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NEURO-ONCOLOGY (P. WEN, SECTION EDITOR)

Novel Therapies for Glioblastoma

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Abstract

Purpose of Review Glioblastoma (GBM) is the most common malignant primary brain tumor, and the available treatment options are limited. This article reviews the recent preclinical and clinical investigations that seek to expand the repertoire of effective medical and radiotherapy options for GBM.

Recent Findings Recent phase III trials evaluating checkpoint inhibition did not result in significant survival benefit. Select vaccine strategies have yielded promising results in early phase clinical studies and warrant further validation. Various targeted therapies are being explored but have yet to see breakthrough results. In addition, novel radiotherapy approaches are in development to maximize safe dose delivery.

Summary A multitude of preclinical and clinical studies in GBM explore promising immunotherapies, targeted agents, and novel radiation modalities. Recent phase III trial failures have once more highlighted the profound tumor heterogeneity and diverse resistance mechanisms of glioblastoma. This calls for the development of biomarker-driven and personalized treatment approaches.

Keywords Glioblastoma · Checkpoint inhibitors · CAR T cells · PARP inhibitors · Radiosensitizers · Radiation

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor, but survival remains poor despite aggressive multimodal treatments. The current standard of care, consisting of maximal surgical resection followed by combined radiation (RT) and temozolomide (TMZ), has remained unchanged since 2005 [1]. Since then, only two therapies have been FDA approved: bevacizumab, initially approved through the accelerated approval program, and tumor-treating fields [2, 3]. Nevertheless, there are continuous efforts to improve survival outcomes that explore multimodal approaches. Here we provide an overview of the emerging therapeutic concepts for GBM spanning immunotherapy, targeted therapy, radiosensitizers, and radiotherapy.

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Immunotherapy

Immunotherapy harnesses the immune system to recognize, target, and kill tumor cells. Efforts in immunotherapy have been most successful in tumors with high tumor mutational burden (TMB) but have yet to yield breakthroughs in GBM. GBM has low TMB despite its profound heterogeneity, rendering it an intrinsically immunologically quiet disease. GBMs are frequently within an immunosuppressive environment that downregulates antigen presentation and disengages infiltrating immune cells [4, 5]. Furthermore, immunotherapies can lead to inflammation within the intracranial space which may result in severe treatment-limiting neurological complications due to increased vasogenic edema, autoimmune encephalitis, and cytokine release syndrome [6, 7].

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Nevertheless, various immunotherapies are explored with the goal to stimulate the immune response against GBM. Table 1 provides an overview of currently ongoing key phase II and III immunotherapy trials within the USA.

Checkpoint Inhibitors

Binding of cytotoxic T lymphocyte antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), which are expressed on immune cells, to their corresponding ligands CD80 or PD-L1/2 on tumor cells, results in reduced T cell activation and proliferation. This allows tumor cells to evade detection and elimination by cytotoxic T cells. Thus, blocking these checkpoint interactions by PD-1/PD-L1- and CTLA-4-targeting antibodies may promote a more effective T cell response against the tumor. While tumor PD-L1 expression has emerged as a potential biomarker for sensitivity to PD-1 blockade in other cancers, expression levels are only detectable in a subset of GBM tumors, vary greatly in different studies, and depend on the PD-L1 assays used [8, 9]. Early attempts to study the combination of PD-1 and CTLA-4 inhibition were complicated by high toxicity but found favorable survival compared with historical controls [10•]. Based on these results, the phase III CheckMate 143 trial evaluated the efficacy of nivolumab compared with bevacizumab in patients with recurrent GBM (rGBM). While the study failed to demonstrate a survival benefit in the nivolumab treatment arm over bevacizumab, there was a small subset of patients that

Table 1 Immunotherapy—ongoing (not yet recruiting, recruiting, or active) multicenter phase II and phase III trials with US locations

