Ongoing Research in Brain Tumor Therapies Provides Hope for the Future

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A SIGNIFICANT AMOUNT OF research into the treatment of brain cancers is being conducted, and with multiple strategies being evaluated simultaneously, hope for future effective treatment options is increasing.

Primary brain cancers are aggressive, resulting in low survival rates, and pose significant challenges to effective treatment.[1] Therapeutic strategies include surgery, chemotherapy, and radiotherapy. Intracranial surgery carries significant inherent risk, and it is difficult to achieve adequate removal of tumor cells because of the difficulty of separating tumor tissue from normal tissue. There are many barriers to effective chemotherapeutic approaches, such as inadequate blood-brain barrier (BBB) penetration, poor drug stability, and adverse events (AEs) due to nonspecific targeting. Moreover, radiotherapy is hampered by tumor cells being inherently resistant to ionizing radiation.[1] Additionally, brain tumors exhibit several characteristics conducive to treatment resistance, such as epigenetic dysregulation, genetic anomalies, cellular plasticity, immunosuppression, and metabolic adaptability.[2]

Because of the numerous mechanisms by which brain tumors resist therapies, many treatment avenues are currently under investigation. **Tabitha M. Cooney, MD**, director of the Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic of the Dana-Farber Cancer Institute and assistant professor of pediatrics at Harvard Medical School, likened today's research to that of the development of chemotherapies for childhood leukemia. "Current research is a modern-day adaptation of the mid-1900s, when childhood leukemia was completely fatal and combinations of different conventional chemotherapies were required to make a difference," Cooney said. "At that time, that approach seemed 'crazy.' The current era will involve combinations across treatment types such as targeted, immune, and conventional therapies."

