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# The Role of PARP Inhibitors in Patients with Primary Malignant Central Nervous System Tumors

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## Opinion statement

Primary malignant central nervous (CNS) tumors are a devastating group of diseases with urgent need for improved treatment options. Surgery, radiation, and cytotoxic chemotherapy remain the primary standard treatment modalities, with molecularly targeted therapies having proven efficacy in only small subsets of cases. Poly(ADP-ribose) polymerase (PARP) inhibitors, which have had immense success in the treatment of extracranial cancers with homologous recombination deficiency (HRD), are emerging as a potential targeted treatment for various CNS tumors. Although few primary CNS tumors display canonical BRCA gene defects, preclinical evidence suggests that PARP inhibitors may benefit certain CNS tumors with functional HRD or elevated replication stress. In addition, other preclinical studies indicate that PARP inhibitors may synergize with standard therapies used for CNS tumors including radiation and alkylating agents and may prevent or overcome drug resistance. Thus far, initial clinical trials with early-generation PARP inhibitors, typically as monotherapy or in the absence of selective biomarkers, have shown limited efficacy. However, the scientific rationale remains promising, and many clinical trials are ongoing, including investigations of more CNS penetrant or more

potent inhibitors and of combination therapy with immune checkpoint inhibitors. Early phase trials are also critically focusing on determining active drug CNS penetration and identifying biomarkers of therapy response. In this review, we will discuss the preclinical evidence supporting use of PARP inhibitors in primary CNS tumors and clinical trial results to date, highlighting ongoing trials and future directions in the field that may yield important findings and potentially impact the treatment of these devastating malignancies in the coming years.

## Introduction

Primary malignant central nervous system (CNS) tumors constitute ~1% of new cancer diagnoses, but account for a disproportionate amount of morbidity and mortality. Relative survival has improved slowly over the past several decades, but 5-year overall survival is still only ~36% averaged across all histologies, indicating a need for additional therapeutic options [1]. Poly(ADP-ribose) polymerase (PARP) inhibitors have emerged as a potential treatment for primary CNS tumors, with investigation focused primarily on adult-type diffuse gliomas and pediatric-type diffuse high-grade gliomas (HGG), as defined by the 2021 WHO classification of tumors of the CNS [2], along with emerging preclinical studies in specific subsets of medulloblastoma and ependymoma.

Among adult-type diffuse gliomas, glioblastoma (GBM) is the most common and most aggressive subtype. Current standard of care treatment consists of maximal surgical resection, followed by chemoradiation with concurrent and adjuvant temozolomide (TMZ), with potential addition of tumor-treating fields (TTF) therapy [3, 4]. Unfortunately, with median survival of just 15 months, recurrences are expected, and second-line therapies, including bevacizumab and other alkylating agents, confer minimal therapeutic benefit. Grade 2 and 3 oligodendroglioma and astrocytoma tumors are characterized by isocitrate dehydrogenase 1 or 2 (IDH1/2) mutations in most cases, and the presence or absence of 1p/19-codeletion, respectively [2, 5]. Though less aggressive than GBM, these gliomas remain uncurable, with recurrences typically occurring over 2–10 years. Standard management consists of surgery, often followed by adjuvant radiotherapy or alkylating agent chemotherapy.

Pediatric HGG are a diverse group of highly aggressive tumors, which are increasingly classified by molecular characteristics. Diffuse midline gliomas (DMG) are characterized by histone H3 lysine 27 (H3K27) alterations, which occur in about ~80% of radiographically diagnosed diffuse intrinsic pontine gliomas (DIPG) [6]. Given their location in the brainstem, these are treated locally with radiotherapy alone, but are universally fatal with median survival of less than 1 year. Pediatric-type hemispheric gliomas are also classified molecularly, and efforts are focused on developing more subtype-specific therapies ranging from targeted chemotherapy to immunotherapy to vaccine therapy, but currently surgical resection and radiation remain the standard of care [7]. Medulloblastoma, standardly treated with surgery, craniospinal irradiation, and multiagent chemotherapy, and ependymoma, managed with surgery and focal radiotherapy, have relatively better outcomes with 5-year survival rates of ~75% and ~85% [8], but still entail considerable morbidity which could be ameliorated with more targeted therapies.

PARP is intricately involved in many aspects of the DNA damage response (DDR), and PARP inhibitors have been successful at targeting non-CNS tumors harboring DDR defects including homologous recombination deficiency (HRD). In primary CNS tumors, potential roles for PARP inhibitors

arise through targeting tumor genetic defects or in generating synergistic effects with other treatment modalities including radiation, chemotherapy, or immunotherapy. Here we will review the rationale and preclinical evidence for use of PARP inhibitors in CNS malignancies and discuss completed and ongoing clinical trials testing PARP inhibitors in this setting.

# Rationale and preclinical evidence for PARP inhibitor use in CNS tumors

## Mechanistic basis of PARP inhibition

The PARP family of enzymes encompasses 17 proteins that catalyze mono- or poly-ADP-ribosylation of target proteins using NAD+ as a substrate and contribute to diverse cellular functions, including DNA damage repair, transcription, and chromatin structure modulation [9]. PARP1 is the dominant member involved in the DNA damage response, accounting for the majority of poly(ADP-ribose) (PAR) synthesis in response to genotoxic stress, with PARP2 and PARP3 playing secondary roles. PARP1 binds to DNA single-stranded breaks (SSBs), where it synthesizes long PAR chains on itself, nearby histones, and additional target proteins, leading to the recruitment, organization, and activation of proteins responsible for DNA repair. PARP1 also plays a role in base excision repair, DNA double-strand break (DSB) recognition and repair, and replication fork protection and restart [10].

