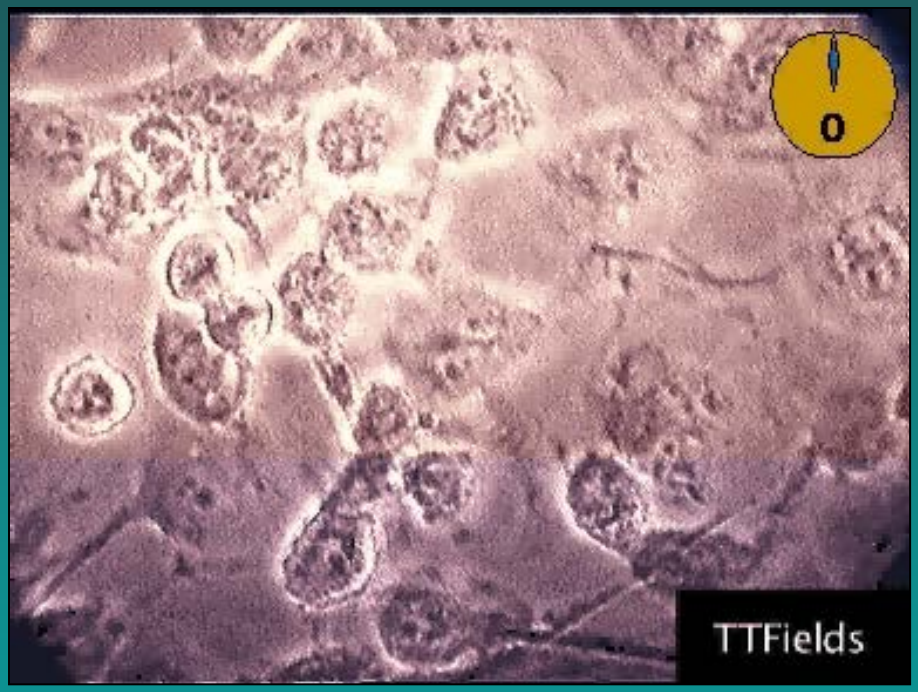
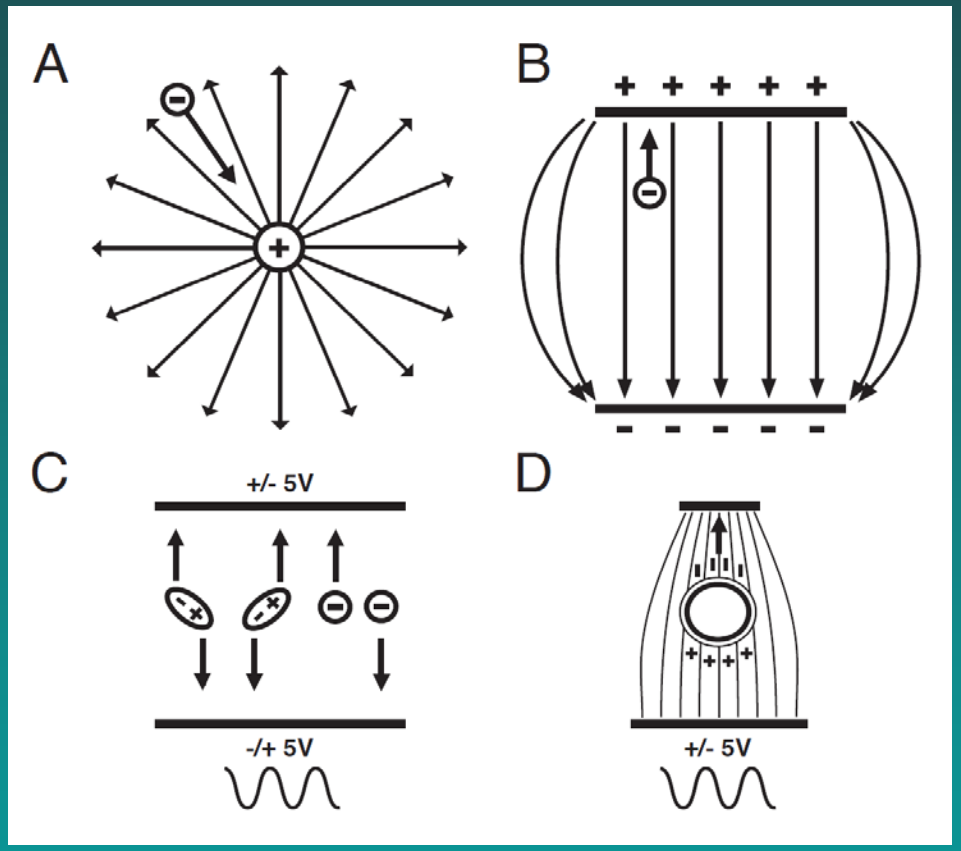
Examining the Role of a Fourth Treatment Modality: Tumor Treating Fields (TTFields)

TTFields: From Bench to Bedside



Stupp R, et al. *Eur J Cancer.* 2012;48(14):2192-2202. Fonkem E, et al. *Exp Rev Neurother.* 2012;12(8):895-899.

Electric Field Effect on Charges and Dipoles



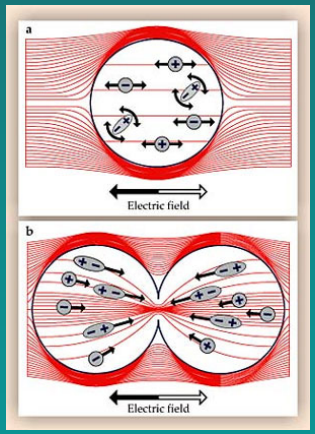
- An electric field is a potential difference in space
- Charges move and dipoles oscillate in a uniform alternating electric field

Gutin P, et al. Presented at: 2012 ASCO Annual Meeting Education Session; June 1-5, 2012; Chicago, Illinois. Available at: http://meetinglibrary.asco.org/content/66664. Accessed September 16, 2013.

