Deciphering Novel Molecular Targets in Neuro-Oncology: An Update

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ABSTRACT: Neuro-oncology is the study of brain and spinal cord neoplasms. Molecular targets and signaling pathways are pivotal in advancing modern healthcare, particularly in personalized medicine. Signaling pathways, which regulate cellular processes such as growth, division, and survival, are frequently dysregulated in cancer. Targeting these pathways has enabled the development of personalized therapies that improve efficacy while minimizing side effects. This approach has led to significant improvements in patient outcomes, reduced treatment toxicity, and a shift toward precision medicine, driving innovation in drug discovery. The integration of molecular targets and signaling pathways into clinical practice highlights their importance for enhancing patient care.

KEY WORDS: personalized therapies, neuro-oncology, drug discovery, precision medicine

I. INTRODUCTION

Neuro-oncology comprises fields that are associated with the study of benign and metastatic brain tumors but are not limited to disorders comprising the spinal cord and peripheral nervous system. This branch of medicine is constantly growing as new areas are being researched and developed.[1,2] Brain tumors are a myriad of different virulent tumors that are difficult to treat with regular treatment methods. Right now, molecular neuro-oncology is formulating new ways on how brain tumors can be treated by pinpointing oncogenic pathways for targeted therapy.[3] Primary brain tumors have many variables in terms of histology, genetics, and outcome which makes it difficult to have a proper diagnosis and treatment. According to the World Health Organization, a separate molecular classification system for CNS tumors has been beneficial.[4] The WHO CNS classification is a system developed by the World Health Organization to classify tumors of the CNS, including those of the brain and spinal cord. The fifth edition of this classification system published in 2021 defines over 40 tumor types and subtypes. The system is always periodically updated based on the latest advances. The changes in this classification are important because it change how CNS tumor patients are treated.[5] The 2021 classification introduced changes in nomenclature and grading and new tumors, particularly pediatric tumors are introduced. It emphasizes the importance of integrated diagnosis and layered reports.[5,6]

Every single brain tumor has its own unique clinical challenges. Despite having many technological advances, treatment options remain limited for certain brain tumors, especially for ones that need better-targeted therapies, because it makes them resistant to current treatment models. Management of brain metastases, or in other words the management of cancer cells from spreading from primary site to secondary one, involves a lot of strategizing and personalized approaches. The

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heterogeneity of the tumors poses a challenge in diagnosis because each individuals treatment will be different. Another major concern in neuro-oncology is the side effects that are present in therapies such as radiotherapy and chemotherapy. Accurate detections of brain tumors early on are important for better outcomes, but screening tools and other tools are not advanced enough yet. The integration of new therapies poses challenges too, because ensuring that they are used safely requires a lot of research and clinical trials.[7]

A molecular target is a molecule found within the neurons or brain tumor cells. Specific to neuro-oncology, there have been many advances in understanding the central nervous system. Glioblastoma is a group of primary malignant brain tumors that has a poor prognosis.[8] However, the options for diagnosis have always been limited, even with patients being diagnosed with radiotherapy and/or chemotherapy.[9] But, through new studies, molecular targeted therapies are achieving anticancer effects. This is due to several interlinked mechanisms that it can go through such as angiogenesis and inhibitions of cell proliferation.[10] It does this by interfering with specific molecules that block cancer growth. These therapies are approved by the US Food and Drug Administration (FDA).[11] The most common molecular targets are protein kinase 9 pathways, cell/cycle apoptosis pathways, and the least common pathways are wnt/β-catenin pathways (Table 1).[12] Molecular targeting differs from other therapies because they damage normal cell proliferation while trying to wipe out cancerous cells which is harmful and has many side effects on other parts of the human body.[13] Targeted therapies have indeed reached remarkable results for various cancer types.[11] Although this type of treatment helps patients, it is difficult for patients to receive personalized care because of the limited availability of different drugs, as they are quite specific and do not have a one-size-fits-all solution. Developing more targeted drugs takes time, so only a fraction of people get the actual treatment they need.[14]