Glioma

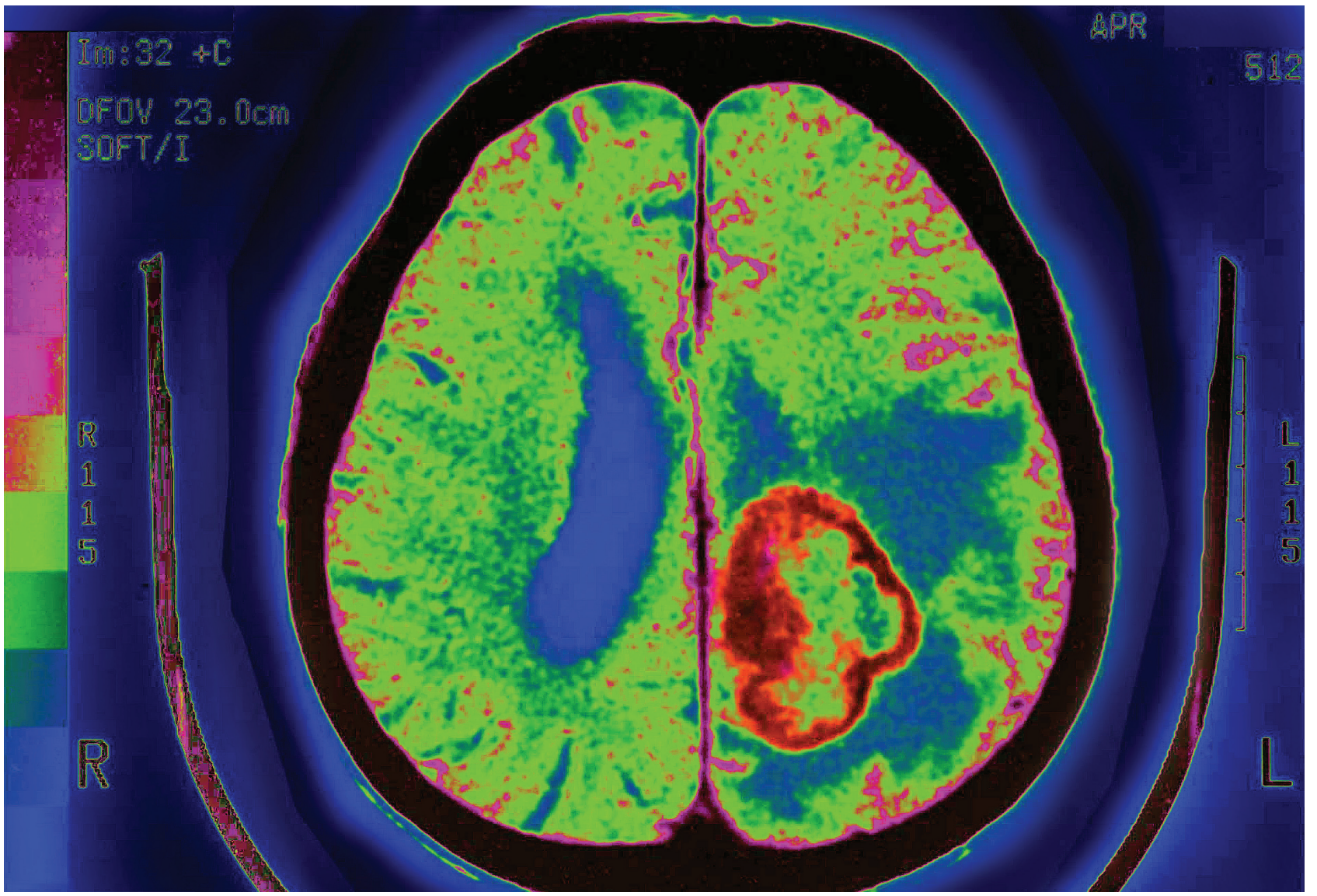
^{186}RNL

^{186}RNL is a nanoliposome containing radioactive rhenium 186 (^{186}Re) that delivers high-energy β and γ particles to a tumor and is administered by convection-enhanced delivery (CED).[3] A recent phase 1/2a dose-escalation trial (ReSPECT-GBM, NCT01906385) evaluated a single administration of ^{186}RNL in patients with recurrent malignant glioma. The 23 included patients who had poor prognostic indicators, a mean of 1.6 prior treatments, and a mean tumor volume of 8.1 mL, and they were spread across 8 dose cohorts receiving 1.0 mCi to 22.3 mCi in 0.6 mL to 8.8mL.[3] The median overall survival (OS) in patients receiving more than 100 Gy mean absorbed radiation dose to the tumor was 22.9 months (95% CI, 8.8-42.3) compared with 5.6 months (95% CI, 1.6-9.4) for patients receiving 100 Gy or less. The median OS for the overall population was 9.4 months (95% CI, 5.8-13.2).[3] A recommended phase 2 dose of 22.3 mCi/8.8 mL is recommended for gliomas less than 15 mL in volume for an upcoming phase 2b trial.

Anlotinib

Anlotinib is a tyrosine kinase inhibitor with numerous targets, including vascular endothelial growth factor receptor (VEGFR) 2, fibroblast growth factor receptor 1, and platelet-derived growth factor receptor β.[4] Preclinical studies identified that the activity of anlotinib against glioblastoma cells, which was enhanced by the addition of temozolomide (Temodar).[4] At the 2022 European Society for Medical Oncology (ESMO) Congress, results were presented from an open-label, single-arm, phase 2 trial of anlotinib in patients with histologically confirmed high-grade glioma who had progressed after surgery followed by radiotherapy and temozolomide (Temodal) chemotherapy (NCT04822805).[5] Once-daily oral anlotinib 12 mg was administered for 14 days every 3 weeks until disease progression or unacceptable

Although few treatment options are currently available to treat patients with various primary brain tumors, primarily glioma and glioblastoma multiforme, ongoing research with various agents are providing hope and promise for new options to be approved in the years to come.



