

MUSELLA

F O U N D A T I O N

BRAIN TUMOR RESEARCH
AND INFORMATION

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Brain cancer is among the most devastating diseases. The majority of patients will never work again. It is now the leading cause of cancer death in children. The costs of the treatments in use are spiraling out of control. The 5 year survival rate is only 5%.

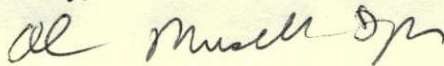
Many experimental treatments show promise – some showing over 25% 5 year survivals in small trials. However, these treatments are not yet available to most patients.

We have an idea on how to safely speed up the FDA approval process, encourage more research and at the same time slash the expenses.

Please look at the attached presentation, which explains the concept. This was designed by a dream team of the leaders in the world of brain tumor treatments and research. Our proposal could be used as a pilot program. If successful, this model could then be applied to all serious diseases.

Feel free to contact me at 888-295-4740 if you would like to discuss this further.

Sincerely,



Al Musella, DPM
President

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A PROPOSAL TO SPEED UP THE SEARCH FOR THE CURE OF BRAIN TUMORS, WHILE SLASHING COSTS AND MAINTAINING SAFETY

Version 40

6/5/2017

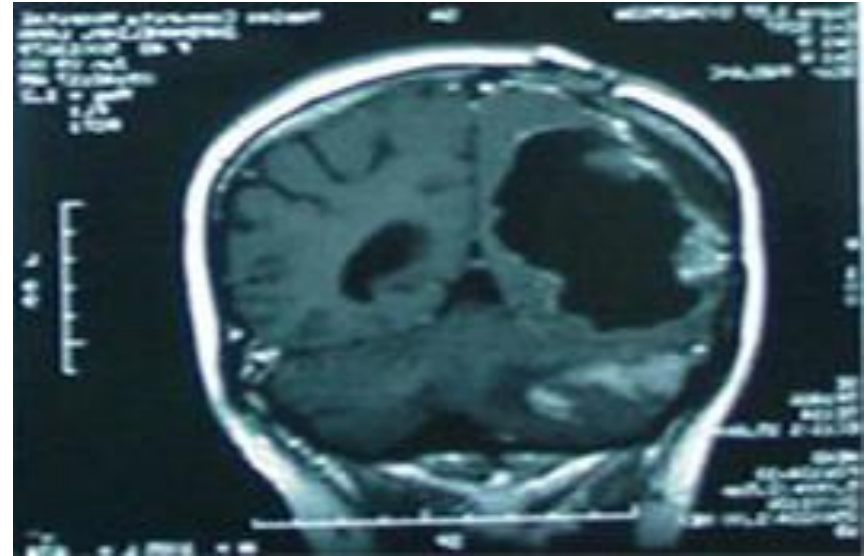
Al Musella, DPM

President

Musella Foundation For Brain Tumor Research & Information, Inc

About Brain Cancer

- Leading cause of cancer deaths in children age 0-19.
- In addition to the problems that all cancer have, brain cancer affects your very being—it changes your personality, ability to communicate, move and take care of yourself, and most patients will never work again.
- Average survival is under 2 years, and the chance of surviving 5 years is only 5%.
- Progress has been slow compared with other types of cancer.



Why is it the progress so slow?

- Brain cancer has the same problems other incurable cancers have: heterogeneity, acquired resistance to treatment, and DNA repair mechanisms
- Brain cancer also has unique problems: The blood brain barrier stops some treatments from getting to the tumor.
- The skull tightly encloses the brain—any swelling has no place to go, so it increases pressure within the skull and shuts off circulation.
- The entire brain is important. You can't just cut out or destroy wide margins without causing neurological problems.

Problems:

1. There are a few experimental treatments that have demonstrated safety and show impressive results in some patients. However, the average patient cannot get access to these potentially life-saving treatments.
2. It is likely that the cure will involve intelligent combinations of treatments, which would be much easier and faster to develop if there were more approved treatments and the results of the combinations were being tracked over time.
3. New treatments are so expensive to develop that most good ideas never get to patients, and those that do get approved have to be priced so high that many patients cannot afford them.

Proposal

We would like to propose
a new approval pathway:

Conditional Approval,
With Mandatory Participation
in a “Virtual Trial”

Conditional Approval

Granted to treatments that:

1. Have proven to be as safe as standard treatments in at least 50 patients.
2. Have shown biologic activity—an improvement in a biomarker, brain scan, progression-free survival, or overall survival.

