Submitted by: Al Musella, DPM & Paul Zeltzer, MD on 10/1/14
Company/Organization: Musella Foundation For Brain Tumor Research & Information, Inc
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NCCN Guidelines Panel: CNS Tumor Panel

Request for reconsideration of NCCN rating of "Alternating electric field therapy" for Recurrent Glioblastoma Multiforme

We respectfully request that the NCCN CNS tumor panel review the latest clinical data in support of inclusion of "Alternating electric field therapy", as delivered by the NovoTTF-100A System, in its clinical guidelines for the treatment of recurrent glioblastoma brain tumors. We ask that the therapy be given a uniform consensus recommendation of Category 2A. We believe that healthcare payers should provide coverage of the device for their members and believe this device provides physicians and patients with an important treatment option for recurrent glioblastoma.

The Musella Foundation For Brain Tumor Research & Information, Inc. is a 501(c) 3 non-profit public charity incorporated in 1997 and dedicated to improving the lives of brain tumor patients. Our mission is to advance the standard of care for brain tumors, both in terms of efficacy and quality of life measurements, by funding new research activities and by promoting education and communication forums. Our organization provides updates on research and treatment advances to the brain tumor community through the Brain Tumor News Blast email list, which has a current subscription of 13,800 families worldwide that are dealing with brain tumors. Through these efforts, we believe our organization is a leading resource for brain tumor patients and caregivers seeking information about treatment options.

We were surprised when the NCCN CNS tumor treatment guidelines for alternating electric field therapy were changed from a category 2b to a Category 3. This was surprising given the fact that all of the new data that has been generated from the time you gave the treatment a category 2b rating to the time you downgraded it to a Category 3 was very positive. Not one negative article came out during that time period. In fact, additional data continues to validate the safety and efficacy of this therapy for patients with recurrent glioblastoma. We base this recommendation on our review of the clinical trial data leading to the FDA approval, numerous published case reports and the reported registry data. We also have extensive personal experience with patients who use the device. We run an online support group dedicated to patients who use or want to use the device (which currently has over 170 members), and we track how patients do with the device. We have some long term survivors in the group, which is unusual in this diagnosis. We also run 10 other online support groups, with over 3,000 brain tumor patients using other treatments, so we get a great perspective on how the Novocure System does compared to other treatments. The Novocure patients do at least as well as patients using any other treatment (most of which have a Category 2A rating) and usually have fewer side effects. If we had to make a decision for ourselves or a family member fighting a glioblastoma, the NovoTTF-100A System would be in the treatment plan.

Recurrent glioblastoma is a rare and deadly disease with an extremely poor prognosis. There are few treatment options approved by the FDA for these patients, and patients deserve a choice in their care. The Novocure NovoTTF-100A System should be available for those who need it. Without a consensus recommendation in the NCCN CNS tumor treatment clinical guidelines, patients and their families face a battle with their insurance companies over coverage. In fact, Medicare is currently deciding whether to cover this treatment for patients and the category 3 recommendation is making access for Medicare patients quite difficult.

The vast majority of recurrent Glioblastoma patients lose the ability to work, and most families immediately develop financial problems. We routinely deal with Glioblastoma patients who forego treatments due to expense. We have helped families fight with insurance companies when Temodar, Gliadel and Avastin were first FDA approved for glioblastomas. We know from experience that inclusion in your guidelines as a category 2A helps make these problems go away, and the last thing our patients need is the stress of worrying about insurance coverage. We understand that the randomized controlled trial did not show outstanding results - but the FDA concluded that it was at least equivalent to the other Category 2A treatments in your guidelines, with less side effects and a higher quality of life for the patients. That alone should support a category 2A recommendation.

Therefore, we support a uniform consensus recommendation of Category 2A by the NCCN CNS Tumors Committee for inclusion of alternating electric field therapy in the treatment guidelines for recurrent glioblastoma patients who are not candidates for surgery or radiotherapy.

We have talked to a lot of neuro-oncologists about this treatment. Some of them love it and use it. Over 100 major brain tumor centers thought enough about this treatment that they became certified in its use and use it on their patients.

