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Abstract Significant progress has been made in the molecular diagnostic subtyping of brain tumors, in particular gliomas. In contrast to the classical molecular markers in this field, p53 and epidermal growth factor receptor (*EGFR*) status, the clinical significance of which has remained controversial, at least three important molecular markers with clinical implications have now been identified: 1p/19q codeletion, *O*⁶-methylguanine methyltransferase (*MGMT*) promoter methylation and isocitrate dehydrogenase-1 (*IDH1*) mutations. All three are favorable prognostic markers. 1p/19q codeletion and *IDH1* mutations are also useful to support and extend the histological classification of gliomas since they are strongly linked to oligodendroglial morphology and grade II/III gliomas, as opposed to glioblastoma, respectively. *MGMT* promoter methylation is the

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Keywords Clinical neurooncology · Molecular diagnostic · Prognostic factor · Malignant gliomas · Clinical trials

Introduction: principles of modern patient care in neuro-oncology

Clinical neuro-oncology has considerably changed and developed within the last decade. Out of the most important diagnostic disciplines, pathology and radiology, two novel strong subspecialties, neuropathology and neuroradiology, have emerged. At modern clinical neuro-oncology centers, management and treatment has become multidisciplinary, including neurosurgery, neurology including epileptology, radiation oncology, medical and pediatric oncology, as well as psychological oncology and palliative care. These disciplines are ideally cooperating under the umbrella of a Neuro-Oncology Center with standardized diagnostic and therapeutic procedures (Fig. 1). Such structures are necessary to face the increasing challenges in neuro-oncology which derive from the vast heterogeneity of intrinsic brain tumors, the increasing rates of involvement of the nervous system by systemic cancer, and the major risk of nervous system complications as significant side effects of current cancer therapies.

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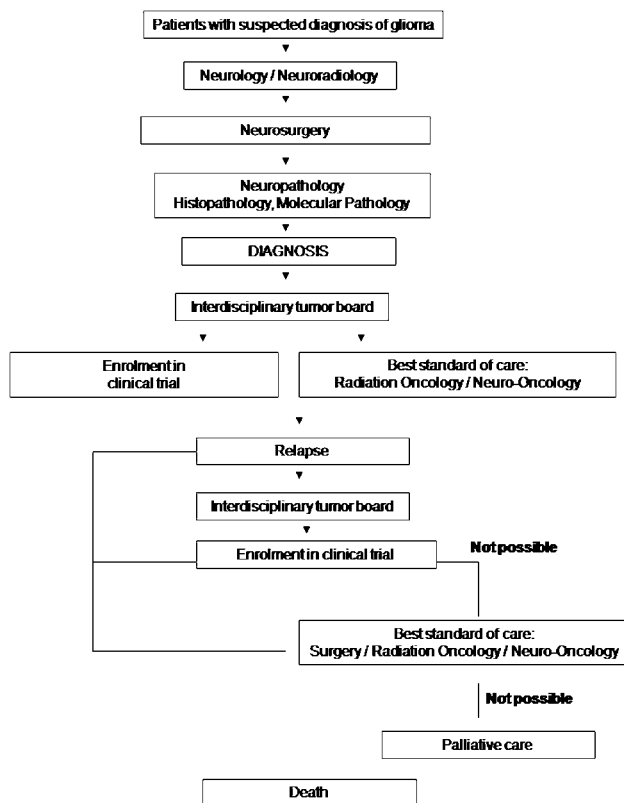