What does Conditional Approval mean?

1. The treatment could be offered as if it had a standard approval. Any doctor could prescribe it for any brain tumor patient.
2. The treatment could not be denied by insurance as being “experimental.” They might not pay—just like they do not like to pay for any new drug—but they just can’t use that excuse.
3. All patients who use a conditional treatment would be required to **participate in a “Virtual Trial” registry** for the duration of the conditional approval period, and to sign a consent form acknowledging and agreeing to the risks inherent in undergoing a treatment whose safety and efficacy have not been fully tested.

FDA Review

- The FDA will conduct reviews periodically.
- If this treatment looks like it is causing more side effects than is acceptable, they remove the conditional approval and the drug may continue on the old pathways.
- If the drug is considered safe and effective, the FDA can upgrade the approval to a full approval. Perhaps a target could be defined, which if reached would trigger full approval such as: a 25 % increase in the number of patients alive at 1 year compared to historic controls.
- Otherwise the conditional approval remains in place.

Conditional Approval Precedents

1. The FDA already has a conditional approval pathway for treatment of cancer (and other diseases) in animals <https://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm413948.htm>.

2. The following countries have conditional approval pathways for cancer treatments:

- Japan
- Canada
- South Korea

South Korea has the most experience. The program started 15 years ago, and they conditionally approved 18 cancer treatments. Only one of those had the approval removed, and it was due to lack of efficacy; it was not a toxicity issue.

3. Federal Regulation: Title 21, Sec 312.84(b) allows the FDA to grant marketing approval for treatments after a Phase 1 trial.

The Brain Tumor Virtual Trial Registry

This is the key to making the concept work.

All patients would participate in the registry for the duration of the conditional approval.

The doctor would submit the treatments the patient is using, any side effects, testing results, as well as dates of progression and of death. This would be done at each visit.

We would collect as much genomic data as is practical and would require data on the biomarkers known to be involved with the treatment.

The registry data (without identifying information, of course) would be available to brain tumor doctors in a simple to use format so they can evaluate the risks and benefits of the conditional treatment and combinations of treatments.

The Virtual Trial App

We will develop a decision support app to help community physicians exploit the registry database.

1. The app allows patient details to be input: tumor type, prior treatments, current status, the most important biomarkers, allergies and any blood test abnormalities such as thrombocytopenia.
2. The app will display all treatments and combinations that have been tried on this type of tumor, which can be sorted in many ways, such as by most effective, best risk/benefit ratio, cost, or least side effects.
3. Clicking on any treatment or combination will display the detailed results for that treatment in similar patients.

With this information, treating physicians can make optimal decisions that balance effectiveness, cost and toxicity.

This tool can be used by community doctors to quickly identify the best combination for individual patients based on the characteristics of the patient and tumor.

It would also allow doctors to avoid treatments that are not helping.

The Virtual Trial database will have an open API so that third parties could develop tools to utilize the data

Alternatives to our proposal:

1. *“Right to Try.”*

Over 30 states have already enacted the “Right to Try” laws, and most others have bills pending. The president is talking about implementing a national Right to Try law.

This law states that a patient can use experimental treatments that have passed a Phase 1 trial. We do not support the “Right To Try” laws because:

- Nobody is observing the results. Each patient’s experiences go to waste, and we will not find out if a treatment is safe, if it is working, and how it interacts with other treatments. Our proposal has the Virtual Trial Registry and app to address this issue.
- Insurance will not pay for these treatments since the FDA did not approve them. In some cases, only the rich can get access. Our approach would allow for insurance to pay.
- Drug companies are resistant to this pathway for fear of FDA retaliation.
- This does nothing to decrease the price of the drug once approved, speed up the approval process and encourage the development of new treatments. Our proposal will.

2. Accelerated Approval / Fast Track / Breakthrough Therapy / Priority Review / Compassionate Use / Investigator sponsored INDs

These FDA programs are a great start, having allowed access to Temodar and Avastin via accelerated approval, but do not go far enough. There are a few experimental treatments that have proven safe and have demonstrated more than a hint of efficacy in Phase 1, 2 and 3 trials, but have not yet been approved. Most of these treatments are not currently available under these pathways yet, and are also unavailable for testing in rational combination therapies—so this system has failed us.

