Alternating Electric Fields Therapy for Recurrent Glioblastoma - NovoTTF-100A System: Updated Outcomes and Toxicity Based on the Analysis of Patient Registry Data
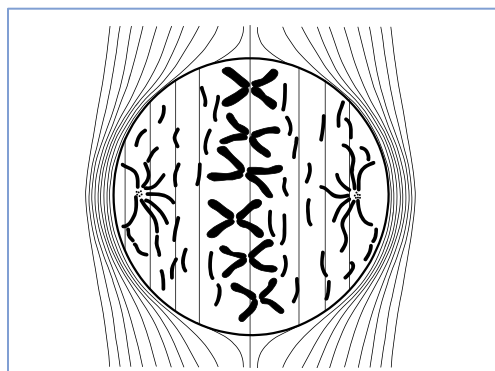
PRiDe (Patient Registry Dataset)

Mrugala MM, Engelhard HH, Butowski N, Tran D, Kew Y, Cavaliere R, Villano J, Bota D, Rudnick J, Sumrall A, Zhu JJ, Wong ET
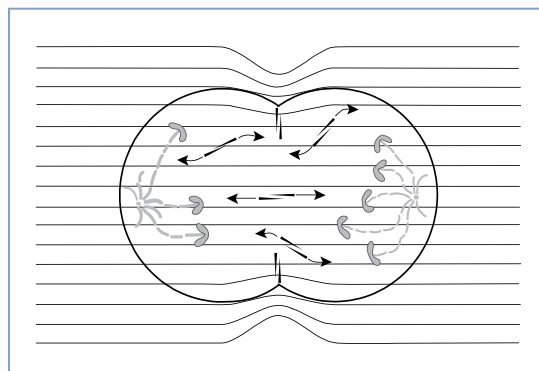
Disclosure slide

- Consultant and research support - Sigma Tau Pharmaceuticals

- Consultant and research support - Novocure

Mechanism of Action: TTFields
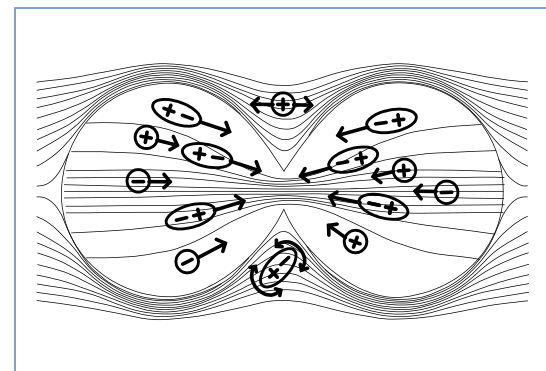## (Tumor Treating Fields)

Metaphase
- Microtubule assembly[1]

Anaphase
- Disrupted cytoplasmic membrane[2]
- Cytoplasmic blebbing[2]
- Asymmetric chromosome segregation[2]

Telophase
- Intracellular dielectrophoresis of macromolecules and organelles[3,4]

TTFields target dividing cancer cells leading to apoptosis[3]