Fig. 1 Interdisciplinary patient care in neuro-oncology

Standards of care in glioma treatment

The current standard of care and treatment options for the most common types of glioma are summarized in Table 1. Some of the treatment recommendations remain controversial, in particular for the management of grade II gliomas. While many authors advocate maximal surgical resection with both therapeutic and diagnostic objective for patients with radiologically well delineated and circumscribed low-grade gliomas, others propose only close follow-up and deferred surgery. However, since the diagnostic specificity of contemporary MRI techniques to separate anaplastic gliomas from suspected low-grade gliomas is limited [23], at least a diagnostic biopsy should be performed even in diffuse, non-delineated tumors. Once diagnosis is established and surgery is not considered, both radiotherapy and chemotherapy are effective treatments [24], with more data available for radiotherapy, but both treatment approaches may carry significant risks of side effects, and there is no indication that early treatment prolongs overall survival or even impacts survival in good quality of life and in a neurologically less impaired condition. For high-risk patients or patients with progressive and symptomatic disease, radiotherapy has historically been the standard treatment, whereas chemotherapy and especially chemoradiotherapy are still investigational.

Long-term toxicity is a particular concern with any treatment in a patient population with a life expectancy of several to many years. Age > 40 years, tumor size > 5–6 cm, tumors crossing the midline, neurologic deficits and contrast enhancement on imaging are considered unfavorable prognostic factors. The presence of 3 or more of these risk factors has been shown to be associated with a significantly shorter survival [17]. More aggressive treatment is commonly recommended for patients with less favorable prognostic factors, but it has remained uncertain whether this patient population derives more benefit from these treatments than patients with favorable prognostic factors [24].

Standard treatment of newly diagnosed anaplastic glioma (WHO grade III) includes resection where feasible, followed by focal radiotherapy up to 60 Gy. Two large international randomized trials have evaluated the benefit of the addition of chemotherapy using procarbazine, CCNU and vincristine (PCV) to radiotherapy, either before or after radiotherapy. No difference in overall survival was shown despite a trend toward improved progression-free survival [4, 28]. Even in the subgroup of presumed chemosensitive oligodendrogliomas, no advantage for the early use of chemotherapy was demonstrated. Recently, the German Neuro-Onkologische Arbeitsgemeinschaft (NOA)-04 trial showed that chemotherapy may substitute for radiotherapy as initial postoperative therapy, with adequate crossover and again no difference in overall survival was shown with either of the sequence strategies [35]. For patients presenting recurrent or progressive disease after prior radiotherapy, temozolomide chemotherapy has demonstrated high response rates in anaplastic astrocytoma and mixed oligoastrocytoma [39] (Table 1).

There is not much controversy in the management of newly diagnosed glioblastoma since a large randomized phase III trial conducted by the EORTC and NCIC demonstrated superiority of concomitant and adjuvant (maintenance) temozolomide chemotherapy in addition to radiotherapy compared to radiotherapy alone. Patients with a WHO performance status of 0–2 and an age up to 70 years were included in this trial [25, 26]. The value of radiotherapy was recently confirmed in a small randomized trial comparing best supportive care (only steroids and supportive medicine) versus radiotherapy alone: median survival was 29 weeks with radiotherapy compared with 16.9 weeks with supportive care only [11]. Based on the overall shorter survival in elderly patients, exclusive radiotherapy, often hypofractionated radiotherapy is proposed to patients over age 65–70 years [20]. Two randomized trials presented in abstract form at the Annual Meeting of the American Society of Clinical Oncology in June 2010 failed to show superiority of primary temozolomide chemotherapy in elderly patients

Table 1 Standards of care for malignant gliomas

	Newly diagnosed	Recurrence or progression ^a
Diffuse astrocytoma WHO grade II	Resection/biopsy and observation or resection/biopsy and radiotherapy	(Re-resection and) radiotherapy or chemotherapy
Oligodendroglioma and oligoastrocytoma WHO grade II	Resection/biopsy and observation or resection/biopsy and chemotherapy or radiotherapy	(Re-resection and) chemotherapy or radiotherapy
Anaplastic astrocytoma WHO grade III	Resection/biopsy and radiotherapy or chemotherapy ^b	(Re-resection and) chemotherapy (temozolomide or nitrosourea) or re-irradiation
Anaplastic oligodendroglioma and anaplastic oligoastrocytoma WHO grade III	Resection/biopsy and chemotherapy (PCV or temozolomide) ^b or radiotherapy ^b or combined modality treatment ^c	(Re-resection and) radiotherapy or chemotherapy (temozolomide or nitrosourea)
Glioblastoma WHO grade IV	Resection/biopsy and radiotherapy and chemotherapy (temozolomide) ^d	(Re-resection and) chemotherapy (temozolomide, nitrosourea) or re-irradiation or bevacizumab ^e