Although the FDA has made compassionate use much easier for doctors, most drug companies are resistant to providing their treatments. We have tried to get the treatments listed later in this presentation. We had a little success years ago with DC-VAX but not in recent years. However, we have not had success recently with any of the other treatments listed. The FDA is not the roadblock in these cases—it is the drug companies who have nothing to gain by participating and face high costs.

3. *21st Century Cures Act*

This law speeds up FDA approvals without giving us the data we need to home in on the cure. It allows the FDA to approve treatments based on lower levels of evidence, such as anecdotal case reports instead of clinical trials.

We do not want that. We want higher levels of evidence. Our registry approach is a new type of clinical trial. Data will be collected and analyzed as if in a traditional clinical trial. Unlike traditional trials, our registry would collect data on real world patients – not just the 5% of perfect patients who qualify for clinical trials.

We need this data to be able to quickly see which treatments work the best, and which do not.

Possible treatments eligible for this pathway

1. **Val-083** – a chemotherapy approved in China for leukemia. Used on over 1,000 patients with good safety profile. In a small trial of patients with the worst prognosis, GBM patients on second or more recurrence after failing Avastin posted results 50% better than any other published treatments. This treatment is not affected by MGMT status and may fill a huge unmet need of patients with unmethylated MGMT. About 55% of GBM patients have unmethylated MGMT, which means the standard treatment has a very small chance of helping them—but this treatment may be able to help these patients

TABLE 6: VAL-083 compared to published literature

Reference	Post Avastin Salvage Therapy	Median Survival from Bevacizumab Failure
Rahman (2014)	nitrosourea	4.3 months
Mikkelsen (2011)	TMZ + irinotecan	4.5 months
Lu (2011)	dasatinib	2.6 months
Reardon (2011)	etoposide	4.7 months
Reardon (2011)	TMZ	2.9 months
Iwamoto (2009)	various	5.1 months
DLM-10-001	VAL-083 (n=22)	8.35 months

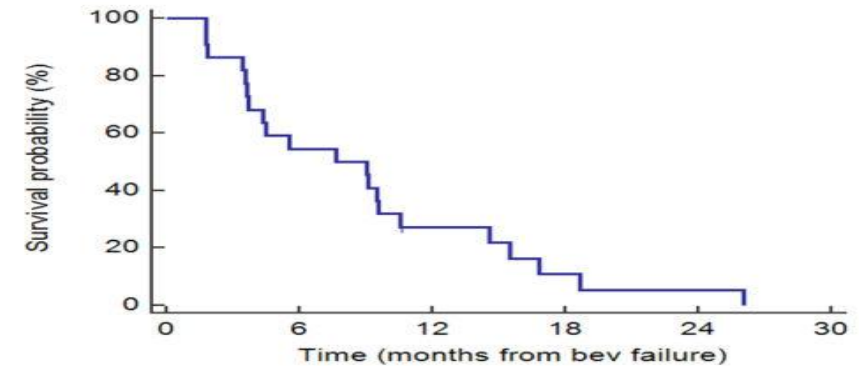


Figure 5: Kaplan Meier plot of patients receiving $\geq 20\text{mg/m}^2$ VAL-083

2. **DC-Vax** – A vaccine with a very good safety record, used in over 350 patients. In small studies, followed for a long time, they report exceptionally high survivals (4-6 years) as noted below. Compare this with the historically quoted 5% who achieved 5-year survival:

“Phase I/II trials conducted out of the University of California, Los Angeles enrolled 39 patients (20 newly-diagnosed GBMs) revealed 33% of patients met or exceeded a median OS of 48.0 months and 27% exceeded a median OS of 72.0 months, with 2 patients alive greater than 10.0 years.”

