MUSELLA
FOUNDATION

BRAIN TUMOR RESEARCH
AND INFORMATION

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 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

Al Musella, DPM
President

1100 PENINSULA BLVD.

HEWLETT, NEW YORK 11557

***Phone*: 888-295-4740** ***Fax*: 516-295-2870** ***E-Mail*: info@virtualtrials.com** ***Web*: http://www.virtualtrials.com**

An Alternative Pathway To FDA Approval of Brain Tumor Treatments

Version 20
3/16/2017

The Need

With currently approved treatments, average survival for the most common brain tumor is only about 2 years.

There are a few experimental treatments that have demonstrated safety and at least some evidence of effectiveness that is equal to or better than the currently approved, standard treatments.

However, under current regulations, it will take years before the average patient can get access to these potentially life-saving treatments.

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.

New treatments are so expensive to develop under current regulations 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

Conditional Approval

Granted to treatments that:

1. Have been tested in a brain tumor clinical trial(s) with at least 25 patients.

2. Have proven to be as safe as standard treatments in at least 50 patients.

3. 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.

2. The treatment could not be denied by insurance as being “experimental”.

3. All patients who use a conditional treatment would be required to participate in a 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.

What happens next?

1. There are regular reviews by the FDA.

2. If the safety is questionable or if the results look worse than the standard treatments, conditional approval is withdrawn and the manufacturer can continue on the standard paths of approval. The FDA cannot use these results against the standard approval tracks, as the patient population is not controlled and patients will be combining other treatments with it.

3. If the results look at least 20% better than the standard treatments, in the first 50 patients over a predetermined period of time, full approval is granted. The company can predefine some subgroups that they wanted to target, and approval could be based on just patients fitting those groups (such as newly diagnosed unmethylated MGMT GBM patients), or some combination with other treatments.

4. If the results are similar to standard treatments, the conditional approval is maintained until the review shows either the treatment is good enough for full approval or bad enough to withdraw approval.

5. The decision to try a conditionally approved drug, alone or in combination, would be up to treating physicians, who could consult with peers through a network linked to the registry.

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 plus 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 so they can evaluate the risks and benefits of the conditional treatment and combinations of treatments.

Registry Trials

The proposed registry will make possible a wide variety of innovative and cost-effective treatment discovery and validation methods.

Retrospective analyses can reveal patterns of biomarker-therapy-response correlations, as well as patterns of cost-(in)efficient utilization.

Registry-based Bayesian Adaptive prospective designs (such as I-SPY and GBM-AGILE) can be significantly more efficient than randomized designs.

Beyond even this, the registry can be used to operate an *optimally efficient* type of trial called “Global Cumulative Treatment Analysis”.

Global Cumulative Treatment Analysis (GCTA)

GCTA [1] includes all registered patients at all sites, all the time, with no exclusion criteria. This offers the potential of enrolling thousands of patients treated in the community who otherwise would not go into trials.

All plausible treatments (including combinations) are under continuous surveillance and consideration. New options are automatically integrated.

A human-machine algorithm, supervised by tumor boards, recommends treatments that simultaneously optimize patient preference, outcome, and information gathering.

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.

Based on a process pioneered by the VA [2], GCTA learns as much as possible from every patient experience. GCTA theoretically optimizes learning, without the need for control arms.

[1] Shrager, J, Tenenbaum, JM (2014a) Rapid Learning Precision Oncology. Nature Reviews Clinical Oncology 11, 109-118.

[2] Fiore, Louis D., et al. "The VA Point-of-Care Precision Oncology Program: Balancing access with rapid learning in molecular cancer medicine." Biomarkers in cancer 8 (2016): 9.

The Virtual Trial App

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

1. Input details about the patient: 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 all combinations that have been tried on this type of tumor, which can be sorted in many ways such as by most effective, most cost 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.

Future versions of the app will support virtual registry trials (see slides 8 and 9), whereby patients could be dynamically assigned to treatment arms based on expert recommendations or clinical outcomes for similar patients.

Alternatives to our proposal:

1. "*Right To Try*".

33 states have already enacted the "right to try laws." 17 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. It is a great start, however:

- 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 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.
- The FDA loses all control—they cannot monitor for safety.
- Drug companies are resistant to this pathway for fear of FDA retaliation.

2. *Accelerated Approval / Fast Track / Breakthrough Therapy / Priority Review / Compassionate Use*

These FDA programs are a great start but do not go far enough, especially with brain tumor treatments. There are 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. These treatments are therefore currently unavailable to the average patient now, and also unavailable for testing in rational combination therapies – so this system has failed us.

