Brain Tumour Initiative:

The Royal Marsden NHS Foundation Trust and
The Institute of Cancer Research supported by:

Alison Fracella Research Trust (AFRT)

We are extremely grateful to the Alison Fracella Research Trust for the support given to The Institute of Cancer Research and Royal Marsden NHS Foundation Trust towards our Brain Tumour Initiative. It is very humbling to hear about the fantastic efforts made by Alison's family and friends to raise awareness about glioblastoma and fund research into new treatments through the Alison Fracella Research Trust. This support, alongside funding from other generous sources, is allowing us to make real advances in our own efforts to combat this deadly disease.

In the last two decades only a single agent (Temozolomide) has reached routine use as an improved treatment to prolong survival in patients with malignant glioma and even with this, the benefits remain modest. The lack of new effective drugs targeting malignant gliomas is due to a number of factors. One is a lack of effectiveness of current drugs, due to poor delivery, resistance mechanisms & redundancy in the activated pathways implicated in tumour progression. This coupled with the limited research activity aimed at early drug development focused on malignant glioma in the UK, is why the support of the Alison Fracella Research Trust is so valuable.

For malignant brain tumours, the current aim of the Neuro-oncology unit at the Royal Marsden Hospital is to develop and implement tailored personalised treatment strategies that match the biological defects in each cancer in combination with the best existing treatment in both adults and children. To this end, we set up a collaboration in 2009 called the Brain Tumour Initiative, combining a number of relevant units within the hospital and the ICR.

The principal future plans are to strengthen this 'bench to bedside' collaboration between the clinical unit and the ICR's drug development team (in the Cancer Research UK Centre for Cancer Therapeutics) as well as with the Neuroscience and Imaging and Pathology team at Kings Healthcare Partners. This will enable us to:

- improve the design of early clinical trials incorporating biomarkers (a molecular feature which makes it useful for measuring the progress of disease or the effects of treatment) through an improvement of the background molecular pathology in primary brain tumours
- increase access to new drugs from both academia and pharmaceutical companies

The programme of biomarker-driven early drug testing has commenced and we are ready to start with the Olaparib (PARP1 inhibitor) study. The innovative design the Olaparib study directly answers some of the problems outlined above which may be responsible for the lack of effectiveness of current treatments for recurrent glioblastoma.

Many anticancer drugs and radiotherapy induce breaks in the DNA, which can lead to cell death if unrepaired. PARP inhibitors block the action of a PARP enzyme which repairs damaged DNA. Therefore the rationale is that its inhibition may increase the effectiveness of radiotherapy and cytotoxic treatments, and this has been already showed in preclinical studies with glioma cell lines.
Clinical studies in breast and ovarian tumours using PARP inhibitors have already been carried out and showed a radiological response in a patient with breast cancer whose cancer had spread to the brain. So far Olaparib has not been tested in people with glioblastoma.

We are also involved in a phase I/II study of an inhibitor with a potential for anti-tumour activity.

Here is the summary of our trials ongoing and in preparation, in patients with newly diagnosed and recurrent glioblastoma:

Ongoing study (first line therapy):

- The Avaglio phase III study with the role of Bevacuzimab as part of first line treatment for GBM
- The Phase I/II trial of BIBW 2992 and radiotherapy with or without temozolomide in newly diagnosed GBM

Studies in preparation (first line therapy):

- A Phase III study of EGFRvIII vaccine study in surgically resected EGFRvIII positive GBM

Studies in preparation (recurrent disease):

- PARP inhibitor trial (CRUK Drug Development Office)
- Cediranib plus Gefitinib study (AstraZeneca/NCRI initiative- NCRI study)

The Phase I/II activity in patients with recurrent high-grade glioma is likely to expand, as there is considerable un-met demand in the UK particularly in terms of the need for new drug testing in this disease. Our 5 year aim, assuming success in finding further sources of funding for neuro-oncology research, is to run a seamless programme of two or three Phase I/II studies per year underpinned by molecular biomarker assessment, proof of principle laboratory studies and functional imaging which will hopefully lead to development of novel effective therapies which are so urgently needed.

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