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PARP inhibitors in gliomas: Mechanisms of action, current trends and future perspectives

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ABSTRACT

Gliomas are the most common primary malignant brain tumours in adults. Despite decades of research into novel therapeutic approaches, the prognosis remains poor. PARP1-2 are critical for DNA repair, cell survival and genomic stability and PARP inhibition (PARPi) may be a promising therapeutic approach for gliomas. Inhibition of PARP activity leads to homologous recombination deficiency (HRD), which, in combination with DNA damage, results in cell death. This review summarises the current knowledge and future perspectives of PARPi in glioma. The available literature was reviewed using PubMed, recent major international oncology congresses were consulted, and ongoing clinical trials were searched using ClinicalTrials.gov.

In translational research, PARPi have demonstrated a strong scientific rationale for their use in the treatment of glioma. They have been evaluated both alone and in combination with radiotherapy, temozolomide, anti-angiogenic agents, immunotherapy and other new drugs in newly diagnosed or recurrent glioma. Most studies were open-label, non-randomised, dose-escalation phase I-II trials. Early results show promising anti-tumour activity, and key challenges include identifying predictive biomarkers, elucidating synergistic effects in combination therapies, addressing the development of resistance, and managing hematological toxicity.

In conclusion, early phase studies have shown promising anti-tumour activity of PARPi that should be confirmed in larger prospective and randomised trials. In addition, the development of novel PARPi with improved blood brain barrier (BBB) penetration and PARP inhibitor activity with new synergistic treatment combinations seems promising and needs to be further explored.

Introduction

Gliomas are the most frequent malignant tumors of the central nervous system in adults, with high aggressiveness, limited therapeutic options and, in most cases, a particularly poor prognosis[1]. Usually, standard treatment involves maximal safe surgical resection followed by radiotherapy and chemotherapy. Recently, vorasidenib, an oral anti-IDH treatment, was shown to extent progression-free survival (PFS) in selected previously untreated, low-risk, IDH-mutant, low-grade gliomas [2]. However, despite this multidisciplinary approach, virtually all

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gliomas recur and the choice of salvage treatment in these cases can be particularly difficult. Among the available options, treatment with nitrosoureas[3–5], temozolomide[5,6], bevacizumab[7–9] or small molecules[10] could be considered, as well as, when possible, surgical re-resection or re-irradiation[11,12]. Careful patient selection, including extensive molecular analysis which has proved feasible in neuro-oncology fields[13], is essential to ensure the most personalized therapy, which is likely to achieve better response rates and improved survival. Poly(ADP-ribose) polymerases (PARPs) are a key component of the DNA damage repair (DDR) mechanism with a crucial role in cell survival and genomic stability[14]. Inhibition of the PARP pathway plays a very important role in oncology, as the loss of the DNA repair mechanism can lead to cell death, even in neoplastic cells. The mechanism of "synthetic lethality" is represented by a genetic interaction in which the simultaneous presence of two genetic events, which individually would have no impact on cell viability, cause cell death when inhibited simultaneously. One of these events could be intrinsic to the cancer cell, such as homologous recombination deficiency (HRD), due to which the cell has a limited ability to repair damage on the DNA chain. In this context, a blockade of the PARP system by means of specific drugs (PARP inhibitors – PARPi), causes the second genetic event, which configures the so-called "synthetic lethality". The inhibition of catalytic activity of PARP-1 and PARP-2 by PARPi leads to DNA single-strand breaks that then result in a DNA double-strand break[14,15]. In addition, the trapping of the PARP-DNA complex by PARPi can lead to the same DNA double helix breaking event: this is considered the most important anti-tumour mechanism of PARPi[15,16]. To date, several PARPi are available in different cancer types, with different indications (breast cancer type 1 susceptibility protein –BRCA-mutation, HRD, no-HRD) and treatment settings[17–20], either as monotherapy or in combination with other oncological drugs[21]. In the field of neuro-oncology, the use of PARPi is not yet considered clinical practice, but there is some evidence that this type of treatment may have a solid rationale in the treatment of glioma patients. In addition, there are several clinical and preclinical data demonstrating high blood–brain barrier penetrance for some of these drugs[22–25]. The aim of this narrative review is to assess the current status and perspectives of the use of PARPi in glioma patients.

Materials and methods

We reviewed the literature published from 2013 to 2024 by conducting an electronic double search of PubMed. For a search strategy we included the key terms (used literaly) "Glioblastoma" OR "high-grade glioma" OR "glioma" AND "PARPi" (e.g. niraparib, olaparib, veliraparib). Based on the abstract appropriate articles were selected. Based on the full-text screening, we excluded studies without relevant information, not in English language, with inadequate experimental design, duplicate papers if a study has been published multiple times or in different versions and retrospective studies.. We also checked the abstracts from the American Society of Clinical Oncology (ASCO), European Association Neuro-Oncology (EANO), European Society for Medical Oncology (ESMO), European Society for Radiotherapy and Oncology (ESTRO) congress from 2020 to 2024. Finally, we looked for ongoing clinical trials considering PARPi as therapy in HGG patients on ClinicalTrials.gov.

Mechanism of action of PARP inhibitors

PARP enzymes, and among them, the best-characterized isoform, PARP1, play a key role in DDR. PARPi contribute to genome instability and exploit potential vulnerabilities of cancer cells with different modalities.

PARP1′s primary function is to bind and promote the repair of DNA single-strand breaks (SSBs) by activating the base excision repair (BER) pathway. PARP1, using NAD + as a substrate, strongly catalyzes the attachment of ADP-ribose polymers (a procedure defined as PARylation) to other nuclear proteins, like histones, effectively recruiting BER components to start DNA repair.[26] The accumulation of SSBs during the cell cycle and DNA replication can lead to double-strand breaks (DSBs), the most relevant DNA insult, repaired by the homologous recombination (HR) pathway. The therapeutic efficacy and potency of PARP inhibition relies on the catalytic inhibition of PAR polymer formation and the consequent accumulation of unrepaired SSBs and, above all, on the formation and trapping of PARP-DNA complexes at the site of SSB, which prevents DNA repair and leads to the further formation and accumulation of lethal DSB, causing collapsing of the replication fork.[27].

