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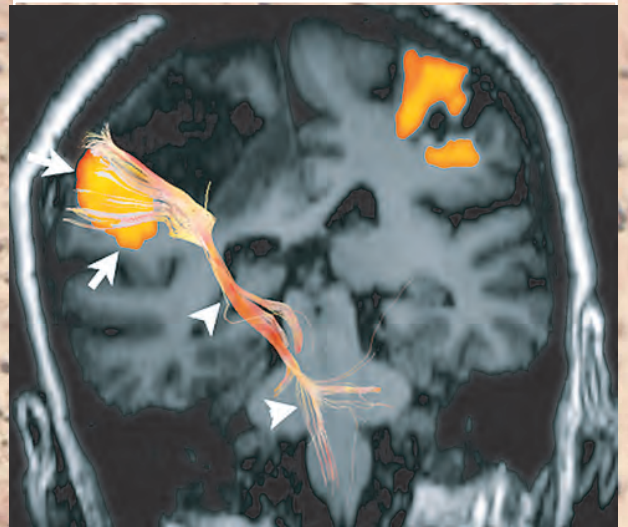
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Interview with Dr Brigitta Baumert about the EORTC Low-Grade Glioma Trial

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Interview with Dr Brigitta Baumert about the EORTC Low-Grade Glioma Trial

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Dear Dr Baumert, can you tell us about the ongoing EORTC “Low-Grade Glioma” trial? What is the rationale and background for this trial?

A: The optimal management of cerebral low-grade glioma (LGG) has not yet been defined. Many patients are treated only when needed. A “need for treatment” is based on several studies, which could clearly identify patient groups based on prognostic factors. Survival seems to be more dependent on specific factors such as age, tumour grade, histological diagnosis, and neurological function. Based on the data of 2 earlier EORTC trials on low-grade glioma, a group of patients with the poorest outcome (= high-risk disease) can be identified and thus needs treatment. This trial has been specifically set up to investigate the optimal treatment paradigm for this patient group with a high-risk disease.

It is a multi-institutional randomized phase-III clinical trial (EORTC 22033-26033) to compare the progression-free survival (PFS) of patients with a low-grade glioma treated with radiotherapy alone versus treatment with temozolomide only. In addition, the impact of genetic deletions of 1p and 19q in low-grade gliomas (LGG) is investigated at the same time: the prognostic effect of tumours with deletion on progression-free survival – overall and by treatment group – and the interaction between treatment and cytogenetic features.

Q: What are the design and the inclusion criteria?

A: Inclusion criteria are histologically confirmed low-grade glioma (LGG) WHO grade II, supratentorial tumour location only, RTOG neurological function 0–3, and not being a candidate for surgical treatment alone as well as presence of high-risk disease or progressive tumours. High-risk disease is determined by the presence of at least one of the following criteria: age ≥ 40 years and/or radiologically proven progressive lesion and/or new or worsening neurological symptoms other than seizures only (eg, focal deficits, signs of increased intracranial pressure, or mental deficits).

In addition to clinical factors, patients are stratified according to a molecular analysis of the 1p/19q status. The central collection of tissue will also allow to subsequently identify additional molecular markers in order to predict individual outcome and response to therapy, therefore the availability of tumour material is an inclusion criterion. Patients with high-risk disease or with progressive tumours are randomized between primary radiotherapy (28 \times 1.8 Gy, 50.4 Gy, control arm) or primary chemotherapy with low-dose TMZ for up to 1 year (12 cycles) (Figure 1). Trial endpoints are progression-free survival, overall survival, but also acute and delayed toxicity, quality of life, and cognitive function.

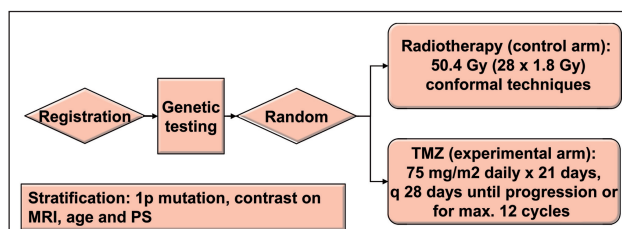


Figure 1. Trial design of the EORTC 22033-26033 intergroup trial with NCI Canada, TROG Australia, and the MRC UK including patients with a low-grade glioma and high-risk disease.

