Mechanisms of Chemoresistance to Alkylating Agents in Malignant Glioma

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Abstract

Intrinsic or acquired chemoresistance to alkylating agents is a major cause of treatment failure in patients with malignant brain tumors. Alkylating agents, the mainstay of treatment for brain tumors, damage the DNA and induce apoptosis, but the cytotoxic activity of these agents is dependent on DNA repair pathways. For example, O6-methylguanine DNA adducts can cause double-strand breaks, but this is dependent on a functional mismatch repair pathway. Thus, tumor cell lines deficient in mismatch repair are resistant to alkylating agents. Perhaps the most important mechanism of resistance to alkylating agents is the DNA repair enzyme O6-methylguanine methyltransferase, which can eliminate the cytotoxic O6-methylguanine DNA adduct before it causes harm. Another mechanism of resistance to alkylating agents is the base excision repair (BER) pathway. Consequently, efforts are ongoing to develop effective inhibitors of BER. Poly(ADP-ribose)polymerase plays a pivotal role in BER and is an important therapeutic target. Developing effective strategies to overcome chemoresistance requires the identification of reliable preclinical models that recapitulate human disease and which can be used to facilitate drug development. This article describes the diverse mechanisms of chemoresistance operating in malignant glioma and efforts to develop reliable preclinical models and novel pharmacologic approaches to overcome resistance to alkylating agents.

Intrinsic or acquired resistance to cytotoxic agents remains the greatest obstacle to the successful treatment of human cancer, and a variety of mechanisms of drug resistance have been identified in human tumors. High-grade malignant gliomas, including glioblastoma and anaplastic astrocytoma, are among the most rapidly growing and devastating cancers. Standard treatment consists of surgery followed by radiotherapy and chemotherapy with alkylating agents. Alkylating agents, including carmustine (bischloroethyl nitrosourea, or BCNU), lomustine (chloroethylnitrosourea), and temozolomide, readily cross the blood-brain barrier and have shown the most activity against malignant glioma. However, despite the ability of these agents to achieve therapeutic concentrations in the brain, malignant gliomas are often resistant to alkylating agents. Identifying and understanding the diverse mechanisms of chemoresistance operating in human tumors and developing effective strategies to overcome resistance is the focus of ongoing preclinical and clinical research.

One important mechanism of resistance to alkylating agents is mediated by the DNA repair enzyme O6-methylguanine methyltransferase (MGMT; refs. 1, 2), which repairs O6-alkylguanine adducts. BCNU and chloroethylnitrosourea are bifunctional alkylating agents that form lethal double-strand cross-links (3). In contrast, the activity of methylating agents such as temozolomide and dacarbazine results in persistent O6-methylguanine adducts that initiate futile cycling of the DNA mismatch repair (MMR) pathway, which ultimately causes DNA double-strand breaks and induction of apoptosis (Fig. 1; refs. 4–6). The methylation damage induced by these agents can be reversed by MGMT. Although many studies have shown that a deficiency of MGMT can increase the sensitivity of high-grade glioma to alkylating agents (7–10), tumors with low levels of MGMT may still exhibit resistance to these drugs (1, 2). This suggests that other mechanisms are also involved in the resistance of some tumors to chemotherapy. For example, a deficiency in MMR can make tumor cells tolerant to mismatched base pairing and mutations in p53, or overexpression of the antiapoptotic protein Bcl-2 or Bcl-XL, can cause resistance to proapoptotic signals. The base excision repair (BER) pathway can also render alkylating agents ineffective by repairing N7-methylguanine DNA adducts that would otherwise be cytotoxic (Fig. 1; ref. 6).

This review will summarize the mechanisms of chemoresistance in malignant glioma and will focus on the development of agents designed to overcome resistance to alkylating agents, with particular emphasis on novel molecules designed to inhibit the BER pathway. An important component...
of this research involves the development of clinically relevant xenograft models for testing novel treatment strategies to overcome chemoresistance. Herein, we will describe a nude mouse serially transplantable xenograft model of glioblastoma multiforme that represents an important tool for testing new agents and treatment strategies.