toxicity occurred. Complete responses (CRs) were observed in 4 of 26 evaluable patients at the data cutoff date, with another 7 experiencing partial responses (PRs), for an objective response rate (ORR) of 42.3% (11/26). A disease control rate of 88.5% was observed with 12 patients presenting with stable disease (SD).[5] The median progression-free survival (PFS) was 8.3 months (95% CI, 3.5-13.1), and the 6-month PFS rate was 64.9%. Any-grade AEs were reported in 19 patients (73.1%), and grade 3 events occurred in 6 patients (23.1%). No AEs greater than grade 3 were observed. These results reveal promising anti-tumor activity and adequate tolerability for patients with recurrent high-grade glioma.[5] Several phase 2 studies evaluating anlotinib in glioblastoma are underway.

Dabrafenib and Trametinib

The combination of the BRAF inhibitor dabrafenib (Tafinlar) and the MEK inhibitor trametinib (Mekinist) has been developed specifically for cancers harboring *BRAF* V600 mutations, including low- and high-grade glioma in adults and pediatric low-grade glioma (pLGG).[6] Results from the phase 2, open-label ROAR basket trial evaluating dabrafenib and trametinib across numerous *BRAF* V600E–mutated cancers in adult patients (NCT02034110) indicated clinically meaningful activity in patients with recurrent or refractory low- and high-grade glioma. The ORR among patients with high-grade glioma was 33% (15/45; 95% CI, 20%-49%), including 3 CRs and 12 PRs, at a median follow-up of 12.7 months.[6] An ▸

Current research in targeted therapies, immunotherapies, and other new treatment modalities are offering hope for effective future treatment options for patients with brain tumors.

ORR of 69% (9/13; 95% CI, 39%-91%), with 1 CR, 6 PRs, and 2 minor responses was observed in patients with low-grade glioma at a median follow-up of 32.2 months. AEs of grade 3 or worse were observed in 53% (n = 31) of patients and included fatigue (9%), headache (5%), and neutropenia (5%).[6]

Dabrafenib with trametinib has also shown efficacy in patients with pLGG, according to data recently presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting. The randomized, phase 2 study included patients aged between 1 and 17 years with *BRAF* V600 mutation–positive gliomas treated in the first-line setting (NCT02684058). Dabrafenib plus trametinib achieved an independently assessed overall response rate of 47% (95% CI, 35%-59%) compared with 11% (95% CI, 3%-25%) in the standard-of-care carboplatin plus vincristine arm (odds ratio, 7.2; 95% CI, 2.3-22.4; $P < .001$).[7] Dabrafenib plus trametinib also produced a clinical benefit rate (CBR; CR + PR + SD at ≥ 24 weeks) of 86% (95% CI, 76%-93%) and a median PFS of 20.1 months (95% CI, 12.8-not estimable) compared with a CBR of 46% (95% CI, 30%-63%) and a median PFS of 7.4 months (95% CI, 3.6-11.8) in the carboplatin plus vincristine arm (HR, 0.31; 95% CI, 0.17-0.55; $P < .001$;).[7] Additionally, fewer grade 3 or greater AEs were observed with dabrafenib plus trametinib (47% vs 94%, respectively) along with fewer discontinuations due to AEs (4% vs 18%). The most frequent AEs in the investigational arm were pyrexia (68%), headache (47%), and vomiting (34%).[7] First-line treatment of pLGG with dabrafenib and trametinib has the potential to significantly improve outcomes compared with traditional chemotherapy based on these significant results.