PARP inhibitors are small molecule compounds that competitively bind the NAD+ binding site, blocking the catalytic activity of PARP. PARP catalytic inhibition hinders repair of DNA SSBs and base lesions, leading to collapse of replication forks during replication and generation of DSBs [11, 12]. In addition, PARP inhibitors can, to varying degrees, non-covalently "trap" PARP at damaged DNA, generating toxic PARP-DNA complexes that cause additional replication fork damage [13, 14]. PARP trapping is largely due to inhibition of its auto-PARylation activity as negatively charged PAR chains facilitate PARP release from DNA, but is influenced by differences in allosteric interactions upon PARP inhibitor binding [15–17].

DNA DSBs induced by either SSB repair inhibition or PARP trapping are proposed to underlie a synthetic lethal interaction between PARP inhibition and homologous recombination (HR) defects, which most commonly arise due to BRCA1 or BRCA2 mutations [11, 12, 14]. More recently, evidence has emerged that PARP plays a role in DNA replication by controlling replication fork speed and sensing unligated Okazaki fragments and that PARP inhibitors induce single-stranded DNA gaps behind the replication fork as a consequence of Okazaki fragment processing defects [18–22]. These ssDNA gaps may lead to toxicity in BRCA-deficient cells either directly or through the induction of DSB formation [18, 23].

## Targeting CNS tumor genetic defects

PARP inhibitors have established activity in BRCA-mutant tumors, but these mutations occur infrequently in primary brain tumors [24]. A variety of other genetic alterations can cause functional HRD leading to PARP inhibitor sensitivity, also referred to as a "BRCAness" phenotype [25]. In CNS tumors, the

most notable examples are IDH1/2 mutations, found in over 70% of grade II–III glioma [5]. IDH1/2 mutations generate neomorphic enzymatic activity leading to excess production of the oncometabolite 2-hydroxyglutarate (2-HG) [26]. 2-HG acts as a competitive inhibitor of the family of α-ketoglutarate-dependent dehydrogenases, which includes histone lysine demethylases and DNA demethylases, resulting in genome-wide epigenetic remodeling [27–31]. Inhibition of lysine demethylase KDM4B, in particular, leads to aberrant histone modifications and masking of local chromatin signaling at sites of DNA DSBs, impairing DSB repair and inducing PARP inhibitor sensitivity [32, 33••]. PARP inhibitor sensitivity is being evaluated clinically in IDH1/2-mutant glioma, as described below.

Several other recurrent CNS tumor genetic changes may confer PARP inhibitor sensitivity via defects in HR or through effects on replication, though have yet to enter the clinical arena. First, upregulation of enhancer of zeste homolog inhibitory protein (EZHIP), a protein that drives H3K27 hypomethylation by inhibiting polycomb repressive complex 2 (PRC2), characterizes group A posterior fossa ependymoma (PFA), the most common and aggressive subtype, as well as DIPG/DMG with H3K27 trimethylation loss but without H3K27M mutations [34–36]. In addition to mimicking the effects of H3K27M mutations, EZHIP overexpression has been shown to suppress HR repair by blocking BRCA2-PALB2 interaction, leading to PARP inhibitor hypersensitivity [37•]. Second, ATRX mutations, which frequently co-occur in IDH1/2-mutant glioma and pediatric-type diffuse hemispheric glioma, H3 G34-mutant, have been linked to increased replication stress [38]. Independently of IDH1/2 mutations, ATRX loss increases PARP inhibitor sensitivity and is a marker for synergy between PARP and ATR inhibitors [38]. Finally, amplification or upregulation of the *MYCN* oncogene occurs in subsets of sonic hedgehog (SHH)–mediated and group 4 medulloblastoma, portends poor prognosis, and is a driver of replication stress, which can be enhanced by PARP inhibitors, leading to mitotic catastrophe [39]. In *MYCN*-amplified medulloblastoma models, PARP is highly expressed in tumor compared to normal cerebellum, and PARP inhibitors in combination with low-dose CHK1 inhibitor are effective in vitro and in vivo [40]. Although some of the cancers described here have been enrolled in clinical trials testing PARP inhibitors, the underlying genetic defects remain to be directly incorporated into molecularly targeted trial design.

## Synergy with radiation and DNA-damaging agents

PARP inhibitors can increase sensitivity to many of the standard DNA-damaging treatments used in CNS tumors including ionizing radiation. In glioma cells, PARP inhibitor–mediated radiosensitization is replication-dependent and likely occurs due to replication collapse at unrepaired SSBs or PARP-DNA trapped complexes [41]. Importantly, normal brain tissue is largely nonreplicating and thus relatively protected from enhanced radiation-induced cytotoxicity mediated by PARP inhibition. The ability of various PARP inhibitors to potentiate radiation sensitivity has been shown in models of glioblastoma, pediatric high-grade astrocytoma, DIPG, medulloblastoma, and ependymoma [42–46]. In a systematic review, the median dose enhancement ratio generated by PARP inhibitors was 1.3 [47], though this conceivable may be further enhanced in tumors with intrinsic DDR defects. Moreover, PARP

inhibitors can radiosensitize glioblastoma stem cells, which have upregulated DDR and may mediate therapeutic resistance [48, 49].

PARP inhibitors also potentiate the activity of other DNA-damaging agents, an effect which in CNS tumors has primarily been studied with TMZ. TMZ is a monofunctional alkylating agent that methylates DNA bases at different sites. Silencing of the DNA direct repair gene $O^6$-methylguanine-DNA methyltransferase (MGMT), which occurs in approximately two-thirds of lower grade glioma and half of GBM, confers sensitivity to TMZ as unrepaired $O^6$-methylguanine lesions trigger cell death in a mismatch repair (MMR)–dependent manner [50–52]. However, intrinsic resistance to TMZ exists in MGMT-expressing tumors and acquired resistance inevitably develops in MGMT-silenced tumors, most commonly due to inactivation of MMR [53–57]. As TMZ also generates substantial $N^7$-methylguanine and $N^3$-methyladenine lesions, which are processed by BER, PARP inhibition has been postulated as a way to re-sensitize resistant cells to TMZ [58]. PARP inhibitors may also promote TMZ sensitivity by blocking PARP-mediated PARylation of MGMT, which has been reported to promote repair of $O^6$-methylguanine lesions [59]. In addition, PARP enzymes other than PARP1 may play a role as PARP inhibitors can restore sensitivity even upon PARP1 knockout in certain MMR-deficient models [60].