The accumulation of DSBs can result in a synthetic lethal interaction between PARP inhibition and homologous recombination defects, most commonly originating from *BRCA1* or *BRCA2* mutations. In the presence of loss of function of *BRCA1/2* genes, the error-prone nonhomologous end-joining (NHEJ) pathway becomes the sole mechanism able to repair DSBs. In this way, when PARP enzymes are inhibited in BRCA-mutated cancer cells, lethal genomic aberrations accumulate, causing cancer cell death.[28].

More recently, new evidence showed that PARP enzymes regulate DNA replication also by controlling replication fork speed and sensing unligated Okazaki fragments. In the presence of Okazaki fragment processing defects, PARP inhibitors induce single-stranded DNA gaps behind the replication fork. These single-strand DNA gaps may lead to DNA toxicity in BRCA-deficient cells, directly or via DSB formation.[29].

Therapeutic Rationale, biomarkers of response and preclinical data of PARPi in gliomas

PARPi showed meaningful activity in some BRCA-mutant and HR deficient tumors and FDA approved their use in prostate, breast, pancreatic and ovarian cancer[30]. However, BRCA mutations are a rare occurrence in primary brain tumors, ranging between 1–3 % in low-grade gliomas and glioblastoma.[31] It is now well known that other genetic alterations can cause HRD, leading to sensitivity to PARP inhibitors, an occurrence also referred to as a "BRCAness" phenotype[32].

IDH mutations are among the best examples of these glioma genetic alterations.[27] *IDH1/2* mutations generate a neomorphic enzymatic activity, producing excess oncometabolite 2-hydroxyglutarate (2-HG) that functions as a competitive inhibitor of histone lysine demethylases and DNA demethylases, resulting in genome-wide epigenetic modifications. Among the others, aberrant histone modifications and masking of local chromatin signaling at sites of DNA DSBs interfere with DSB repair, potentially inducing PARPi sensitivity. [33] In this context, the PARPi olaparib impaired the growth of *IDH1* mutated tumor xenografts. [34] In another study, olaparib significantly enhanced temozolomide (TMZ) activity in *IDH1*-mutated glioma cells. [35] The role of O6-methylguanine-DNA methyltransferase (*MGMT*) activity as a biomarker of response to PARPi in gliomas is yet elusive. Veliparib significantly improved ($P < 0.001$) the efficacy of TMZ in glioblastoma patient-derived, *MGMT*-methylated, xenografts tumors[36]; in other studies PARP inhibition restored TMZ sensitivity in *MGMT* unmethylated glioblastoma murine models and glioblastoma cell lines. [37,38].

Phosphatase and tensin homolog (PTEN) deficiency, caused by loss-of-function mutations or gene deletions, is a common genetic feature in gliomas, typically associated with a worse prognosis and detected in a high portion of glioblastoma patients. Significantly, PTEN loss impairs homologous recombination repair. [39] Deletion of *PTEN* caused susceptibility to veliparib in glioma cell lines; moreover, veliparib also improved TMZ efficacy in PTEN-deficient glioblastoma allografts[40]. In another study, the combination of the topoisomerase I inhibitor LMP400 with niraparib led to synergistic cytotoxicity by various mechanisms, with an efficacy significantly more pronounced in PTEN-deleted than in PTEN-wild type glioma cells[39].

Importantly, PARPi may also combine synergistically with RT. Several mechanisms can facilitate this synergy in gliomas, such as interfering with the repair of DNA damages induced by ionizing radiation, impairing radio-resistance driven by glioma stem cells and tumor hypoxia, and enhanced delivery through disrupted blood–brain barrier [41] (See Fig. 1).

In another interesting study by Wu S. et al[42], EGFR amplification emerged as a potential selection biomarker to predict sensitivity to PARP inhibition, specifically talazoparib. Indeed, in the glioblastoma population, analysing data from derived glioma sphere-forming cells and in vivo glioma models, the authors showed that talazoparib significantly increased DNA damage, increased PARP DNA trapping and suppressed tumour growth in EGFR-amplified models but not in unamplified models.

Early-Phase clinical studies of PARPi in gliomas

Niraparib, veliparib, olaparib, and, more recently, pamiparib and NMS-293 are the PARPi investigated in gliomas for which early clinical data are available. Hematological toxicity was a significant concern in PARPi clinical development, both when used as monotherapy or in combination with RT and alkylating agents, in some cases leading to premature trial interruption[43]. Another critical issue for clinical efficacy in glioma is the capability of PARPi to cross the BBB. Olaparib is a known substrate of the P-glycoprotein efflux pump that impairs distribution through intact BBB, although effective penetration was demonstrated in the clinical setting [28,42]. Niraparib and pamiparib are more brain-penetrant, with brain-to-plasma (B:P) ratios of 0.1 and 0.2, respectively, while veliparib and, above all, NMS-293 show higher brain accumulation[26,45].

Niraparib combined with TMZ was investigated in a multicenter, open-label, two-part study in patients with recurrent, advanced solid tumors[46]. In the dose escalation part, patients received increasing doses of niraparib (30, 40, 70 mg once daily) in combination with a fixed dose of TMZ (150 mg/m2 on 5/28 days treatment cycles), to define the recommended phase 2 dose (RP2D) of the combination. Part B intended to explore the efficacy and tolerability of two cohorts of recurrent GBM (rGBM) and melanoma patients but was never opened. Nineteen patients were treated, with thrombocytopenia (52.6 %) and neutropenia (31.6 %) being the most common severe adverse events (AEs). At 70 mg dose level, all three patients experienced grade 4 thrombocytopenia, and thus niraparib 40 mg QD + TMZ 150 mg/m2 was established as RP2D, despite the occurrence of two dose-limiting toxicities (DLTs) grade 4 thrombocytopenia among 10 cases. One GBM patient reported a partial response (PR), while two other patients, with a diagnosis of melanoma and ovarian carcinoma, had stable disease (SD). More recently, niraparib was tested in a phase 0/2 trial. Radiologically newly diagnosed GBM patients received four days of niraparib (300/200 mg QD) before elective surgery planned 3–5 or 8–12 h following the last dose. Tumor tissue from enhancing and non-enhancing areas, cerebrospinal fluid (CSF), and plasma samples were collected. Patients with *MGMT* unmethylated exceeding the prespecified pharmacokinetics (PK) in the non-