### Mechanisms of Chemoresistance

**MGMT.** The DNA repair enzyme MGMT seems to play a major role in resistance to temozolomide and other alkylating agents by removing alkyl groups from the O6 position of guanine (11). The protective effect of MGMT has been shown in human cell lines (12) and in human xenograft models (13). For example, studies with MGMT knockout mice revealed that fibroblasts and bone marrow cells were significantly more sensitive to the toxic effects of temozolomide compared with cells from MGMT wild-type mice (14). Moreover, retrovirus-mediated transfer of the human MGMT gene to cells that are deficient in endogenous MGMT activity results in high levels of resistance to temozolomide and other alkylating agents (15).

**In vivo** studies that used mixtures of MGMT-positive and MGMT-negative colon cancer cell lines injected into nude mice and exposed to BCNU showed that the extent of MGMT expression in mixed xenografts correlated directly with their sensitivity to BCNU (16). Xenografts with 0% to 10% MGMT-positive cells grew rapidly in the presence of BCNU (Fig. 2; ref. 16). Pretreatment with a selective MGMT inhibitor, O6-benzylguanine, has been shown to suppress MGMT activity for ~6 hours and sensitize xenografts containing MGMT-positive cells to BCNU (16). Similarly, other studies showed that inhibition of MGMT with O6-benzylguanine promotes the increased antitumor activity of temozolomide both in vitro (17–19) and in vivo (13, 20). Thus, direct removal of O6-methylguanine by MGMT seems to be a major mechanism of resistance to the cytotoxic effects of alkylating agents.

In human cancer, the MGMT gene is not commonly inactivated by mutation; loss of MGMT function is most frequently caused by promoter region hypermethylation.
Preclinical studies have shown that methylation of discrete regions of the MGMT promoter is associated with epigenetic silencing of the gene, loss of MGMT expression (23, 24), and diminished DNA repair activity. Tumors with methylated MGMT promoters are more sensitive to alkylating agents, whereas tumors with unmethylated MGMT promoters express high levels of the enzyme and are more resistant to alkylating agents (10). From a clinical standpoint, MGMT promoter methylation is associated with improved response to alkylating agents, as evidenced by improved survival in patients with high-grade gliomas who are treated with BCNU or temozolomide (25–27). Therefore, MGMT promoter methylation may predict the therapeutic response to alkylating agents (10). Several ongoing studies are investigating the correlation between MGMT methylation status and temozolomide sensitivity. These studies are also investigating whether increasing the dose intensity of temozolomide treatment could overcome the resistance mediated by MGMT.

The MMR pathway. The MMR pathway is critical for mediating the cytotoxic effect of O^6^-methylguanine. The MMR pathway is comprised of several proteins (hMLH1, hPMS2, hMSH2, hMSH3, and hMSH6) and is programmed to correct errors in DNA base pairing which arise during DNA replication. Defects in this system cause resistance to temozolomide, presumably because the cell becomes tolerant to the mispairing of O^6^-methylguanine with thymine. During DNA replication, DNA polymerase mispairs O^6^-methylguanine with thymine, which triggers MMR-dependent removal of the mispaired thymine. However, the O^6^-methylguanine remains, and subsequent mispairing of O^6^-methylguanine with yet another thymine leads to repetitive rounds of MMR (17, 28, 29). It has been proposed that this futile cycling of the MMR system induces double-strand breaks, which in turn, triggers p53-dependent cell cycle arrest and apoptosis (30). Consequently, tumors that are deficient in MMR are relatively resistant to the cytotoxic effects of alkylating agents such as temozolomide. In fact, many tumors are known to be deficient in MMR. For example, hereditary nonpolyposis colon cancer is caused by mutations in the hMLH1 or hMSH2 genes (31). Therefore, the cytotoxicity of temozolomide is low in colon cancer cell lines harboring these mutations (32). Deficiency in MMR also occurs in a number of sporadic human cancers due to methylation of the hMLH1 gene promoter, although this is not known to occur in malignant glioma. Of the 60 cell lines in the National Cancer Institute tumor panel, five are deficient in hMLH1 activity, and these cell lines are all resistant to temozolomide (33).