In vitro, PARP inhibitors reliably restore the activity of TMZ in MGMT-expressing or MMR-deficient glioma or medulloblastoma cells, while generally having a limited effect on MGMT-deficient cells that are already highly TMZ-sensitive [58–63]. In contrast, in vivo studies using patient-derived xenograft models have suggested that the sensitizing effects of PARP inhibitors are limited to those with intrinsic TMZ sensitivity, possibly because PARP inhibitor concentrations needed to induce re-sensitization are difficult to achieve clinically, at least with certain PARP inhibitors [64–66]. Co-treatment with PARP inhibitors in TMZ-sensitive cells has also been shown to prevent the emergence of TMZ resistance [67]. In light of these preclinical findings, PARP inhibitors have been investigated in human trials in both TMZ-naive and TMZ-resistant tumors, as discussed below.

## Combination with immunotherapy

Tumors exploit inhibitory immune checkpoints, such as cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), to suppress T cell effector function and escape immune surveillance [68]. Antibodies targeting CTLA-4 and PD-1/PD-L1 pathways block the interaction of inhibitory molecules with their ligand on tumor cells or antigen-presenting cells, thereby reinvigorating the anti-tumor immune response [68]. Immune checkpoint blockade (ICB) has shown substantial clinical efficacy in patients with various solid tumors but only subsets of patients respond [68]. Putative predictive biomarkers of ICB response include high tumor mutational burden (TMB), increased number of tumor-infiltrating lymphocytes (TILs), an inflammatory gene signature, positive PD-L1 expression, and MMR deficiency/microsatellite instability [69–72]. GBM is considered to have an immunologically "cold" tumor microenvironment, with low TMB and multiple immunosuppressive mechanisms [73–75]. Consequently, ICB has been largely ineffective in clinical trials of adult GBM, with two randomized controlled trials failing to show a benefit with nivolumab over bevacizumab in recurrent GBM or with

the addition of nivolumab to RT and TMZ in newly diagnosed GBM [73, 76, 77]. Nevertheless, observed responses with ICB in pediatric patients with recurrent hypermutant GBM harboring germline MMR deficiencies suggest it may still hold promise for the treatment of primary CNS tumors [78, 79]. These findings also beget the prospect of targeting DNA damage repair pathways in order to sensitize gliomas to ICB.

In other solid tumors, PARP inhibition has been shown to enhance tumor immunogenicity and response to ICB through DNA damage–induced activation of immune recognition pathways and increased neoantigen formation [80–82]. In the setting of HRD, PARP inhibition creates DSBs resulting in cytosolic dsDNA fragments that are detected by cGMP-AMP synthase (cGAS), ultimately leading to activation of stimulator of interferon genes (STING) and production of type I interferons (IFNs) [82–85]. The enhanced expression of proinflammatory cytokines and chemokines serves to increase recruitment of TILs [83, 86–88]. Through DNA damage–mediated generation of type I IFNs and inhibition of GSK3β, PARP inhibitors have also been shown to induce a compensatory increase in the expression of PD-L1 [70, 82, 84–86, 88, 89]. The genomic instability induced by PARP inhibition may also serve to increase TMB, thereby leading to more tumor-specific neoantigens that can be recognized by cytotoxic T cells, as has been seen in the setting of MMR-deficient tumors [71, 90–92]. Moreover, via release of type I INFs and other proinflammatory cytokines, PARP inhibition has been shown to enhance antigen presentation by increasing expression of major histocompatibility complex class I (MHC I) on tumor cells and promoting the recruitment and activation of antigen-presenting cells [83, 87, 88, 93]. Of note, while TMB has emerged as a biomarker of ICB response in multiple tumor types, treatment-induced hypermutation has not been consistently associated with ICB response in GBM [72, 91, 94, 95].

As described previously, IDH1/2 mutations confer a "BRCAness" phenotype and sensitivity to PARP inhibitors, making these tumors prime candidates in which to explore PARP inhibitor and immunotherapy combinations. However, in addition to inducing HR defects, 2-HG accumulation has also been shown to impair T cell recruitment via decreased tumor cell production of CXCL10 and impaired T cell activity [96, 97]. In turn, inhibition of mutant IDH1/2 results in increased PD-L1 levels, improved T cell infiltration, and enhanced response to ICB in mouse models [96, 98]. Additional studies are needed to elucidate the interplay between DNA damage–mediated immune activation, IDH1/2-induced BRCAness, and 2-HG-mediated immunosuppression.

## PARP inhibitors under clinical investigation in CNS tumors

No PARP inhibitors are yet approved for treatment of CNS tumors, but those currently under clinical investigation in the brain tumor setting include the following: three of the four PARP inhibitors that are currently FDA-approved for other indications (olaparib, niraparib, and talazoparib), the highly investigated PARP inhibitor veliparib, two PARP inhibitors with clinical approval in China for ovarian cancer (pamiparib and fuzuloparib), and two novel compounds designed for CNS penetration and PARP1 selectivity (AZD9574 and NMS-293) (Table 1).