Immunotherapy for Glioblastoma

*Debebe Theodros, Dane Moran, Tomas Garzon-Muvdi and Michael Lim**

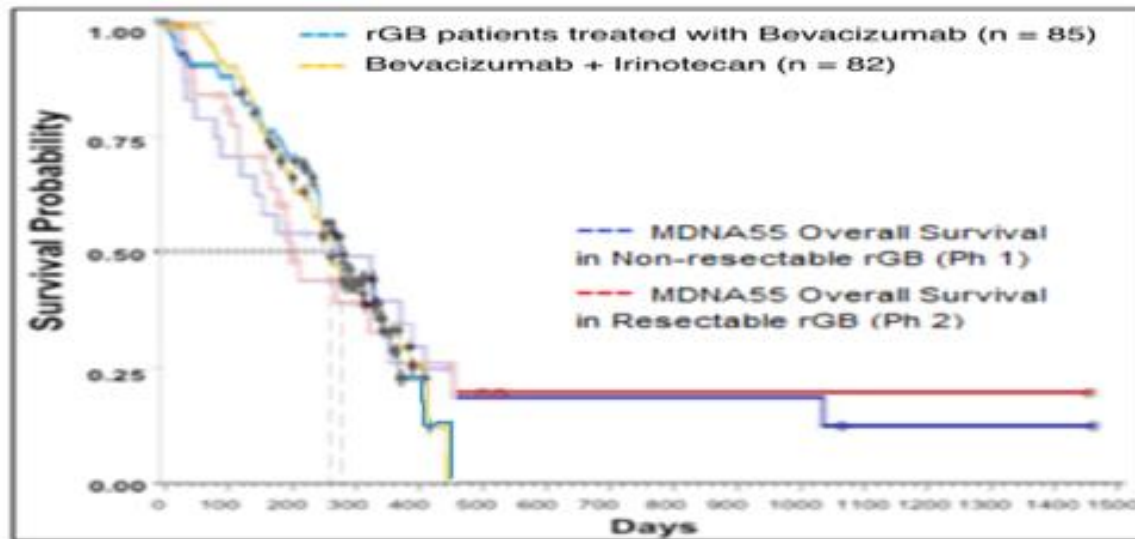
<https://www.omicsonline.org/open-access/immunotherapy-for-glioblastoma-2155-9899-1000464.php?aid=81333>

3. **ICT-107** – Another vaccine that has reported a small increase in median survival, but with excellent safety with a long survival tail. There are many multi-year survivors.

“Updated survival data presented by Dr. Phuphanich at the 2016 SNO meeting showed that 19% of patients had long-term remission of greater than 8 years, with the longest remission being 9.6 years. Also, 38% of patients demonstrated long-term survival of greater than 8 years, with the longest survivor greater than 10.2 years. Immune response data showed a correlation between survival and cancer-stem-associated expression, and a trend toward greater CD8 T cell cytokine responses in long-term survivors.”

<http://investors.imuc.com/releasedetail.cfm?ReleaseID=1000488>

4. **MDNA55** – An immunotherapy that targets IL-4, which is found on about 75% of GBMs, and very little or none on normal brain cells. Tested in over 75 patients with no significant toxicities. In 66 recurrent GBM patients, they had a 56% response rate with an outstanding 20% complete response rate after just one injection. The graph below compares these results with recent trials, where all patients died by day 450. With MDNA55, some patients are still alive at day 1,500.

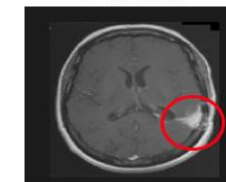
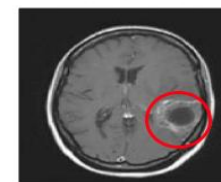


Efficacy in Non-Resected Recurrent GB (n=25)

High Objective Response Rate



Complete Response (CR): 5/25



Partial Response (PR): 9/25

5. Trans Sodium Crocetinate (TSC)

A 56-patient, Phase 2, clinical trial of glioblastoma multiforme patients incorporated TSC into the standard of care by administering TSC during radiation therapy. The results were published in *Journal of Neurosurgery*, 126: 460-66, 2017, which showed 2-year survival of 36%. This trial showed tumor regression in 2/3 of the tumor-bearing patients -- with complete (100%) regression occurring in 11 patients. Of particular importance was that patients unable to have initial surgery (biopsy only) did exceptionally well in this trial with 40% of the 15 patients in that subgroup surviving for 2 years as compared to around 10% survival seen for that subgroup in other trials. There is a huge unmet need for treatments that can be used on inoperable GBM tumors.

TSC was well-tolerated, with no serious adverse events (SAE's) occurring. In 3 clinical trials in which a total of 140 patients have received TSC, no SAE's have occurred in any of the trials.

Conditional Approval Immediate Impact

Approving just the treatments mentioned could have a huge impact on brain cancer patients right now. With current treatments, only about 5% of adult GBM patients will live 5 years. Using just one of the treatments mentioned might bring that up to 20-25%, saving about 6,000 American lives a year. Using these treatments as tools in a toolbox to combine therapies might bring that up much higher, to the point of having true hope where there is none right now—all with just one swipe of the pen to enact this Conditional Approval program.