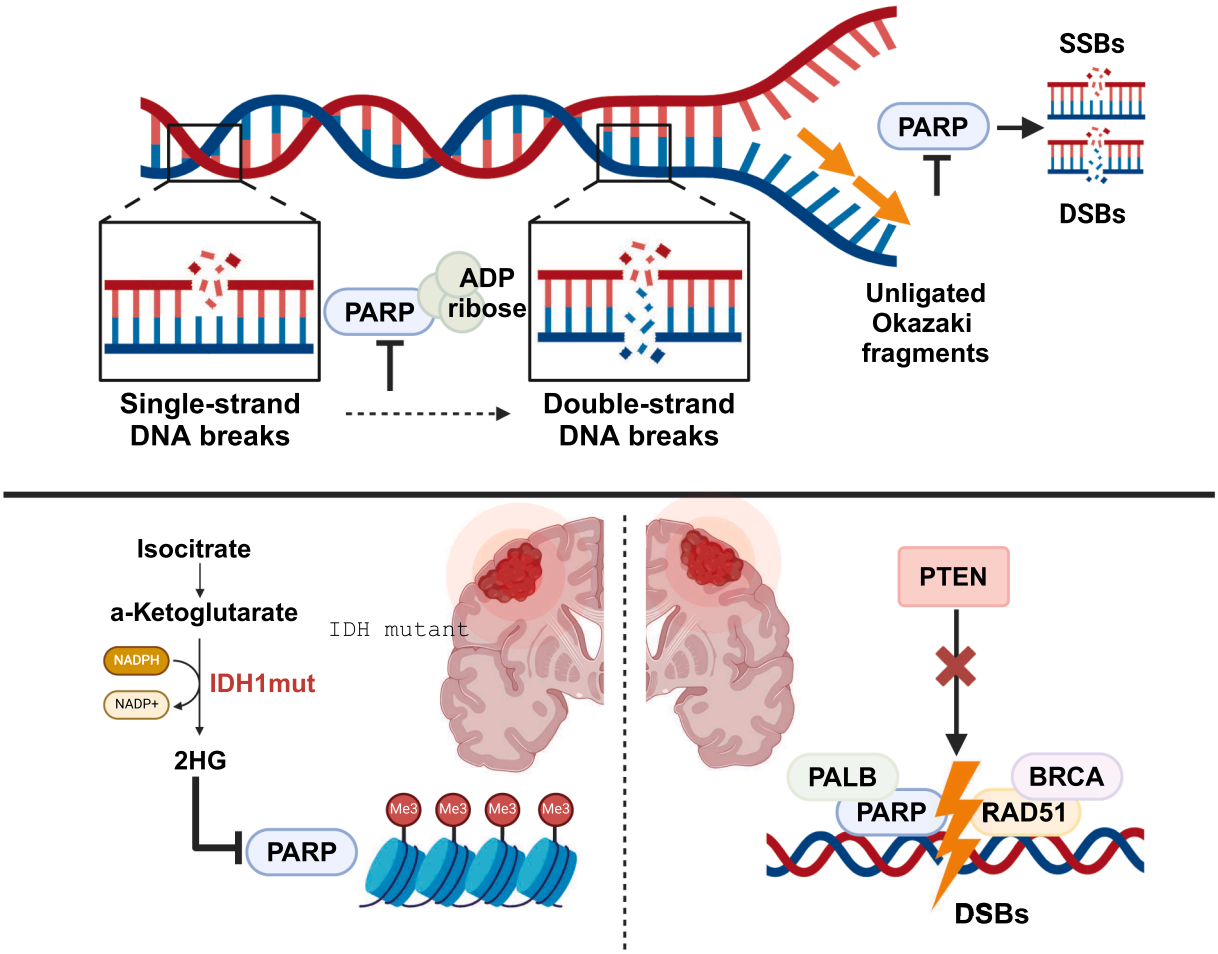

Fig. 1. PARPi mechanisms of action and key pathways involved in synthetic lethality. PARP = Poly ADP-ribose polymerase; SSB = Single-Strand Breaks; DSBs = Double-Strand Breaks; IDH = Isocitrate Dehydrogenase; 2HG = 2 hysroxyglutarate; ADP = adenosin diphosphate; PTEN = Phosphatase and tensin homolog; PALB = Partner and Localizer of BRCA2; BRCA = breast cancer gene).

enhancing tumor were considered eligible for the therapeutic expansion phase of niraparib plus RT followed by maintenance with niraparib single agent. All 35 patients enrolled in the Phase 0 part of the trial reached the PK threshold, with a mean unbound concentration of niraparib of 253.2 nM in 32 evaluable tumor specimens. Moreover, the suppression of PAR levels after ex vivo radiation was observed in 75 % of the patients (18/24). Eleven out of 18 patients with unmethylated *MGMT* were treated in phase 2 of the study. Three life-threatening thrombocytopenia occurred among the first six patients treated at 300 mg daily, and therefore, the starting dose was lowered to 200 mg, without other treatment-related serious AEs observed. At time of data cut-off, mPFS was 11.7 m[47]. These promising activities and results led to start a phase 3 randomized study to evaluate the efficacy of niraparib in MGMT unmethylated GB (GLIOFOCUS).