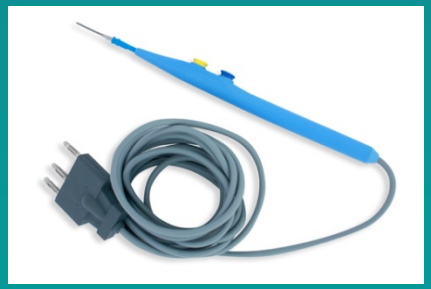
Use of Electric Fields in Medical Devices

Cardiac pacemaker; <1KHz
LOW

Tumor treating fields; 100-300kHz
MEDIUM



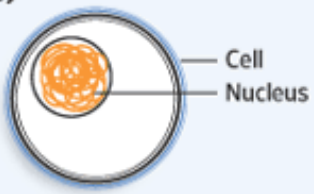
Diathermy; > 1 MHz
HIGH



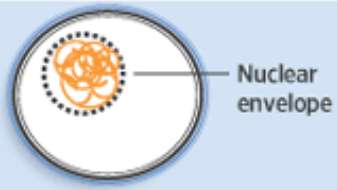
Disrupting Cancer-Cell Division

Normal Cell Divison (Mitosis)

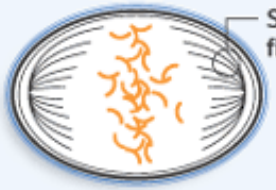
The cell DNA is doubled in preparation for division.



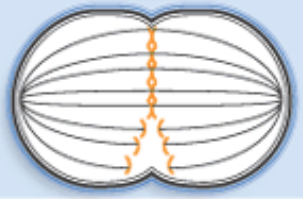
The cell's nuclear envelope disintegrates.



Spindle fibers form.

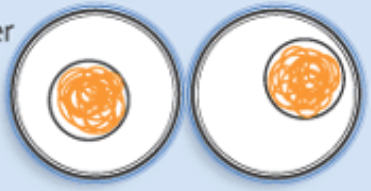


Chromosomes align in the center of the cell and attach to the spindle fibers.



Chromosomes move toward the two poles and the cell begins to cleave.

Two identical 'daughter cells' are formed.



Mitosis with Device

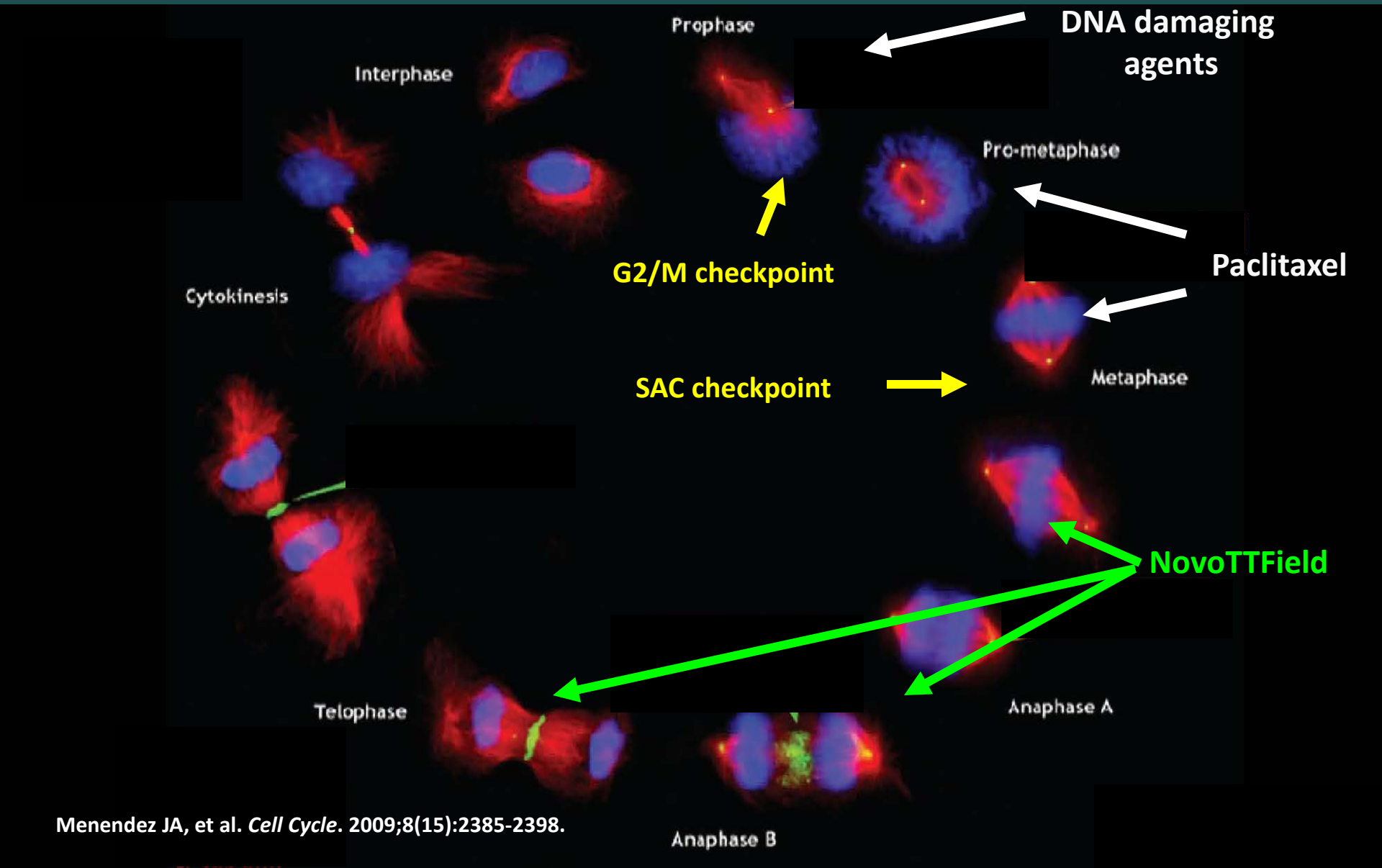
The device delivers alternating electrical fields to the cancer cells by means of insulated electrodes on the surface of the scalp. Healthy brain cells don't divide, and the electrical fields generated by the device don't affect them.