The intrinsic potency of different PARP inhibitors correlates most closely with their PARP trapping potential, which itself is dependent on both their

**Table 1. PARP inhibitors under clinical investigation in primary CNS tumors**

| PARP inhibitor | Approved disease indications | Relative PARP1 inhibition potency | Allosteric retention type [17] | Relative trapping potency | PARP1 vs PARP2 selectivity | Intact blood–brain barrier penetration | Standard monotherapy dosing |
|---|---|---|---|---|---|---|---|
| **Olaparib** (LYNPARZA, AstraZeneca) | Breast, ovarian, pancreatic, and prostate cancer | 1 | Type I (neutral) | 1 | No [136] | Low* B:P = 0.02 [107] | 300 mg BID |
| **Veliparib** (AbbVie) | N.A. | 0.1–1 [136] | Type III (pro-release) | <0.1 [13, 16] | No [136] | High B:P = 0.3–1 [66, 108] | 400 mg BID |
| **Niraparib** (ZEJULA, GlaxoSmithKline) | Ovarian cancer | 0.1–0.8 [136] | Type III (pro-release) | ~0.1–2 [13, 16] | No [136] | Moderate B:P = 0.09 [107] | 200–300 mg BID |
| **Talazoparib** (TALZENNA, Pfizer) | Breast cancer | 1–80 [136] | Type I (neutral) | ~100 [99] | No [136] | Low B:P = 0.02 [106, 107] | 1 mg BID |
| **Pamiparib** (BeiGene) | Ovarian Cancer (China) | ~1 [100] | N.D. | 1 [100] | No [100] | Moderate B:P = 0.2 [107] | 60 mg BID |
| **Fuzuloparib** (Jiangsu Hengrui Pharmaceuticals) | Ovarian cancer (China) | ~1 [137] | N.D. | N.D. | N.D. | N.D. | 150 mg BID |
| **AZD9574** (AstraZeneca) | N.A. | ~1 [103] | N.D. | N.D. | >8000-fold [103] | High B:P = 0.3–0.8 [109] | N.D. |
| **NMS-293** (Nerviano Medical Sciences) | N.A. | ~1 [101] | N.D. | <<1 [102] | >200-fold [102] | Very high B:P = 4–10 [102] | N.D. |

Abbreviations: *B:P*, brain-to-plasma ratio; *BID*, twice daily
*Olaparib has been shown to penetrate recurrent GBM with mean tumor to plasma ratio of 0.25 [105••]

catalytic inhibition and allosteric retention type [13, 16, 17]. Talazoparib is the strongest PARP trapping inhibitor, followed by olaparib, niraparib, and pamiparib all with similar trapping potencies, followed by veliparib which has significantly less trapping [13, 16, 99, 100]. NMS-293 has been reported to be non-PARP trapping [101], while data for fuzuloparib and AZD9574 are not yet available. Non-PARP trappers such as veliparib have limited single agent potency and are typically investigated in combination with cytotoxic agents. All the PARP inhibitors listed have approximately equipotent activity against PARP1 and PARP2, except for the next-generation compounds AZD9574 and NMS-293 which have >8000-fold and >200-fold selectivity for PARP-1 respectively [102, 103]. It is thought that PARP-2 inhibition may contribute to hematologic toxicity and so PARP-1 selectivity may confer an improved toxicity profile while maintaining tumor control efficacy [104].

The various PARP inhibitors also differ in their pharmacokinetic and pharmacodynamic properties, with penetration of the blood–brain barrier being a key parameter for CNS tumor efficacy. Olaparib and talazoparib are known substrates of the P-glycoprotein efflux pump and have poor distribution to brain tissue in the presence of an intact blood–brain barrier [105••, 106, 107]. However, as described below, phase 0 clinical trial data suggests olaparib may sufficiently penetrate tumors with a disrupted blood–brain barrier [105••]. Niraparib and pamiparib have moderately improved brain-to-plasma (B:P) ratios (0.1 and 0.2), veliparib and AZD9574 have high intact brain penetration (B:P ~0.3-1), and NMS-293 may have substantially higher CNS accumulation (B:P ~4-10) [66, 101, 107–109].

# Clinical trials of PARP inhibitors in CNS tumors

## IDH1/2-mutant glioma PARP inhibitor trials

Based on the preclinical studies demonstrating that IDH1/2 mutations confer susceptibility to PARP inhibitors, several clinical trials have been initiated testing PARP inhibitors in IDH1/2-mutant gliomas (Table 2). Two clinical trials (OLAGLI and ETCTN10129) testing standard dose olaparib as monotherapy have recently reported results [110, 111]. The OLAGLI trial enrolled 35 patients with recurrent high-grade IDH-mutant glioma after radiotherapy and at least one line of alkylating chemotherapy while ETCTN10129 enrolled 15 patients in the glioma cohort with recurrent IDH1/2-mutant contrast-enhancing glioma. In both studies, pre-specified primary endpoints of 6-month progression-free survival (PFS-6) or overall response rate (ORR) by RANO criteria were not met, although there was some demonstration of benefit in these heavily pretreated populations, with prolonged SD seen in subsets of patients.

Ongoing studies in IDH1/2-mutant glioma are investigating PARP inhibitors with improved CNS penetration or in combination with alkylating chemotherapy, with an emphasis on correlative studies to determine intratumoral drug activity. ABTC-1801 is testing the combination of pamiparib and TMZ in recurrent IDH1/2-mutant glioma. Preliminary phase 0 data demonstrated mean unbound concentrations of pamiparib of >20-fold the in vitro $IC_{50}$ for PARP inhibition in both enhancing and non-enhancing tumors. In the phase I component of the study, the regimen of pamiparib 60 mg twice daily and low-dose metronomic TMZ (20 mg daily) was found to have tolerable hematologic toxicity and will be used as the recommended phase II dose (RP2D) [112•]. The PNOC017 trial is similarly testing pamiparib in combination with TMZ in