Category	Target	Agent	Disease	Trials (phase)
Checkpoint inhibitor	PD-1	Cemiplimab	Newly diagnosed	NCT03491683 (I/II),
			Recurrent	NCT04006119 (II)
		Nivolumab	Newly diagnosed	NCT04195139 (II), NCT02617589 (III), NCT02667587 (III)
			Recurrent	NCT02017717 (III), NCT03452579 (II), NCT03743662 (II)
			Recurrent	NCT02327078 (I/II)
		Pembrolizumab	Newly diagnosed	NCT03018288 (II)
			Recurrent	NCT03661723 (II), NCT03797326 (II), NCT02798406 (II)
	PD-L1	Avelumab	Newly diagnosed	NCT02968940 (II),
		Durvalumab	Newly diagnosed	NCT02336165 (II)
			Recurrent	NCT02336165 (II)
	CTLA-4	Ipilimumab + nivolumab	Newly diagnosed	NCT03367715 (II)
		Ipilimumab + nivolumab	Recurrent	NCT02017717 (III)
	IDO	Indoximod	Newly diagnosed	NCT04047706 (I)
		Epacadostat	Recurrent	NCT02327078 (I/II)
Peptide vaccine	Autologous gp96-associated peptides	HSPPC-96 ± pembrolizumab	Newly diagnosed	NCT03018288 (II)
		HSPPC-96 ± bevacizumab	Recurrent	NCT01814813 (II)
	Onco-mimics of TAAs and TSNs	EO2401 + nivolumab	Recurrent	NCT04116658 (I/II)
	gpB and pp65	VBI-1901	Recurrent	NCT03382977 (I/II)
	WT1	DSP-7888 + bevacizumab	Recurrent	NCT03149003 (II)
	Survivin	SurVaxM	Newly diagnosed	NCT02455557 (II)
DC vaccine	Autologous TAAs	AV-GBM-1	Newly diagnosed	NCT03400917 (II)
	pp65	pp65-DC	Newly diagnosed	NCT02465268 (II)
Viral therapy	IL-12	Ad-RTS-hIL-12 + cemiplimab	Recurrent	NCT04006119 (II)
Direct oncolytic virus	Defective Rb/p16 pathway	Ad5-DNX-2401 + pembrolizumab	Recurrent	NCT02798406 (II)
	CD155	PVSRIPO	Recurrent	NCT02986178 (II)

PD-1 programmed cell death protein 1, *PD-L1* programmed death-ligand 1, *CTLA-4* cytotoxic T lymphocyte-associated protein 4, *IDO* indoleamine 2,3-dioxygenase, *gp* glycoprotein, *HSPPC-96* heat shock protein peptide complex-96, *TAAs* tumor associated antigens, *TSNs* tumor-specific neoantigens, *WT1* Wilms tumor gene 1 protein, *DC* dendritic cell, *IL-12* interleukin 12, *Rb* retinoblastoma, *CD155* poliovirus receptor

experienced durable treatment response to nivolumab [11•]. A separate phase III trial, CheckMate-498, also failed to meet its primary overall survival (OS) endpoint when evaluating radiation and nivolumab versus radiation and temozolomide for patients with MGMT-unmethylated newly diagnosed GBM (nGBM) (NCT02617589) [12]. The CheckMate-548 trial evaluates the addition of nivolumab vs placebo to standard-of-care radiation and temozolomide in MGMT-methylated GBM patients. Preliminary results did not show a statistical difference in progression-free survival (PFS) between treatment arms, but observation of study subjects is ongoing to evaluate for differences in OS (NCT02667587) [13]. The accompanying correlative studies in these national clinical trials are investigating biomarkers that may identify patients who are likely to respond to checkpoint blockade. One emerging predictor of treatment response may be the mutational load of the individual tumor, as responses to checkpoint inhibition have been reported in patients with germline mutations in DNA mismatch repair (MMR) enzymes [14, 15]. There is emerging data suggesting that neoadjuvant administration of PD-1 antibodies prior to resection of rGBM may induce an antitumor immune response and possibly improve outcomes [16].

Chimeric T Cell Receptors

Tumor-specific T cells can be generated by genetically modifying autologous T cells to express chimeric antigen receptor (CAR) constructs. Upon binding to their respective surface-exposed tumor antigen, CAR-T cells proliferate and activate an immunostimulatory cascade, resulting in cytotoxic attack on the antigen-bearing tumor cell. Early studies targeting a variety of tumor antigens have demonstrated the overall feasibility and safety of CAR-T therapy [17–20]. In a phase I trial evaluating epidermal growth factor receptor variant III (EGFRvIII)–directed CAR-T, tissue analyses from post-CAR-T surgical intervention found that most subjects had specific loss or decreased expression of EGFRvIII [20•]. Such antigen escape mechanisms may limit the durability of responses to CAR-T therapy but also provide evidence of the successful targeting of EGFRvIII. Recently, bispecific T cell engagers (BiTEs) have been proposed as a solution against antigen escape. These bicistronic constructs target EGFRvIII but then recruit untransduced bystander T cells against wild-type EGFR [21••]. CAR-T BiTEs demonstrated minimal toxicities and antitumor activity against heterogeneous tumors, highlighting a promising avenue for future developments in CAR-T therapy.