To its credit, the FDA has in the past embraced “toolkit” licensing for HIV/AIDS and some orphan drugs. It is time to extend this model to GBM and other devastating cancers.

This pathway will also break down most barriers to the development of new therapies, allowing for a quick influx of new treatments that under current regulations would be too financially risky to try.

How will it save money?

The cost to take a drug from the idea stage to FDA approved treatment has more than doubled in the last 10 years, to exceed \$2.5 BILLION, and takes over 10 years¹. Over 90% of the treatments that start a phase 1 trial will never make it to FDA approval.

According to the Manhattan Institute, https://www.manhattan-institute.org/pdf/fda_05.pdf, 91% of these costs are for the Phase 3 trials, 8% for Phase 2 trials and less than 1% for Phase 1 trials.

By doing away with Phase 2 and 3 trials, we can save 99% of the development costs and cut 8 or more years off of the process. This would allow us to try new and riskier (from a financial point of view) ideas that would be impossible to raise funding for under the current system.

This will give us a new generation of treatments that are reasonably priced. It would—for the first time—bring competition, where treatments that have similar effects would then compete on price.

1. <https://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/>

Conditional Approval Benefit to Patients

- Faster access to a wider range of treatments.
- Ability to choose among many different treatment options.
- Significantly cheaper treatments.
- Insurance may cover these treatments.
- The patient's doctor has more tools in the toolbox to use instead of shoehorning them into using the handful of available treatments. A perfect example is the drug Temozolomide, which is used on all GBM patients, even though it has been shown to have very little chance of success with the 55% of GBM patients having unmethylated MGMT. It is used because there is no better approved alternative.

Conditional Approval Benefit to the FDA

The “Right to Try” alternative pathway cuts out the FDA oversight completely. With our Conditional Approval proposal, the FDA plays an important role in monitoring these treatments to keep us safe.

The new administration has promised to cut the time it takes to get approval and the costs involved, without supplying a plan. Our proposal fits their mandate and keeps the FDA in control.

Conditional Approval Benefit to Pharma and Researchers

Our Virtual Trial Registry database will transform the everyday practice of oncology into a global adaptive search for better treatments and cures, allowing drug companies to:

- Significantly cut the time and expense of developing new treatments.
- Keep the costs of treatment down. The industry is under fire for the cost of new treatments.
- Explore riskier approaches that have the chance to cure diseases instead of safe options that make small improvements.
- Explore how their treatment works in combinations that are impractical to try in traditional trials – possibly showing a large benefit that would have remained undiscovered using traditional trials.
- Identify why current treatments fail, and design new treatments to fill the gaps.

Conditional Approval Benefit to Insurance Companies

The cost of new treatments has gotten out of hand. Using a common combination of only 2 of the most recently approved treatments for GBM cost about \$55,000 per month, and the vast majority of private insurance companies are paying for this combination.

Our plan would allow for competition. Many new drugs would be approved quickly. We talked to some of the companies developing the drugs mentioned here today, and they are willing to keep the price of their conditionally approved drugs at or below the cost of the current standard of care drugs. Perhaps that could be a requirement of conditional approval.

Preliminary talks with an executive at a major health insurance company revealed that they would be willing to cover conditionally approved treatments as long as the total monthly cost is similar or less than the cost of the standard of care.

Summary

The first advances in oncology occurred at a time when there were no regulations. Doctors had ideas, and put them to work immediately. They adjusted and combined treatments as needed until they were optimized and became standard treatments. Many types of cancer were cured by this work.

It is obvious that the way to attack our incurable cancers is to use a combinational approach. We probably have the necessary tools in the toolbox today—but we are not allowed to use them because they are not yet approved.

Our brain cancer patients do not have decades to wait for our regulatory system. When faced with certain death, we believe it is acceptable to not have 100% proven safety and, therefore, **we are requesting a pilot project to test this system on brain cancer (or perhaps any disease with less than a 50% chance of surviving 5 years).**

Contacts & Supporters

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- Paul Zeltzer, MD, Professor of Neurosurgery, UCLA Medical Center, CA
- Lloyd Zucker, MD. Director, Florida Neuroscience Institute

Life and death decisions should not be made based on regulations—they should be based on what is best for the patient, as determined by the patient and his/her doctors.