Veliparib was first evaluated in a randomized phase I/II study among TMZ-treated, HGG. Veliparib was tested at a previously defined maximum-tolerated dose (MTD) of 40 mg and randomized in combination with two TMZ schedules (75 mg/m2 21/28 days −arm 1- versus 150–200 mg/m2 5/28 days −arm 2-). Among all patients enrolled, 74 received and progressed to bevacizumab (BEV), while 151 were BEV-naïve. The overall incidence rate of grade 3/4 myelosuppression was 20.0 %; the 5/28 day treatment schedule was far better tolerated. Only two BEV-treated patients remained progression-free at six months, while nine of the 53 BEV-naive patients remained progression-free at six months. Median overall survival (OS) did not significantly differ between the two treatment arms in both BEV-treated and in BEV-naïve patients[48]. More recently, a multicenter phase 1 clinical study evaluated veliparib in combination with RT and TMZ in newly diagnosed GBM patients; as per protocol, six patients who had already completed concurrent chemoradiation were initially enrolled into a safety-cohort of six weeks of treatment with veliparib 10 mg BID and TMZ 75 mg/m2 QD. In this safety cohort, only one patient experienced DLT (grade 4 thrombocytopenia). In the subsequent part of the study, among twelve patients receiving veliparib 10 mg BID and concurrent six-week chemoradiation with TMZ, four patients showed severe myelosuppression that also persisted after a de-escalation to veliparib administered every other week, as 3 of 6 patients had DLT (2 thrombocytopenia and one neutropenia). Due to the unacceptable hematological toxicity, the study was terminated early [49].

The first clinical data on olaparib came out from a phase 1 study exploring the combination with TMZ in rGBM patients. The trial consisted of a pilot study (Stage 1) to confirm tumor penetrance, followed by Stage 2, with dose-escalation and dose-expansion cohorts. In Stage 1, three patients received olaparib 200 mg BID for seven doses prior to surgical resection, and olaparib was detectable above the lower limit of quantification in all tumor samples. Stage 2 patients received different doses and schedules of olaparib and TMZ for 42 days of a 56-day cycle. Twenty-nine patients were evaluated for safety in the dose-escalation part of the study, with a total of one grade 3 neutropenia, one grade 2 thrombocytopenia, one grade 3 vomiting, and one toxic death, leading to de-escalation and defining MTD/RP2D as olaparib 150 mg 1–3 days per week, plus TMZ 75 mg/m2 daily. Ten patients were evaluable in the dose expansion cohort at this dose level. Regarding efficacy, 14 out of 36 patients (39 %) remained progression-free at six months (9 treated in the dose escalation cohorts and 5 in the dose expansion cohort); this result was considered not sufficient to further pursue development of Olaparib/TMZ combination in this population [44]. To exploit the feasibility and potential of radio-sensitizing effect, olaparib was later tested in the newly diagnosed setting. In the phase 1, dose-escalation, PARADIGM trial, olaparib (dose ranging from 50 mg QD to 200 mg BID) was given concurrently with hypofractionated radiation (40 Gy in15 fractions) in newly diagnosed elderly (>70 years) or frail GBM patients (PS ECOG 2). Among the sixteen patients enrolled, treatment was well-tolerated, with only one DLT observed (grade 3 agitation related to olaparib); hematological toxicity was not an issue, as only a grade 1 thrombocytopenia was reported. MTD was not reached, and RP2D was established at olaparib 200 mg BID. mOS and mPFS were 10.8 months and 5.5 months, respectively. The olaparib − radiation combination did not negatively affect cognitive function as measured by the Mini-Mental State Examination.[50] The PARADIGM-2 included two parallel phase I studies of olaparib/RT or olaparib/ RT/TMZ in newly diagnosed < 70 years old GBM patients stratified by *MGMT* status tested centrally by central pyrosequencing. *MGMT* unmethylated patients received daily Olaparib plus standard RT (60 Gray in 30 fractions). Dose escalation was completed without DLTs among 43 treated patients, and RP2D was defined as Olaparib 300 mg BID. The mOS of the 42 eligible patients was 14.1 months, and survival rates at 12 and 24 months were 64.3 % and 16.7 %, respectively. The RP2D cohort was then expanded to 29 patients. At the time of data presentation, six patients were alive, with a median follow-up time of 22.9 months. mOS was 14.2 months (12.2–16.9); 12- and 24-month OS 69.0 % (56.5–78.5) and 24.1 % (14.8–34.8) respectively. Dose escalation in the *MGMT* methylated group is still ongoing.[51] Moreover, a recently presented phase 1/2a study assessed the safety and tolerability of olaparib combined with the standard Stupp regimen as first-line treatment in newly diagnosed, unresectable GBM patients. Patients received RT (60 Gy/30 fractions/6 weeks), concurrent TMZ (75 mg/m^2), and olaparib along RT until four weeks after the end of RT; during the maintenance period TMZ (150 mg/m^2, days 1–5 every 28 days, for six cycles) plus olaparib at the MTD up to disease progression or unacceptable toxicity were administered. The study included two sequential dose escalations (DE1, DE2) of olaparib by a Time-To-Event Continual Reassessment Method to split both periods for DLT assessment. Overall, 30 patients were enrolled, and 16 and 11 pts were eligible for determining MTD1 and MTD2, respectively. In DE1, 4 DLTs (thrombocytopenia G3-4, neutropenia G4) were described, and the MTD1 was defined as olaparib 100 mg BID days 1–3. In the DE2, one DLT occurred (thrombocytopenia G4), and olaparib 100 mg BID days 1–3 of a 28-day cycle was confirmed as MTD2[52].