Vaccines

Vaccine strategies facilitate immune recognition by stimulating an antigen-specific effector T cell response against tumor-specific antigens (TSAs) or tumor-associated antigens (TAA). The inaugural EGFRvIII peptide vaccine, rindopepimut, showed impressive responses in early-phase studies, but failed to demonstrate survival benefit in a phase III evaluation of nGBM, possibly due to antigen escape in the tumor [22]. Of note, a phase II study of bevacizumab with rindopepimut in rGBM demonstrated encouraging results over the placebo arm. However, validation in larger clinical trials is warranted before more definite conclusions can be drawn [23].

SurVaxM is a peptide vaccine targeting survivin, a member of the inhibitor of apoptosis protein family [24]. A single-arm phase II study found benefits in both PFS and OS and, consequently, a prospective randomized trial is planned [25••]. Other vaccine strategies rely on personalized target antigen selection and/or inclusion of multiple peptides and have demonstrated favorable safety profiles with evidence of T cell response against tumor antigens [26, 27••, 28].

In addition to the peptide vaccines described above, dendritic cell (DC) vaccines rely on autologous DCs that are activated, e.g., by exposure to tumor lysate ex vivo. Data from a phase III trial investigating DCVax, an autologous tumor lysate-pulsed DC vaccine, suggest that survival may be improved compared historical controls. However, data from the treatment vs placebo arm of this study have not yet been unblinded and there was a high crossover rate into the treatment arm, thereby complicating interpretation of the study result [29•]. Other DC vaccines targeting multiple antigens or proteins derived from cytomegalovirus (CMV), which have been found to selectively re-activate in immunosuppressed conditions such as in GBM, are also actively explored [30, 31, 32••, 33].

Viral Therapy

Viral-mediated gene therapy involves the selective delivery of a gene of interest using viral vectors. Toca-511 encodes for a deaminase that locally transforms externally administered Toca FC to 5-fluorouracil that locally depletes tumor and immunosuppressive myeloid cells [34]. While Toca-511/-FC led to encouraging results in early clinical trials, it failed to demonstrate survival benefit in a phase III trial of rGBM [35]. In contrast, VB-111 delivers a pro-apoptotic chimeric protein into angiogenic endothelial cells [36]. A phase II trial examining a primed regimen of VB-111 demonstrated survival benefit in rGBM, but results were not supported in the unprimed phase III study [37]. Currently, a phase II trial involving Ad-RTS-hIL-12 is underway after encouraging preliminary results (NCT04006119) [38]. Ad-RTS-hIL-12 is an adenoviral gene vector that delivers recombinant human interleukin-12 (hIL-12). Transcription of the hIL-12 transgene only occurs in the presence of the activator ligand, veledimex, which is administered orally.

In contrast to gene therapies that are being delivered via viral vector, other approaches use direct administration of oncolytic viruses that selectively replicate in tumor cells to elicit cytotoxic effects and stimulate the immune response. PVSRIPO, an attenuated polio-rhinovirus chimera, recognizes the poliovirus receptor CD155 which is widely expressed in neoplastic cells. Early studies demonstrated safe intratumoral infusion of PVSRIPO and encouraging survival [39]. DNX-2401, a replication-competent adenovirus that uses tumor-specific integrins as an entry point to exert oncolytic effects, demonstrated dramatic responses in a phase I dose escalation trial [40]. Both therapies are now undergoing phase II evaluation alone or in combination with checkpoint blockade (NCT02798406, NCT02986178).

Targeted Therapies

Despite the vast heterogeneity of genetic and epigenetic alterations seen in GBM, there are three hallmark pathways that are commonly dysregulated and represent possible targets for therapies: receptor tyrosine kinase (RTK)/Ras/phosphoinositide 3-kinase (PI3K), p53, and retinoblastoma (Rb) [41]. Alterations within these pathways may be targeted using small molecule inhibitors or monoclonal antibodies with the goal of inhibiting these driver pathways. Currently, numerous clinical studies are ongoing (Table 2).