TABLE 1: Some of the molecular targets of neuro-oncology

Drug	Molecular target	Cancer type	Ref.
Bevacizumab	VEGF	Glioblastoma	15
Nimotuzumab	EGFR		16
Temozolomide + Nivolumab and Radiotherapy	Unmethylated O6-methylguanine-DNA-methyltransferase (MGMT) promoter		17
Crizotinib	Anaplastic Lymphoma Kinase (ALK), ROS1, c-MET		22
Ipilimumab	Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)		24
Imatinib	BCR-ABL, c-KIT, and platelet-derived growth factor receptor alpha (PDGFRA)	Various cancers	18
Ivosidenib (IVO)	Mutant IDH1	Glioma	19
Erlotinib	EGFR	Non-small cell lung cancer (NSCLC) with brain metastases	20
Vemurafenib	BRAF V600E mutation	Pediatric brain tumors	21
Palbociclib	Cyclin-dependent kinases 4 and 6 (CDK4/6)	Medulloblastoma	23
Everolimus	Mammalian target of rapamycin (mTOR)	Diffuse intrinsic pontine glioma (DIPG), high-grade glioma (HGG)	25
Ribociclib	Cyclin-dependent kinases 4 and 6 (CDK4 and CDK6)		25

II. NEURO-ONCOLOGY TYPES

Primary brain tumors encompass a wide range of types, and they each affect different parts of the central nervous system.[26] There are over 100 primary brain tumors and each is then categorized as benign and malignant.[2] Benign brain tumors are not cancerous and slower-growing tumors. They have distinct borders, which means that they don't invade surrounding tissues or other parts of the body. The treatment is the removal of the tumor, or it may become malignant.[27]

Malignant tumors are the opposite of a benign brain tumor. They are cancerous and develop very fast. They have irregular borders and spread throughout the body with a process called metastasis. There are various treatment methods for malignant brain tumors, such as "surgery, radiotherapy, chemotherapy, immunotherapy, or a combination of therapies to prevent the cancerous spread."[27] Malignant brain tumors are harder to treat as they mostly only have a five-year survival rate of not greater than 35%.[28] The symptoms and complications almost always relate to the specific anatomical area the tumor affects. Some symptoms such as focal or lateralized symptoms include hemiparesis, which is weakness on one side, aphasia, which is difficulty with speech, and visual field deficits. These symptoms progress over many days or weeks. Sometimes, in cases of leptomeningeal disease, symptoms can involve multiple areas of the CNS. These are some uncommon symptoms, but there are common symptoms such as headaches, nausea and vomiting, mental changes, gait difficulties, cranial nerve palsies, and radicular pain.[26] Some of the most common types of tumors are described below.

A. Gliomas

Gliomas are the most frequent type of adult primary CNS tumors.[29] Subtypes are diffuse astrocytomas, oligodendrogliomas, and oligoastrocytomas. Glioblastomas, the most common tumor, are also the most aggressive form of astrocytoma.[2] Also, a small percentage of gliomas are linked to Mendelian disorders such as neurofibromatosis, tuberous sclerosis, and Li-Fraumeni syndrome. But now with more and more research, genomic studies have provided more insight that will help cure and improve success rates with biomarkers. Some are O6-methylguanine-DNA methyltransferase (MGMT) methylation, Isocitrate dehydrogenase (IDH) mutation, Glioma cytosine–phosphate–guanine (CpG) island methylator phenotype (G-CIMP).[30]

B. Astrocytomas

Astrocytomas are a type of glioma that originate from astrocytes, star-shaped cells in the CNS. They grow and spread in the brain, meaning they are diffusely infiltrative tumors, which make it much harder to cure as they are constantly spreading.[31] They are difficult to treat with even advanced histopathological tools. Because this type of glioma is very infiltrative, it is tough to differentiate it from other brain lesions. This response is more apparent when using less sensitive methods such as CT scans. Astrocytomas can mimic stroke-like symptoms, causing misdiagnosis. MRI is the best standard for brain tumor diagnosis, but because astrocytomas have such irregular shapes and growth patterns, it makes it challenging to tell. Because they rapidly progress, especially after initial misdiagnosis, it highlights the aggressive nature of this type of tumor. Even though basic MRI models produce profound knowledge on CNS brain tumors, contrast-enhanced MRI and advanced sequences such as perfusion or diffusion-weighted imaging are needed to obtain sufficient detail for diagnosis. It is needed for distinguishing astrocytomas from other CNS lesions. Taking this tumor out with complete surgical resection is often unsuccessful because it is constantly spreading. Along with all of this, these tumors are often resistant to standard therapies such as radiotherapy, chemotherapy, and other long-term management.[32] Either way, the role of MRI is crucial in diagnosis and management, and does is used to make as much headway as possible. It's used for initial detection, assessment of tumor location, and tumor grade evaluation. MRI shows enhancement patterns, edema (swelling), and/or necrosis (dead tissue), which are seen in more aggressive astrocytoma, and tumor borders. There are many advanced MRI techniques. To get insight on how the tumor affects surrounding brain tissue