The electrical field interferes with the production of spindle fibers...

...and disrupts the even distribution of the chromosomes...

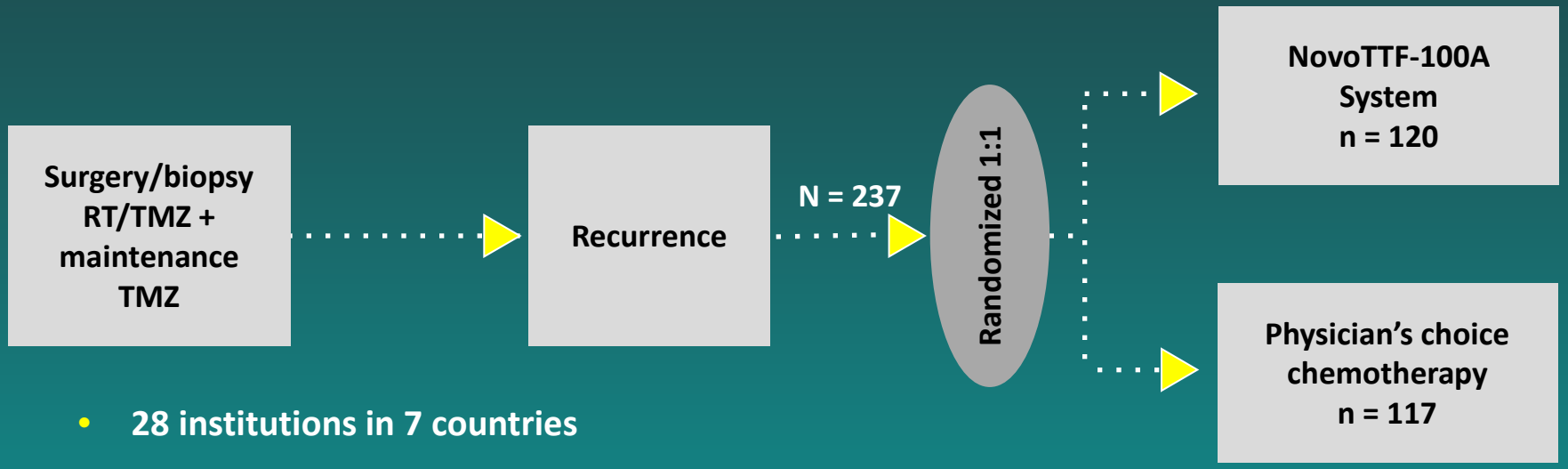
...causing structural disruption and cell fragmentation.

Tumor Treating Fields Appear to Affect Cells After DNA Damaging Agents and Spindle Poisons



Menendez JA, et al. *Cell Cycle*. 2009;8(15):2385-2398.

EF-11: Phase III Study in Recurrent Glioblastoma



- 28 institutions in 7 countries
- Stratification
  - Treatment center
  - Surgery prior to trial entry
- Other inclusion criteria
  - Radiologically confirmed disease progression
  - Karnofsky performance status ≥70%

Primary endpoint: Overall survival
Secondary endpoints: PFS, 6-month PFS, 1-year survival, radiologic response, quality of life (QoL)

Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

EF-11: Patient Characteristics

	NovoTTF-100A System (n = 120)	Active control (n = 117)
Age (year), median (range)	54 (24-80)	54 (29-74)
Gender, (male), n (%)	92 (77)	73 (62)
Histology		
Glioblastoma, %	100	100
Prior lower grade glioma, n (%)	10 (8)	9 (8)
Karnofsky performance status, median (range)	80% (50-100)	80% (50-100)
Steroid use at enrollment		
Yes, n (%)	55 (46)	62 (53)
No, n (%)	55 (46)	49 (42)
Unknown, n (%)	10 (8)	6 (5)
Largest tumor diameter at randomization (cm), median (range)	6.1 (0-15.2)	5.5 (0-16.2)
Interval from initial glioma diagnosis (month), median (range)	11.8 (3.2-99.3)	11.4 (2.9-77.1)

Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

EF-11: Prior Treatments in Subjects

	NovoTTF-100A system (n = 120)	Active control (n = 117)
1st recurrence, n (%)	11 (9)	17 (15)
2nd recurrence, n (%)	58 (48)	54 (46)
3rd or greater recurrence, n (%)	51 (43)	46 (39)
Surgery		
Debulking before enrollment, n (%)	33 (28)	29 (25)
Debulking at any stage, n (%)	95 (79)	99 (85)
Biopsy only, n (%)	25 (21)	18 (15)
Radiotherapy, %	100	100
With concomitant temozolomide, n (%)	103 (86)	96 (82)
No concomitant temozolomide, n (%)	15 (13)	20 (17)
Unknown, n (%)	2 (1)	1 (1)
Prior adjuvant (maintenance) temozolomide, n (%)	100 (83)	89 (76)
Median number of cycles (range)	4 (0–19)	3 (0–27)
Prior bevacizumab, n (%)	23 (19)	21 (18)

Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

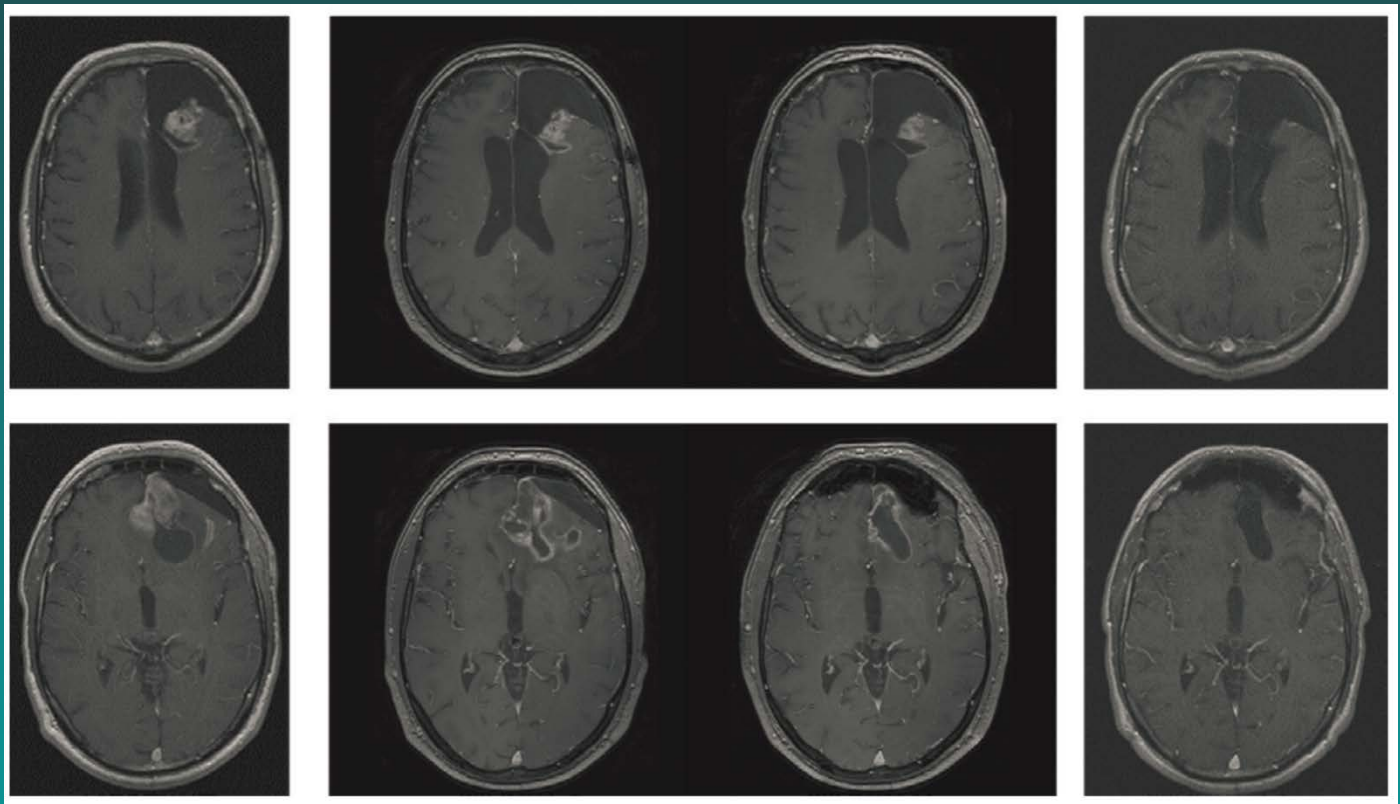
EF-11: Active Control Chemotherapy Regimens

Therapy	Number of patients (%)*
Bevacizumab	36 (31)
Irinotecan	36 (31)
BCNU/CCNU	29 (25)
Carboplatin	15 (13)
Temozolomide	13 (11)
PCV	10 (9)
Other	7 (7)
None	4 (3)

*Multiple listings possible; some agents given in combination
BCNU/CCNU, lomustine/carmustine; PCV, procarbazine + lomustine + vincristine chemotherapy regimen

Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

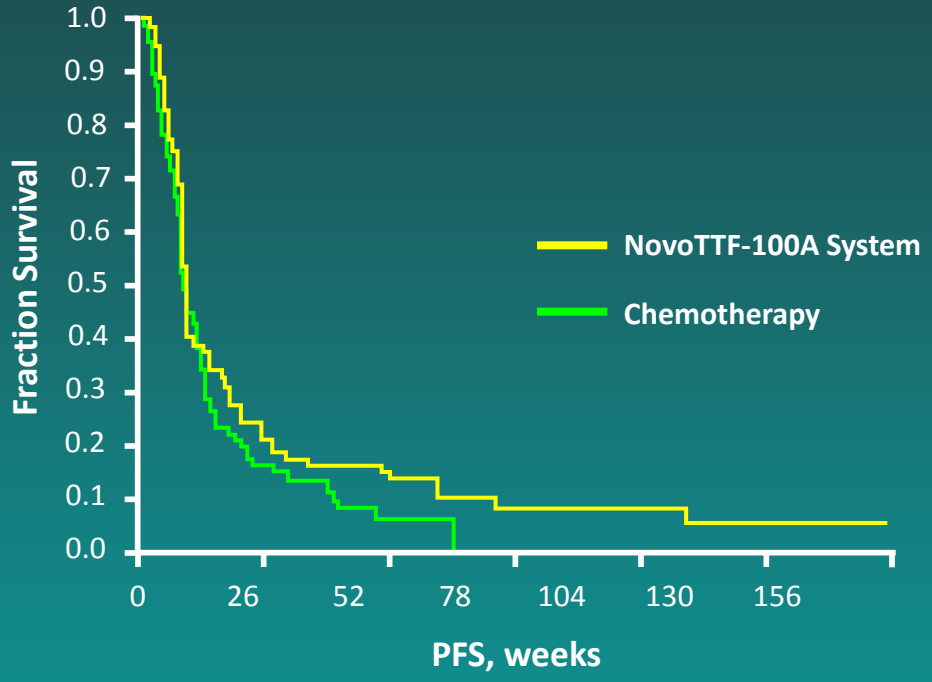
Delayed Response or Pseudoprogression While on NovoTTF-100A Therapy



- MRI of a complete responder treated with NovoTTF-100A Therapy
  - Transient progression or pseudoprogression occurred at 2 months after starting NovoTTF-100A Therapy
  - Partial response was noted only after 6 months and complete response was noted after 12 months

Wong ET, et al. *Neuro Oncol.* 2012;14:vi65-vi85 (suppl 6; abstr NO-47).