Small Molecule Inhibitors

Small molecule inhibitors targeting RTKs, notably EGFR, have been extensively studied in GBM. EGFR amplifications are detected in 50% of cases, with approximately half of these expressing the EGFRvIII mutation [42]. Despite successes of EGFR inhibitors in other cancers, including in intracranial disease, studies have failed to show a survival benefit in GBM [43], possibly because of relatively low intratumoral drug levels. In addition, the molecular heterogeneity of GBM and activation of multiple RTK pathways simultaneously may limit the efficacy of single target regimens as downstream signaling gets activated through parallel pathways [44]. Nonetheless, there are small subsets of GBMs with driver mutations such as BRAF V600E that show response to RAF or RAF/MEK inhibitors, or oncogenic fusions such as NTRK, that also have high response rates [45–47].

Small molecule inhibitors with multitarget inhibitory effects may circumvent these issues of heterogeneity and pathway redundancy but may also lead to increased toxicity. Regorafenib, an oral multikinase inhibitor, inhibits multiple targets involved in tumor angiogenic, stromal and oncogenic pathways [48]. A randomized phase II trial comparing regorafenib to lomustine found increased OS in recurrent disease, warranting further clinical evaluation [49•]. Currently, regorafenib is being evaluated in both nGBM and rGBM as part of GBM AGILE, a phase II/III international platform trial with Bayesian adaptive randomization designed to evaluate multiple treatment combinations (NCT03970447) [50••].

ONC201 is a small molecular antagonist of dopamine receptor D2/3 (DRD2/3) and mitochondrial caseinolytic protease P activator that induces p53-independent cell apoptosis [51, 52]. In a phase II trial in molecularly unselected rGBM, single agent ONC201 was well-tolerated and led to a near complete objective response in a patient possessing a H3-K27M mutation [53]. Since then, several clinical studies are evaluating ON201 for patients with progressive H3K27M mutant gliomas (NCT03295396, NCT02525692, NCT02525692).

Another target of interest is the cyclin dependent kinase (CDK) family. Efforts to target cyclin CDK 4/6 were driven by the observation that many brain cancers overexpress cyclin D1, which binds CDK 4/6 to cause dysregulated G1/S progression. Several small molecule inhibitors of CDK4/6 have been investigated in GBM, including palbociclib, ribociclib, and abemaciclib. Trials of single agent palbociclib and ribociclib failed to demonstrate any survival difference in rGBM despite adequate tissue pharmacokinetics [54, 55••]. Preclinical models using abemaciclib demonstrated antitumor activity that was potentiated with TMZ and improved blood-brain barrier (BBB) penetrance compared with palbociclib [56]. Abemaciclib recently demonstrated intracranial benefit in metastatic breast cancer and is currently undergoing clinical evaluation in multiple trials for GBM (NCT02981940) [57]. Abemaciclib is also being investigated as part of INSiGhT, another ongoing platform trial evaluating precision medicine approaches to GBM treatments (NCT02977780) [58••]. CDK 4/6 targeting therapy may synergize with checkpoint inhibition in glioblastoma, as was demonstrated in a recent preclinical model [59].

Monoclonal Antibodies

Monoclonal antibodies (mAbs) represent another class of molecules than can be used to inhibit tumor driver pathways. Included in this class is bevacizumab, which targets vascular endothelial growth factor (VEGF) and blocks angiogenesis. Bevacizumab received accelerated FDA approval after encouraging phase I/II results [2], but two phase III studies only found extended PFS and no OS benefit [60, 61]. Nevertheless, bevacizumab is often used to manage symptomatic disease given its antiedema effect and has received full FDA approval to treat rGBM. Monoclonal Abs directed against EGFR have also been developed, notably cetuximab, which failed to show survival benefits in a phase II trial [62]. One limiting factor in the therapeutic efficacy of mAbs may be incomplete BBB penetration, which is exacerbated by their large size.