Drug companies are resistant to providing their treatments via compassionate use as the data can only be used against them and not help them. They are allowed to charge patients, but insurance will not pay—so only the rich can use this pathway if the company decided to charge. Most of the treatments mentioned in a later slide are not available via compassionate use.

These approval pathways still require many more patients, and usually a randomized control group, which skyrockets the costs involved and the time needed to get approval. A large number of patients are doomed to use what was the standard of care at the start of the trial.

3. GBM AGILE trial

This is a giant leap forward in clinical trial design. It allows for screening combinations of experimental and off-label treatments in a clinical trial environment. However, it has some limitations:

1. A small committee decides which treatments to use in these combinations and only a small number can be tested simultaneously.
2. Patients do not get access to the treatment they and their doctor think is best for them—they get randomized into one of the available arms of the trial.
3. Pediatric and low Karnofsky score patients are excluded at this point.
4. If successful, a treatment must still go through more years of expensive trials to get approved.
5. This trial does nothing to reduce the price of the treatments.
6. Only a small minority of GBM patients enroll in clinical trials—about 10%. This trial will have a limit of about 3,000 patients worldwide over a few years, which unfortunately excludes the vast majority of GBM patients.

4. 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 to be able to select a treatment plan based on solid evidence based research. Our registry approach is a new type of clinical trial. Data will be collected and analyzed as rigidly as if in a traditional clinical trial. We need this data to be able to quickly see which treatments work the best, and which do not.

The 21st Century Cures act will give us more tools in the toolbox, and allow oncologists to prescribe more combinations, but without requiring participation in the registry, the experiences of these patients are going to waste and do not help the next patients.

5. "Free To Choose Medicine"

This proposed pathway uses the concept of "Observational Approval". Similar to our plan, it includes a registry to track outcomes and allows for treatments to be sold after phase 1 trials. It goes much further than our proposal in that it includes all treatments, not just for serious diseases. This has been in use in Japan since 2013 (but only for regenerative medicine.)

We feel that there is a big difference in the level of proof of safety and efficacy required when treating a disease where there is a very small chance at survival vs. treating a less serious disease.

Our plans differ from current pathways in when and how this proof is provided. Currently, this proof is provided before patients are able to get access to the treatment. With our plans, preliminary proof is provided in the phase 1 trials, but the registry detects side effects and efficacy while patients are allowed access to the drug, so early adopters of the treatment might not have all of the information needed. This is acceptable with incurable brain cancer, much less so with diseases that already have other approved treatments that at least help.

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 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 still 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 Pitfalls

Elimination of phase 3 trials would remove the proof needed that a treatment shows a small improvement over standard treatments. However, we are looking for major improvements, and using advanced **Bayesian statistics** on our registry data can bring us close enough to the level of proof needed to select an effective treatment cocktail for patients. We are aware that there have been many cases where phase 3 results fail to show a benefit compared to earlier phase results. Our registry will catch those cases and if it is shown that a treatment is not working, it simply will not be used.

There is an entire industry built around running phase 3 clinical trials. Jobs may be lost. Times change, and the challenge now is to mine data from this registry and find the best treatments and weed out the unhelpful ones. New research is needed to find why treatments do not work on particular individuals and design a way around that so eventually all patients can be helped.

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, 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.

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
Mikkelson *(2011)*	TMZ + irinotecan	4.5 months
Lu *(2011)*	dasatinib	2.6 months
Reardon *(2011)*	etoposide	4.7 months
Reardon *(2011)*	TMZ	2.9 months
Iwomoto *(2009)*	various	5.1 months
DLM-10-001	***VAL-083 (n=22)***	**8.35 months**