EF-11: Progression-Free Survival in the ITT Population



	NovoTTF-100A treatment (n = 120)	Chemotherapy (n = 117)
Median PFS, months	2.2	2.1
Log-rank *P* value	0.16	
HR (95% CI)	0.81 (0.60–1.09)	
PFS 6-month (95% CI)	21.4% (13.5–29.3)	15.1% (7.8–22.3)
P value	0.13	

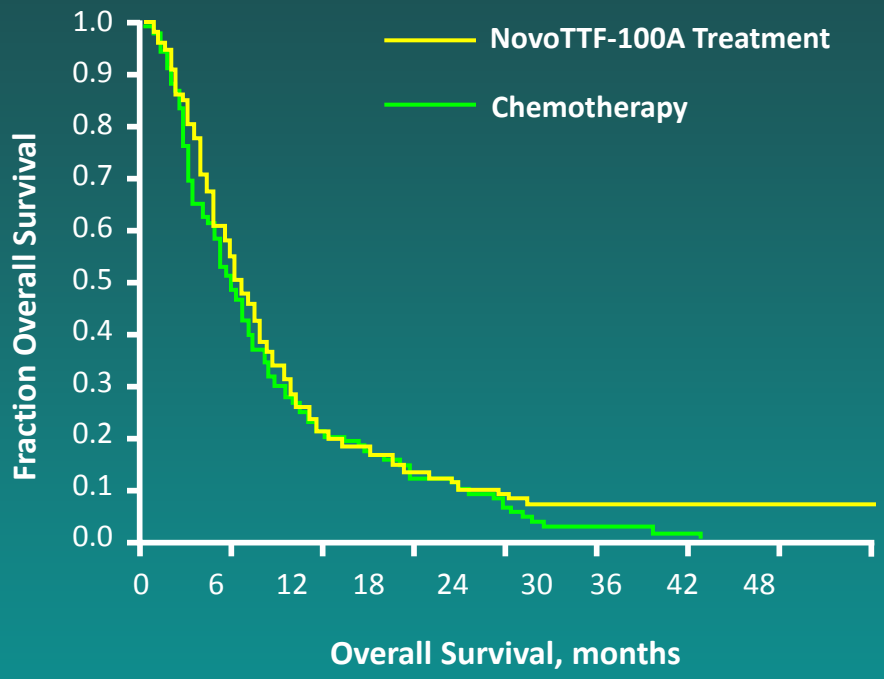
At risk	0 w	13 w	26 w	39 w	52 w	65 w	78 w	91 w
NovoTTF-100A	120	38	19	14	11	6	4	3
BPC	117	34	14	10	3	1	0	0

- Objective radiological responses
  - NovoTTF-100A Treatment group (n = 14)
  - Chemotherapy group (n = 7)