^a Please note that treatment at recurrence or progression depends on prior therapy

^b See NOA-04 trial [35]

^c See EORTC 26951 and RTOG 94-02 [4, 28]

^d See EORTC 26981-22981 NCIC CE.3 [25, 26]

^e See [12] and Table 3

[15, 36]. In fact, the German NOA-08 trial even shows that primary temozolomide alone is not non-inferior to primary radiotherapy alone [36]. A concomitant treatment strategy is currently evaluated in a NCIC-EORTC randomized trial.

There is no accepted standard treatment for patients recurring after prior chemoradiotherapy. Treatment options depend on the delay after prior therapy, the patient's general and neurological condition, and the requirement for high-doses of corticosteroids. Cytotoxic options to be considered are reexposure to temozolomide, possibly with a metronomic or dose-intense regimen, at least in patients failing during adjuvant rather than after adjuvant temozolomide or nitrosoureas [34]. A number of targeted or antiangiogenic agents have failed to demonstrate measurable efficacy in randomized trials, e.g., erlotinib, imatinib, or most recently, enzastaurin. The monoclonal antibody to vascular endothelial growth factor (VEGF), bevacizumab, has received substantial attention over the last 2 years. Based on impressive radiological response rates, decreased steroid requirements, but in the absence of a randomized trial or the demonstration of a survival advantage, bevacizumab has received accelerated conditional FDA approval in 2009, however, the European Medicines Agency (EMA) denied extension of the market application [7, 12]. Despite occasional undeniable benefit, many questions and concerns regarding utility, indication, dose and schedule and efficacy remain for bevacizumab use in malignant glioma [38].

Significance of molecular diagnostics in clinical trials

Molecular diagnostics allows identifying subgroups and subtypes of glioma with a similar genetic profile. This enrichment of more homogeneous patient populations may lead to more uniform tumor responses in specific molecular constellations. In particular, for therapy with modern targeted agents, such a selective approach is warranted, as it will exclude patients least likely to benefit from an investigational treatment strategy. Furthermore, as many of these molecular markers carry a strong prognostic value, stratification for known clinical and molecular prognostic markers is important to adequately evaluate the outcome and value of the new agent. In contrast to prognostic markers that will estimate the outcome in a treatment-independent manner, e.g., older glioma patients do worse than younger glioma patients, predictive markers are of value only in the context of a specific therapy, e.g., hormone receptors in breast cancer or *MGMT* promoter methylation in glioblastoma. However, in reality, markers are often to some extent both of prognostic and of predictive value. Examples of molecular marker used for selection or stratification within clinical trials are given in Figs. 2, 3 and 4.

Thus, patient enrolment may be limited to patients having gliomas with a particular molecular phenotype, e.g., *MGMT* promoter methylation in the CENTRIC trial for newly diagnosed glioblastoma. Further, molecular markers can be determined upfront and used for patient

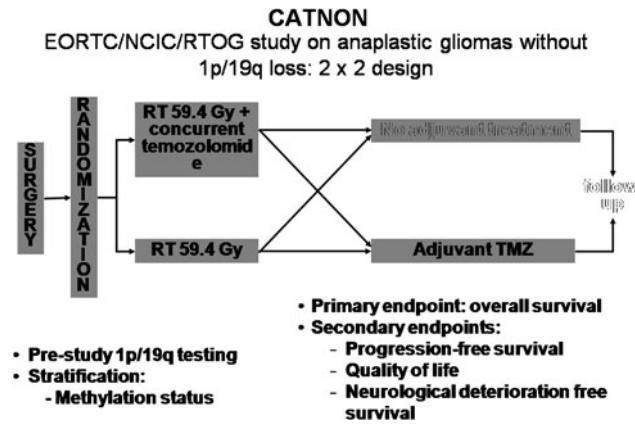


Fig. 2 Clinical trial designs based on molecular diagnostics: CATNON (<http://www.ClinicalTrials.gov> Identifier NCT00626990)