diffusion tensor imaging (DTI) and functional MRI (FMRI) are used. MR spectroscopy and perfusion MRI measure biochemical changes in the brain and measure blood flow in the tumor, respectively.[33] According to demographics, the cerebrum, cerebellum, brain stem, and spinal cord are most likely to be affected by the percentage that is 63.8%, 4.8%, 3.5%, and 1.8%, respectively.

Symptoms vary depending on the location of the tumor, but they typically include seizures, headaches, and focal neurological deficits such as changes in motor function, sensory perceptions, or speech difficulties. The prognosis and survival rate also vary depending on age, tumor size, and tumor location.[34] Endothelial growth factor receptor vIII (EGFRvIII) is a mutant variant of the EGFR. This is most involved in the increase of astrocytoma cells. It has been studied for its role in promoting uncontrolled cell division and tumor growth. IDH1 (codon 132) and IDH2 (codon 172) mutations are key biomarkers. IDH-mutant DA is normally associated with better prognosis and survival whereas IDH-wild type DA is not, and is more aggressive.[35] PMMRDIA (Primary Mismatch Repair-Deficient IDH-Mutant Astrocytomas) are aggressive tumors found mostly in children and young adults, the average age being 14. Even with IDH mutations, the median survival is only 15 months. PMMRDIA has multiple mutations, and microsatellite instability (genetic abnormalities) is common.[36] Several other molecular markers have been tested but not limited to diffuse Astrocytomas associated with ATRX mutations, TP53 mutations, and MGMT methylation.[34]

C. Oligodendrogliomas

Oligodendrogliomas, or ODG are rare, widespread tumors that develop in the white matter in the brain. They can be classified into low-grade oligodendrogliomas and high-grade oligodendrogliomas.[37] The methods for grading low-grade and high-grade ODG's methods are based on traditional histology and not on well-established biomarkers, making it difficult for treatment. Just like astrocytomas, because they have various shapes and sizes, it causes difficulty in imaging the tumor, making it harder to treat.[38] Regarding growth, infiltrative growth patterns are more common in tumors with intact 1p/19q. Compared with tumors having 1o/19q loss, this type has much more infiltrative behavior. Either way, any of these types of tumors have infiltrative growth patterns, they just vary.[39] Survival rates get lower the higher the age and histologic tumor grade, making older patients face much more significant challenges.[40] For grade II oligodendrogliomas, the mean survival time was 74 months and for grade III, it was 39 months. Likewise, the mean age at diagnosis is 42 years for grade II, and for grade III, it is 49 years.[41] In the 2021 World Health Organization (WHO) Classification of Tumours of the Central Nervous System, oligodendrogliomas are specifically characterized by IDH mutations and 1p/19q co-deletion. They are required for diagnosis. These tumors are generally graded as WHO grade II or grade III. Grade II is low-grade, whereas grade II is anaplastic.[42] As for MRI scans for oligodendrogliomas, they are the key to diagnosing and managing the tumor. They are superior to CT scans in assessing tumor extent and cortical involvement. One of the main issues in diagnosing oligodendrogliomas is differentiating it from other forms of clear cell neoplasms even with all the newer technologies to help.[43] Hematoxylin-eosin stained slide assessment under a standard light microscope is what the diagnosis for this tumor relies on. The difficulty for diagnosis is also because there are mixed tumors with astrocytomas as well, making oligoastrocytomas tumors. They are clonal neoplasms, meaning it underwent some type of genetic mutation, and not two different tumors colliding.[44] Oligodendrogliomas have microscopic cells that migrate throughout the brain. So, even after surgical resection, it is still hard to get cured fully because of the leftover microscopic cells.[45] The symptoms of this tumor cannot be exactly pinpointed. It depends on where and how it progresses. The symptoms are mainly seizures or cognitive and/or deficits. It differs from low-grade oligodendrogliomas and high-grade oligodendrogliomas.[46]