1. Kirson E, Gurvich Z, Schneiderman R, et al. *Cancer Res*. 2004;64(9):3288-3295. **2**. Lee SX, Wong ET, Swanson KD. [SNO abstract CB-013]. *Neuro Oncol*. 2012;14(suppl 6):vi7vi20.
3. Kirson ED, Dbalý V, Tovarys F, et al. *PNAS*. 2007;104(24):10151-10157. **4**. Gutin PH, Wong ET. *Am Soc Clin Oncol Educ Book*. 2012;32:126-131.
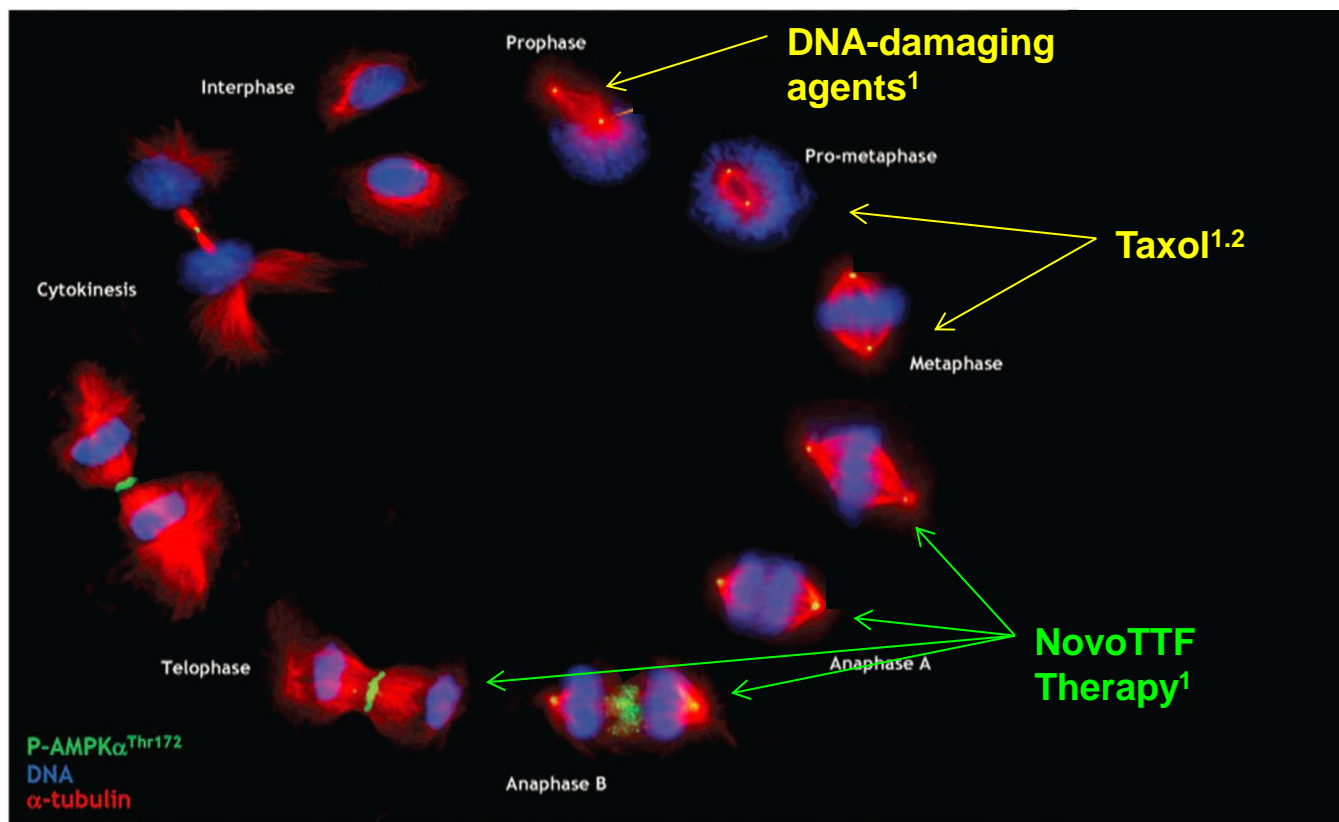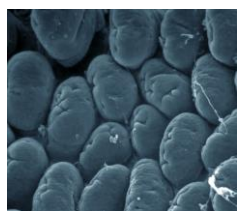
TTFields - Mechanism of Action

Image modified from Vazquez-Martin A, Oliveras-Ferraros C, Mendeendez JA. *Cell Cycle.* 2009;8(15);2385-2398. **1.** Wong ET, Lee SX, Swanson KD. [SNO abstract CB-013]. *Neuro Oncol*. 2012;14(suppl 6):vi7-vi20. **2.** Horwitz SB. *Ann Oncol*. 1994;5 Suppl6:S3-S6.
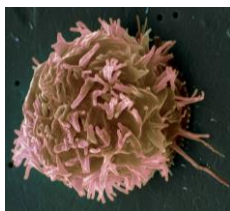
In Vitro Evidence of Mechanism of Action