Pamiparib has been explored in a multi-arm phase 1b/2 dose-escalation/expansion study, combined with RT in newly diagnosed GBM with unmethylated *MGMT* (arm A, N = 60), with RT and TMZ in unmethylated newly diagnosed GBM (arm B, N = 9), and with TMZ in methylated/unmethylated rGBM patients (arm C, N = 47). The most common severe AEs were anemia (10 %) in Arm A, decreased neutrophil and white blood cell count (each 22 %) in arm B, anemia, fatigue, and decreased lymphocyte count (each 11 %) in arm C. In Arms A/B and Arm C, mOS and mPFS were 4.4 months, 1.8 months, and 12.7 months, 7.3 months, respectively. Overall, the manageable safety profile and preliminary efficacy data support the further evaluation of these combinations in GBM [53]. Another phase 1 study evaluated pamiparib in combination with metronomic low-dose TMZ in recurrent, IDH-mutant gliomas. Pamiparib's starting dose was 60 mg BID and TMZ dose 20 mg daily, with dose de-escalation levels for anticipated hematological toxicity. Among the first six patients, one experienced a DLT (grade 3 neutropenia and thrombocytopenia), while two additional patients had grade 2 neutropenia, supporting pamiparib 60 mg BID with TMZ 20 mg QD as RP2D. Two patients remained on study treatment at 12 + and 10 + months, while a third progressed at 10.1 months (PFS-6 43 %). Importantly, in the enhancing and non-enhancing tumor specimens of two resected patients, the mean unbound pamiparib concentrations were 198 and 160 nmol/L, being 20-fold the in vitro half maximal inhibitory concentration (IC50) for PARP inhibition[54].

A recent phase 0 clinical trial investigated the PK and pharmacodynamics (PD) of pamiparib in patients with newly diagnosed (arm A) and rGBM (arm B). Patients received four days of pamiparib 60 mg BID prior to the planned surgery. Pamiparib achieved pharmacologically active concentrations in both arms with the mean unbound in the non-enhancing region of 171.5 nM and 162.5 nM, respectively, exceeding the PK threshold to qualify for the expansion phase of the study. Radiation-induced PAR expression was 2.44 fold in untreated control vs 1.16 in Arm A and 0.82 in Arm B. The mPFS was 5.8 and 3.1 months in Arm A and B, respectively[55].

Finally, preliminary results from a phase 1/2 study of NMS-293, a new agent with a 200-fold selectivity for PARP-1, possibly reducing myelosuppression due to the sparing of PARP-2 inhibition, were recently presented. NMS-293 was combined with TMZ 150 mg/m2 QD on days 1–5 of a 28-day cycle in patients with recurrent gliomas. No $\geq$ grade 3 treatment-related adverse events were described, with mainly grade 1 events reported. Among fourteen patients, a GBM patient had a confirmed PR, another GBM patient a complete response on enhancing non-target lesions, and a patient IDH-mutant, grade 3 astrocytoma, had an unconfirmed PR[56] The promising activity in terms of response and acceptable tolerability led to plan a dedicated Phase 2 trial in relapsed glioblastoma.. Table 1 summarizes the early phase clinical trials of PARPi in gliomas with available clinical data.

Clinical use of PARPi in glioma: Phase II and III trials

As previously presented, various phase I/II studies have investigated the use of PARPi in combination with chemotherapy and RT, showing greater potential for therapeutic efficacy. In this section, we present phase II-III clinical data of PARPi used in the concomitant treatment phase of newly diagnosed and recurrent glioma patients. Clinical trial (phase II-III) using PARPi for glioma patients are summarized in Table 2.

The phase II VERTU trial[57] explore the combination of veliparib and RT in newly diagnosed *MGMT*-unmethylated GBM. A total of 125 patients were randomized 2:1 to receive in the experimental arm veliparib and concurrent RT, followed by adjuvant veliparib plus TMZ vs standard arm of concurrent TMZ and RT, followed by adjuvant TMZ. Primary endpoint was PFS at six months with secondary endpoints OS, PFS at nine months, toxicity, feasibility and quality of life. Despite veliparib was safe when added to chemoradiotherapy, $\leq$ 30 % of patients on the experimental arm experienced grade 3–4 toxicity and the most common adverse event (G3-G4) was thrombocytopenia (17 %), neutropenia (12 %) and seizures (11 %), in this patient setting, limited clinical benefit was highlighted. Median PFS was 5.7 months (95 % CI: 3.9–6.5 months) and 4.2 months (95 %CI: 2.4–5.7 months) in the experimental and in the standard arm respectively. Median OS was 12.7 m (95 %CI: 11.4–14.5 m) in the experimental arm vs 12.8 m (95 % CI: 9.5–15.8 m) in the standard arm. A Phase II-III study evaluating veliparib plus TMZ versus TMZ alone following the combination phase of radiochemotherapy in patients with newly diagnosed *MGMT*-methylated GBM (Alliance- NCT02152982)[58] has been completed and results were presented at ASCO 2022: 447 pts were enrolled and the PFS was almost identical between the two groups, with a median of 13.2 months with veliparib versus 12.1 months with placebo ($p = 0.31$), the mOS was 28.1 months with veliparib and 24.8 months with placebo ($p = 0.15$). Another study, has evaluated the efficacy and activity of veliparib plus concurrent chemoradiation with TMZ in newly diagnosed IDHwt GBM or IDHmut-grade 4 astrocytoma patients (NCT03581292)[58] but failed to improve outcome compared to clinically and molecularly matched historical control cohorts. Iniparib, a prodrug already used in BRCA2-mutated pancreatic cancer and triple negative breast cancer[59,60] has been evaluated as a possible therapy in newly diagnosed GBM patients. In this study, Blakeley et al [61] enrolled 81 patients with newly diagnosed GBM in a single-arm multicenter phase 2 trial to receive iniparib with concurrent chemo-radiotherapy with TMZ compared to a historical control[62]. The primary endpoint was OS; secondary end point was frequency of toxicity associated with iniparib. Despite the evidence in only a single arm, iniparib shows potential antitumor activity (mOS 21.6 m, HR 0.44, 95 %CI: 0.35–0.55) versus historical control. Treatment-emergent G3 adverse events occurred in 27 % of patients (thrombocytopenia 18 %, neutropenia 10 % and fatigue 5 %).