D. Oligoastrocytomas

Oligoastrocytomas are classified as WHO grades II or III tumor that are a mixture of two neoplastic

cells found in oligodendrogliomas and astrocytomas.[47] Oligodendrogliomas need both *IDH*-mt and 1p/19q co-deletion. Astrocytomas are put into two categories, *IDH wild-type (IDH*-wt) and *IDH*-mt.[48] Astrocytomas have TP53 and ATRX mutations as well.[49] However, oligoastrocytomas are a subset of these two tumor cells mixed. Oligodendroglioma cells are in a honeycomb pattern in a uniform matter whereas astrocytomas have a looser structure. Oligoastrocytomas have both cell types in the tumor.[50] Based on studies, if the tumor is smaller than 5 cm, the survival outcomes and behavior resemble those of oligodendrogliomas, which tend to have a better prognosis. But in contrast, for tumors 5 cm or larger, survival patterns and aggressiveness are more like more aggressive astrocytomas,[51] the most seen symptom of this tumor is epileptic seizures, followed by fatigue[52] before the concept of oligoastrocytomas, the regimens of oligodendrogliomas and astrocytomas overlapped, making it hard to clearly determine the tumor. Because oligoastrocytoma is a mixture of two different tumor cells, the treatment approach is varied. Neuro-oncologists are more concerned with making sure that they choose the right therapy rather than focusing on the prognosis.[53] As per drugs to treat this, PCV, procarbazine, lomustine, and vincristine are three chemotherapy drugs that may help. In the RTOG 9802 trial, PVC combined with radiation therapy showed that there was a median of 13.3 years rather than the median of just 7.8 years for patients only undergoing radiation therapy. But, this is not set because there are different outcomes based on different subgroups of this tumor regarding IDH mutations and 1p/19q codeletion statuses.[54]

III. MOLECULAR TARGETS OF NEURO-ONCOLOGY

A molecular target in neuro-oncology specifically refers to a molecule found within the neurons or brain tumor cells. They are often a protein or a receptor.[55] There are many important signaling pathways, but some are more prominent than others. Signaling pathways or normally started by something called ligands.[56] Some of these targets include phosphatidylinositol-3-kinase (PI3K) Akt, mammalian target of rapamycin (mTOR), EGFR, vascular endothelial growth factor (VEGF) among others. Each of these targets does something different. PI3K/Akt and mTOR signaling pathways focus on aspects of cell growth and survival. PI3K/Akt pathway supports cell survival under environments with low nutrients, oxygen, and other conditions which makes it easier for cancer progression. mTOR mainly focuses on processes essential for cell growth, cell cycle progression, and metabolism, which is what makes these pathways go hand in hand.[57] EGFRs play a role in tissue development in organs such as the skin, liver, and gut. When this factor's signal is shared with other receptors, it amplifies the original signal causing cancer growth, which is why EGFR is associated with more aggressive tumor behavior.[58] Less aggressive gliomas are seen with IDH mutant gliomas.[59] There are different drugs for each of these pathways, for example, erlotinib targeting EGFR and bevacizumab targeting VEGF.[60] Conventional therapies such as surgery and chemotherapy do not suffice, and neuro-oncology is complicated. However, precision medication seems promising and is rapidly changing with new data incoming.[2,61]