**Table 2. Completed and ongoing trials of PARP inhibitors in primary CNS tumors**

| Study | PARP inhibitor | Phase | Status | *n* | Cancer criteria | Treatment arms | Results/primary endpoints |
|---|---|---|---|---|---|---|---|
| *IDH1/2-mutant glioma PARP inhibitor trials* | | | | | | | |
| OLAGLI NCT03561870 | Olaparib | II | Completed | 35 | Recurrent IDH1/2-mutant HGG | Olaparib 300 mg BID | Primary endpoint (PFS-6) not met [110] |
| ETCTN10129 NCT03212274 | Olaparib | II | Completed (cohort A) | 15 (cohort A) | Recurrent IDH1/2-mutant contrast-enhancing glioma (cohort A) | Olaparib 300 mg BID | Primary endpoint (ORR) not met, but prolonged SD observed in patients with grade 2/3 tumors [111] |
| ABTC-1801 NCT03914742 | Pamiparib | 0/I/II | Active not recruiting | 60 | Recurrent IDH1/2-mutant glioma | Phase 0/1: pamiparib + TMZ (dose escalation)Phase 2: pamiparib 60 mg BID + TMZ 20 mg QD | Pamiparib achieved active concentrations in enhancing and non-enhancing tumor; RP2D established; tumor response by RANO criteria (phase II) [112•] |
| PNOC017 NCT03749187 | Pamiparib | 0/I | Recruiting | 78 (est.) | Newly diagnosed or recurrent IDH1/2-mutant glioma in adolescents and young adults | Phase 0: pamiparib × 7 days ➔ surgery ➔ pamiparib + TMZ<br>Phase I: pamiparib + TMZ | Intratumoral drug concentration; safety and tolerability |
| TAC-GReD NCT04740190 | Talazoparib | II | Recruiting | 33 (est.) | Recurrent HGG with IDH1/2 mutation or other DDR deficiency | Talazoparib 0.75 mg (D1-4 Q7D) + carboplatin AUC 1.5 (D1 Q7D) + WBRT 2 Gy (D1 of cycle 1) | PFS-6 by RANO criteria |
| CERTIS1 NCT05417594 | AZD9574 | I/II | Recruiting | 195 (est., all arms) | Recurrent IDH1/2 mutant glioma (module 2) | AZD9574 + TMZ (dose escalation) (module 2) | Safety and tolerability |
| NCT05406700 | Niraparib | 0 | Not yet recruiting | 16 (est.) | Recurrent IDH1/2-mutant non-enhancing glioma | 1. Niraparib × 28 days ➔ surgery ➔ niraparib<br>2. Surgery ➔ niraparib | Intratumoral drug concentration |
| NCT05076513 | Niraparib | 0 "trigger" | Recruiting | 42 (est.) | A. Newly diagnosed GBM<br>B. Recurrent IDH1/2-mutant glioma | A. Niraparib × 4 days ➔ surgery ➔ niraparib + RT ➔ Niraparib maintenance | Intratumoral drug concentration; PFS-6 in patients with |

**Table 2.** (Continued)

| Study | PARP inhibitor | Phase | Status | *n* | Cancer criteria | Treatment arms | Results/primary endpoints |
|---|---|---|---|---|---|---|---|
| | | | | | | B. Niraparib × 4 days ➔ surgery ➔ niraparib maintenance | demonstrated PK/PD effects |
| *Glioblastoma trials of PARP inhibitors in combination with TMZ and/or RT* | | | | | | | |
| NCT00770471 | Veliparib | I/II | Completed | 24 | Newly diagnosed GBM | Veliparib 10 mg BID + RT 60 Gy in 30 fractions + TMZ 75 mg/m$^2$ QD | Regimen not tolerated due to dose-limiting hematologic toxicity [113] |
| NCT01026493 | Veliparib | I/II | Completed | 215 | Recurrent GBM previously treated with TMZ | 1. Veliparib 40 mg BID + TMZ 75 mg/m$^2$ (D1-21 Q28D)<br>2. Veliparib 40 mg BID + TMZ 150-200 mg/m$^2$ (D1-5 Q28D) | Primary endpoint (PFS-6) not met; 20% grade 3/4 myelosuppression [114] |
| VERTU ACTRN12615000407594 | Veliparib | II | Completed | 125 | Newly diagnosed unmethylated MGMT GBM | 1. Veliparib 200 mg BID + RT 60 Gy in 30 fractions ➔ veliparib 40 mg BID (D1-7 Q28D) + TMZ 150-200 mg/m$^2$ (D1-5 Q28D)<br>2. TMZ 75 mg/m$^2$ + RT 60 Gy in 30 fractions ➔ TMZ 150-200 mg/m$^2$ (D1-5 Q28D) | Primary endpoint (PFS-6) not met: 46% in experimental arm and 31% in standard arm, not significantly improved from historically benchmark of 53% [115•] |
| A071102 NCT02152982 | Veliparib | II/III | Completed | 447 | Newly diagnosed methylated MGMT GBM | 1. RT + TMZ ➔ veliparib 40 mg BID (D1-7 Q28D) + TMZ 150-200 mg/m$^2$ (D1-5 Q28D)<br>2. RT + TMZ ➔ placebo + TMZ 150-200 mg/m$^2$ (D1-5 Q28D) | No significant improvement in OS (HR 0.89, $p$=0.15) or median OS (28.1 vs. 24.8 mo.) [116•] |
| OPARATIC NCT01390571 | Olaparib | I | Completed | 48 | Recurrent GBM | 1. Olaparib 200 mg BID × 7 days ➔ surgery<br>2. Olaparib + TMZ (dose escalation) | Olaparib detected in all tumor core and margin specimens at doses sufficient for in vitro radiosensitization; hematological toxicity necessitated reduced and intermittent dosing [105••] |