Niraparib, a selective PARP1/2 inhibitor, has been tested in newly diagnosed GBM in a phase 0–2 trial (NCT05076513). In this multi-center study[63], niraparib demonstrated high penetration across the blood–-brain barrier, reaching pharmacologically relevant concentrations in both non-enhancing and enhancing GBM tissue and cerebrospinal fluid. The results of the phase 2 were presented at ASCO 2024 congress analyzing 20 newly diagnosed *MGMT*-unmethylated GBMM patients treated with a concomitant phase of Niraparib and RT followed by niraparib alone: the median OS was 20.3 months with a median PFS of 11.7 months; these data were much higher if compared to historical controls of Stupp protocol where the median OS for newly diagnosed *MGMT*-unmethylated GBM patients was 12.7 months. Yet, the safety was good with 48 % of the patients reporting grade 3–4 adverse events. Based on these promising results, an international, randomized phase 3 trial (GLIOFOCUS trial) has recently started (NCT06388733) in order to evaluate niraparib versus temozolomide in adult patients with newly diagnosed *MGMT*-unmethylated GBM.

Olaparib is PARP1/2 selective inhibitor already approved for breast and ovarian cancer BRCA 1/2 mutated [62,63]. A single-arm phase 2 trial [64] enrolled and treated 15 patients with recurrent IDH1/2 mutant glioma with olaparib as a single agent. The primary endpoint was ORR and secondary endpoints PFS, OS and the duration of response. In this patient cohort, olaparib showed a mPFS of 3.63 m (95 %CI 1.87–5.53) and mOS of 20.7 m (95 %CI 13.77-NR) in intention to treat population. Nine patients (60 %) achieved SD and 6 (40 %) patients PD. A subgroup analysis according to WHO 2021 central nervous system tumors classification[65] was performed. mPFS for patients with grade 2 and/or 3 was 5.2 m (95 %CI 3.63–9.2) vs 1.8 m (95 %CI 1.77-NR) in those with grade 4 (CDKN2A altered). The mOS was 29.5 m (95 %CI 19.87-NR) and 15.17 m (95 %CI 9.1-NR) in grade 2/3 glioma and grade 4 glioma patients respectively. This trial, despite the limited sample size, suggest a clinical benefit in select patients demonstrated clinical benefit of olaparib (prolonged stable disease) in a selected population of recurrent low-grade glioma: grade 2 and grade 3 IDH1/2 mutant glioma without CDKN2A alteration. A French study[66] analyzed olaparib activity in 35 recurrent IDH mutant HGG patients; most of them received olaparib after 2 prior line of chemotherapy (77 %); 31 % of the patients had a grade 2 glioma while 69 % of the patients had a grade 3 or 4 glioma; this study did not reach its pre-defined threshold for activity being PFS-6 of 31.4 % (a PFS-6 $>$ 50 % was considered necessary to further investigations) even if 2 patients (6 %) reported an objective response and 40 % had a stable disease as their best response. Median PFS and median OS were 2.05 and 15.9 months, respectively; noteworthy, oligodendroglioma patients reported the higher PFS-6 (53.4 % vs 15.7 %) than astrocytomas supporting further evaluations in this population.

Tumor treating fields (TTF) is a novel cancer treatment (antimitotic) using alternating electric fields, FDA approved for the treatment of rGBM that show clinical improvement also in newly diagnosed GBM [67,68]. A Phase 2 trial (NCT04221503) combining niraparib with TTF is ongoing.

Recently, the results of another clinical trial (Phase II) (NCT04740190)[69] evaluating the combination of talazoparib with carboplatin and RT in recurrent HGG with DNA damage repair deficiency (DDRd) was presented at ASCO 2024 congress with modest results having a mPFS of 3.5 ms and a 1y-OS rate of 30 %.

The synergistic role of combining antiangiogenic treatment and PARPi has been extensively studied in ovarian cancer [70]. In this context, a phase 2 trial (NCT02974621) is ongoing in patients with rGBM in combination with olaparib and cediranib (oral VEGF inhibitor) versus bevacizumab (FDA approved for rGBM), results not yet available. Moreover, the combination of olaparib with durvalumab (a PD-1 inhibitor) resulted in limited efficacy with no synergistic effect[71].

Future perspectives

PARPi have solidified their place in the therapeutic landscape for BRCA-mutant and HR deficient breast, ovarian, pancreatic and prostate cancer. In the often challenging field of neuro-oncology, there is emerging potential for the use of PARPi in the treatment of glioma, with several clinical trials currently underway.

Table 1
Early phase studies of PARPi in gliomas with available clinical data.