Table 2 Targeted therapy—ongoing (not yet recruiting, recruiting, or active) multicenter phase II and phase III trials with US locations

Target	Agent	Disease	Trials (phase)
2-gp1	Bavituximab	Newly diagnosed	NCT03139916 (II)
ANG/TIE2	Trebananib	Recurrent	NCT01609790 (II)
BRAFV600E/MEK	Dabrafenib + trametinib	Newly diagnosed	NCT03919071 (II)
		Recurrent	NCT02684058 (II)
	Encorafenib + binimetinib	Recurrent	NCT03973918 (II)
BTK	Acalabrutinib	Recurrent	NCT02586857 (II)
CDK 4/6	Abemaciclib	Newly diagnosed	NCT02977780 (II)
		Recurrent	NCT02981940 (II)
cMET/VEGFR	Cabozantinib	Recurrent	NCT02885324 (II)
CSF1	Pexidartinib	Newly diagnosed	NCT01790503 (I/II)
CXCR4	USL-311	Recurrent	NCT02765165 (I/II)
DRD2/ClpP	ONC201	Recurrent	NCT03295396 (II), NCT02525692 (II)
EGFR/HER	Neratinib	Newly diagnosed	NCT02977780 (II)
EGFR/HER2/SRC	Tesevatinib	Recurrent	NCT02844439 (II)
GSK-3b	9-ING-41	Recurrent	NCT03678883 (I/II)
	Belinostat	Newly diagnosed	NCT02137759 (II)
HIF-2a	PT2385	Recurrent	NCT03216499 (II)
mIDH1	Olutasidenib	Recurrent	NCT03684811 (I/II)
mTOR	nab-Sirolimus	Newly diagnosed	NCT03463265 (II)
		Recurrent	NCT03463265 (II)
	Everolimus	Newly diagnosed	NCT01062399 (I/II)
mTOR/DNA-PK	CC-115	Newly diagnosed	NCT02977780 (II)
MnSOD mimetic	BMX-001	Newly diagnosed	NCT02655601 (II)
PARP	Olaparib	Recurrent	NCT03212274 (II), NCT02974621 (II)
	Pamiparib	Newly diagnosed	NCT03150862 (I/II)
		Recurrent	NCT03150862 (I/II), NCT03914742 (I/II)
	Veliparib	Newly diagnosed	NCT02152982 (II/III)
PI3K	Buparlisib	Recurrent	NCT01349660 (I/II)
PI3K/mTOR	Paxalisib	Newly diagnosed	NCT03522298 (II)
Proteasome	Marizomib	Newly diagnosed	NCT03463265 (II)
		Recurrent	NCT03463265 (II), NCT02330562 (I/II)
ROS1/TRK/ALK	Repotrectinib	Unspecified	NCT04094610 (I/II)
VEGFR	Lenvatinib + pembrolizumab	Recurrent	NCT03797326 (II)
	Cediranib	Newly diagnosed	NCT01062425 (II)
		Recurrent	NCT02974621 (II)
	Tanibirumab	Recurrent	NCT03856099 (II)
VEGFR/TIE2/MANY OTHERS	Regorafenib	Newly diagnosed	NCT03970447 (II/III)
		Recurrent	NCT03970447 (II/III)
XPO1	Selinexor	Recurrent	NCT01986348 (II)
TROP-2	IMMU-132	Recurrent	NCT01631552 (I/II)

2-gp1 beta-2 glycoprotein 1, *BTK* Bruton's tyrosine kinase, *ANG* angiopoetin, *TIE2* angiopoetin-1 receptor, *CDK* cyclin-dependent kinase, *cMET* tyrosine-protein kinase MET, *VEGFR* vascular endothelial growth factor receptor, *CSF1* colony-stimulating factor 1, *CXCR4* CXC chemokine receptor type 4, *DRD2* dopamine receptor D2, *ClpP* caseinolytic protease P, *EGFR* endothelial growth factor receptor, *HER* human epidermal growth factor receptor, *EphB4* ephrin type B receptor 4, *GSK-3b* glycogen synthase 3 beta, *HDAC* histone deacetylase, *HIF-2a* hypoxia inducible factor 2 alpha, *mIDH1* mutant isocitrate dehydrodrenase 1, *mTOR* mammalian target of rapamycin, *DNA-PK* DNA-dependent protein kinase, *MnSOD* mitochondrial manganese superoxide dismutase, *PARP* poly(ADP-ribose) polymerase, *PI3K* phosphoinositide 3-kinase inhibitor, *ROS1* proto-oncogene tyrosine-protein kinase ROS, *TRK* tropomyosin receptor kinase, *ALK* anaplastic lymphoma kinase, *TROP-2* tumor-associated calcium signal transducer 2, *XPO1* exportin 1, *ADC* antibody-dependent conjugate