DSP-0390

Gliomas support rapid growth by upregulating cholesterol synthesis, and increased expression of genes associated with cholesterol synthesis correlates with poorer patient survival. DSP-0390 is a small-molecule inhibitor of emopamil-binding protein that selectively kills glioblastoma cells by inhibiting de novo cholesterol synthesis.[8] In preclinical research, DSP-0390 has shown significant antitumor activity in orthotopic xenograft models of human glioblastoma. A phase 1 trial in patients with recurrent, high-grade glioma (NCT05023551) is under way in the United States and Japan. The dose-expansion phase will enroll 20 to 40 patients with measurable WHO grade IV glioblastoma that has progressed after primary therapy, who will receive once-daily oral DSP-0390.[8]

Tovorafenib

Tovorafenib (DAY101) is an oral, small-molecule, type II pan-RAF inhibitor that is highly selective and able to penetrate the central nervous system.[9] In addition to targeting the *BRAF* V600E mutation, tovorafenib also targets *RAF* gene fusions; however, unlike type I BRAF inhibitors, tovorafenib does not result in activation of the MAPK pathway via RAS-dependent paradoxical activation. In a phase 1 trial (PNOC014) of tovorafenib in pediatric patients with recurrent/progressive low-grade glioma, a clinical benefit was observed in 7 of 8 patients with tumors containing *RAF* fusions. The drug was also well tolerated.[9] Initial results from the ongoing, open-label, single-arm phase 2 FIREFLY1 trial (NCT04775485; PNOC026) of tovorafenib in pediatric patients with *RAF*-altered recurrent or progressive LGG appear promising, according to a news release from earlier this year. An overall response rate of 64% and CBR of 91%, with 14 PRs and 6 patients with SD, were observed in 22 patients evaluable by Response Assessment for Neuro-Oncology (RANO).[10] Tumor shrinkage of 19% to 43% was noted in all 6 patients with SD. Both patients with *BRAF* fusions and the *BRAF* V600E mutation who had previously received MAPK-targeted therapy were among the responders, and all responders remained on therapy.[10] A global phase 3 clinical trial (FIREFLY-2/LOGIC) is set to evaluate the efficacy and safety of tovorafenib monotherapy compared with investigator's choice of 1 of 3 chemotherapy options in patients with newly diagnosed pLGG with an activating *BRAF* mutation.

Regarding progress in pLGG, Cooney said, "Pediatric oncologists now understand low-grade glioma is a chronic illness that places significant burden on patients and families and this era of RAF inhibition is very exciting and appealing. Not only are we trying to discern the short-term benefit of these agents, but also if we can achieve long-term benefits to quality of life and patient burden resulting in the ability to thrive in their normal educational and social attainments."

Cooney believes the outlook is positive for targeted agents in general. "We're in early phases and I think in the decade ahead we will improve our understanding of incorporating the right molecularly targeted agents with the right patients and becoming more sophisticated and assertive with potential combination strategies."

Glioblastoma Multiforme

L19TNF

The pro-inflammatory cytokine tumor necrosis factor (TNF) has the potential to initiate an immune response against tumor cells, according to the results of the phase 1/2 GLIOMOON trial (NCT03779230), but its application has been hindered by significant AEs when dosed to achieve desired activity levels.[11] L19TNF was developed in the hopes of specifically targeting tumor cells by fusing an antibody (L19) that binds an epitope of fibronectin specific to the extracellular matrix of tumor cells. Recently, results from a preclinical trial of L19TNF in combination with PD-1 inhibitors, the VEGF inhibitor bevacizumab (Avastin), or the chemotherapy lomustine, were presented at ESMO 2022.[12] In 2 immunocompetent orthotopic glioma mouse models, L19TNF with lomustine resulted in the strongest increase in lymphoid cells infiltrating the tumor and robust synergistic anti-tumor activity, ultimately curing the most tumors in mice, and no drug activity was observed in immunodeficient mice. The combination of L19TNF and lomustine has entered a phase 1/2 trial (GLIOSTAR; NCT04573192) and appears to be well tolerated in the first few patients dosed. PRs (2/6) and durable SD have been observed so far, including in patients with the inherently negative prognostic indicator of an unmethylated *MGMT* promoter. Of the 2 patients with a PR, 1 had a 98% reduction in tumor size from baseline and the other had an 83% reduction.[12]