A. Drug-Targeting Growth Factors

Drug-targeting growth factors are aimed at interfering with the molecular signaling pathways to reduce cell proliferation leading to cancer. Growth factor receptors are proteins found on the cell surface that leads to a bunch of different signals, but if dysregulated can cause problems in the cells causing cancer and also resist apoptosis, which is programmed cell death.[62] EGFR is associated with particularly aggressive tumors, which is why EGFR is more commonly expressed in many tumors because it is often overexpressed. Once EGFR is activated, it triggers a cascade of signaling events through several pathways such as the PI3K/AKT pathway, the MAPK/ERK pathway, and the JAK/STAT pathway. This in turn does a lot with cell survival, proliferation, metastasis, and angiogenesis, making it the perfect target to focus on. which is involved in cell survival and metabolism, which is why it is better to target EGFR rather than the pathways itself.[63] EGFR is part of the ErbB family of tyrosine kinase. This family also includes HER2/*neu* (erbb2), HER3 (erbB3),

and HER4 (erbB4).[64,65] Drugs such as gefitinib and erlotinib are classified as cancer therapies, specifically tyrosine kinase inhibitors, which can help reduce and inhibit tumors with EGFR. Although up to date, there have been five EGFR inhibitors, three being tyrosine kinase inhibitors and the others being antibodies such as Cetuximab, a monoclonal antibody.[66]

B. Drugs Targeting the Ras Signaling Pathway

The Ras signaling pathway is a critical communication system made with several regulators that regulate processes such as cell growth, differentiation, and survival.[67] The Ras family is a family of proteins of small GTPases, H-Ras, N-Ras, and the two K-Ras isoforms, K-Ras4A and K-Ras4B.[68] Ras is activated by growth factors or other signals. Ras proteins, in turn, transmit signals, primarily the MAPK and PI3K/AKT pathways, which can lead to either positive or negative effects on apoptosis.[69] These downstream pathways regulate cell cycle progression, apoptosis, and mechanisms that are critical to cell maintenance and function.[68] Cancer cells utilize Ras signaling pathways because the pathway is disrupted due to mutations that cause Ras proteins to be continuously active. That gives way to uncontrolled cell division and enhances the survival of cancer cells.[67] Because of this, it has been highlighted as a target, but directly targeting Ras proteins has been challenging because of the structure. This means that it makes it harder for drugs to effectively bind and inhibit them. Therefore, scientists target the processes and proteins that support Ras rather than Ras itself.[2] In cancers, the Ras pathway can be a driving force behind oncogenesis. This is because of mutated Ras proteins that are known as H-Ras, K-Ras, and N-Ras, which are the driving force behind oncogenesis, or upstream and downstream effectors leading to a dysregulated pathway.[70] Studies have estimated that cancers with Ras mutations can be seen in 19% of all cancer cases, with about 3.4 million new cases globally each year.[71] There are several drugs that target the Ras signaling pathway to inhibit it.

Farnesyltransferase inhibitors (FTIs) drugs block a key enzyme that supports Ras function but with a combination of other inhibitors.[72] A key process in Ras activity is called farnesylation. Faryeslyation is catalyzed by the enzyme farnesyltransferase, which is what FTIs try to inhibit.[73] FTIs were originally developed to block the activity of mutated Ras proteins[74]; however, more recent studies are showing that FTIs may target a different protein instead of Ras. Other drugs used for cancer treatment are Lonafarnib, a well-known drug for FTIs,[75] and Tipifarnib, which is undergoing clinical trials.[76] These drugs might be more effective for tumors where the normal (wild-type) Ras is overactive, rather than tumors with mutated Ras.[77] Other types of inhibitors are MEK and ERK inhibitors. Moreover, mainly what they do is block downstream signals that Ras proteins use to drive cell division, which disrupts tumor growth. The RAS-RAF-MEK-ERK pathway is one of the most important signaling pathways in cells and plays a major role in cell development by inhibiting MEK or ERK, therapies could block the last steps in the pathway, potentially preventing the cancerous cells from growing. Trametinib and cobimetinib are MEK inhibitors.[78] They are approved, but ERK inhibitors such as Ulixertinib (BVD-523) are still undergoing clinical trials.[79] However, studies have shown that cells may have developed resistance to MEK inhibitors that still rely on the MAPK pathway for their growth and survival.[80] Targeting later steps such as ERK could still work, which is why combining MEK and ERK inhibitors would be the best option.[81] It is, however, important to note that these drugs and approaches in general are still under active research (Fig. 1).