Effects on Cells Are Frequency Specific and Inversely Related to Cell Size[1-3]
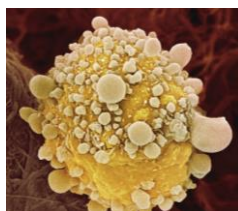
Normal Intestine[4]	Breast Cancer[2]	Pancreatic Cancer[3]	NSCLC[2]	Ovarian Cancer[4]	GBM[1,2]	SCLC[4]
~50 kHz	120 kHz	150 kHz	150 kHz	200 kHz	200 kHz	240 kHz
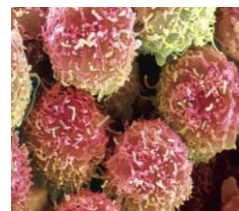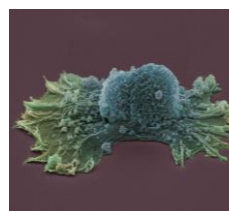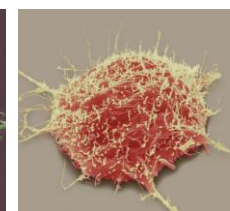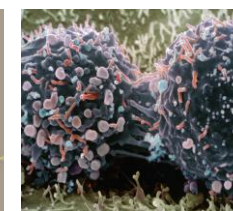
1. Kirson E, Gurvich Z, Schneiderman R, et al. *Cancer Res*. 2004;64(9):3288-3295. **2**. Kirson ED, Dbalý V, Tovarys F, et al. *PNAS*. 2007;104(24):10151-10157. **3**. Giladi M, Schneiderman RS, Porat Y, et al. *Pancreatology*. 2014;14(1):54-63. **4.** Novocure data on file. Images used with permission from Steve Gschmeissner/Science Photo Library.

NovoTTF-100A system was approved by FDA for recurrent GBM in 2011

Images used with permission from Novocure.

PRiDe (Patient Registry Dataset)

METHODS

◆ Data from <u>recurrent GBM patients</u> treated with NovoTTF-100A system in the United States between <u>October 2011 and November 2013</u> were captured

◆ Patients provided consent to use their PHI to advance the understanding of NovoTTF Therapy

◆ Baseline patient characteristics were assessed by manual patient chart review

◆ Overall survival (OS) was assessed using the Social Security Death Date Registry

STATISTICAL ANALYSIS

◆ Retrospective OS and treatment duration curves were constructed using the Kaplan-Meier method

◆ OS in the registry dataset was compared to the survival of patients receiving NovoTTF Therapy in EF-11 study (ITT group) using a log-rank test

◆ Patient characteristics prognostic for survival with NovoTTF Therapy were assessed using a Cox proportional hazards model (P value of .15)

◆ Subgroup analyses were performed on the patient characteristics found to be significantly correlated with OS

PRiDe–Baseline Patient Characteristics

		PRiDe NovoTTF Therapy[1] (n=457)	EF-11 NovoTTF Therapy[2] (n=120)	EF-11 Active Chemotherapy[2,a] (n=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)
	10-60	19.0%	NA	NA
	70-80	46.6%	NA	NA
	90-100	30.9%	NA	NA
	Unknown	3.5%	NA	NA
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%
	RT + temozolomide	>77.9%	86%	82%
	Debulking surgery	>63.9%	79%	85%
	Carmustine wafers	>3.7%	NA	NA

KPS, Karnofsky performance status; NA, not applicable; RT, radiotherapy.[a]Active chemotherapy, including bevacizumab.

1. Novocure data on file. **2.** Stupp R, Wong ET, Kanner AA, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

PRiDe – Overall Survival

Legend:
- PRiDe NovoTTF Therapy (n=457)
- EF-11 NovoTTF Therapy (n=120)
- EF-11 Active Chemotherapy (n=117)