Poly(ADP-ribose)polymerase. Another important mechanism of resistance to alkylating agents is the BER pathway, which is thought to be involved in the repair of N^7^-methylguanine and N^3^-methyladenine DNA adducts (Fig. 1; ref. 6). These are the most common DNA adducts created by temozolomide, accounting for ~90% of all methylation events. Poly(ADP-ribose)polymerase (PARP-1) plays a pivotal role in the BER pathway. This enzyme is activated by DNA strand breaks and is expressed at high levels in most human cell lines. This led to the investigation of PARP inhibitors as a means of increasing the cytotoxic activity of temozolomide. Inhibition of BER would be expected to increase the cytotoxicities of N^7^-methylguanine and N^3^-methyladenine lesions, which are otherwise readily repaired in most normal cells and tumor cells with an intact BER pathway. In particular, PARP inhibitors would be expected to dramatically enhance the cytotoxicity of temozolomide in MMR-deficient cells because these cells tolerate O^6^-methylguanine DNA adducts (34).

Apoptosis-regulating genes. In addition to the resistance mechanisms described above which involve DNA repair, chemoresistance in gliomas may be influenced by dysregulation of apoptosis-regulating genes and proteins. For example, loss of normal p53 function, up-regulation of Bcl-2 or Bcl-X_L, or overexpression of epidermal growth factor receptor (EGFR) can disrupt the normal apoptotic response to DNA damage. It is well known that p53 plays a central role in detecting DNA damage and regulating the signaling pathways required to mediate apoptosis. Murine tumors deficient in Trp53 (the gene that encodes p53 in mice) and cell lines that express mutant Trp53 are less sensitive to gamma-irradiation or chemotherapy (35). Reintroduction of wild-type Trp53 by adenoviral transfer restores sensitivity to cytotoxic agents, resulting in the apoptosis and suppression of tumor growth in nude mice (36, 37). Wild-type p53 interacts with the promoters of a variety of genes, including EGFR, MDM2, and Bcl-2. Wild-type p53 increases the transcriptional activity of the EGFR and MDM2 genes and represses the transcription of Bcl-2 (38). Based on the analysis of patient tumor samples, inactivation of p53 occurs in >50% of primary glioblastomas, and this is associated with the up-regulation of Bcl-2 (17, 39, 40). Consistent with these findings, up-regulation of either Bcl-2 or EGFR expression in glioma cell lines has been correlated with drug resistance and decreased apoptotic response in vitro (41, 42). EGFR is the most frequently amplified and mutated oncogene in de novo malignant glioma, and several clinical as well as histopathologic studies have suggested that the presence of EGFR amplification might affect the response of malignant gliomas to chemotherapy (43). In one study, overexpression of a tumor-derived mutant form of EGFR known as variant III (EGFRvIII) in wild-type p53-expressing human glioma cells resulted in resistance to cisplatin (41). However, this mutation is not known to confer resistance specifically to alkylating agents. The mechanism involved was suggested to be the suppression of drug-induced apoptosis, which was largely mediated by...
increased expression of Bcl-XL and subsequent inhibition of caspase-3–like protease activation. Although dysregulated expression of EGFR, MDM2, and Bcl-2 frequently occurs in glioblastoma multiforme, none of these changes in gene expression have been clearly identified as an independent prognostic factor for either the biological behavior of gliomas or patient survival (44). Additional studies into the mechanisms regulating apoptosis and sensitivity to DNA damage may reveal new strategies for overcoming the resistant phenotype of glioblastoma multiforme.

Given the important role of temozolomide in the treatment of gliomas and the probable dependence of its activity on MGMT activity, a recent study has sought to better characterize the molecular pathways mediating temozolomide cytotoxicity in human malignant glioma cell lines in terms of MGMT, Bcl-2, and p53 expression (42). This study showed that forced expression of Bcl-XL protein attenuates temozolomide cytotoxicity in MGMT-negative LNT-229 cells but not in MGMT-positive LN-18 cells. Neither irradiation nor dexamethasone modulated MGMT activity or temozolomide sensitivity in this paradigm. Abrogation of p53 wild-type function with RNA interference or expression of a dominant-negative p53 mutant also conferred resistance to temozolomide. Conversely, agents such as CP-31398 that stabilize the wild-type conformation of p53 sensitize glioma cells to temozolomide (45). These data suggest that wild-type p53 activity is necessary for sensitivity to alkylating agents. Furthermore, because low-grade gliomas have a high incidence of p53 mutations, they may be less sensitive to temozolomide. However, these conclusions are limited by the preclinical paradigm applied and may not accurately reflect the clinical situation.