However, some of the neuro-oncologists dismiss it out of hand without looking at the data. We think they associate it with a type of alternative treatment popular many years ago that was obviously a fake. The Novocure system is different. This was developed the correct way – hard work, years of intensive lab research, large human trials, FDA approval and then the registry of patients who used the device after approval. There is a lot of 3rd party research published which paints a picture that this treatment is indeed appropriate for recurrent glioblastoma. Please make sure the reviewers read the latest research on the treatment before making a snap decision. A copy of the latest research – a report on 457 patients with recurrent glioblastoma – is attached below. When reviewing it, keep in mind the results reported with all of the other glioblastoma treatments that you rated higher.

And finally – if possible, please change the description from “Alternating electric field therapy” to “Tumor Treatment Field Therapy” and/or “NovoTTF-100A System“ to match the descriptions that Medicare uses.

Sincerely,

Al Musella, DPM and Paul Zeltzer, MD

NOVOTTF™ THERAPY FOR RECURRENT GLIOBLASTOMA

PRiDe (**P**atient **R**eg**i**stry **D**atas**e**t)

FDA Approved Indication

- NovoTTF-100A System is FDA approved for use as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM), following confirmed disease recurrence after receiving chemotherapy.
- The device is intended to be used as monotherapy as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.
- Please refer to the Instructions For Use (IFU) for full prescribing information or visit novottftherapy.com

PRiDe
Methods

- Data from recurrent GBM patients in the United States who started NovoTTF Therapy between October 2011 and November 2013 were captured[1]
- Patients provided consent to use their PHI to advance the understanding of NovoTTF Therapy[1]
- Baseline characteristics were assessed by manual patient chart review
- OS was collected using the Social Security Death Date Registry and obituaries

GBM, glioblastoma; OS, overall survival; PHI, protected health information.

NovoTTF Therapy is approved for the treatment of recurrent glioblastoma. Refer to the IFU for full prescribing information.

1. Wong ET, Engelhard HH, Tran DD, et al. ASCO Proceedings 2014; Publication-Only Abstract # e13033.

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PRiDe
Baseline Demographics

		PRiDe NovoTTF Therapy[1,2] (n=457)
Age (years)	Median (range)	55 (18-86)
Gender	Male	67.6%
	Female	32.4%
KPS	Median (range)	80 (10-100)
	10-60	19.0%
	70-80	46.6%
	90-100	30.9%
	Unknown	3.5%
Recurrence	Median (range)	2 (1-5)
	1st	33.3%
	2nd	26.9%
	3rd-5th	27.4%
	Unknown	12.5%
Prior Treatments	Bevacizumab	>55.1%
	RT + temozolomide	>77.9%
	Debulking surgery	>63.9%
	Carmustine wafers	>3.7%

KPS, Karnofsky performance status; RT, radiotherapy.

1. Wong ET, Engelhard HH, Tran DD, et al. ASCO Proceedings 2014; Publication-Only Abstract # e13033.
2. Novocure data on file.

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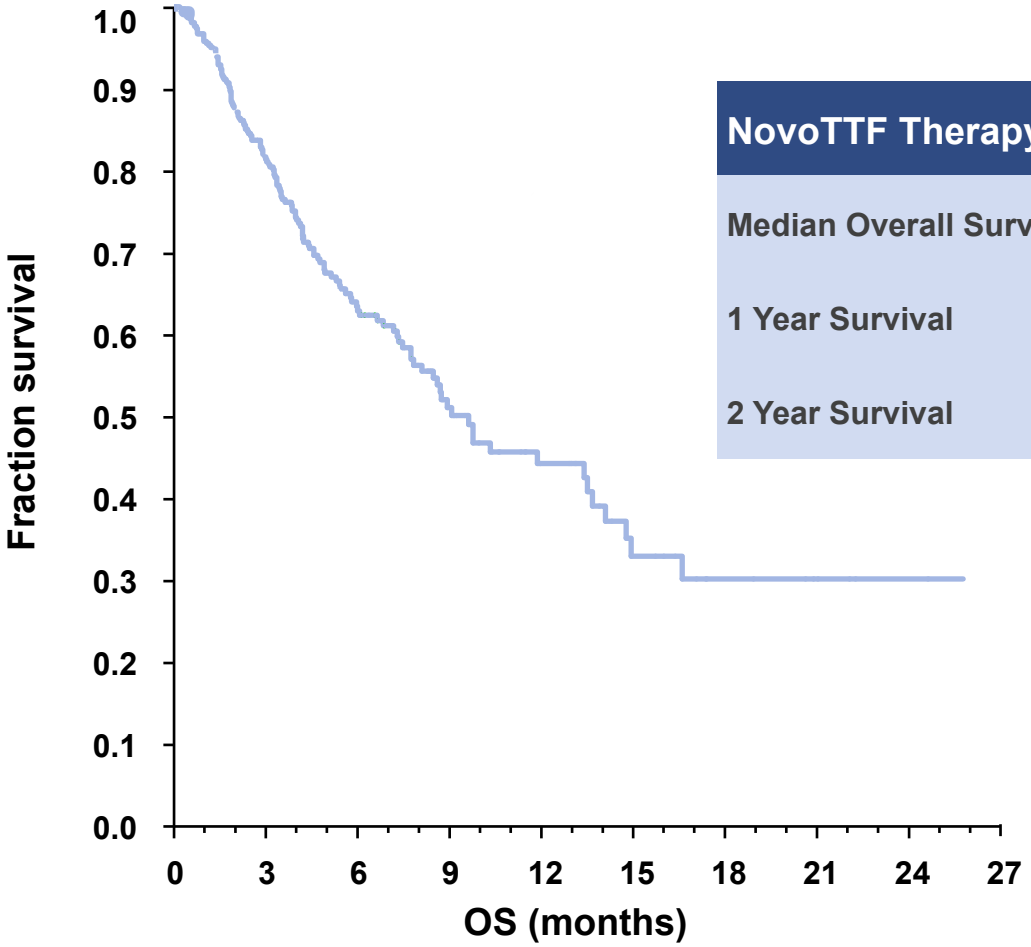
PRiDe
Survival Outcomes