Antibody Drug Conjugates

Antibody drug conjugates (ADCs) are composed of an antibody linked to a cytotoxic compound, enabling targeted delivery of biologically active payloads. ADCs can be classified into cytotoxins, immunotoxins, or radioimmunotherapies depending on whether the accompanying compound is an antimitotic agent, bacterial toxin, or radioisotope, respectively. Depatuxizumab mafodotin (Depatux-M, ABT-414) was designed to bind cells with EGFR amplifications and release monomethyl auristatin F, an anti-microtubule toxin that halts cell proliferation and causes cell death. A phase II trial (INTELLANCE 2) studying Depatux-M in EGFR amplified rGBM suggested improved survival when combined with

TMZ. However, the phase III trial in nGBM (INTELLANCE 1) was halted after an interim analysis showed no survival benefit (NCT02573324) and is no longer being developed [63]. A second EGFR-targeting ADC, ABBV-221, was evaluated in a phase I trial in advanced solid tumors, including GBM, that was terminated due to safety concerns (NCT02365662) [64]. ABBV-321, a third-generation ADC, uses a pyrrolobenzodiazepine payload and is being evaluated in a phase I trial that includes patients with GBM (NCT03234712).

Radiosensitizers

Radiosensitizers refer to a group of targeted therapeutics that enhance the efficacy of radiation. DNA repair pathways promote resistance to ionizing radiation, which depends on the induction of DNA damage for cytotoxic effects, and thus have emerged as targets for radiosensitization. TMZ is a well-recognized radiosensitizer that is administered concurrently with radiation and can stabilize radiation-induced DNA damage. Through activation of the MMR and ataxia telangiectasia-mutated (ATM) pathways, TMZ causes cells to arrest in the more susceptible G2/M cell phase and enhances the DNA-damaging effects of radiation [65]. While the survival benefit of adding TMZ to radiation is well established and remains the current standard of care for glioblastoma, recurrence rates remain high and therefore continue to fuel interest in the development of other radiosensitizers.

Poly-(ADP-Ribose)-DNA Polymerase (PARP) Inhibitors

PARP inhibitors target poly-(ADP-ribose)-DNA polymerase (PARP), a family of proteins implicated in the base excision repair (BER) pathway and have primarily been used in the treatment of homologous repair (HR) deficient cancers. While GBMs do not generally exhibit HR deficiency, the observation that PARP-inhibitory effects are limited to replicating cells only has fueled interest in PARP inhibitors to potentiate tumor control from radiation while sparing normal tissues [66]. Clinical evaluation of several PARP inhibitors in glioblastoma were limited by poor BBB penetration and hematological toxicities, but recent work has demonstrated that olaparib, veliparib, and pamiparib can reach therapeutic levels in situ [67–69]. Two phase I/II trials studying olaparib are underway: the PARADIGM trial, in which nGBM patients receive olaparib with hypofractionated RT, and PARADIGM-2, in which nGBM patients receive olaparib and standard fractionated RT with or without TMZ (CRUKD/13/034, CRUKD/16/010). Early results from both studies demonstrated that radiation with olaparib alone is well-tolerated and, if dosed intermittently, when combined with TMZ [67]. Preliminary results from the VERTU trial, a randomized phase II evaluation in MGMT-unmethylated nGBM, found chemoradiation with TMZ and veliparib to be well tolerated but did not improve outcomes [69]. Veliparib is also being evaluated in a phase III trial in MGMT-methylated nGBM with adjuvant temozolomide and the results will be available soon (NCT02152982).

DNA-PK Inhibitors

DNA-dependent protein kinase (DNA-PK) mediates DNA repair through both non-homologous end-joining (NHEJ) and HR pathways, and its deregulation is associated with radioresistance in multiple cancers [70]. Inhibition of DNA-PK has been shown to downregulate elements of double strand break (DSB) repair and sensitize GBM cell lines to ionizing radiation [71, 72]. CC-115, a dual of inhibitor of mammalian target of rapamycin (mTOR) kinase and DNA-PK, was recently shown to infiltrate GBM tissue to near plasma levels after oral administration [73]. As such, a phase II study examining the use of CC-115 with concurrent RT is underway (NCT02977780).