**Table 2.** (Continued)

| Study | PARP inhibitor | Phase | Status | *n* | Cancer criteria | Treatment arms | Results/primary endpoints |
|---|---|---|---|---|---|---|---|
| PARADIGM ISRCTN52658296 | Olaparib | I | Completed | 16 | Newly diagnosed GBM, not a candidate for standard chemoradiation | Olaparib (dose escalation) + short-course RT 40 Gy in 15 fractions | Olaparib well tolerated with RT, with RP2D of Olaparib 200 mg BID [117] |
| PARADIGM-2 ISRCTN51253312 | Olaparib | I | Recruiting | 50 (est.) | A. Newly diagnosed methylated MGMT GBM<br>B. Newly diagnosed unmethylated MGMT GBM | A. Olaparib (dose escalation) + RT 60 Gy in 30 fractions + TMZ 75 mg/m$^2$ ➔ olaparib × 4 weeks ➔ TMZ × 6 cycles<br>B. Olaparib (dose escalation) + RT 60 Gy in 30 fractions ➔ Olaparib × 4 weeks | Safety and tolerability [118] |
| OLA-TMZ-RTE-01 NCT03212742 | Olaparib | I/II | Recruiting | 79 (est.) | Unresectable or partially resectable GBM | Olaparib (dose escalation or RP2D) + RT 60 Gy in 30 fractions + TMZ 75 mg/m$^2$ QD ➔ olaparib (dose escalation or RP2D) + TMZ 150 mg/m$^2$ (D1-5 Q28D) | RP2D (phase I); 18-month OS (phase II) [119] |
| NCT03150862 | Pamiparib | I/II | Completed | 116 | A/B. Newly diagnosed unmethylated MGMT GBM<br>C. Recurrent methylated or unmethylated MGMT GBM | A. Pamiparib 60 mg BID + RT 60 Gy in 30 fractions ➔ pamiparib 60 mg BID + TMZ 60 mg (D1-7 Q28D)<br>B. Pamiparib 60 mg BID + RT 60 Gy in 30 fractions + 60 mg TMZ (weeks 1 and 5) ➔ pamiparib 60 mg BID + TMZ 60 mg (D1-7 Q28D)<br>C. Pamiparib 60 mg BID + TMZ 60 mg (D1-7 Q28D) | Modified disease control rate 68.8% in Arm A, 80.0% in Arm B; ORR 9.1% in Arm C [121] |
| NCT04614909 | Pamiparib Olaparib | 0/II | Recruiting | 30 (est.) | A. Newly diagnosed GBM<br>B/C. Recurrent GBM | A/B. Pamiparib 60 mg BID ×4 days ➔ surgery ➔ (if PK response) pamiparib | Systemic plasma PK profile parameters, intratumoral drug concentration (phase 0). PFS-6 in |

**Table 2.** (Continued)

| Study | PARP inhibitor | Phase | Status | *n* | Cancer criteria | Treatment arms | Results/primary endpoints |
|---|---|---|---|---|---|---|---|
| | | | | | | + RT ➔ pamiparib + TMZ<br>C. Olaparib 200 mg BID ×4 days ➔ surgery ➔ (if PK response) olaparib + RT ➔ olaparib + TMZ | participants with demonstrated PK response (phase II). |
| NCT01294735 | Niraparib | I | Completed | 19 | Advanced cancer | Niraparib (dose escalation) + TMZ 150 mg/m$^2$ QD | RP2D established (40 mg QD), with dose-limiting thrombocytopenia in 20% at the RP2D [122] |
| NCT05297864 | Niraparib | II | Recruiting | 45 (est.) | Recurrent HGG | Niraparib 200–300 mg QD | Safety and tolerability; disease control rate by RANO criteria |
| NCT04715620 | Niraparib | II | Recruiting | 30 (est.) | Recurrent GBM | Niraparib 200–300 mg QD + RT 55 Gy | PFS-6 |
| NCT04552977 | Fuzuloparib | II | Not yet recruiting | 50 (est.) | Recurrent GBM | Fuzuloparib + TMZ | PFS-6 |
| NCT04910022 | NMS-293 | I/II | Recruiting | 125 (est.) | Recurrent GBM | 1. NMS-293 (dose escalation or RP2D) D1-7 Q28D + TMZ D1-5 Q28D<br>2. Lomustine (Phase II) | Safety and tolerability; PFS-6 |
| *PARP inhibitor-immunotherapy trials* | | | | | | | |
| NCT03991832 | Olaparib | II | Recruiting | 9 (cohort A) | Recurrent IDH1/2-mutant glioma (cohort A) | Olaparib 300 mg BID + durvalumab 1500 mg IV every 4 weeks | Preliminary results: regimen well tolerated, but demonstrates limited activity (1 OR, 2 SD, 6 PD) [127] |
| NCT05188508 | Olaparib | II | Recruiting | 57 (est.) | Recurrent glioma with IDH1/2 mutation or other HR defect | Pembrolizumab 200 mg IV D1 Q21D + (starting cycle 3) olaparib 200 mg BID D1-7 Q21D + TMZ 50 mg/m$^2$ D1-7 Q21D | ORR |
| NCT05463848 | Olaparib | II | Not yet recruiting | 78 (est.) | Recurrent GBM | Olaparib BID D1-7 Q21D + TMZ D1-7 Q21D + pembrolizumab D1 Q42D | Tumor-infiltrating lymphocyte density, PFS-6 |

**Table 2.** (Continued)

| Study | PARP inhibitor | Phase | Status | *n* | Cancer criteria | Treatment arms | Results/primary endpoints |
|---|---|---|---|---|---|---|---|
| *Pediatric brain tumor PARP inhibitor trials* | | | | | | | |
| PBTC-027 NCT00994071 | Veliparib | I | Completed | 29 | Recurrent pediatric brain tumors | Veliparib (dose escalation) + TMZ (dose escalation) | RP2D established (veliparib 25 mg/m$^2$ BID + TMZ 135 mg/m$^2$ D1-5 Q28D) [128] |
| PBTC-033 NCT01514201 | Veliparib | I/II | Completed | 66 | Newly diagnosed DIPG | Veliparib (dose escalation or RP2D) + RT ➔ veliparib 25 mg/m$^2$ BID + TMZ 135 mg/m$^2$ (D1-5 Q28D) | RP2D established (veliparib 65 mg/m$^2$); primary endpoint (OS compared to historical controls) not met [129] |
| ACNS1721 NCT03581292 | Veliparib | II | Active not recruiting | 115 (est.) | Newly diagnosed pediatric HGG | Veliparib 65 mg/m$^2$ + RT ➔ veliparib 25 mg/m$^2$ BID + TMZ 135 mg/m$^2$ (D1-5 Q28D) | EFS |
| ADVL1411 NCT02116777 | Talazoparib | I/II | Completed | 40 | Recurrent pediatric solid tumors | Talazoparib (dose escalation or RP2D) + TMZ (dose escalation or RP2D) | RP2D established (talazoparib 0.6 mg/m$^2$ BID D1, QD D2-6 Q28D + TMZ 30 mg/m$^2$ QD D2-6 Q28D); of 13 subjects with CNS tumors, there were 1 PR and 5 SD, including 3 prolonged SD [130] |