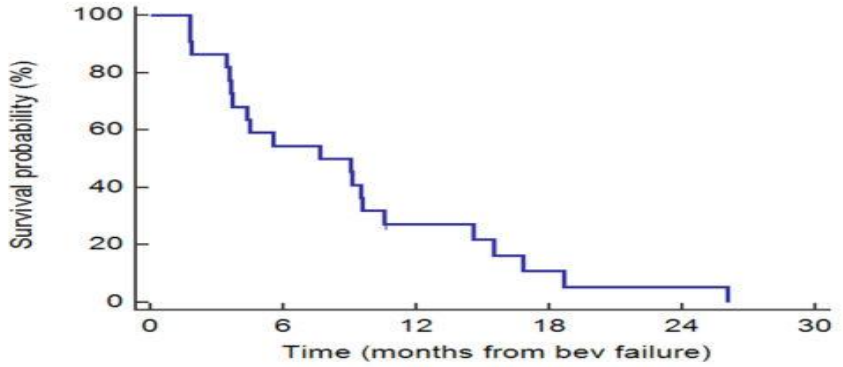


Figure 5: Kaplan Meier plot of patients receiving ≥20mg/m² VAL-083

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 4- and 6- year survivals as noted below. Compare this to 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 and excellent safety with a long survival tail. For the minority of patients that it helps, it also helps for long time. 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. **Toca 511** – Gene therapy. Good safety record, reported a significant increase (compared to historical controls who have a median survival of 7.1 months after recurrence) in overall survival for recurrent GBM. There are a few long-term survivors who appear to be cured with no tumor and perfect functioning years after stopping treatment.

"Overall survival for recurrent high-grade glioma was 13.6 months (95% confidence interval, 10.8 to 20.0) and was statistically improved relative to an external control (hazard ratio, 0.45; P = 0.003). "

http://stm.sciencemag.org/content/8/341/341ra75

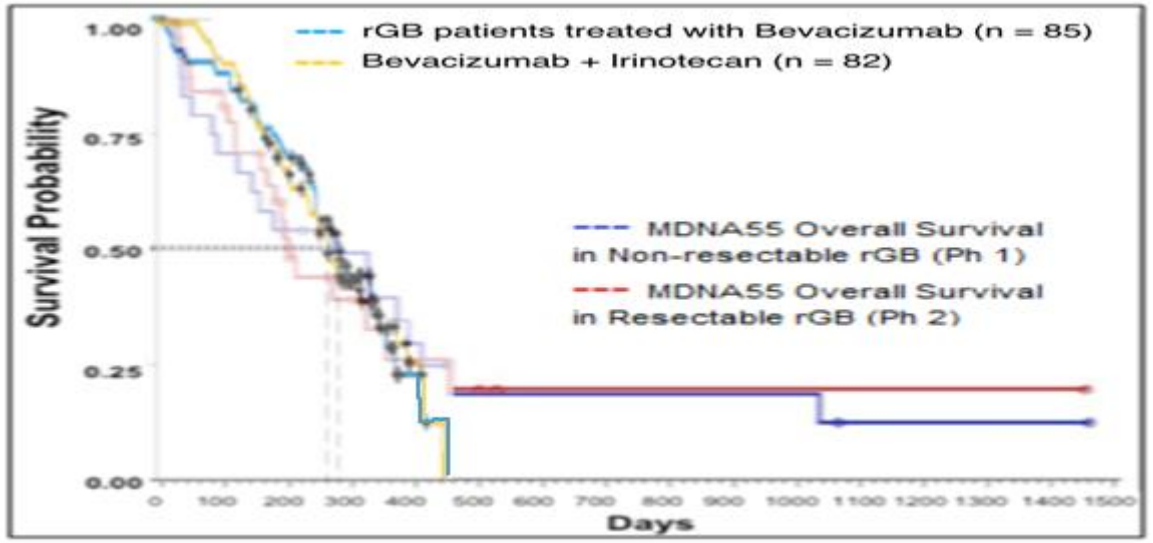
5. **Gliolan** (5-ALA) – A dye used during surgery to allow surgeon to better see where the tumor is, allowing more tumor to be removed, and improving survival. It has been used on **60,000** patients worldwide with absolute safety. It is approved for use in 33 countries, and is a standard treatment in Europe. It is absolutely criminal that this is not approved in the USA.

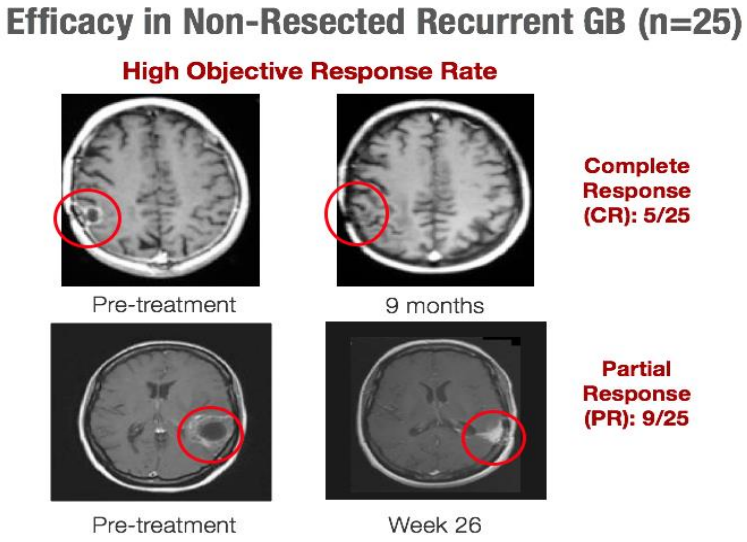
"The study included 251 evaluable cases. CR and PFS6 rates were significantly higher in the group of patients treated surgically with 5-ALA: CR, 67% versus 45%, p=.000; PFS6 for patients with grade IV tumours, 69% versus 48%; p=.002. The differences retained their significance and magnitude after adjusting for all covariates including age, functional status, and whether gliomas were located in eloquent areas."