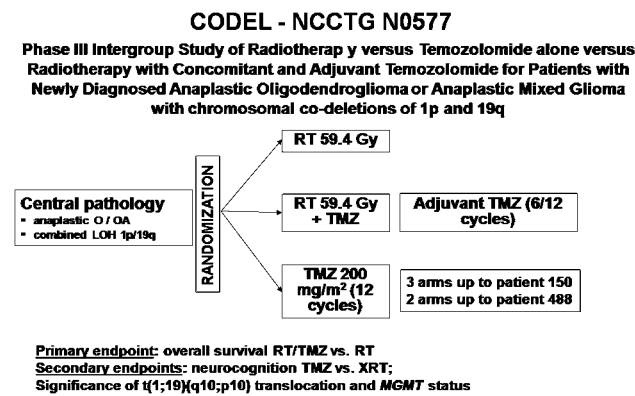
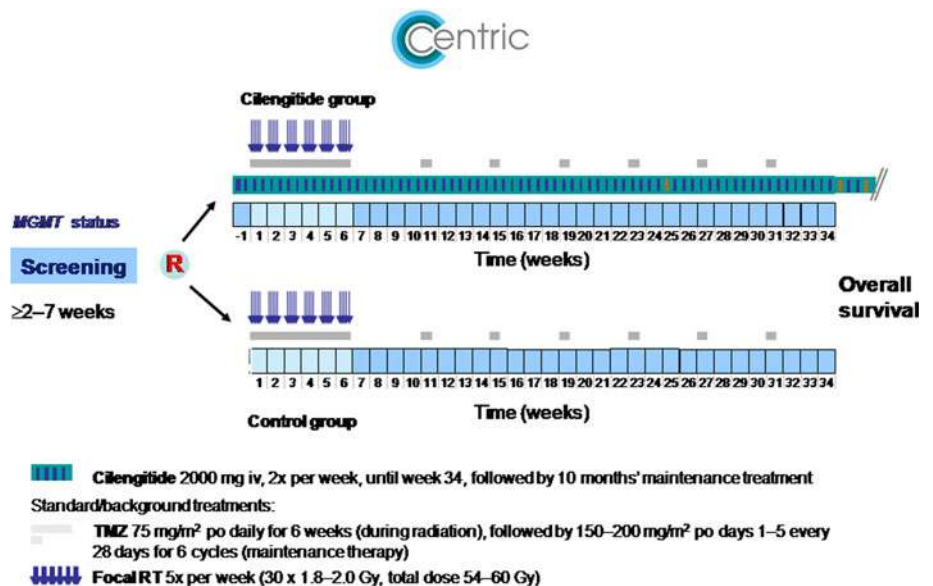


Fig. 3 Clinical trial design based on molecular diagnostics: CODEL (<http://www.ClinicalTrials.gov> Identifier NCT00887146)

stratification, in order to prevent imbalances of favorable versus non-favorable prognostic subgroups between treatment arms. Ultimately, molecular diagnostics may be used

Fig. 4 Clinical trial design based on molecular diagnostics: CENTRIC (<http://www.ClinicalTrials.gov> Identifier NCT00689221)



to determine whether specific biomarkers predict outcome in response to a specific type of treatment. In this regard, a prognostic marker is commonly considered a marker that allows estimating the outcome in a treatment-independent manner, whereas a predictive marker allows estimates of outcome depending on treatment. For instance, the 1p/19q codeletion (see below) is strongly predictive of a favorable outcome in patients with grade III gliomas treated with radiotherapy or chemotherapy [4, 28, 29, 35]. In contrast, analyses of patients with grade II gliomas managed by surgery alone showed the 1p/19q deletion to be associated with slower growth in a French series [19], but not with time to progression in a German study [31].