Preclinical Models Testing Strategies to Overcome Chemoresistance

Efforts to develop new strategies to overcome chemoresistance underscore the need for reliable preclinical models to test these strategies. Ideally, robust preclinical models would facilitate the development of optimal therapeutic regimens so that only the most effective treatment regimens are moved forward into the clinical testing. These model systems could be used to develop predictive markers for treatment response that would guide the development of new agents or individualized therapies, thereby minimizing patients’ exposure to ineffective treatment approaches.

**Cell culture models.** Several cell culture models have been used to show the role of MGMT in resistance to temozolomide. For example, studies with Chinese hamster ovary cells lacking endogenous MGMT expression have shown that overexpression of MGMT confers resistance to temozolomide (46). Similarly, established glioma cell lines have provided a model for studying the correlation between MGMT levels and sensitivity to various alkylating agents (12). Although cell culture models are valuable for the design of cancer therapies, these models do not consistently predict tumor response to cytotoxic or biological agents in the clinical setting. Cultured cell lines do not necessarily reflect the biology or heterogeneity of primary tumors nor their therapeutic response to treatment and may have less relevance in the clinical setting than in vivo models.

**Transgenic mouse models.** Transgenic mouse models are genetically defined animal models that allow for testing of therapies that are targeted specifically at the affected pathways (47). For example, transgenic mice have been engineered to recapitulate key genetic features of glioblastoma multiforme such as mutant EGFR; such mice are excellent for the evaluation of specific molecular mechanistic questions. However, because of limited genetic diversity, these models may be less useful for identifying the multiple mechanisms of sensitivity and resistance found in the spectrum of genetically diverse tumors found in patients.

**Xenograft models.** In xenograft models, established cell lines are often grown as subcutaneous flank (heterotopic) or intracranial (orthotopic) tumors. However, orthotopic xenografts created from established glioblastoma cell lines generally fail to recapitulate the infiltrative growth pattern of primary human glioblastomas; instead, they tend to form solid masses at the injection site, compressing rather than invading the parenchyma (48–51). In addition, the growth of tumor cell lines in culture can lead to a high degree of selection, causing the loss of important gene alterations that are common among primary glioblastomas such as EGFR gene amplification (52, 53). Glioblastoma cell lines established from primary tumors with amplified EGFR and/or EGFR mutations invariably lose this amplification and mutation through prolonged cell culture. This observation suggests that the growth advantage associated with increased EGFR expression and the
constitutively active mutant form of the receptor (e.g., EGFRvIII) is specific to the in vivo environment and that high-level EGFR signaling may in fact be a disadvantage for in vitro tumor cell growth (52, 53). Although the use of heterotopically grown cell lines offers some insight into tumor biology, prolonged selection of these cell lines in cell culture limits their clinical relevance for understanding patient tumor responsiveness to chemotherapeutic or biological agents.

Recently, the amenability of a serially transplantable nude mouse xenograft model was indicated for testing novel therapeutics and for answering key biological and clinical questions regarding mechanisms of resistance, drug dosing, and combination strategies (54, 55). In this model (Fig. 3), glioblastoma tissue samples were obtained from patients, and serially propagated in the flank of athymic nude mice. This method of propagation allows the preservation of key morphologic and histopathologic features, such as the presence of necrosis, similar to those of the primary glioblastomas from which they were derived (Fig. 4). By establishing and maintaining multiple glioblastoma xenografts in this manner, a genetically diverse panel of glioblastoma tumors is available for testing novel therapeutic strategies.

With the test panel approach, therapies are routinely evaluated against intracranial tumors that are established from short-term cultures of freshly resected flank tumors. Single-cell suspensions are stereotactically injected into the brains of nude mice (Fig. 3), and this results in a nearly 100% rate of successful engraftment. Analysis of the resulting intracranial tumors shows that these tumors maintain key histopathologic features of the original tumor, such as a highly invasive growth pattern and nuclear pleomorphism (Fig. 5). Therefore, it is expected that the chemosensitivity of the serially propagated human tumor would likely be comparable to that of the patient tumor from which it was derived, and that this model would predict the activity of chemotherapies used alone or in combinations. Indeed, MGMT promoter methylation is faithfully maintained from the original patient tumor specimen. Among a panel of xenografts developed at the Mayo Clinic, the proportion of xenografts that exhibit MGMT promoter methylation (~45%) was similar to that reported in a series of primary tumors (26).