ATM/ATR Inhibitors

DSBs result in cell cycle arrest and subsequent DNA repair through activation of the ATM and ataxia telangiectasia and Rad3-related (ATR) pathway. Consequently, upregulation of either ATM or ATR signaling has been associated with radioresistance in GBM stem cells [74, 75]. Preclinical GBM models have suggested that the efficacy of ATM inhibition is dependent on the presence of p53 mutations but have been unable to decouple whether this dependency is due to p53 or G1/S checkpoint deficiency [76]. A phase I dose-escalation trial assessing concurrent AZD1390, a novel ATM inhibitor, and intensity-modulated radiation (IMRT) is currently recruiting patients and has treatment arms for nGBM and rGBM (NCT03423628).

Radiotherapy

Conventional RT for GBM relies on a standard dose fraction size of 180–200 cGy delivered using photon beams. Current standard-of-care treatment involves the concurrent use of TMZ and RT to doses of 60 Gy to the post-operative bed [1]. In elderly and poor performance status patients, a modified hypofractionated RT (> 2 Gy fractions) approach is used and has yielded fewer adverse events and less treatment burden. Dose-escalation attempts to improve control with photon radiation have resulted in increased tissue injury with no additional survival benefit [77]. As a result, there is a growing interest to explore non-conventional RT sources and regimens.

Particle Therapy

Proton beam therapy (PBT) and carbon ion RT (CIRT) exhibit a signature Bragg peak pattern that results in lower dose distal to the target of interest and sharp lateral penumbra [78]. As a result, nearby organs at risk are spared to a greater extent and target volumes can be reduced, decreasing the risk for treatment-related neurocognitive decline. While the benefit of reducing treatment toxicities is limited by the poor survival in GBM, the ability to avoid radiosensitive normal tissues may alleviate immunosuppression typically seen in radiation and bolster responses to immunotherapy [79].

Dose-escalation studies of PBT in both nGBM and rGBM disease have been evaluated**.** PBT boosts after photon radiation have yielded cumulative doses of up to 96.6 Gy with some grade 3 toxicities [80, 81]. The authors note that the majority of recurrences were outside the 90-Gy equivalent (GyE) area, suggesting that higher doses are required to control disease**.** PBT has also been shown to be safe and yield favorable survival when patients with difficult-to-treat recurrent GBM, as defined by large tumor sizes or proximity to dose-limiting organs, were re-irradiated with and without TMZ [82•]. Currently, a randomized phase II trial is comparing the efficacy of frontline PBT to dose-escalated photon IMRT in nGBM with overall survival as a primary endpoint (NCT02179086). A separate phase II study is underway, evaluating cognitive failure and local control after IMRT or PBT (NCT01854554). The results from these studies will be crucial in informing whether PBT may play a role in frontline disease management.

Carbon ions are speculated to be reduce hypoxia-induced tumor resistance and were found to be effective against cell-lines radioresistant to conventional RT [83, 84]. CIRT is further associated with more double-strand breaks and, compared with photon radiation, is less dependent on the timing of treatment. However, this also raises concerns for higher rates of cell kill in normal tissue given the slow speed of treatment, during which movement may introduce uncertainty [85]. It is important to note that there are currently only a few centers worldwide capable of delivering CIRT which may preclude widespread evaluation and provision of CIRT for GBM [86].

Early studies have suggested a favorable toxicity profile for intracranial CIRT. When delivered concurrently with TMZ, toxicity was infrequent, and simulated survival curves demonstrated a potential survival benefit [87]. As such, the phase II CLEOPATRA trial was designed to compare CIRT or PRT boost to macroscopic tumor following concurrent photon therapy and TMZ for nGBM. The results of the study have yet to be published, even though the trial has not actively accrued patients since 2013 (NCT01165671). The CINDERELLA trial, a randomized phase I/II study, was designed to compare CIRT against fractionated stereotactic RT in recurrent gliomas [87]. Recent results from the dose-escalation phase I portion of the trial demonstrated safe re-irradiation with 10–16 fractions of 3 Gy [88•].

Zap-X Gyroscopic Radiosurgery

Zap-X is a self-contained linear accelerator (LINAC) radiation device dedicated to intracranial and cervical spine stereotactic radiosurgery (SRS) [89]. The creators of Zap-X Radiosurgery Systems claim that treatment verification can be performed using a closed-loop system, as opposed to open-loop algorithms used in conventional SRS, that examines the beam after it has exited the patient in real time, thus providing an independent quality assurance step throughout treatment [90]. As a self-shielded system that eliminates the need for traditional radiation vaults, the installation of Zap-X can be simplified, which can reduce the cost of SRS [91]. A 3-MV LINAC, lower than the 6–15-MV range used in conventional SRS, is used as the source of radiation [92]. The Zap-X Gyroscopic Radiosurgery platform was FDA-cleared in 2017 and began its first clinical treatments of brain tumors in 2019. However, no clinical results have yet to published.