Abbreviations: *BID*, twice daily; *EFS*, event-free survival; *est.*, estimated; *HGG*, high-grade glioma; *ORR*, overall response rate; *OS*, overall survival; *PFS-6*, 6-month progression-free survival; *PD*, pharmacodynamics; *PK*, pharmacokinetics; *PR*, partial response; *QD*, daily; *RANO*, response assessment in neuro-oncology; *RP2D*, recommended phase II dose; *RT*, radiotherapy; *SD*, stable disease; *WBRT*, whole brain radiotherapy

newly diagnosed or recurrent IDH1/2-mutant glioma in young adults, also with a phase 0 component to evaluate intratumoral drug concentration. Talazoparib is being tested in combination with carboplatin in recurrent HGG with IDH1/2 mutations or other DDR deficiencies, using low-dose single-fraction whole brain radiotherapy to improve drug brain penetration (TAC-GReD trial). AZD9574 is being tested in recurrent IDH1/2-mutant non-enhancing glioma in module 2 of the CERTIS1 trial (NCT05406700). Finally, two phase 0 trials (NCT05406700 and NCT05076513) are investigating brain penetration of niraparib and biomarkers of drug response in IDH1/2-mutant glioma.

## Glioblastoma trials of PARP inhibitors in combination with TMZ and/or radiotherapy

The preclinical findings suggesting that PARP inhibition can induce radiosensitization and mitigate TMZ resistance in glioblastoma models have been a predominant focus of PARP inhibitor trials in CNS tumors, with multiple different PARP inhibitors being tested in a variety of different regimens. Veliparib was the first PARP inhibitor to be combined clinically with radiotherapy and TMZ in the treatment of newly diagnosed GBM, but was found to have unacceptable dose-limiting hematologic toxicities in combination with concurrent chemoradiation even when given at a low dose of 10 mg twice daily (4 of 12 patients with dose-limiting thrombocytopenia) and even with de-escalation to every other week administration of veliparib (3 of 6 patients with dose-limiting hematological toxicity) (NCT00770471) [113]. Three subsequent trials have thus combined veliparib with radiotherapy or TMZ independently but overall have yielded negative results. Veliparib in combination with TMZ was investigated in a phase I/II trial in patients with recurrent GBM previously treated with TMZ but failed to improve 6-month PFS (NCT01026493) [114]. More recently, the randomized phase II VERTU trial investigated veliparib and radiotherapy followed by adjuvant veliparib and TMZ, with standard concurrent radiotherapy and TMZ followed by adjuvant TMZ as control arm, in patients with newly diagnosed MGMT promoter-unmethylated GBM [115•]. There were similar toxicity and health-related QOL outcomes between arms, but no improvement in survival compared to historical benchmarks. Of note, the trial was non-comparative in design and insufficiently powered to detect moderate differences in survival. Finally, the complementary Alliance A07112 trial, a large randomized placebo-controlled trial investigating the addition of veliparib to adjuvant TMZ in newly diagnosed MGMT promoter-methylated GBM, found no significant improvement in OS or PFS with veliparib [116•]. An unplanned analysis suggested that concurrent veliparib may limit the emergence of TMZ resistance in subsets of cancers, but this remains to be further investigated. Correlative translational studies from both the VERTU and Alliance trials, including expression or polymorphisms of DNA repair genes, have yet to be reported.

Olaparib has been tested in several GBM trials, starting with the OPARATIC trial, which evaluated the pharmacokinetics, safety, and tolerability of olaparib and TMZ for recurrent GBM. As with veliparib, olaparib exacerbated TMZ-related hematological toxicity, but dose reduction of olaparib to 150 mg 3 days/week was determined to be tolerable with daily TMZ 75 mg/m$^2$ [105••]. Olaparib was detected in all tumor core and margin specimens at doses sufficient for in vitro radiosensitization, despite failing to cross the blood–brain barrier in preclinical models. The PARADIGM study performed dose escalation of olaparib with

radiotherapy in patients with newly diagnosed GBM who were not eligible for standard chemoradiation. In this setting, olaparib was well tolerated at doses up to 200 mg twice daily, which notably are higher than those achievable in patients receiving radiotherapy to extracranial sites [117]. Ongoing trials are testing olaparib with both TMZ and radiotherapy to determine optimal dosing. PARADIGM-2 is a phase I study stratified by MGMT promoter methylation status evaluating concurrent and adjuvant olaparib with radiotherapy and TMZ in the MGMT-methylated cohort and with radiotherapy alone in the MGMT-unmethylated cohort [118]. Contemporaneously, the OLA-TMZ-RTE study is dose-escalating olaparib in combination with the conventional Stupp regimen [3] in newly diagnosed unresectable or partially resectable GBM [119]. Both PARADIGM-2 and OLA-TMZ-RTE have planned correlative studies of candidate predictive biomarkers including analysis of DNA repair pathways.

Pamiparib, niraparib, fuzuloparib, and NMS-293 are currently in early phase studies. Pamiparib was studied in combination with radiotherapy and/or TMZ in a phase I/II trial in newly diagnosed or recurrent GBM (NCT03150862). Pamiparib at a dose of 60 mg twice daily was generally well tolerated and resulted in a modified disease control rate of 69.8% in the upfront setting and an ORR of 9.1% in the recurrent setting, supporting further evaluation of these combinations [120, 121]. An ongoing phase 0 study with exploratory phase II component is comparing pharmacokinetics and intratumoral drug exposure of pamiparib versus olaparib, with patients displaying a pharmacokinetic response going on to receive concurrent PARP inhibitor, radiotherapy, and TMZ (NCT04614909). A phase I study of niraparib in advanced cancer established a maximum tolerated dose (MTD) of 40 mg daily with TMZ and showed activity in one subject with GBM (NCT01294735) [122], while two ongoing phase II studies are investigating full-dose niraparib alone or in combination with radiotherapy for recurrent GBM (NCT05297864, NCT04715620). Finally, fuzuloparib and NMS-293 are being tested in combination with TMZ in recurrent GBM in phase II and I/II trials (NCT04552977, NCT04910022).