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—Tabitha M. Cooney, MD

Veliparib

PARP is an important component of the DNA damage repair mechanism. Resistance to temozolomide is common in patients with brain tumors, and DNA damage repair is 1 mechanism implicated in the development of resistance.[12] Therefore, combining temozolomide with the PARP inhibitor veliparib has the potential to counteract these mechanisms and has proved significantly beneficial in glioblastoma patient-derived xenografts with *MGMT* promoter hypermethylation.[13] Unfortunately, recent results from the phase 2/3 Alliance A071102 trial (NCT02152982) assessing veliparib or placebo with adjuvant temozolomide in patients with newly diagnosed glioblastoma harboring *MGMT* promoter hypermethylation were unremarkable. No significant differences between the combination of temozolomide with veliparib and temozolomide with placebo were observed among the 421 patients receiving treatment, in terms of median OS (28.1 vs 24.8 months, respectively; $P = .15$) or median PFS (13.2 months vs 12.1 months; $P = .31$).[13] However, the veliparib combination did result in a trend in extended survival following retreatment with temozolomide at first recurrence, with a median post-recurrence OS of 17.0 months vs 12.6 months in the placebo arm ($P = .03$).[13] Therefore, the addition of veliparib to temozolomide therapy may still benefit a subset of patients with glioblastoma; identifying which patients will benefit, though, remains a challenge.

Atezolizumab

Overall, immune checkpoint inhibitors (ICIs) have demonstrated little efficacy against glioblastoma. Previously published results indicated that atezolizumab (Tecentriq) in combination with temozolomide and radiation therapy provided modest efficacy in 60 patients with newly diagnosed glioblastoma and unknown *MGMT* methylation status.[14] In post hoc analyses of a phase 1/2 trial (NCT03174197), investigators continued to search for markers identifying patients who benefited from the addition of atezolizumab. Unfortunately, T-cell levels and PD-L1 expression did not correlate with outcome; however, glial fibrillary acidic protein emerged as a potential negative predictive biomarker.[15] Results of further analysis of data from this trial, in terms of baseline tumor genome and gut microbiota, were recently presented at ASCO 2022. Three sequencing methods (whole exome [WES], somatic copy number alteration [SCNA], and RNA-seq) identified *EGFR* aberrations as being associated with relatively worse median OS compared with patients with *PTEN* alteration–rich tumors, and patients with identified *IDH1* mutations exhibited the longest median OS.[16] A gene set enrichment analysis identified a group of tumor genes with roles in lymphocyte activation and immune response that was enriched in patients with longer OS ($P < .01$). Distinct fecal bacterial taxa were also associated with OS (*Ruminococcus spp.*) and treatment response (*Eubacterium spp.*), warranting further investigation.[16]

Selinexor

Exportin-1 (XPO1) is a nuclear export protein that is overexpressed in several solid tumors, which is associated with poor outcomes. Inhibition of XPO1 reactivates tumor suppressor proteins and reduces translation of oncogene mRNAs.[17] The oral medication selinexor (Xpovio) is a selective inhibitor of XPO1 that readily crosses the BBB and is effective in various solid and hematologic tumors.[17] Selinexor was recently evaluated in 76 adults with recurrent glioblastoma and a Karnofsky performance status of 60 or greater in the phase 2 KING trial (NCT01986348), which was later terminated by the sponsor. Selinexor was administered at various doses, with patients planning to undergo cytoreductive surgery receiving up to 3 doses twice weekly (n = 8). Patients not undergoing surgery received dosages of 50 mg/m^2 twice weekly (n = 24), 60 mg twice weekly (n = 14), or 80 mg once weekly (n = 30). The 6-month PFS rate, the primary end point, was highest in the patients who received 80 mg once weekly (17%; 95% CI, 7.78%-38.3%), with a RANO-response rate of 10% (95% CI, 2.1%-26.5%).[17] A single fatal AE occurred, and 26 patients (34%) across all treatment groups experienced serious AEs. An exploratory analysis found that patients with mutations in *PDX1, EP400,* or *DOCK8* tended to survive longer than others.[17] Ongoing clinical trials in glioblastoma are evaluating selinexor in combination with temozolomide (NCT04216329) and standard-of-care chemotherapy (NCT04421378).