In contrast, 80% of glioblastoma cell lines have a methylated MGMT promoter. This xenograft model shows that primary human glioblastomas, which are propagated in the flank and transplanted orthotopically, closely resemble the human microenvironment, particularly in relation to growth characteristics and invasive properties.

### PARP Inhibitors

There is considerable interest in modulating the activity of PARP-1 in the clinical setting for the treatment of both cancer and nonmalignant diseases. Potential applications in the nonmalignant setting have recently been reviewed (56, 57). In the realm of cancer therapy, preclinical models have shown that inhibition of PARP-1 can potentiate the activity of both radiotherapy and a variety of chemotherapeutic agents (58–64), and PARP-1 inhibitors have also shown single-agent activity against certain tumor cell lines (65, 66). These observations have stimulated considerable interest in these agents as anticancer therapy. AG-14361 is a potent inhibitor of PARP-1, with an inhibition constant in the nanomolar range, and AG-014699, a potent tricyclic indole with an inhibition constant of <5 nmol/L, is a close analogue and the first PARP inhibitor to enter clinical trials in patients with cancer (67). AG-014699 was developed through a collaborative program.

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**Fig. 4.** Morphology and histopathology of glioblastomas grown in the flank. Flank tumors recapitulated human tumor morphology as evidenced by the presence of (A) high cellularity and mitotic activity (arrows) and (B) necrosis (closed arrows) and vascular endothelial proliferation (open arrows).

**Fig. 5.** Growth of intracranial tumors established from flank xenografts. A representative section of an orthotopic tumor displays a close resemblance to primary tumors regarding advanced stage of growth. The tumor revealed high cellularity (open arrow) and invasion into corpus callosum (closed arrow).
The effects of AG-14361 on the cytotoxicity of temozolomide were studied using two genetically matched cell lines; the parent cell line was MMR-deficient, and the matched cell line was MMR-proficient by virtue of the transfer of chromosome 3 (68). As expected, AG-14361 enhanced temozolomide cytotoxicity in both MMR-proficient and MMR-deficient cell lines, but the degree of enhancement was greater in the MMR-deficient cell lines (3.7- to 5.2-fold increase compared with only a 1.5- to 3.3-fold increase in the MMR-proficient cell lines). The enhanced potentiation of temozolomide activity in MMR-deficient cells compared with MMR-proficient cells suggests that it might be possible to selectively enhance the antitumor activity of temozolomide in the clinical setting using a PARP inhibitor because normal tissue (particularly the hematopoietic system) would be MMR proficient, whereas tumors may be MMR deficient. Although, as with any agent that enhances the cytotoxic potential of a chemotherapy drug, the addition of a PARP inhibitor may cause significant added toxicity. The phase I study with AG-014699 showed that a normal dose of temozolomide could be safely administered in combination with a PARP inhibitor (69). However, in the phase II study in patients with metastatic melanoma, a significant proportion of patients required a 25% reduction of the temozolomide dose or treatment delays because of myelosuppression (70).

The phase I trial of AG-014699 in combination with temozolomide for the treatment of solid tumors (primarily metastatic melanoma) was divided into two parts (69). The first part of the study was designed with a pharmacodynamic end point to show significant (at least 50%) PARP inhibition in peripheral blood lymphocytes 24 hours after the first dose of AG-014699. Temozolomide 100 mg/m² (50% of the standard dose) was given in combination with AG-014699 (escalating doses from 1 to 12 mg/m²) daily for 5 days every 28 days. The reduced dose of temozolomide was initially used in the event that inhibition of PARP potentiated the known myelosuppressive effects of temozolomide. Significant inhibition of PARP-1 was shown at all dose levels investigated. Inhibition was profound and sustained for 24 hours at doses of >8 mg/m² and in all patients (n = 12) treated at 12 mg/m² (Fig. 6). Moreover, the combination of 12 mg/m² of AG-014699 with 100 mg/m² of temozolomide was not toxic. In the second part of the study, patients with metastatic melanoma (exclusively) were treated with 12 mg/m² of AG-014699 and escalating doses of temozolomide. All patients consented to tumor biopsies to allow assessment of target tissue PARP inhibition. During this part of the study, it was possible to administer a full dose of temozolomide (200 mg/m²) with 12 mg/m² of AG-014699 without additional toxicity being observed while achieving significant tumor PARP inhibition (~60% below baseline activity) in tumor tissue 5 hours after dosing. The 5-hour time point was selected, because at that time point, temozolomide is known to cause maximum DNA strand breaks (71); this would be the optimal time to have maximal PARP inhibition in order to achieve effective chemopotentiation. Maximum PARP inhibition in tumor biopsies has been observed with the highest dose of AG-014699 investigated (18 mg/m²); however, this dose also enhanced the myelosuppressive effects of temozolomide, leading to dose reductions and delays.