The EORTC trial 22033-26033 is a randomized phase III study that evaluates primary chemotherapy with temozolomide versus radiotherapy in patients with grade II astrocytic brain tumors. Patients are stratified for 1p loss to make sure that prognostically similar patient populations are randomized into both arms. MGMT promoter methylation will be assessed to determine whether the MGMT status allows to predict specifically the benefit derived from temozolomide chemotherapy.

For anaplastic oligodendroglial tumors, the 1p/19q codeletion has traditionally been an important molecular marker linked to a better prognosis, whereas other markers have not gained major clinical significance (Table 2). The RTOG 94-02 and EORTC 26951 prospective randomized trials which compared radiotherapy alone with radiotherapy followed by PCV, or PCV followed by radiotherapy, demonstrated that the 1p/19q codeletion was associated with longer progression-free survival and overall survival and that this effect was independent of the initial treatment, radiotherapy alone or radiotherapy with (neo-)adjuvant chemotherapy [4, 28]. Thus, the 1p/19q status could no

Table 2 Molecular markers in glioma: prognostic or predictive?

	Grade II gliomas	Grade III anaplastic gliomas	Grade IV glioblastoma
P53 mutations	No	No	No
EGFR amplification	No	No	No
1p/19q codeletion	Controversial	Prognostic (pos.)	Rare
<i>MGMT</i> promoter methylation	Controversial	Prognostic (pos.)	Predictive for alkylating agent chemotherapy
IDH 1/2 mutations	Prognostic (pos.)	Prognostic (pos.)	Rare, prognostic (pos.)

longer be claimed to specifically predict chemosensitivity and therefore also not be used to guide treatment decisions in terms of radiotherapy versus chemotherapy. In contrast, it is solely a prognostic marker at present. This conclusion was supported by the NOA-04 trial which enrolled 318 patients with all three types of anaplastic glioma and randomized between radiotherapy alone and chemotherapy alone, using either the PCV regimen or temozolomide [35]. Again, the 1p/19q codeletion was linked with a favorable outcome irrespective of initial therapy. Based on EORTC 26951 and RTOG 94-02 [4, 28], EORTC, NCIC, RTOG, MRC and HUB designed separate trials for 1p/19q-intact and 1p/19q-codeleted tumors irrespective of the morphological subtype of anaplastic glioma (Figs. 2, 3). The four-armed trial CATNON for patients without 1p/19q loss examines the role of temozolomide in the concurrent or adjuvant setting with radiotherapy, or both. Patients are stratified for *MGMT* gene promoter methylation status. CODEL, the companion protocol for 1p/19q-codeleted tumors, will compare radiotherapy alone, temozolomide chemotherapy alone and radiochemotherapy using temozolomide, thus combining features of NOA-04 [35] and EORTC 26981-22981 NCIC CE.3 [25, 26].

The EORTC NCIC trial for temozolomide in newly diagnosed glioblastoma had shown an increase of the median survival from 12.1 to 14.6 months and of the 2-year survival rate from 10 to 26% when temozolomide was added to radiotherapy. The benefit from temozolomide was particularly prominent in patients with tumors exhibiting *MGMT* promoter methylation [8]. The difference in progression-free survival among the *MGMT*-methylated patients of 5.9 months with radiotherapy alone versus 10.3 months with radiotherapy plus temozolomide suggested that indeed *MGMT* promoter methylation is a predictive molecular marker for benefit from temozolomide. No confirmation of this finding from another trial may be expected, since radiotherapy alone is no longer an accepted standard of care control arm in trials except for older patients with glioblastoma. Many ensuing phase II trials that examined radiotherapy plus temozolomide plus another (novel) agent confirmed that *MGMT* promoter methylation was at least prognostic in newly diagnosed glioblastoma. Compared with the historical data base of the

EORTC NCIC trial [8, 25], a gain in median progression-free survival specifically in patients with glioblastoma with *MGMT* promoter methylation was observed in a trial examining the first-in-class integrin-targeting polypeptide, cilengitide [27]. Accordingly, the CENTRIC trial, a cooperative effort of EORTC and Merck Serono, seeks approval for cilengitide specifically in the subset of patients (30–35%), whose glioblastomas exhibit *MGMT* promoter methylation.