C. Drugs Targeting the Phosphoinositide 3′ Kinase (PI3K)/Akt Pathway

PI3K is a critical signaling cascade involved in carcinogenesis, proliferation, invasion, and metastasis of tumor cells.[82] This signaling pathway, including mTOR, is frequently overlapped with RAS, which means targeting any one of them will target this pathway as well, but they each have their mechanisms.[83] PI3KS are enzymes that modify lipid molecules by adding a phosphate group to the 3'-OH group of inositol phospholipids, producing PI(3,4,5)P3, a second messenger. When receptor

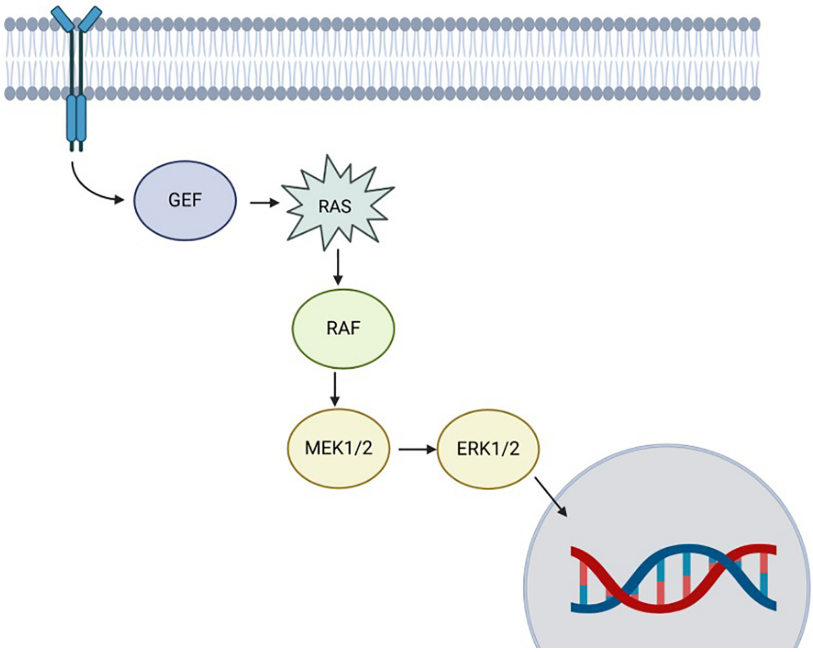

FIG. 1: The key steps in the Ras signaling pathway begins with the activation of a cell surface receptor by an external ligand. This activates the associated GTPase Ras through GEF. Once activated, Ras triggers a cascade of downstream signaling events, including the activation of the Raf-MEK-ERK kinase cascade, which regulates various cellular processes such as growth, differentiation, and survival. (Figure was generated using www.BioRender.com with an academic license.)

protein tyrosine kinases (RPTKs) are activated, PI3Ks generate PI(3,4,5)P3 and PI(3,4)P2 at the cell membrane. These lipid products recruit Akt, a key signaling protein, to the inner plasma membrane. From there, AKT initiates downstream signaling.[83] Continuous activation of PI3K/ AKT can lead to the PIK3C gene being produced excessively, altering pathway regulation.[84] Dysregulation has been seen many times over many different cancers. Cells are mutated and genetically altered, and the deregulation means it counteracts efforts to inhibit it. Therefore, inhibiting AKT may be an option for treating cancer with these types of tumors.[82] However, different studies and investigations have found that monotherapy is not very reliable, so a combination of targeted therapy is a better option.[85] There are different types of inhibitors in the pathway. Dual PI3K/mTOR inhibitors are one of the more useful inhibitors as they inhibit both of those respective pathways. NVP-BEZ235 (Dactolisib) inhibits the kinase activity of both PI3K and mTOR, preventing the reactivation of compensatory signaling loops often triggered by single-agent therapies.[86] *In vitro* efficiency, NVP-BEZ235 effectively reduced glioblastoma cell proliferation and induced apoptosis in various cell lines.[87] Isofom-specific PI3K inhibitors exist, and they are designed to target individual PI3K isoforms, reducing toxicity compared to pan-PI3K inhibitors. This type of inhibitor is particularly effective in tumors with specific molecular alterations, making them ideal for precision medicine. This selectivity can improve therapeutic activity. This approach can potentially offer more tailored and effective cancer therapies while minimizing side effects seen with broader inhibitors.[88] PI3Kα isoform is heavily involved in activating the PI3K/ AKT pathway in GBM cells. Alpelisib, a selective PI3Kα inhibitor, successfully blocked PI3K/AKT activation and reduced the growth of GSC-derived neurospheres, suggesting PI3Kα's critical role in GBM progression.[89] Idelalisib is a small-molecule inhibitor that specifically targets the delta isoform