Study identifier	Phase	Intervention	Patients population	No. of pts	Safety	Efficacy	Other results
NCT01294735 Kurzrock et al. 2014 [46]	1	Niraparib 30/40/70 mg QD + TMZ 150 mg/m^2 QD	Recurrent advanced solid tumors	19	Five grade 4 thrombocytopenia; one grade 4 neutropenia	1 PR in GBM patient	
NCT05076513 Metha et al [47]	0/2	Phase 0: Niraparib 300/200 mg qd before surgery Phase 2: Niraparib + RT	Phase 0: Newly diagnosed GBM Phase 2 MGMT unmethylated, resected GBM achieving niraparib PK threshold in non-enhancing tumor tissue	35 (11 enrolled in Phase 2)	Three cases of life-threatening thrombocytopenia on niraparib 300 mg Niraparib 200 mg well tolerated	mPFS 11.7 *m*	All patients enrolled in phase 0 met the niraparib PK threshold in the non-enhancing tumor
NCT01026493 Robins et al. 2016 [48]	1/2	ARM 1: Veliparib 40 mg BID + TMZ 75 mg/m^2 21/28 days ARM 2: Veliparib 40 mg BID + TMZ 150–200 mg/m^2 5/28 days	Recurrent, TMZ-refractory, high-grade gliomas	151 BEV-naïve 74 BEV-refractory	Arm 1 vs 2, BEV-refractory: grade 3/4 neutropenia 12.6 % vs 8.1 %, grade 3/4 thrombocytopenia 25 % vs 5.4 % Arm 1 vs 2, BEV-naive: Grade 3/4 neutropenia 19.1 % vs 4,1% grade 3/4 thrombocytopenia 16.4 % vs 8.2 %	BEV-refractory: Two pts progression-free at six months; one CR. mOS 4.7 months in both arms 1 and 2 BEV-naive: Nine patients progression-free at six months; one CR and one PR mOS 10.3 mo in arm 1, 10.7 mo in arm 2	
NCT00770471 Kleinberg et al. 2023 [49]	1	Veliparib 10 mg BID + TMZ 75 mg/m^2 +/- RT	Newly diagnosed GBM	6 treated with Veliparib 10 mg BID + TMZ 75 mg/m^2 (safety group) 12 treated with Veliparib 10 mg BID + TMZ 75 mg/mq + RT (concomitant group) 6 treated with Veliparib 10 mg BID every other week + TMZ 75 mg/mq + RT (de-escalation group)	Safety group: One grade 4 thrombocytopenia Concomitant group: Three grade 4 thrombocytopenia; one patient with severe neutropenia/thrombocytopenia/anemia De-escalation group: Three DLT (2 thrombocytopenia, one neutropenia)	mOS 13 mo OS-24: 25 %	
NCT01390571 Hanna et al. 2020 [42]	1	Stage 1 (pilot study to confirm olaparib brain penetration): olaparib 200 mg BID for seven doses prior to surgery Stage 2 (dose escalation/expansion phase):Olaparib + TMZ 50–75 mq/m^2	rGBM	3 in Stage 1 32 in Stage 2, dose-escalation phase 13 in Stage 2, dose expansion phase	Stage 2, dose-escalation: One grade 3 neutropenia, one grade 2 thrombocytopenia, one grade 3 vomiting, one toxic death Among 16 pts treated at RP2D (Olaparib 150 mg days 1–3 per week + TMZ 75 mg/m^2 QD): Three grade 3/4 anemia, seven 3/4 lymphopenia, four thrombocytopenia	Among 36 evaluable pts: PFS6 39 %	Olaparib was detected in all tumor samples of stage 1 pts and all evaluable core and tumor margin samples of the whole study population
PARADIGM trial (1 dose escalation)	1	Olaparib (50 mg QD/100 mg QD/100 mg /200 mg BID/200 mg	Newly diagnosed elderly or frail GBM	16	1 DLT (grade 3 agitation olaparib-related); only one grade 1	mOS10.8 mo mPFS 5.5 mo	Olaparib + RT did not impair cognitive function

(*continued on next page*)

Table 1 (*continued*)

Study identifier	Phase	Intervention	Patients population	No. of pts	Safety	Efficacy	Other results
Derby et al. 2024 [50]		BID) + RT (30 Gy in 15 fractions)			thrombocytopenia RP2D established at 200 mg BID		
PARADIGM 2 Derby et al. 2023 [51]	1	Unmethylated: Olaparib + RT (60 Gy in 30 fractions) Methylated: Olaparib + CTRT	Newly diagnosed MGMT unmethylated GBM and methylated (<70 years, ECOG 0–1)	43 unmethylated 24 methylated	No DLT RP2D established at 300 mg BID	Overall population mOS 14.1 mo OS-12 64.3 % OS-24 16.7 % RP2D cohort mOS 14.2 mo OS-12 69 % OS-24 24.1 %	
NCT03212742 Stefan et al. 2023 [52]	1/2a	Olaparib + RT (60 Gray in 30 fractions) + TMZ (75 mg/m^2 during RT, 150 mg/m^2 during maintenance)	Unresectable, newly diagnosed GBM	30 16 evaluable in RT period; 11 pts evaluable in maintenance period	RT period 4 pts with DLT (G3/4 thrombocytopenia, G4 neutropenia) Maintenance period One DLT (thrombocytopenia G4) MTD 100 mg BID days 1–3 in both groups		
NCT03150862 Piotrowki et al. 2020 [53]	1b/2	ARM A: Pamiparib + RT ARM B: Pamiparib + RT + TMZ ARM C: Pamiparib + TMZ	Newly diagnosed, MGMT unmethylated GBM (Arm A- B) rGBM (Arm C)	Arm A: 60 Arm B: 9 Arm C: 47	Arm A anemia (10 %) Arm B leuko-neutropenia (22 %) Arm C anemia (11 %), fatigue (11 %) decreased lymphocyte count (11 %)	Arm A/B mPFS 4.4 mo mOS 12.7 mo Arm C mPFS 1.8 mo mOS 7.3 mo	
NCT03914742 Schiff et al. 2021 [54]	0/1	Pamiparib 60 mg BID + TMZ 20 mg QD	Recurrent IDH mutant glioma	6	One DLT (grade 3 neutropenia and thrombocytopenia)	PFS-6 43 %	Mean pamiparib unbound concentrations 20-fold the in vitro IC50 for PARP inhibition in two esected patients
NCT04614909 Schiff et al. 2021 [55]	0	Four days of pamiparib 60 mg BID before surgery	Newly diagnosed (arm A) and recurrent (arm B) GBM	Arm A: 20 Arm B: 14		Arm A mPFS 5.8 mo Arm B mPFS 3.1 mo	Pamiparib achieved pharmacologically active concentrations in both arms
NCT04910022 Geurts et al. 2023 [56]	1/2	NMS-293 + TMZ 150 mg/m^2	Recurrent gliomas	21 (14 evaluable for response)	No DLT or grade ≥ 3 TRAEs	One confirmed PR and one CR on enhancing non-target lesion in GBMpts One unconfirmed PR in an IDH mutant, grade 3, astrocytoma	

Abbreviation: BEV bevacizumab; CR complete response;DLT dose-limiting toxicity; GBM Glioblastoma; Gy Gray; IC50 Half maximal inhibitory concentration;; MGMT O^6-methylguanine-DNA methyltransferase; mOS median overall survival;; MTD maximum tolerated dose; OS-12 overall survival at 12 months; OS-24 overall survival at 24 months; PARP Poly (ADP-ribose) polymerase; PFS progression-free survival; PK pharmacokinetics; PR partial response; RP2D recommended phase 2 dose; RT radiotherapy; TMZ temozolomide; TRAEs treatment-related adverse events; rGB recurrent glioblastoma.