NovoTTF Therapy[1]	N = 457
Median Overall Survival	9.6 mos
1 Year Survival	44%
2 Year Survival	30%

OS, overall survival.

1. Wong ET, Engelhard HH, Tran DD, et al. ASCO Proceedings 2014; Publication-Only Abstract # e13033

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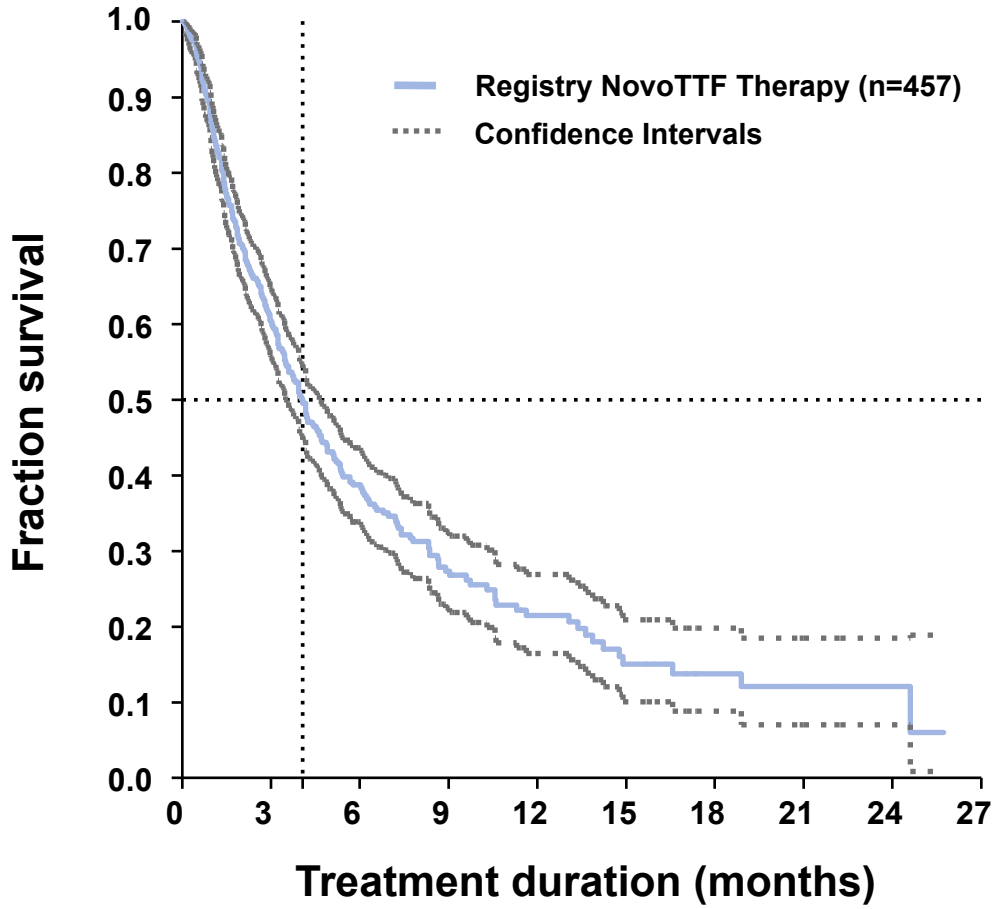
PRiDe
Treatment Duration[1,2]

Median treatment duration = 4.1 months (95% CI, 3.5 to 4.8)



CI, confidence interval.