Observational, retrospective study of the effectiveness of 5-aminolevulinic acid in malignant glioma surgery in Spain (The VISIONA study).

https://www.ncbi.nlm.nih.gov/pubmed/23870657

6. **MDNA55 –** An immunotherapy which 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 1 injection. The graph below compares these results to recent trials, where all patients died by day 450. With MDNA55, some patients are still alive at day 1500.





7. **Agenus Prophage vaccine (HSPPC-96)**, a vaccines which (along with the vaccine on the next slide) demonstrates how trials can be misleading and even lead to halting the development of useful treatments. Both had outstanding data in early trials, but failed later stage trials. Each might not show enough effect on the selected endpoints by themselves to consider the trials a success, but they may play a role in a combination of therapies which may have a huge impact.

With HSPPC-96, a trial in 46 newly diagnosed patients has a median overall survival of 23.8 months (compared to about 18 months with standard of care), with a few long term survivors. NO significant side effects. However, they found a subgroup that did much better, with an average of 44.7 months for patients with low PD-L1 levels. The most recent trial (for recurrent GBM) failed – it showed no improvement over a group of patients treated with Avastin, but those patients were not selected for this marker and were in worse shape. Under our plan, a community oncologist would be able to look at this data, prescribe the vaccine and add in a checkpoint inhibitor – with the results being tracked in our registry to see how it performs.

8. **Rintega** – a vaccine against EGFRvIII. Results in large trials were outstanding, with no significant side effects. 25 % of the recurrent GBM patients were alive after 2 years compared with NONE in the control group.

The large pivotal phase 3 trial actually showed good results compared to historical matched controls, but it did not beat the control arm. The control arm was an immune enhancer which is actually part of Rintega. It was chosen because an earlier trial had to be stopped when patients in the control group dropped out. These patients knew they were randomized to the control group because the treatment group patients developed mild inflammation at the injection site, so for the new trial, the immune enhancer was used to produce the same inflammation in the control group so patients wouldn't know which group they were in.

Again – this is a treatment that needs to be part of our toolbox to use in rationally constructed combination therapies. However, because of the design of the phase 3 trials, it will forever be lost to us.

Conditional Approval Immediate impact

Approving the treatments mentioned could have a huge impact on brain cancer patients right now. With current treatments, only about 5% of patients will live 5 years. Using just one of the treatments mentioned might bring that up to 25%, saving about 6,000 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.

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 painfully obvious that the way to cure our currently 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. For example, there are reports that combining the vaccines with immune modulators can make them more effective. But we can not just combine them now as the vaccines are not approved and cannot be obtained outside of trials. 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

- Al Musella, DPM President, Musella Foundation For Brain Tumor Research & Information, Inc.
  888-295-4740 Musella@virtualtrials.com [Contact person]
- Marty Tenenbaum, PhD Cancer Commons 650-530-3636 jmt@cancercommons.org [Contact Person]
- Lisa Kaminsky President, The Brad Kaminsky Foundation
- John A. Boockvar, MD, Feinstein Institute for Medical Research
- Henry S. Friedman, MD, The Preston Robert Tisch Brain Tumor Center at Duke, NC
- Roberta Hayes, Ph. D., St. Johns University, NY
- Linda Liau, MD, Ph.D., UCLA Medical Center, CA
- Mark Levin, MD, Private Practice, Bergen, NJ
- John E Morrissey Chairman, Richard M Schulze Family Foundation
- Hideho Okada MD, PhD, UCSF, CA
- Jeff Shrager PhD, Cancer Commons
- Lee Tessler, M.D., Long Island Brain Tumor Center, NY
- Paul Zeltzer, MD, UCLA Medical Center, CA

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.