The encouraging PARP inhibition observed in this phase I study provided the rationale for a phase II study of the combination of AG-014699 and temozolomide in patients with metastatic melanoma. Forty-six patients were treated with temozolomide (200 mg/m²) and AG-014699 (12 mg/m²) daily for 5 days every 28 days (70). This study confirmed that temozolomide can be administered in the presence of a PARP inhibitor with only minor dose reductions being required because of hematologic toxicity; 18 (39%) patients required a dose reduction of temozolomide to 150 mg/m². Moreover, this study met its primary objective (i.e., an increase in the response rate compared with historical data with temozolomide alone), and this combination also seems to improve time to progression.

Other PARP-1 inhibitors are now entering early clinical development in a range of malignant indications. For example, there are plans for INO-010 to enter clinical studies in combination with temozolomide both in patients with metastatic melanoma and in patients with malignant glioma (PARP 2005 Conference). Although PARP inhibitors for clinical...
In recent years, our understanding of the pathways responsible for repairing DNA damage and rendering cancer cells resistant to chemotherapy has greatly improved; consequently, effective strategies to modulate clinical resistance to cytotoxic agents are evolving. DNA damage caused by temozolomide is repaired by BER, removed by MGMT, or tolerated in MMR-deficient cells. Modulation of the first two pathways of resistance is now becoming a clinical possibility.

Early clinical trials with MGMT inhibitors such as O\(^6\)-benzylguanine have been completed [reviewed by Hegi et al. (26)], and this article reviews the promising initial results of trials investigating the modulation of temozolomide resistance with PARP-1 inhibitors. Inhibition of PARP activity would, in addition, allow PARP inhibitors to act as radiopotentiators because the DNA damage caused by radiotherapy consists of single- and double-strand breaks (62). Repair of both types of lesions is known to involve the recruitment of PARP-1 (77). Therefore, the use of a potent PARP inhibitor as part of a multimodality therapy with temozolomide and radiotherapy in patients with glioblastoma multiforme may have particular clinical relevance and might significantly improve therapeutic benefit in this group of patients.

Developing effective treatment regimens is a major challenge in malignant glioma, and identification of a reliable preclinical model that could recapitulate human disease would facilitate this process. The murine serially transplantable xenograft model is simple and reproducible and maintains most of the characteristics of primary human glioblastoma. This model preserves the molecular phenotype and invasiveness of glioblastoma xenografts, which is critical for investigating molecularly targeted agents. The combination of flank tumor genetic characterizations with a procedure for initiating intracranial xenografts makes this model an invaluable tool for multiple neuro-oncology research applications. The versatility and applicability of this preclinical model will contribute to the elucidation of the molecular mechanisms of chemoresistance, which should ultimately result in the identification of more effective therapeutic strategies for malignant glioma.

Conclusions and Future Directions

Inhibitors (74, 75). However, genetic or epigenetic defects in tumors and would be expected to confer sensitivity to PARP-gous recombination repair have also been reported in human homologous recombination as a result of epigenetic some spontaneous malignancies may also be deficient in of promoter methylation has been reported, suggesting that Furthermore, suppression of BRCA protein expression because of promoter methylation has been reported, suggesting that some spontaneous malignancies may also be deficient in homologous recombination repair as a result of epithelial gene silencing (73). Other acquired defects affecting homolo- gous recombination repair have also been reported in human tumors and would be expected to confer sensitivity to PARP inhibitors (74, 75). However, genetic or epigenetic defects in homologous repair pathways are exceedingly rare in gliomas (76), and it is unlikely that monotherapy with PARP inhibitors will be clinically useful in patients with brain tumors.

References

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