1. Wong ET, Engelhard HH, Tran DD, et al. ASCO Proceedings 2014; Publication-Only Abstract # e13033
2. Novocure data on file.

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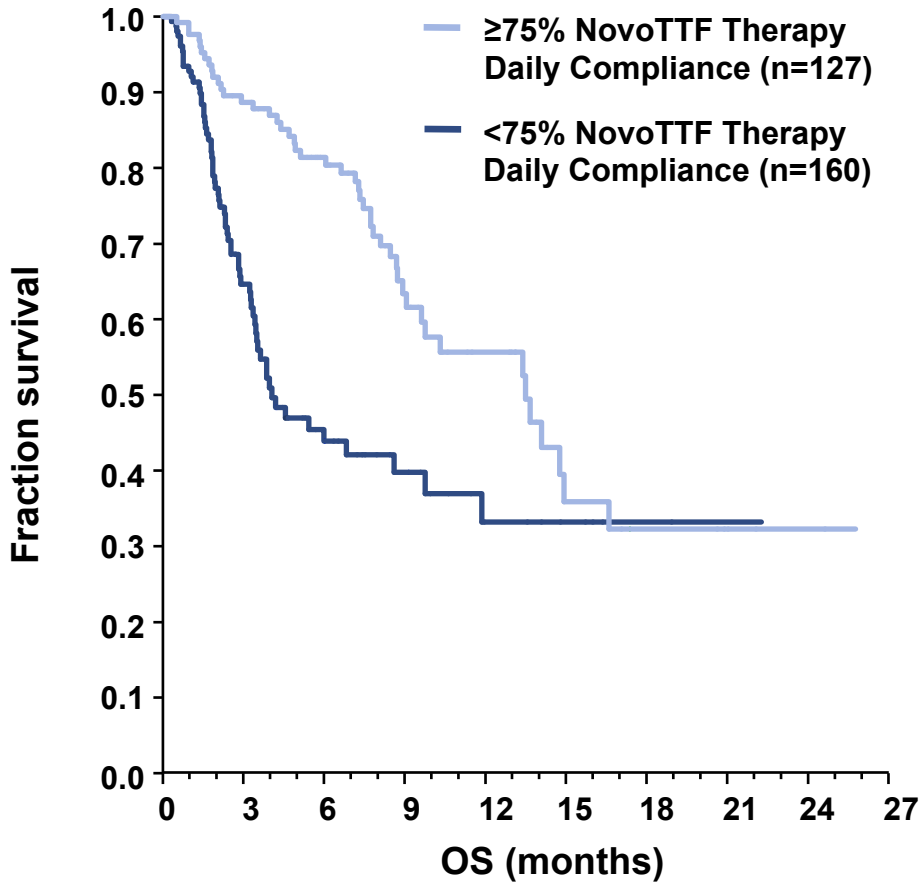
PRiDe

Overall Survival by Compliance[1]

Compliance data available for 287 of 457 registry patients



Median OS	Months
≥75% compliance	13.5
<75% compliance	4.0

Log-rank (Mantel-Cox) Test	
Chi square	18.44
df	1
P value	<.0001

≥75% vs <75% Daily Compliance	
HR	0.43
95% CI of ratio	0.29 to 0.63

CI, confidence interval; df, degrees of freedom; HR, hazard ratio; OS, overall survival.