Y-axis: Fraction Survival
X-axis: OS (months)
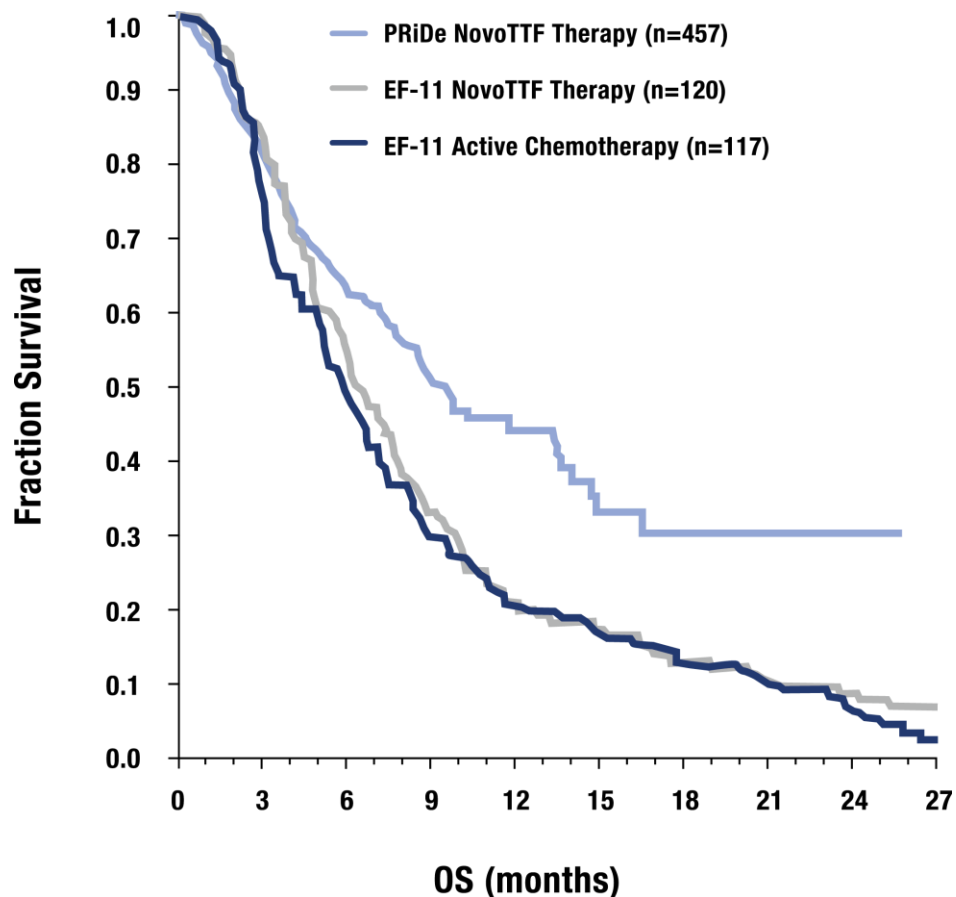
Median OS	Months
PRiDe NovoTTF Therapy[1]	**9.6**
EF-11 NovoTTF Therapy[2]	6.6
EF-11 Active Chemotherapy[2]	6.0

Log-rank (Mantel-Cox) Test[1]	
P value	0.0003

PRiDe vs EF-11 NovoTTF Therapy[1]	
HR	0.66
95% CI	0.50-0.86

CI, confidence interval; HR, hazard ratio; OS, overall survival.
1. Novocure data on file. **2.** Stupp R, Wong ET, Kanner AA, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

PRiDe – One- and Two-Year Survival Rates and Median Treatment Duration

	PRiDe NovoTTF Therapy[1] (n=457)	EF-11 NovoTTF Therapy[2] (n=120)	EF-11 Active Chemotherapy[2] (n=117)
1-Year survival	44%	20%	20%
2-Year survival	30%	9%	7%

Median treatment duration in PRiDe was 4.1 months (95% CI, 3.5-4.8)

1. Novocure data on file. **2.** Stupp R, Wong ET, Kanner AA, et al. *Eur J Cancer*. 2012;48(14):2192-2202.

PRiDe − Overall Survival by Compliance[1]

Compliance data available for 287 of 457 registry patients

Legend:
- ≥75% NovoTTF Therapy Daily Compliance (n=127)
- <75% NovoTTF Therapy Daily Compliance (n=160)