BPC, physician's choice chemotherapy

Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

EF-11: Overall Survival in the ITT Population

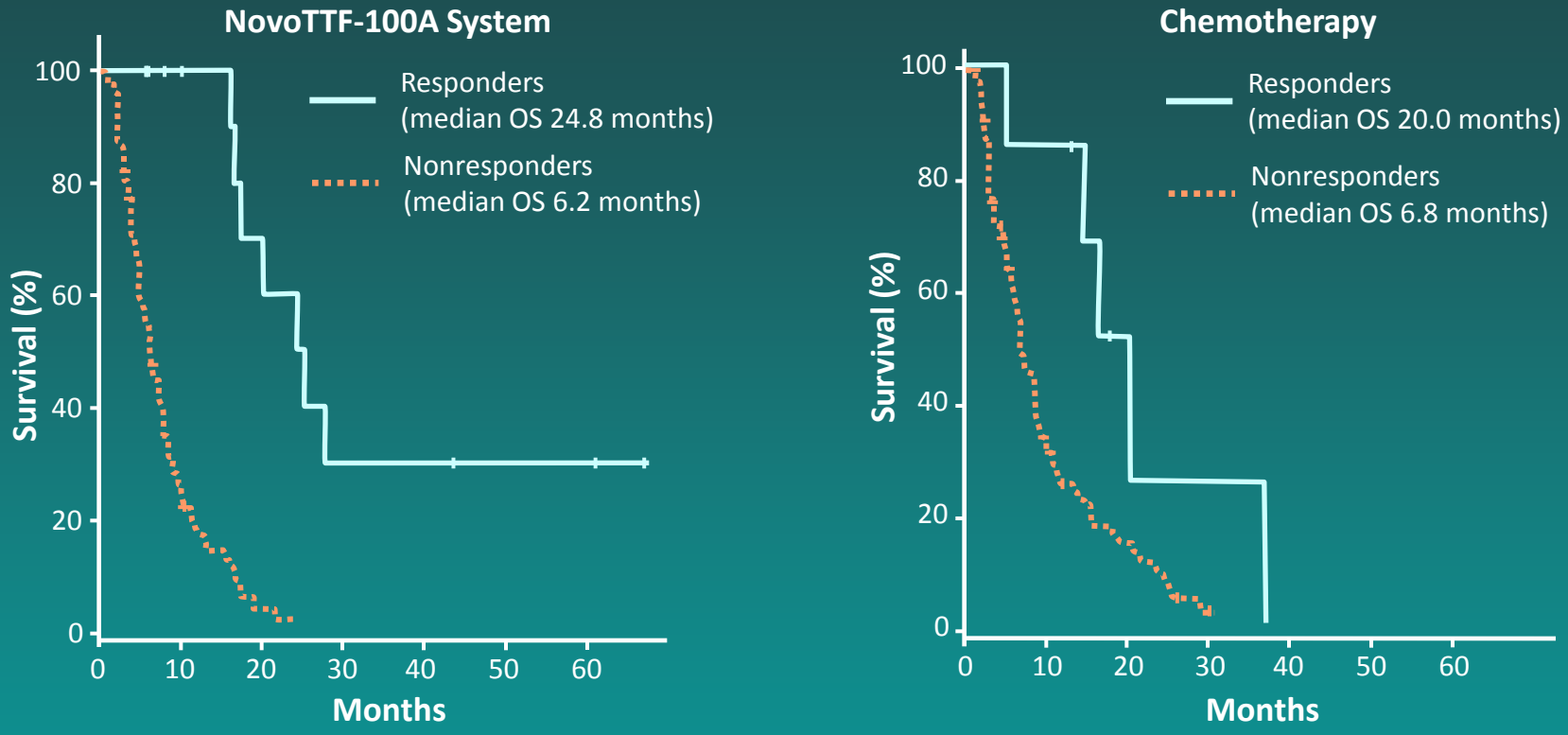


At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m	42 m	48 m
NovoTTF-100A	120	63	24	15	9	7	4	2	1
BPC	117	56	22	14	6	2	1	0	0

	NovoTTF-100A treatment (n = 120)	Chemotherapy (n = 117)
Median OS, months	6.6	6.0
Log-rank *P* value	0.27	
HR (95% CI)	0.86 (0.66 – 1.12)	
1-year survival	20%	20%

Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

EF-11: Overall Survival in Responders vs Nonresponders

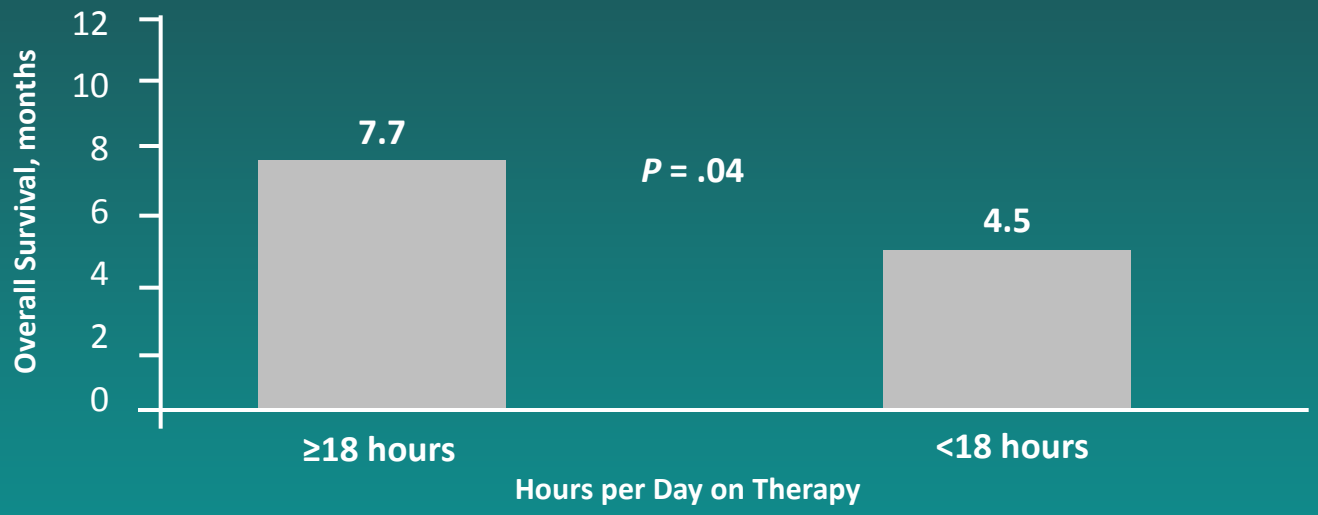


- **14 of 120 (11.7%) patients exhibited a radiological response while on NovoTTF-100A therapy, median time to response of 8.4 months (95% CI, 6.9-9.9 months)**
- **7 of 117 (6.0%) patients exhibited a radiological response while receiving BPC chemotherapy, median time to response of 5.8 months (95% CI, 3.6-8.0 months)**
- **Three complete responses were seen on trial**
- **All three were from patients in the NovoTTF-100A system cohort**

Wong ET, et al. *Neuro Oncol.* 2012;14:vi65-vi85 (suppl 6; abstr NO-47).

EF-11: Correlation Between Overall Survival and Treatment Compliance

Subgroup analysis of patients receiving NovoTTF-100A therapy



- 78% of patients completed 4 weeks of therapy (1 cycle)
- >80% of patients were compliant 75% of the time
- Median compliance was 86% (range 41%-98%) translating to a mean use of 20.6 hours per day

EF-11: Treatment-Emergent Adverse Events ≥Grade 2

	NovoTTF-100A treatment (n = 116)		Chemotherapy (n = 91)	
	≥Grade 2 (%)	Grade 3/4 (%)	≥Grade 2 (%)	Grade 3/4 (%)
Hematological	3	0	17	4
Leukopenia	0	0	5	1
Neutropenia	0	0	2	1
Thrombocytopenia	1	1*	7	2
Gastrointestinal disorders	4	1	17	3
Abdominal pain	0	0	3	0
Diarrhea	0	0	6	2
Nausea	2	0	7	0
General deterioration and malaise	5	1	6	1
Infections	4	0	8	1
Skin rash (transducer arrays)	2	0	0	0
Metabolism and nutrition disorders	4	1	6	3
Renal and urinary disorders	3	1	3	0