1. Novocure data on file.

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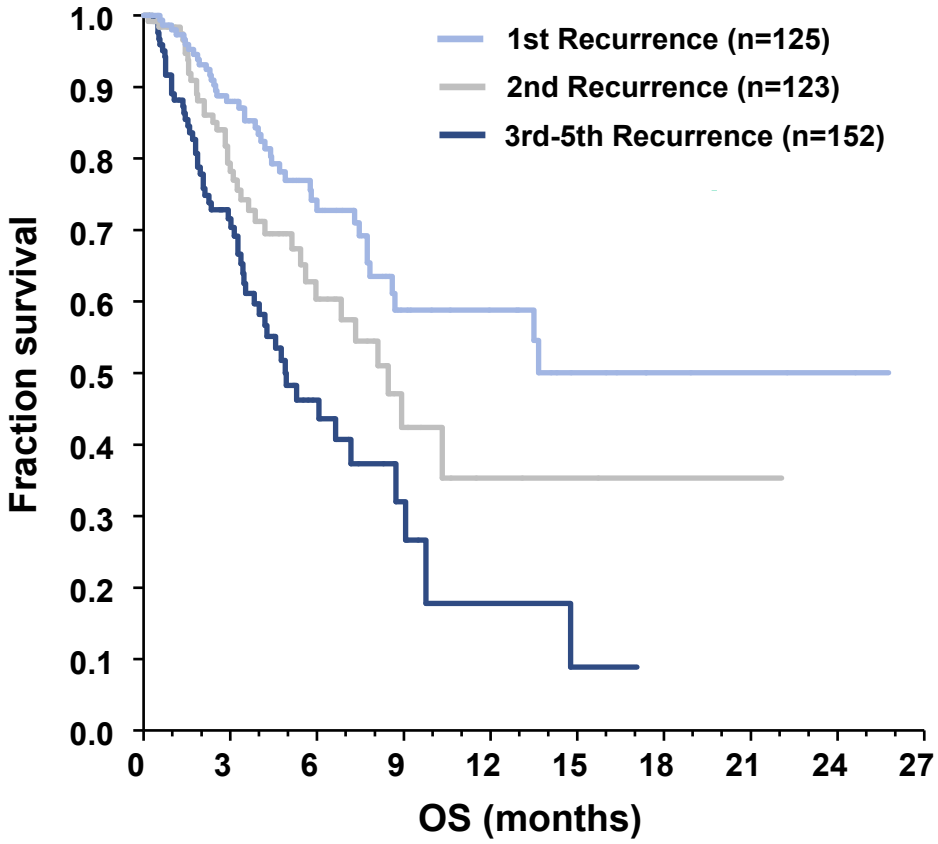
PRiDe: Overall Survival by Prognostic Factors

PRiDe

Overall Survival by Number of Recurrence[1]



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

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.

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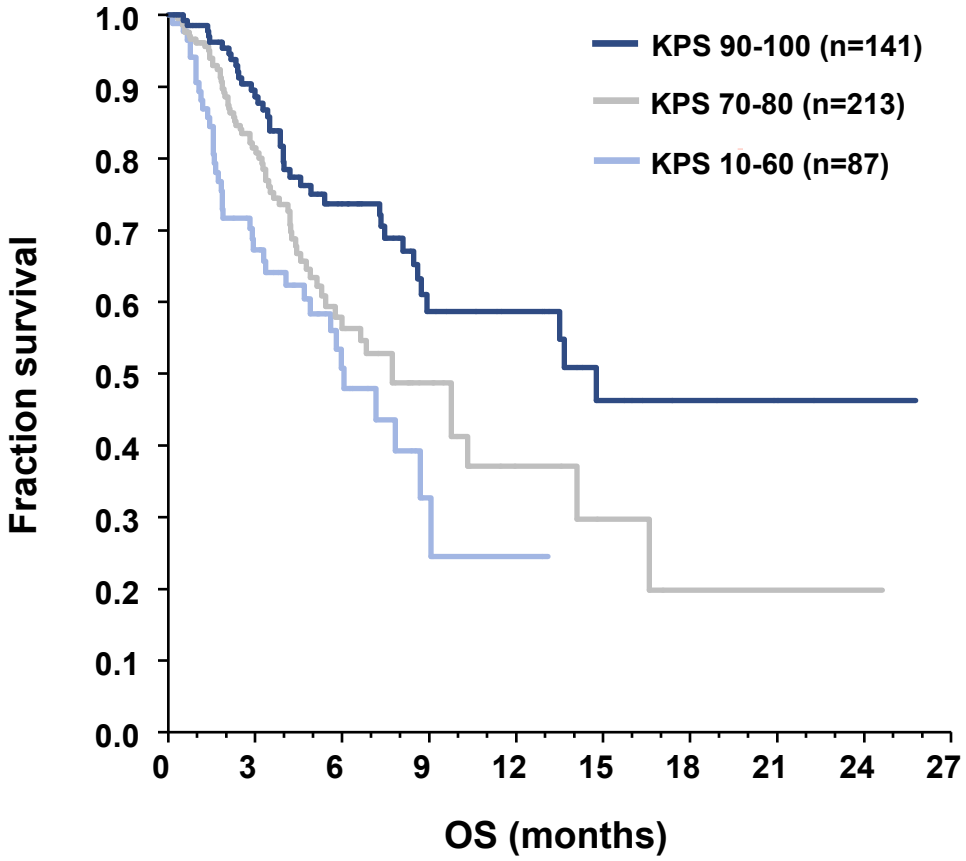
PRiDe
Overall Survival by KPS[1]