GammaTile

GammaTile was recently FDA-cleared for the treatment of newly diagnosed and recurrent brain tumors. GammaTile involves the permanent placement of encapsulated radioactive Cesium-131 seeds in the surgical cavity. Results of patients with recurrent tumors treated to 60 Gy demonstrated the feasibility and safety of this approach (NCT03088579) [93, 94].

FLASH Radiotherapy

FLASH RT uses ultra-high dose rates (> 30–100 Gy/s vs. conventional 0.1 Gy/s) and has been hypothesized to reduce radiation-induced toxicities while maintaining tumor responses [95]. Preclinical models showed that ultra-high dose rates reduced reactive oxygen species, neuroinflammation, and rates of cognitive deficits compared with conventional dose rates [96, 97]. In studies using GBM cell lines, FLASH and conventional RT yielded similar tumor control [98]. The ability to reduce normal tissue injury may allow for higher maximum tolerated doses and improve therapeutic and cognitive outcomes. To date, only a single reported patient has undergone FLASH RT for the treatment of subcutaneous T cell lymphoma which resulted in a durable response with minimal toxicities [99•]. Despite promising preclinical models demonstrating the neuroprotective effects of the FLASH RT effect, reports exhibit considerable heterogeneity as some studies were unable to induce the FLASH effect and found increased toxicity levels [100, 101].

Laser Interstitial Thermal Therapy

Though not considered a form of radiation, laser interstitial thermal therapy (LITT) has emerged as potential cytoreductive technique for patients who are not candidates for open craniotomies. In LITT, a laser-tip probe is inserted into the centroid of the tumor to deliver low-powered thermal energy. The probe is then controlled by the surgeon and guided by real-time MRI thermography [102]. The first in-human trial evaluating LITT used the NeuroBlate System in rGBM [103]. Median survival was encouraging at 316 days. Of ten patients treated, two suffered neurological deterioration due to the treatment, possibly due to unexpected patterns of thermal energy deposition during the procedure. LITT is currently undergoing investigation in conjunction with other pharmacotherapies for recurrent GBM (NCT03341806, NCT03022578, NCT03277638). In the newly diagnosed setting, a phase I feasibility study on frontline LITT using the NeuroBlate System was terminated due to failure to enroll (NCT02880410).

Conclusion

Glioblastoma is the most common malignant brain tumor and, despite significant efforts and a multitude of preclinical investigations and clinical studies, has no effective therapies and poor prognosis. Ongoing efforts focus on various immunotherapeutic strategies, targeted agents, and novel radiotherapy approaches. Despite the successes in early-phase clinical studies, a number of immunotherapies and targeted therapies have failed to be of significant benefit. In the face of tremendous tumor heterogeneity and multifaceted resistance mechanisms in glioblastoma, this calls for an improved patient stratification in future clinical trials based on molecular tumor subtypes and refinement of possible biomarkers as predictors of response to the respective therapy. Especially in patients with recurrent GBM, optimal patient stratification based on molecular tumor markers may be challenging because current tumor specimens are rarely available and the molecular tumor characteristics may have changed since the last surgical tissue specimen was obtained due to treatment and as part of the natural evolution of glioblastoma pathology [104, 105]. Therefore, non-invasive or minimal-invasive ways to assess biomarker status are required to form a dynamic personalized approach tailored to changing tumor characteristics. Lastly, it is difficult to decouple whether negative results of many studies are due to pharmacodynamic (low efficacy despite target inhibition) or pharmacokinetic (low therapeutic levels due to BBB) failure. In addition, the synergistic effects of combining immunotherapy, targeted therapy, and radiation may prove crucial to targeting GBM, which is well-known to develop resistance to and progresses on any of the currently available therapies.

Compliance with Ethics Guidelines

Conflict of Interest E. Liu has nothing to disclose.

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Dr. Kurz reports that she is the principal investigator on two immunotherapy studies that have been mentioned in this work (NCT02968940, NCT03367715).

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- • Of importance
- •• Of major importance

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