

Dear Al,

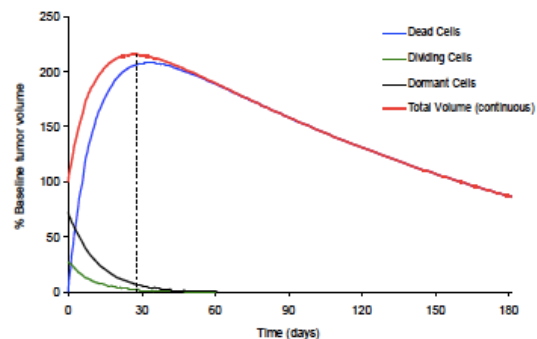
Peter Melnyk passed your email along to me to answer the question about the length of time to see a treatment effect that you asked on behalf of one of the support group members. The group member wanted to know why there was not an immediate response seen when using NovoTTF 100A.

As you know Novocure conducted extensive evaluations using tumor treating fields in the laboratory setting before beginning use in humans.

From that research a kinetic model was developed. Two slides that we use in certification training for physicians discuss the expectation about when to see a response.

## In Vitro Kinetic Effect of TTFields

- Kinetic modeling of compartmental tumor growth was used to test the time needed to achieve tumor growth reversal using TTFields
- Tumor growth reversal is not immediate
- Tumor growth reversal is seen only if TTFields are applied continuously for several weeks



Kirson et al., *Clin Exp Metastasis*, 2009 DOI10.107/S10585-009-9262-Y

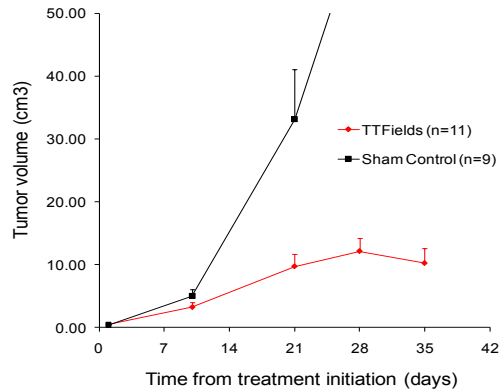
As you can see from the slide above the effect of NovoTTF on dividing cells begins fairly quickly after the fields are applied (the green line), the number of dead cells increases (the blue line) but it isn't until around the 30 day mark that a decrease in overall tumor volume (red line) is able to be seen.

Similar results were seen when we performed tests in live animals.

The tumor growth rate slowed as seen in the red lines and continued to accelerate in the control group. But a decrease in the overall tumor volume isn't seen until after 4-5 weeks.

# In Vivo Kinetic Effect of TTFields

- Tumor growth reversal is not immediate
- Tumor growth reversal was seen after 4 weeks, if TTFields were applied continuously
- This validates the findings of the in-vitro kinetic model



TTFields treated vs sham treated rabbits with deep solid tumors – 5 continuous weeks of treatment

Kirson et al., *Clin Exp Metastasis*, 2009 DOI10.107/S10585-009-9262-Y

I am attaching the original paper that discussed the work for your reference.

I know it is a little bit difficult for people to grasp. There are a few key points. Tumor treating fields only have an effect on cells that are in the process of actively dividing. The data show that tumor cell division is slowed when the device is applied but it is not until the 4th week or so mark that an overall reduction in tumor size can be seen on MRI. As the cancer cells die off it takes some time for the immune system to discard the waste products of the dead cells. MRIs look at the size of the overall tumor and can not tell the difference between cells that are alive and dead.

I hope that the information is what you are looking for and that it helps the patients to understand why it takes at least 4 weeks to see a decrease in overall tumor volume. If you want to discuss this, or need some additional information please do not hesitate to let me know. I am happy to help in any way I can.

Sincerely,

**Laura Benson**  
**Vice President, Medical Affairs**  
**Novocure**  
**212.767.7533**

The US Food and Drug Administration (FDA) has approved the NovoTTF-100A System for use as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM), following histologically – or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.