Y-axis: Fraction Survival
X-axis: OS (months)
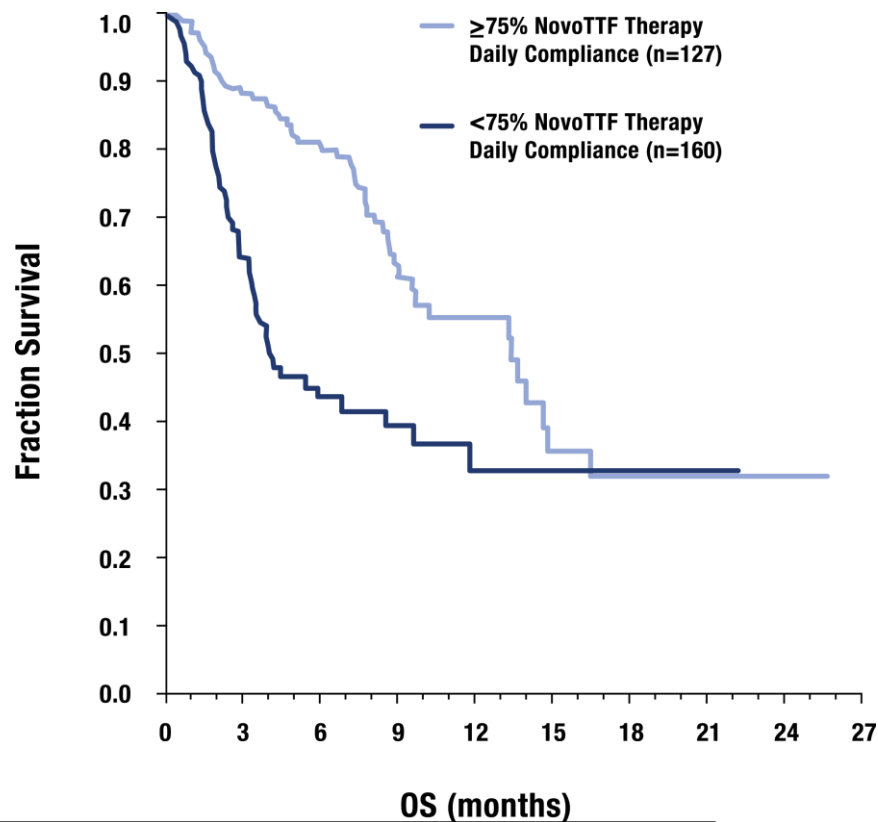
Median OS	Months
Compliance ≥75%	13.5
Compliance <75%	4.0

Log-rank (Mantel-Cox) Test	
Chi square	18.44
df	1
P value	<0.0001

Daily Compliance ≥75% vs <75%	
HR	0.43
95% CI	0.29-0.63

CI, confidence interval; HR, hazard ratio; OS, overall survival.

1. Novocure data on file.

PRiDe – Overall Survival by the Number of Recurrence[1]

1st Recurrence (n=125)
2nd Recurrence (n=123)
3rd-5th Recurrence (n=152)
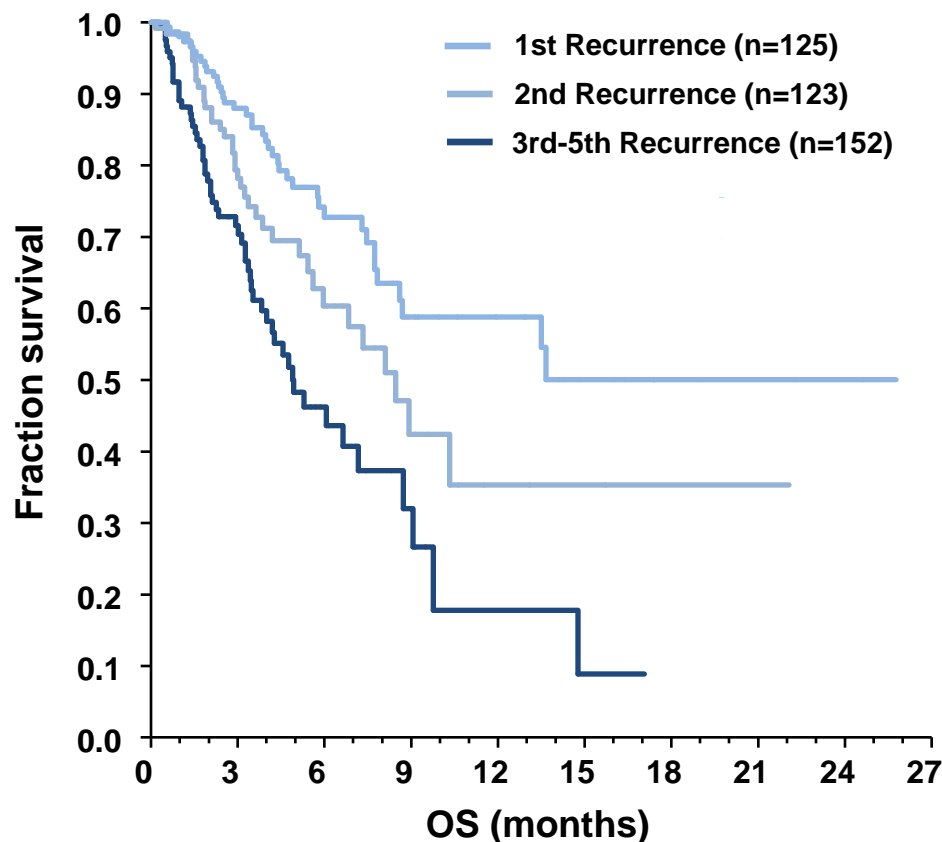
Median OS	Months
1st recurrence	20.0
2nd recurrence	8.5
3rd-5th recurrence	4.9

Log-rank (Mantel-Cox) Test	
Chi square	24.88
df	2
P value	<0.0001

1st vs 2nd Recurrence	
HR	0.6
95% CI	0.4-0.9
P value	0.0271

1st vs 3rd-5th Recurrence	
HR	0.3
95% CI	0.2-0.5
P value	<0.0001

HR, hazard ratio; OS, overall survival.