NT-I7

Radiotherapy and temozolomide therapy often result in extended systemic lymphopenia, which reduces patient survival.[18,19] NT-I7 (efineptakin alfa) is a first-in-class, long-acting recombinant interleukin-7 agent that has been shown to reverse lymphopenia, increase cytotoxic CD8-positive T cells (both systemically and within the tumor), and improve survival in mice with orthotopic gliomas.[18,19] In an ongoing phase 1/2 trial in patients with high-grade gliomas treated with chemoradiation (NCT03687957), NT-I7 was well tolerated. Treatment resulted in increased cytotoxic T cells and natural killer cells along with rapid increases in key cytokines and chemokines.[18] Because of the promising outlook for NT-I7, the FDA granted orphan drug designation to NT-I7 for the treatment of glioblastoma.[20]

VBI-1901

Over 90% of glioblastomas express the cytomegalovirus antigens, including gB and pp65, which are often targeted by CD4 and CD8-positive T cells, respectively.[21] VBI-1901 is a vaccine immunotherapeutic consisting of a gB/pp65-enveloped virus-like particle plus adjuvant. A phase 2a trial (NCT03382977) is evaluating VBI-1901 in patients with first-recurrent glioblastoma. Administration route is based on adjuvant: intradermal for GM-CSF (n = 10) or intramuscular for $ASO1_B$ (n = 10). OS rates at 12 months were 60% for the GM-CSF arm and 70% for the $ASO1_B$ arm, with 18-month rates of 30% and approximately 30% to 40%, respectively.[21] One patient in the GM-CSF arm was progression free at 2 years, and their tumor had reduced in size by 93% from baseline. Immunologic tolerance was not observed with prolonged monthly dosing.[21] Because of promising trial results, the FDA has granted fast track and orphan drug designations to VBI-1901 for glioblastoma treatment.[21,22] Additionally, the phase 2a study has been expanded, and a VBI-1901 arm has been added to the phase

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Brain Tumors

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2 INSIGhT trial (NCT02977780) evaluating numerous therapeutic interventions for glioblastoma.[22]

VAL-083

VAL-083, a bifunctional DNA-targeting agent, causes cell death by creating interstrand DNA cross-links at N7-guanine, culminating in lethal double-strand breaks.[23] Additionally, VAL-083 acts as a radiosensitizer against glioblastoma cancer stem cells in vitro and is not affected by *MGMT*-mediated chemoresistance per in vitro and in vivo studies.[23] A recent phase 2 trial (NCT03050736) evaluated VAL-083 in combination with radiation therapy in newly diagnosed, *MGMT*-unmethylated glioblastoma. The initial dose-escalation stage evaluated patients across doses of 20, 30, or 40 mg/m^2/day for 3 days every 21 days in combination with standard radiation treatment. In the second, dose-expansion stage, up to 20 additional patients were enrolled at the 30 mg/m^2/day dose (total n = 25).[23] The median PFS for all patients was 9.3 months (95% CI, 6.4-12.0), with a median OS of 19.6 months (95% CI, 14.0-22.4). As of the data cutoff, 18 patients (62.1%) had died. Concentrations of VAL-083 in the cerebrospinal fluid were as high or higher compared with plasma.[23] VAL-083 was granted fast track designation by the FDA earlier this year.[24]