Thus, altogether, molecular diagnostics of gliomas may serve the purposes to allow for the definition of more homogeneous patient populations as exemplified in CATNON and CODEL for anaplastic gliomas or CENTRIC for glioblastoma (Figs. 2, 3, 4) or may, in the future, be used to test whether specific treatments are active depending on the absence or presence of a specific molecular marker. While 1p/19q status and *MGMT* status are thus already used for patient enrolment, the determination of *IDH1* mutations may assume an important diagnostic role in the near future. Glioblastomas with *IDH1* mutations have a much better prognosis and putatively a different histogenetic origin, further supported by the recent discovery of a glioma-CpG island methylator phenotype (G-CIMP) associated with *IDH1* mutations [16]. CIMP has been identified also in other cancers, best known from colon cancer, and usually defines a distinct subtype with different epidemiology and distinct clinical and molecular features [9]. Hence, future glioblastoma trials should either exclude these patients or introduce a stratification for the *IDH1* mutation status.

Significance of molecular diagnostics in the routine diagnostic assessment

Considerable efforts have been made for two decades to implement molecular diagnostics in the subclassification of glioblastoma, often with the view to aid clinicians in decision making. Such studies have traditionally focused on molecular lesions that are thought to be involved in the molecular pathogenesis of glioblastoma, e.g., mutations of p53 or *phosphatase-and-tensin-homolog-on-chromosome-ten* (PTEN) or amplification of the epidermal growth factor receptor (*EGFR*) or cyclin-dependent kinase (*CDK*) 4

genes. Interestingly, however, once the glioblastoma phenotype has been established, the absence or presence of these lesions does not correlate with the outcome of patients treated according to current standards of care [32]. In fact, none of the molecular markers available today, including those compiled in Table 2, are particularly helpful in daily decision making. Furthermore, targeting the EGFR signaling pathway using small molecule inhibitors has not shown the benefit hoped for [2]. Available data from clinical trials does not support particular treatments or treatment strategies based on the molecular profile. This is particularly true for grade II gliomas, where the prognostic role of all molecular markers with the exception of *IDH1* mutations has remained more controversial. Probably there is a prognostic role of 1p/19q and *MGMT* promoter methylation in low-grade gliomas, too, but the magnitude of effect may be smaller than in anaplastic gliomas [10]. Accordingly, molecular markers cannot be used to decide whether a patient should receive genotoxic therapy or not, and if so, radiotherapy or chemotherapy. While *IDH1* mutations are prognostically favorable across all grades of gliomas (Table 2) [21], no study has demonstrated a link between this molecular lesion and benefit from a specific type of treatment [6].

Among anaplastic gliomas, anaplastic oligodendroglial tumors were traditionally believed to have a better prognosis than anaplastic astrocytomas, while mixed oligoastrocytomas were attributed an intermediate prognosis, and chemosensitivity was believed to be linked to the 1p/19q codeletion [4]. It has become clear that the 1p/19q codeletion is predictive for a more favorable course in response to either chemotherapy with PCV or temozolomide or radiotherapy, and, in fact, in anaplastic gliomas, this is true for *MGMT* promoter methylation as well as *IDH1* mutations [29, 30, 35]. These three favorable markers are not independent, but partly associated, e.g., the 1p/19q codeletion lost significance upon the multivariate analysis of the

NOA-04 trial when *MGMT* and *IDH1* status were included in the analysis, whereas *IDH1* mutation and *MGMT* promoter methylation were strongly correlated in other studies [30]. In conclusion, all three markers are helpful in daily clinical routine because they provide powerful information for patient counseling in terms of overall prognosis, yet, there is no rationale to base treatment decisions on either of these markers.