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

KPS 90-100 vs 70-80	
HR	0.6
95% CI	0.4-0.9
P value	0.0070

KPS 90-100 vs 10-60	
HR	0.4
95% CI	0.2-0.6
P value	<0.0001

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.

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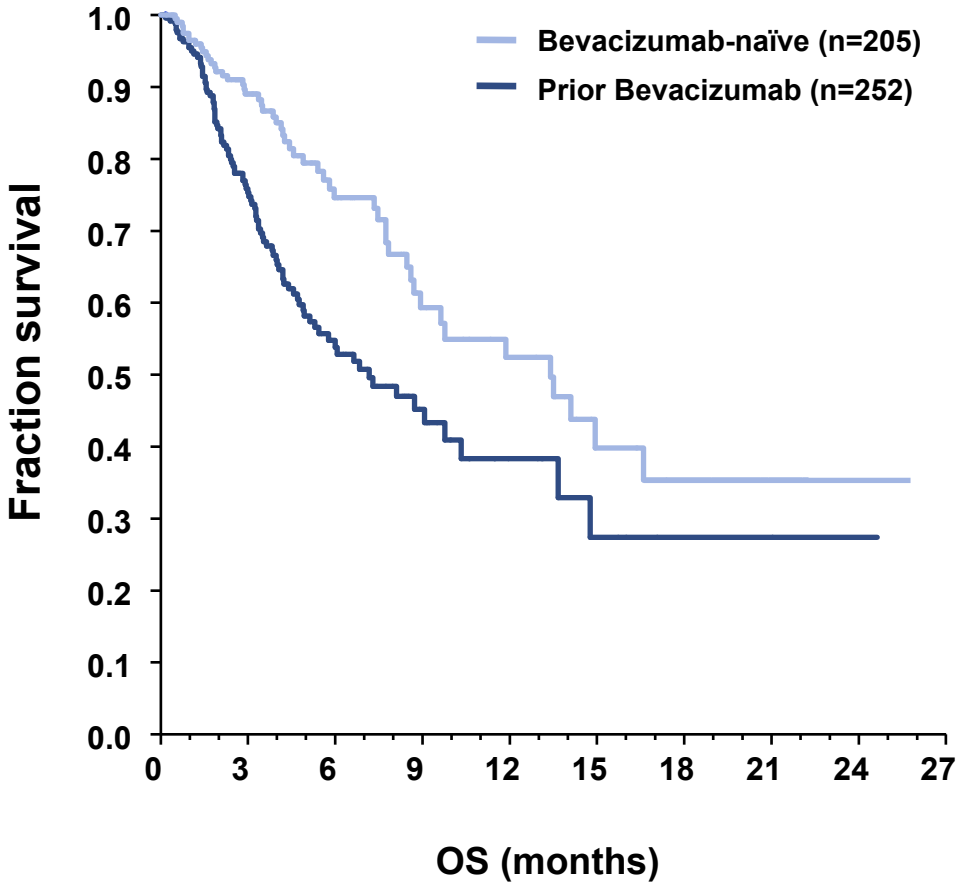
PRiDe

Overall Survival by Prior Bevacizumab Treatment[1]



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; HR, hazard ratio; 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.

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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.

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PRiDe
Conclusions

- The PRiDe dataset represents 457 patients treated in the United States between October 2011 and November 2013[1]
  - Novocure believes this represents about 5% of the treated recurrent GBM population in the United States[2]
- OS with NovoTTF Therapy is significantly longer in the real-world setting than that 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]
  - PRiDe dataset confirms that at least 18 hours of treatment per day with NovoTTF Therapy achieves longer survival outcomes
- The PRiDe dataset confirms that certain prognostic factors are predictive for survival[5]
  - Bevacizumab-naïve patients
  - Performance status
  - Use in 1st recurrence
- 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]

GBM, glioblastoma; OS, overall survival.

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.

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