Neuroblastoma

The humanized anti-GD2 monoclonal antibody naxitamab (hu3F8; Danyelza) is approved by the FDA in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) as consolidation treatment for chemorefractory high-risk neuroblastoma (HR-NB) that is in remission.[25] However, the approval does not include patients with progressive disease, for whom response to treatment is rare. A recent phase 2 trial (NCT03189706) evaluated the combination of naxitamab, irinotecan, temozolomide, and sargramostim, aka "HITS," in patients with HR-NB.[25] HITS was administered to 8 patients with HR-NB refractory to induction chemotherapy and 82 patients with up to 6 previous relapses.[25] CRs were observed in 26% of patients, PRs in 11%, and SD in 27%.[25] Objective responses were noted in 64% of all patients, with the following breakdown by patient subgroups: 25% of *MYCN*-amplified, 100% of refractory, 61% of relapsed, 64% previously receiving irinotecan and temozolomide, 68% previously receiving naxitamab, and 42% previously receiving dinutuximab, irinotecan, and temozolomide. No immunogenicity was observed.[25] These results indicate naxitamab is effective against chemoresistant HR-NB. This agent continues to be evaluated in phase 2 trials.

Other Brain Tumors

Paxalisib

The FDA recently granted orphan drug designation to paxalisib, a PI3K inhibitor that acts upstream of mTOR and easily crosses the BBB. Paxalisib is being investigated in malignant glioma (glioblastoma and diffuse intrinsic pontine glioma).[26] Recently, results were presented at the American Association for Cancer Research 2022 Annual Meeting from 2 different combinations of paxalisib in atypical teratoid/rhabdoid tumors. Paxalisib extended median survival from 40 to 54 days (P = .001) in orthotopic xenograft models of atypical teratoid/rhabdoid tumors and exhibited synergistic effects with TAK580 (a pan-RAF inhibitor that also easily crosses the BBB) to further slow tumor growth.[27] In a separate evaluation, paxalisib also behaved synergistically with the histone deacetylase 1/3 inhibitor RG2833 to decrease cell growth and increase apoptosis.[28] The investigators concluded that these paxalisib-based combinations would make excellent candidates in future clinical trials.

Sonodynamic Therapy

Use of low-intensity ultrasound in combination with sonosensitizers is a potential new method of eradicating tumor cells known as sonodynamic therapy.[29] However, achieving the right concentration of sonosensitizers within the tumor itself is a challenge. The FDA recently awarded orphan drug and fast track designations to Alpheus Medical's CV-01 sonodynamic therapy for the treatment of brain cancers.[29] A multicenter trial (NCT05362409) is currently recruiting patients with recurrent high-grade glioma to receive 5-aminolevulinic acid (5-ALA) solution orally as a sonosensitizer prior to CV-01 ultrasound, a treatment that will be repeated every 4 weeks.[30]

Cooney said sonodynamic therapy is a newer modality being considered across national trial developments in combination with epigenetic modifiers or immunotherapeutics. "I anticipate this approach being a part of our trial evaluations in the years ahead, but once safety, tolerability, and proper agents have been identified, the question becomes scalability."

Outlook

Although it appears there are no significant changes coming to the treatment landscape for brain tumors in the next couple of years, Cooney is hopeful for the future. "We've entered a hopeful era, to truly reduce morbidity for highly survivable tumors that we haven't seen before," she said. "For aggressive tumors we have hope that some of these agents will have a role to play, but that depends on our ability to become quite sophisticated and efficient in trial design and determining exactly what that role is and what the other players are."

In terms of improving trial design, Cooney discussed the importance of patient engagement in treatment protocols and evaluations. "We are trying to engage the patient and family communities much more in trial design to create protocols that will help us determine the activity of these drugs. Are they getting into the tumor space? What is the mechanism regarding local and systemic effects? This relies on a family's or patient's willingness to pursue tumor biopsies or serial [cerebrospinal fluid] collections, but it also speaks to the need for participant-reported outcomes via embedded surveys." Cooney believes these approaches will allow for more rapid and accurate assessments of the effects of these agents. **TT**

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