1p/19q codeletions and *IDH1* mutations are rare in glioblastomas and may even be considered incompatible with the diagnosis of glioblastoma in the future. In contrast, *MGMT* promoter methylation is often advocated as a valuable biomarker allowing to guide treatment decisions in glioblastoma patients even outside clinical trials. This common practice should be discouraged for many reasons, as recently reviewed elsewhere [33]: only the methylation-specific PCR has repeatedly provided clinically useful prognostic information, whereas all other techniques of assessing the *MGMT* status must be considered experimental and require further study; even the methylation-specific PCR did not yield reproducible data across laboratories; and withholding temozolomide on the basis of an unmethylated *MGMT* promoter test means withholding the only proven active drug against glioblastoma from a majority of patients.

Clinical perspectives for molecular diagnostics

The promising development of anti-angiogenic agents in glioblastoma (Table 3) calls for the search for novel prognostic or predictive markers which might guide the choice for or against agents with specific modes of actions in the future. For instance, one might predict that only glioblastomas expressing high levels of VEGF will respond to bevacizumab or cediranib, whereas sensitivity to cilengitide would require expression of the corresponding target integrins, $\alpha_v\beta_3$ and $\alpha_v\beta_5$, on blood vessels or tumor cells or

Table 3 Vasculature-targeting agents explored in registration trials for glioblastoma

	Mode of action	Newly diagnosed	Recurrent
Bevacizumab	VEGF antibody	Phase II combination with RT/TMZ → TMZ safe [14] Phase III recruiting (AVAGLIO)	Phase II promising [7, 12]
Cediranib	VEGF receptor antagonist	Phase II combination with RT/TMZ → TMZ planned (RTOG)	Phase II monotherapy promising [1] Phase III combination with lomustine (REGAL ^a)
Cilengitide	Integrin antagonist	Phase II combination with RT/TMZ → TMZ promising [27] Phase III recruiting (CENTRIC)	Phase II monotherapy promising [18]
Enzastaurin	PKC β -antagonist	Phase I combination with RT/TMZ → TMZ concluded [3]	Phase I/II promising for response, but not PFS [13] Phase III monotherapy negative [37]

^a <http://www.ClinicalTrials.gov> IDENTIFIER NCT00777153

both. Visualization of the target molecule in vivo by molecular imaging might be a technology in the future to detect and monitor molecular markers for targeted therapies [22]. Although intuitive, such studies have not yet been performed or at least did not yield conclusive results. This resembles the so far unsuccessful efforts at identifying prospectively the minority of glioma patients which derive benefit from EGFR inhibitors. These unexpected failures are likely due to the underestimation of the complexity of the targeted cancer-relevant pathways. Efforts are ongoing to devise respective combination strategies [2].

Despite these drawbacks, there has been significant progress in supporting and supplementing the histological classification of gliomas with an increasing spectrum of molecular markers with strong prognostic impact, and it appears not too optimistic to assume that it may not take long until the first markers with predictive power for specific treatments become available, as also seen in some few other cancers.

Even today, the increasing use of molecular testing if only for prognostic assessment has resulted in problems and challenges that urgently need to be addressed: how are such tests standardized, should there be reference laboratories, should most neuropathology units offer these tests, and, finally, how can such a broadening of the neuropathological diagnostic repertoire be financed to make it available to most oncology centers in many countries? It is unlikely that neuro-oncologists will always be so lucky as to take an unexpected finding from high-throughput analyses, such as the *IDH1* mutations back to routine with a simple PCR or more recently even a mutation-specific antibody that can easily be incorporated into standard immunohistochemistry procedures [5].

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