1. 1. Wong ET et al. In Proceedings from the 16th Biennial Canadian Neuro-Oncology Meeting; June 12-14, 2014; Halifax, Nova Scotia. Clinical Science Oral Abstract Presentation C7.

PRiDe – Overall Survival by KPS[1]

Legend:
- KPS 90-100 (n=141)
- KPS 70-80 (n=213)
- KPS 10-60 (n=87)

Y-axis: Fraction survival (0.0–1.0)
X-axis: OS (months) (0–27)
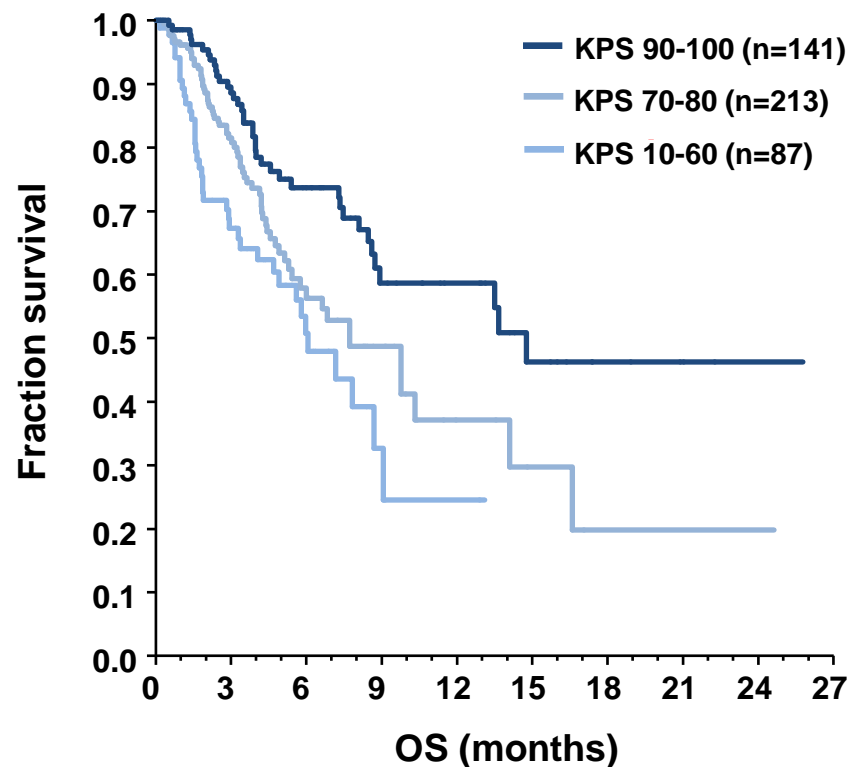
Median OS	Months
KPS 90-100	14.8
KPS 70-80	7.7
KPS 10-60	6.1

Log-rank (Mantel-Cox) Test	
Chi square	16.12
df	2
P value	0.0003

CI, confidence interval; df, degrees of freedom; KPS, Karnofsky performance status; OS, overall survival.