## PARP inhibitor-immunotherapy trials

To date, the majority of clinical data regarding the efficacy of combined PARP inhibition and ICB has come from trials in patients with extracranial solid tumors. Early results have indicated the combination of PARP inhibition and ICB is generally well tolerated with evidence of anti-tumor activity in a subset of patients with germline BRCA1/2 mutations and relapsed ovarian carcinoma and HER2-negative metastatic breast cancer [123–126].

There is emerging data on combined PARP inhibition and ICB in glioma, with several clinical trials currently in progress. In a phase 2 basket trial of olaparib in combination with durvalumab in IDH-mutant solid tumors (NCT03991832), early interim results from the glioma arm ($N$ = 9) showed the combination is generally well tolerated although there was limited anti-tumor activity with only 1 patient demonstrating a partial response and a median PFS of 2.5 months [127]. A non-randomized phase II trial is investigating the combination of pembrolizumab with olaparib and TMZ in patients with recurrent gliomas (NCT05188508). This trial includes patients with grade II and III IDH-mutated gliomas as well as IDH wild-type gliomas with genetic mutations in HR genes. A recently initiated randomized phase II trial is studying

pembrolizumab, olaparib, and TMZ in recurrent GBM (NCT05463848). This trial includes a surgical "window-of-opportunity" in which a cohort of patients will receive treatment before and after surgical resection allowing for evaluation of the immunomodulatory effects in the tumor microenvironment.

### Pediatric brain tumor PARP inhibitor trials

A Pediatric Brain Tumor Consortium (PBTC) phase I trial of veliparib and TMZ was performed to evaluate the pharmacokinetics and MTD of veliparib in combination with TMZ in recurrent pediatric brain tumors (PBTC-027). As in the adult setting, dose reductions were required of TMZ due to high hematological toxicity, and the RP2D was veliparib 25 mg/m$^2$ twice daily and TMZ 135 mg/m$^2$ daily [128]. This study was followed by the PBTC-033 phase I/II trial in upfront DIPG in which veliparib 65 mg/m$^2$ twice daily was combined with radiotherapy followed by adjuvant veliparib and TMZ at the previously established RP2D. The treatment was tolerated, but the study was closed at interim analysis due to lack of survival benefit compared with historical controls [129]. This regimen is now being tested in newly diagnosed pediatric HGG without H3K27M mutations in ACNS1721, with the hypothesis that drug entry and efficacy may differ between brainstem and hemispheric HGG. Planned exploratory analyses will investigate associations of tumor genomic, transcriptomic, and epigenetic alterations and germline alterations in HRD and energy metabolism genes with treatment response and outcome. Finally, talazoparib was investigated in combination with TMZ in a large study of recurrent pediatric solid tumors including CNS tumors (ADVL1411). Results revealed promising activity in CNS tumors with 1 PR and 5 SD, including 3 prolonged SD, in 13 subjects with CNS malignancies, which may prompt further study particularly given the relatively poor blood–brain barrier penetration of talazoparib and the low dose of TMZ used in the study [130].

## Toxicity considerations

PARP inhibitors are generally well tolerated as monotherapy, with fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea), and hematological changes (anemia, thrombocytopenia, and neutropenia) being the most common side effects. Adverse event rates are comparable across the different approved PARP inhibitors [131]. In CNS trials, PARP inhibitors are also relatively well tolerated in combination with partial brain radiotherapy at doses comparable to standard monotherapy regimens [115•, 117]. In contrast, concurrent PARP inhibitor and alkylating chemotherapy exacerbate hematological toxicity, requiring significant dose reductions to 20–25% of standard monotherapy doses and/or intermittent dosing strategies. Thus, one critical issue being addressed in early phase studies is whether dose reductions necessary for co-treatment with TMZ will be sufficient to yield active intratumoral drug concentrations and ultimately clinical benefit.

## Future perspectives

PARP inhibitors have revolutionized cancer therapy for BRCA-deficient cancers and confer benefit in tumors harboring other HR defects or more generally

displaying platinum sensitivity. In addition, this potential is now recognized to expand to other BRCAness phenotypes and to open the door for novel combination strategies in HR-proficient cancers. In CNS tumors, there is strong preclinical evidence that PARP inhibitors can target tumors with altered pathways related to HR or replication stress and can synergize with standard brain cancer therapies. However, early results from clinical trials testing monotherapy olaparib in IDH1/2-mutant tumors and veliparib combined with radiotherapy or TMZ in GBM and pediatric HGG have been disappointing. These results suggest that PARP inhibitors alone in non-BRCA-mutant tumors may be insufficient and that clinically active drug delivery, which must include penetration of both enhancing and non-enhancing tumor, remains a challenge in malignant brain tumors. A variety of next-generation PARP inhibitors with potential for greater efficacy (with enhanced PARP trapping or PARP1 selectivity) or improved brain penetration are currently under investigation. In addition, advances in drug delivery across the blood–brain barrier, for example, using nanoparticles or convention-enhanced delivery, may allow for more effective PARP inhibitor treatment strategies [132–134]. Finally, accumulating preclinical data also suggests a role for combining PARP inhibitors with other DNA damage response modulators, for example, ATR or CHK1 inhibitors [38, 40, 135]. Altogether, the use of PARP inhibitors in the treatment of primary CNS tumors remains promising and carefully designed trials incorporating validated biomarkers and tissue endpoints will be critical for their success.

## Declarations

### Conflict of Interest

S. Gueble and J. Vasquez declare that they have no conflicts of interest. R. Bindra reports grants and personal fees from Modifi Bio, outside the submitted work. In addition, R. Bindra has a patent 62/344,678 pending to Yale.

### Human and Animal Rights and Informed Consent

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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