(p110δ) of phosphoinositide 3-kinase (PI3K). Unlike other PI3K isoforms, PI3Kδ is predominantly expressed in hematopoietic cells, which include B cells. By inhibiting PI3Kδ, idelalisib blocks several key cellular signaling pathways that are essential for the survival of malignant B cells, making it effective therapeutic strategies for B cell malignancies.[90] Conversely, Pan-PI3K targets all four isoforms of class I PI3K, α, β, γ, and δ. This is why they are referred to as pan-inhibitors. The goal of using these drugs is to block the entire PI3K signaling pathway But because of their broad-spectrum activity, it means they also inhibit PI3K in normal cells, which can cause adverse events (AEs) and off-target toxicity. This limits their ability to be used effectively at higher therapeutic doses, often leading to treatment discontinuation due to side effects.[88] Buparlisib has clinical potential as a pan-PI3K inhibitor in various cancers as it demonstrates its excellent brain penetration, crucial for treating intracranial tumors. It shows effective target inhibition.[91] Akt inhibitors are another type of inhibitor in cancer treatment. Akt, which is also known as Protein Kinase B, is a key regulator of processes such as cell survival, growth, migration, and differentiation. It is often overactive in various cancers, including breast, lung, and ovarian. The PI3K pathways require Akt phosphorylation at two key sites, Thr308 and Ser473. These play a major role in tumor progression. While this is promising, the drugs have to overcome the complexity of Akt's multiple isoforms with other signaling molecules. Clinical trials with Akt inhibitors have been ongoing, but the inhibitors' effectiveness has been limited, so even though progress has been made, Akt inhibition remains a challenging but still crucial area in cancer therapy development.[92] Ipatasertib is a selective Akt kinase inhibitor studied for solid tumors.[93] But, in essence, all of these drugs have demonstrated varying levels of bioavailability, brain penetration, and efficacy in clinical studies, which indicate their potential for precision therapies (Fig. 2).

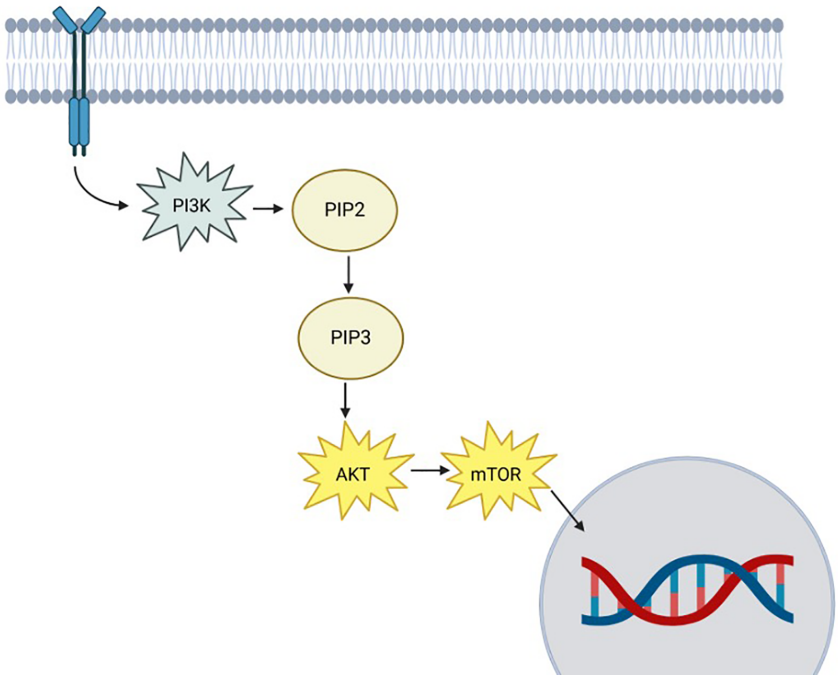

FIG. 2: This diagram shows how the PI3K/AKT pathway works. When growth factors bind to cell surface receptors, they activate PI3K, which produces PIP2 amd PIP3. It then activates AKT, a protein that triggers cell survival, growth, and metabolism. AKT also activates mTOR. Mutations in any part of this pathway can lead to uncontrolled cell growth and cancer. (Figure was generated using www.BioRender.com with an academic license.)