1. Wong ET et al. In Proceedings from the 16th Biennial Canadian Neuro-Oncology Meeting; June 12-14, 2014; Halifax, Nova Scotia. Clinical Science Oral Abstract Presentation C7.
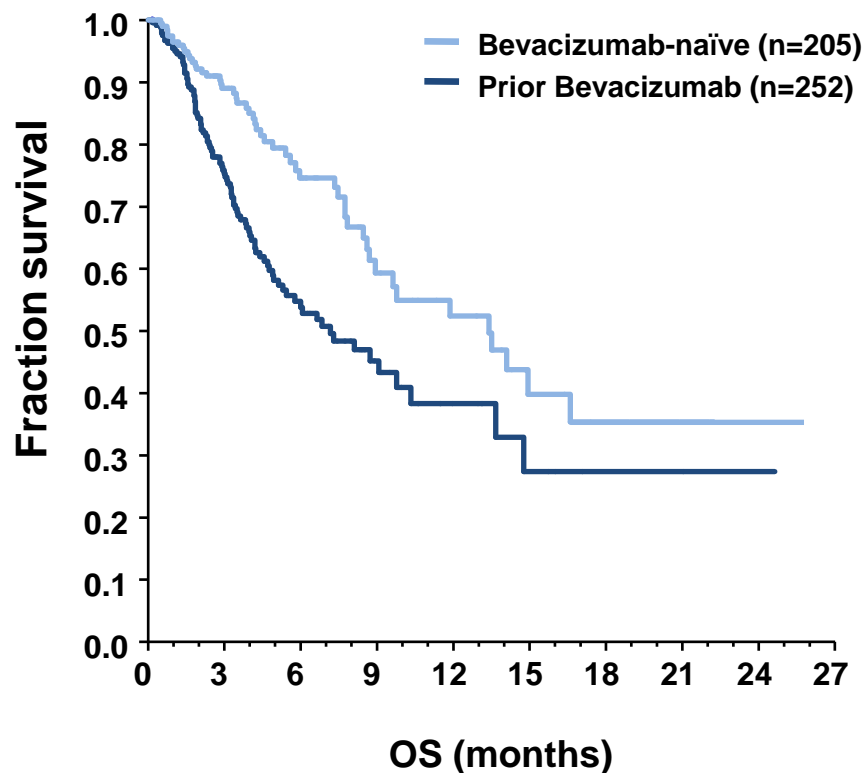
PRiDe – Overall Survival by Prior Exposure to Bevacizumab[1]

Fraction survival (y-axis): 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.0

OS (months) (x-axis): 0, 3, 6, 9, 12, 15, 18, 21, 24, 27

Bevacizumab-naïve (n=205)
Prior Bevacizumab (n=252)

Median OS	Months
Bevacizumab-naïve	13.4
Prior bevacizumab	7.2

Log-rank (Mantel-Cox) Test	
Chi square	14.54
df	1
P value	0.0001

Bevacizumab-naïve vs Prior Bevacizumab	
HR	0.54
95% CI	0.39-0.74

CI, confidence interval; df, degrees of freedom; KPS, Karnofsky performance status; OS, overall survival.
1. Wong ET et al. In Proceedings from the 16th Biennial Canadian Neuro-Oncology Meeting; June 12-14, 2014; Halifax, Nova Scotia. Clinical Science Oral Abstract Presentation C7.

PRiDe − Safety Analysis[1]

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
Vascular disorder	1.6
Weakness	1.4
Infections	1.4
Eye disorder	1.3

1. Novocure – data on file

PRiDe − Conclusions

◆ The PRiDe dataset represents 457 patients treated with NovoTTF-100A system in the United States between October 2011 and November 2013 (estimated 5% of all GBMs) [1]

◆ OS with NovoTTF Therapy is significantly longer in the real-world setting than what was observed in the EF-11 pivotal trial[3,4]
  - ◆ **Median OS: 9.6 vs 6.6 months**
  - ◆ **1-Year survival: 44% vs 20%**
  - ◆ **2-Year survival: 30% vs 9%**

◆ Compliance is a clear predictor of survival on NovoTTF Therapy[3,4]

◆ The PRiDe dataset confirms that certain prognostic factors are predictive for survival[5]
  - ◆ Performance status
  - ◆ Early introduction of therapy (first recurrence)
  - ◆ Bevacizumab-naïve patients

◆ No new safety signals have been detected in the real-world setting[3]

◆ Skin irritation was the only common device-related adverse event, which is consistent with the results from the EF-11 pivotal trial[3,4]

1. Wong ET, Engelhard HH, Tran DD, et al. ASCO Proceedings 2014; Publication-Only Abstract # e13033. **2.** Ostrom QT, Gittleman H, Farah P, et al. *Neuro Oncol*. 2013;15(suppl 2):ii1-ii56. **3.** Novocure data on file. **4.** Stupp R, Wong ET, Kanner AA, et al. *Eur J Cancer*. 2012;48(14):2192-2202. **5.** Wong ET et al. In Proceedings from the 16th Biennial Canadian Neuro-Oncology Meeting; June 12-14, 2014; Halifax, Nova Scotia. Clinical Science Oral Abstract Presentation C7.