*Thrombocytopenia from prior chemotherapy; normalized subsequently

Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

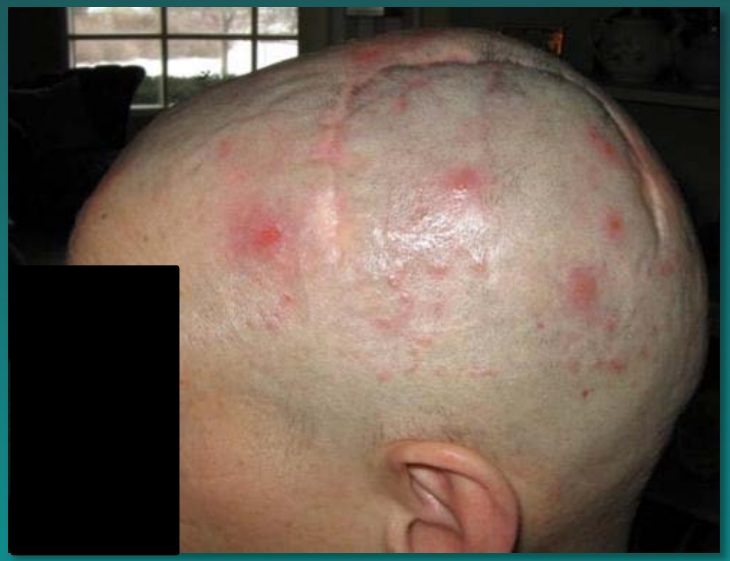
EF-11: Treatment-Emergent Adverse Events ≥ Grade 2

	NovoTTF-100A treatment (n = 116)		Chemotherapy (n = 91)	
	≥Grade 2 (%)	Grade 3/4 (%)	≥Grade 2 (%)	Grade 3/4 (%)
Nervous system disorders	30	7	28	7
Brain edema	0	0	2	0
Cognitive disorder	2	1	2	1
Convulsion	7	2	5	2
Dysphasia	2	0	1	0
Headache	8	1	6	0
Hemianopsia	1	0	3	1
Hemiparesis	3	1	2	1
Peripheral neuropathy	2	0	2	0
Psychiatric disorders	5	0	4	0
Respiratory disorders	1	0	3	1
Vascular disorders	3	1	4	3
Pulmonary embolism	1	1	2	2
Hypertension	1	0	1	1
Deep vein thrombosis	1	0	1	0

Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

EF-11: NovoTTF-100A Treatment-Related Adverse Events (All Grades)

	NovoTTF-100A treatment* (n = 116) n (%)
Medical device site reaction	18 (16)
Headache	4 (3)
Malaise	2 (2)
Muscle twitching	1 (1)
Fall	1 (1)
Skin ulcer	1 (1)



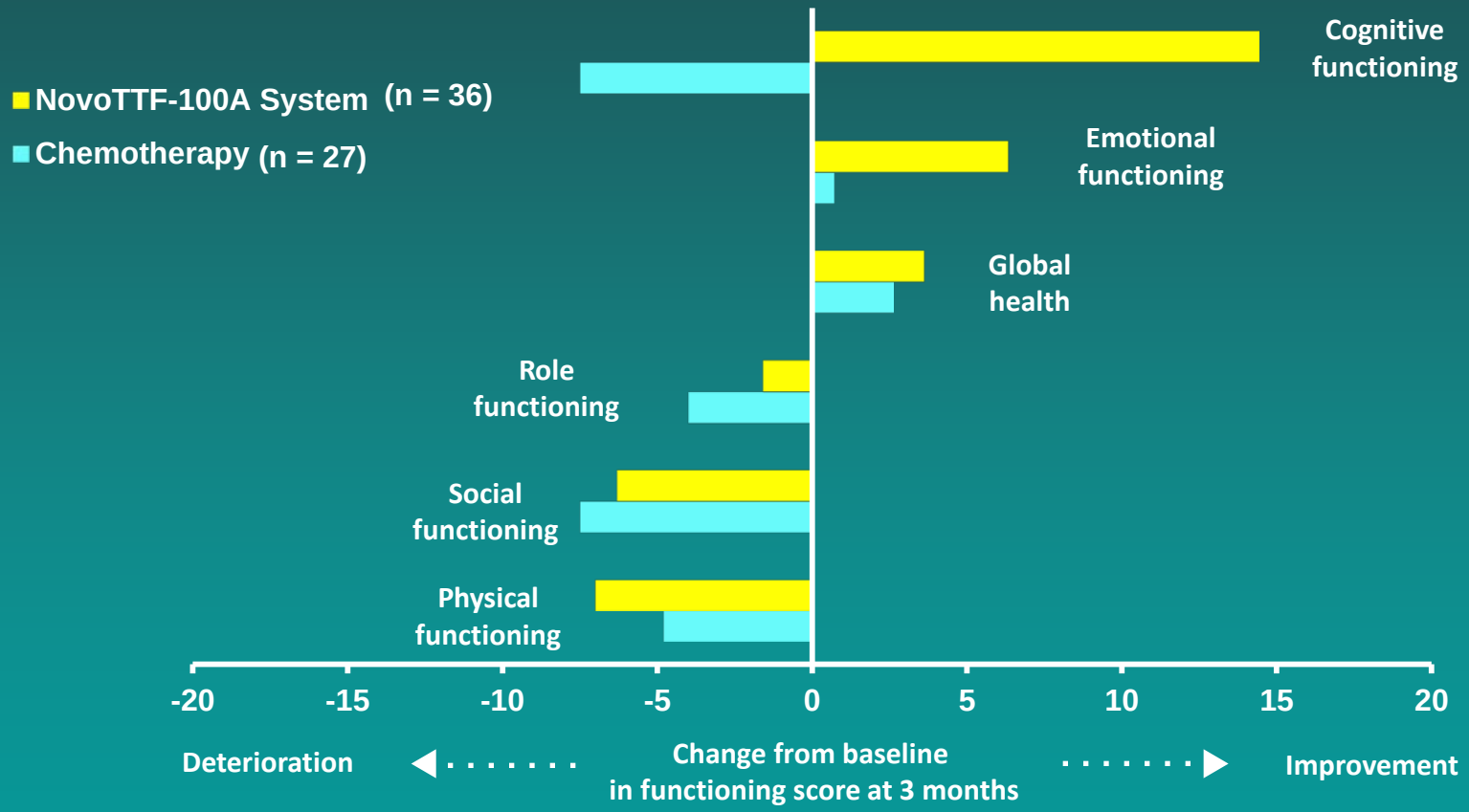
Grade 2 skin irritation underneath transducer arrays[1]