Understanding the mechanisms of resistance to PARP inhibition is critical. It has been suggested that PARP resistance may occur through several processes, including restoration of the HHR pathway, increased PARylation activity, and pharmacological alterations[72]. To overcome PARP resistance, the optimal combination of PARPi with other treatment strategies is urgently needed. In this regard, exploring the synergistic effects of PARPi with radiotherapy, chemotherapy and immunotherapy is essential for glioma patients. Vorasidenib has demonstrated to extent progression-free survival in low-risk, low-grade gliomas and a potential synergistic effect with PARPi in this population with BRACness characteristics should be investigated to improve clinical benefit. Another potential drugs increasing PARPi activity could be inhibitors of cell cycle checkpoint kinases ATR, CHK1 and WEE1; indeed, preclinical studies have shown a synergistic effect with these combinations[73].

Yet, PARPi has been shown to upregulate PD-L1 levels on tumour

Table 2
Phase II/III studies PARPi in glioma.

Study Identifier	Drug	Phase	Design	Patients population	No. of pts	Status	Results
Sim, H-W et al (Vertu) [57]	Veliparib	2	EXP: Veliparib + RT → Veliparib + TMZ ST: TMZ + RT → TMZ	Newly diagnosed GBM (unmethylated)	125	Completed	mPFS 5.7 m vs 4.2 *m* mOS 12.7 m vs 12.8 *m*
NCT02152982 (Alliance) [58]	Veliparib	2/3	EXP: Veliparib + RT → Veliparib + TMZ ST: TMZ + RT → TMZ	Newly diagnosed GBM (methylated)	447	Completed	mPFS 13.2 m vs 12.1 *m* mOS 28.1 m vs 24.8 *m*
NCT03581292 [58]	Veliparib	2	EXP:Veliparib + RT + TMZ → Veliparib + TMZ ST: TMZ + RT → TMZ	Newly diagnosed IDHwt-GBM or IDHmut-Astro4	37 23IDHwt-GBM 14 IDHmut-A4	Completed	1y-PFS 29 %; 1y-OS 67 % 1y-PFS 57 %; 1y-OS 90 %
Blakeley et al. [61]	Iniparib	2	RT + TMZ + Iniparib	Newly diagnosed GBM	81	Completed	mOS 21.6 *m*
NCT04221503	Niraparib	2	TTF + Niraparib	rGBM	30	Recruiting	/
NCT03212274 Fanucci et al. [64]	Olaparib	2	Olaparib	Recurrent IDH1 and IDH2 mutant glioma	15	Completed	mPFS 3.63 *m* mOS 20.7 *m*
NCT04740190 (TAC-GReD) [69]	Talazoparib	2	RT + Carboplatin + Talazoparib	Recurrent high grade glioma (DDRd)	33	Completed	mPFS 3.5 *m* 12 m-OS 30 %
NCT02974621	Olaparib	2	EXP: Cediranib maleate + Olaparib ST: Bevacizumab	rGBM	70	Active, not recruiting	/
NCT05076513 [63]	Niraparib	2	Niraparib + RT	Newly diagnosed GBM (unmethylated)	20	Completed	mPFS 11.7 *m* mOS 20.3 *m*
NCT03991832 [71]	Olaparib	2	Olaparib + Durvalumab	Recurrent IDHmut gliomas	29	Completed	mPFS 1.9 *m* mOS 9.5 *m*
NCT03561870[66]	Olaparib	2	Olaparib	Recurrent IDHmut HGGs	35	Completed	mPFS 2.05 *m* mOS 15.9 *m*
NCT06388733	Niraparib	3	EXP: Niraparib + RT → Niraparib ST: TMZ + RT → TMZ	Newly diagnosed GBM (unmethylated)	450	Recruiting	/

Abbreviations: EXP, experimental; ST, standard; RT, radiotherapy; TMZ, temozolomide; GBM, glioblastoma; mOS, median overall survival; mPFS, median progression free survival; m, months; PFS-6 m, progression-free survival rate at six months; TTF, tumor treating fiels; rGBM, recurrent GBM; HGG = high-grade gliomas

cells, providing a rationale for using these drugs with immune checkpoint inhibitors; however, a recent study showed no efficacy of the combination of olaparib plus durvalumab in recurrent high-grade glioma[66]. To improve the penetration of PARPi across the blood–brain barrier, treatment with low-intensity pulsed ultrasound, such as the Sonobird (@Carthera) implantable device, may be of interest; indeed, two recent studies have shown that the device increases intracerebral drug penetration[74,75].

Further translational research is needed to identify biomarkers to allow a better selection of patients and an optimal combination of therapeutic strategies mostly in IDH-mutant glioma patients given their increase sensitivity to PARPi[28] Although most clinical trials analyzing PARPi enrolled heterogeneous glioma patients with different clinical and molecular characteristics, no strong activity of PARPi was seen in IDH mutant glioma compared to IDHwt glioma. Recent works demonstrated that the amplification of MYC/MYCN and CDK18 expression could be potential biomarkers of PARPi activity and it will be extremely important to conduct prospective studies exploring this concept also in glioma patients[76]. Another question is if the methylation status of MGMT may be a predictor of PARPi efficacy; however, according to a translational study PARPi could sensitize TMZ in unmethylated MGMT GBM by inhibition of PARylation and subsequent reduction of MGMT function[38]. PTEN deletion may be another potential biomarker of PARPi activity and as described above it should be more investigated in glioma patients receiving PARPi [39].

Several studies have demonstrated that loss of PARP1 is the major driver of synthetic lethality, so the trapping of PARP2 to DNA may not be required to achieve anticancer activity[77]. Being PARP2 inhibition particularly linked to the adverse events related to PARPi, a selective inhibition of PARP1 is currently under investigation to permit a future well tolerated combination with other agents [78].

In conclusion, the glioma trial scenario emphasizes precision oncology, molecular profiling, and innovative immunotherapies. PARPi could complement these advances by disrupting DNA repair pathways and increasing treatment efficacy[79]. In addition, the development of novel PARPi with improved BBB penetration, the combination with other synergistic therapies and more potent PARP inhibitor activity is progressing and promises new and exciting treatment options[78].

Declaration of Competing Interest

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