Q: Which groups, countries and how many centres participate in the trial?

A: This is an international intergroup study conducted by the European Organisation for Research and Treatment of Cancer (EORTC) together with the National Cancer Institute of Canada (NCIC) Clinical Trials Group, the Tasmanian Radiation Oncology Group (TROG) from Australia, and the Medical Research Council (MRC) from the United Kingdom. Overall, there are 78 participating institutions from Europe, Canada, Australia/New Zealand and one from Singapore. Within Europe, there are about 13 participating countries including Great Britain.

Q: Do you have any translational or biological investigation in this trial?

A: Indeed, there is an accompanying translational research package to this trial. Beside the fact that this study is the first to use a stratification based on molecular markers (changes in genes 1p/19q) to identify patients that benefit most from either radio- or chemotherapy we will conduct additional translational research based on this tissue material. We are searching for biomarkers, cancer-relevant molecular pathways, and new targets, as well as diagnostic, prognostic, and predictive biomarkers. The programme is set up to understand underlying molecular mechanisms for successful treatment of LGG. The tumour tissue will be characterized for genome-wide aberrant DNA methylation and respective associations with clinical parameters including response to therapy.

The generated molecular data will also identify tumours that should not be treated as low-grade gliomas despite favourable characteristics. Identifying new treatment strategies: because of the limited treatment options for LGG, new treatment options should be identified. Tumours depend on their acquired genetic changes for growth and a rational way to identify novel treatments is to use these changes to target the tumour. A growing number of drugs that target such changes have shown significant clinical benefit. We will therefore analyze

and screen for frequently mutated genes like IDH1 and others in order to identify potential new treatment strategies. The aim is to identify potential therapeutic drugs that act on the identified affected pathways and can be entered into future clinical trials and, thus, new treatment options.

Q: *Do you have quality of life and neurocognitive evaluation along with the study?*

A: Indeed, this study features both quality-of-life and neurocognitive evaluations. Quality of life (QoL) is included as a secondary endpoint. The hypothesis is that the use of primary temozolomide may have better QoL outcomes because of deferring radiotherapy and thus late radiation-induced toxicity. QoL is measured by a standardised questionnaire in a longitudinal setting.

Late radiation-induced toxicity consists for a larger part of the development of neurocognitive side effects as, for example, a decrease in short-term memory. The assessment of neurocognitive functioning is conducted as a side study. Patients are tested at baseline, before treatment, and repeatedly thereafter every 6 months to detect potential changes over time.

Like the stratification based on genetic tumour characteristics, this is the first study to have a prospectively conducted neuropsychological evaluation based on a standardized test battery specifically designed for this study purpose.

Q: *How is the recruitment going on and when do you expect to reach the accrual goal? When can we get the first results?*

A: We have reached the recruitment target with an inclusion of 707 patients and about 470 patients randomized. However, it is important to note that the second study step, the randomisation, is still open to allow further registered patients to be randomised. Therefore, a registered patient can still be randomized and treated as per protocol after the study has been closed for patient registration (Figure 1). We may expect first preliminary results within the next 2 years.

Also, recently, first results of the accompanying quality assurance programme for radiotherapy have been published [1]. This study had an accompanying detailed quality assurance programme reviewing the irradiation technique of the centres involved with regard to compliance of the protocol guidelines and radiation treatment technique. We observed that strict evaluation by digital review of radiotherapy resulted in overall grades of larger protocol deviations of about 30 %.

Thank you very much!

Brigitta Baumert is the study coordinator (along with study co-chair Roger Stupp) for the EORTC 22033-26033 trial entitled, "Primary chemotherapy with temozolomide vs radiotherapy in patients with low-grade gliomas after stratification for genetic 1p loss: a phase III study".

Reference:

1. Fairchild A, Weber DC, Bar-Deroma R, et al. Quality assurance in the EORTC 22033-26033/CE5 phase III randomized trial for low grade glioma: the digital individual case reviews. *Radiother Oncol* 2012; 103: 287–92.

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