

GBM AGILE

“A Story of Convergence, Commitment, Collaboration, and Compassion”

Glioblastoma Multiforme – GBM is the most common and aggressive form of adult malignant brain cancer. An enigmatic and deadly disease, GBM will be diagnosed in over 12,000 Americans this year and in tens of thousands more around the globe. Five-year survival for GBM is less than 5 percent (median survival is one year), and worse, these dismal statistics have not changed for decades. Although GBM is often referred to as a rare disease, its human and economic cost is staggering.

A “Big Idea” for GBM Emerges – We are entering a new era of precision medicine where the hope is that the diagnosis and treatment of a number of diseases, especially cancer, will be based on the “molecular profile” of a patient’s tumor. However, that hope is yet to be realized for GBM patients, as although hundreds of GBM clinical trials have tested numerous therapies, treatment options have not changed significantly for decades. The major advance in GBM treatment occurred a decade ago when a phase 3 study showed that survival in patients who received a drug called temozolomide in combination with radiation therapy improved by approximately two months. This is the current standard of care for GBM. This dismal picture is further amplified by the fact that there are essentially no biomarkers for GBM that could drive drug development and ultimately enable GBM patients to benefit from precision medicine. This unsettling and unacceptable reality led to the organization of think tanks in 2013-14 (convened by Drs. Ann Barker, Web Cavenee and Al Yung) to “rethink” GBM: what do we know - and not know about GBM – and what can we do to build a real knowledge base and in parallel change patient outcomes for the better? The concept of planning, designing and conducting an adaptive trial for GBM that included the large number of ethnically diverse patients afforded by the cooperation of the U.S., China, Australia and Germany (to ensure that we can learn why agents do or do not work) was endorsed by the group of scientists and advocates – and a “big idea” – GBM AGILE – was on the move!

Why this “Big Idea” – An Adaptive Trial for GBM: The adaptive trial design concept provides a unique, efficient and innovative approach to ensure that we learn from every patient entering the trial (we have learned very little from previous standard trials). Using a Bayesian, statistically driven design and incorporating biomarkers to divide GBM into subclasses, GBM AGILE will more rapidly and efficiently test single agents and combinations of drugs, biologics, etc. Beyond increasing the numbers of agents tested and the speed of the screening process, effective therapies can

progress quickly and more cost-effectively to “graduate” from GBM AGILE – and move on to a confirmatory phase 3 registration trial. Similarly, agents that do not work can be dropped from the trial – again more efficiently and quickly. The adaptive design also addresses one of the other major barriers in identifying effective drugs for GBM – the lack of validated biomarkers. Since GBM AGILE is a standing trial that will learn from every patient, as the trial proceeds it will be possible to qualify and even validate selected biomarkers. Finally, experts who also worked on the design and implementation of I-SPY 2 (an adaptive trial for breast cancer) are bringing “lessons learned” to GBM AGILE. For example, a master protocol for GBM AGILE is in development with the FDA.

Status of GBM AGILE – “Crowdsourcing Knowledge”: GBM AGILE, which began as a small “coalition of the willing” determined to improve the survival of GBM patients, has evolved into a relatively large global “force” of over 130 neurosurgeons, neuro-oncologists, pathologists, imagers, basic and clinical neuroscientists, etc. This unprecedented GBM AGILE Global Team is led by an Executive Committee and organized around the work of ten committees - each working to build and share the knowledge needed to shape the adaptive design and master protocol for GBM AGILE. The groups meet regularly by phone and in-person – challenged by aligning people and time zones across the globe – to pursue the numerous goals and tasks needed to design and implement GBM AGILE. GBM AGILE members pay their travel expenses and donate their time to this remarkable effort. This is perhaps the first example of “crowdsourcing knowledge” to build a trial that incorporates all that we know about GBM. This “knowledge crowdsourcing” model will prove to be of great value as we strive to break down silos and build knowledge bases to ensure that precision medicine is available to all patients – especially those with “rare” diseases. Although there is much work ahead, including meeting the challenges of raising the funds to implement GBM AGILE, the great news is that GBM AGILE has transitioned from a big idea, to a “global coalition” to a global “force” well on its’ way to making GBM AGILE a reality in 2016 – which is a beacon of hope for all current and future GBM patients!

“The GBM AGILE Global Team is creating a knowledge-based adaptive standing clinical trial (learning system) – that can identify more effective therapies faster and more efficiently – for the benefit of GBM patients”