*NovoTTF-100A System instructions for use

1. Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

EF-11: Quality of Life Assessment

Improved cognitive and emotional functions in patients treated with NovoTTF-100A system compared to patients treated with chemotherapy



Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

Conclusions of EF-11 trial

1. The NovoTTF-100A system shows comparable efficacy with cytotoxic chemotherapies

2. Patients treated with NovoTTF-100A experienced lower toxicity and a better quality of life than those treated with chemotherapies

The PRiDe Dataset: An Analysis of Patient Registry Data N = 457

- All recurrent glioblastoma patients in US treated with Novo TTF (October 2011–November 2013)
- OS in PRiDE compared to OS of patients receiving NovoTTF therapy in EF-11 trial (ITT group)
- Patient characteristics prognostic for survival with NovoTTF Therapy were assessed
- Subgroup analyses performed on patient characteristics were correlated with OS

Wong ET, et al. Proceedings of the American Society Of Clinical Oncology Annual Meeting. 2014: Abstract #e13033.
Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

Baseline Demographics

		PRiDe dataset	EF-11 NovoTTF[1] therapy	EF-11 active chemotherapy[1]
	N	457	120	117
Age (years)	Median (range)	55 (18-86)	54 (24-80)	54 (29-74)
Gender	Male	67.6%	77%	62%
	Female	32.4%	23%	38%
KPS	Median (range)	80 (10-100)	80 (50-100)	80 (50-100)
Recurrence	Median (range)	2 (1-5)	2 (1-5)	2 (1-4)
	1st	33.3%	9%	15%
	2nd	26.9%	48%	46%
	3rd-5th	27.4%	43%	39%
	Unknown	12.5%	0%	0%
Prior treatments	Bevacizumab	>55.1%	19%	18%
	Radiotherapy + temozolomide	>77.9%	86%	82%
	Debulking surgery	>63.9%	79%	85%
	Carmustine wafers	>3.7%	NA	NA

1. Stupp R, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

Safety Analysis (> 2%)

Adverse event	Percentage of patients (n = 457)
Skin reaction	24.3
Heat sensation	11.3
Neurological disorder	10.4
Seizure	8.9
Electric sensation	7.7
Headache	5.7
Pain / discomfort	4.7
Fall	3.9
Psychiatric disorder	2.9
Gastrointestinal disorder	2.9
Fatigue	2.5

PRiDe Overall Survival

	PRiDe dataset	EF-11 NovoTTF therapy[1]	EF-11 active chemotherapy[1]
Median treatment duration	4.1 months (95% CI, 3.5-4.8)	2.2 months (95% CI, 2.1-2.4)	2.1 months (95% CI, 2.0-2.9)
Median compliance	70% (range, 12-99)	86% (range, 41-98)	NA
Median OS	9.6 months (95% CI, 8.0-13.7)	6.6 months	6.0 months
HR of PRiDe vs others / *P* value	—	HR = 0.66 (95% CI) *P* = .0003	HR = 0.58 (95% CI) *P* = .0001
1-/2 -year survival	44% / 30%	20% / 9%	20% / 7%

1. Stupp R et al. *Eur J Cancer*. 2012;48(14):2192-2202.

PRiDe OS: Prognostic Factors

	Median OS (months)	HR	*P* value
Daily compliance			
≥75%	13.5	0.4 (95% CI, 0.3-0.6)	<.0001
<75%	4		
Bevacizumab use			
Naïve	13.4	0.5 (95% CI, 0.4-0.7)	.0001
Prior use	7.2		
Debulking surgery			
No	8.9	1.1 (95% CI, 0.8-1.5)	.7927
Yes (any)	9.8		

PRiDe OS: Prognostic Factors (2)

	Median OS (months)	HR	*P* value
KPS			
90-100	14.8	—	—
70-80	7.7	0.6 (95% CI, 0.4-0.9)	.0070[a]
10-60	6.1	0.4 (95% CI, 0.2-0.6)	<.0001[b]
Number of recurrences			
1st	20	—	—
2nd	8.5	0.6 (95% CI, 0.4-0.9)	.0271[c]
3rd-5th	4.9	0.3 (95% CI, 0.2-0.5)	<.0001[d]

[a] KPS 90-100 compared to KPS 70-80. [b] KPS 90-100 compared to KPS 10-60.
[c] First recurrence compared to 2nd recurrence. [d] First recurrence compared to 3rd through 5th recurrence.

Conclusions of TTF Trials

- Combined total of nearly 700 patients: EF-11 (N = 237) + PRiDe (N = 457), represents the most robust dataset published in recurrent glioblastoma
- Safety profile benign
- OS with PRiDe similar to EF-11 phase III study[1]
  - Median OS of 9.6 versus 6.6 months
  - 1-year survival 44% versus 20%
  - 2-year survival 30% versus 9%
- PRiDe confirms prognostic factors that predict survival:
  - Compliance ≥18 hours/day
  - Bevacizumab-naïve patients
  - Performance status
  - Use in first recurrence

1. Stupp R, et al. *Eur J Cancer* 2012;48(14):2192-2202.