D. Drugs Targeting mTOR

mTOR, or the mammalian target of rapamycin, is a protein kinase. mTOR plays a critical role in regulating protein synthesis, autophagy, and other cellular processes essential for growth and survival. Dysregulated mTOR signaling is seen in diseases other than cancer, such as diabetes. Recent advances have enhanced the understanding of mTOR's functions and regulation, which is helpful for clinical interventions in disease treatment.[94] mTOR is a 289-kDa serine-threonine kinase belonging to the PI3K-related kinase (PIKK) family. mTOR operates within two distinct multiprotein complexes, mTORC1 and mTORC2, which are very important. mTORC1 consists of the mTOR catalytic subunit, Raptor, which handles assembly and substrate recruitment, mLST8, whose role remains unclear, and the negative regulators PRAS40 and Deptor. In its inactive state, PRAS40 and Deptor inhibit mTORC1 by binding to the complex, but their phosphorylation during activation reduces this inhibition, enabling mTORC1 to promote downstream signaling. mTORC2 is composed of Rictor, mSIN1, Protor-1, mLST8, and Deptor. Rictor and mSIN1 stabilize the complex, while Deptor acts as an inhibitor, similar to its role in mTORC1. The protein mLST8 is critical for the stability and activity of mTORC2, with its absence significantly impairing the complex's function.[95] mTORC1 is seen inside of various cellular compartments, including mitochondria, neuronal membranes, the nucleus, endoplasmic reticulum, Golgi, and lysosome surfaces, with activation predominantly occurring on lysosomes.[96] mTORC2 regulates metabolism, growth, and survival by activating AKT through phosphorylation at key sites, with RICTOR being essential for this process. Its activity is influenced by various signals.[97] mTOR is quite important because it is a critical regulator of cellular processes, which is why it is included in the involvement in tumorigenesis. Despite significant progress in understanding mTOR, many aspects remain unclear, especially concerning mTORC2's activation, regulation, and interplay with mTORC1.[98] Everolimus (Afinitor) is an mTOR inhibitor. It was approved in 2009 for targeted-therapy refractory mRCC, and demonstrated significant efficacy in the RECORD study, improving progression-free survival (PFS) to 4.0 months compared to 1.9 months for placebo. While effective, it requires careful management of side effects such as stomatitis and pneumonitis, emphasizing patient-centered care in clinical use.[99] Temsirolimus is another inhibitor, specifically a mTORC1 inhibitor. Despite its efficacy, challenges such as immune suppression, metabolic side effects, and drug resistance highlight the need for ongoing research to optimize its use in cancer therapy for this inhibitor.[100] Sirolimus (rapamycin), originally isolated from *Streptomyces hygroscopicus* for its antifungal properties, has demonstrated significant antitumor and immunosuppressive effects. It is effective in preventing organ transplant rejection and potentially useful in cancer therapy and is currently being studied for its antiproliferative effects in cancer treatment.[101] Ridaforolimus is an inhibitor It shows a cytostatic mode of action, halting tumor cell growth without causing immediate cell death. In preclinical studies, it demonstrated antitumor effects in various tumor cell lines and mouse models, particularly with intermittent dosing. Ridaforolimus' effective dosing strategies may offer a potential therapeutic approach with minimized side effects.[102] A preclinical study showed that combining Vistusertib, a dual mTORC1/2 inhibitor, with paclitaxel resulted in additive effects on cell growth inhibition and significantly reduced tumor volumes (Fig. 3).

E. Drugs Targeting the Sonic Hedgehog (Shh)/Patched (PTCH) Pathway

The Hh signaling pathway, particularly the Shh component, plays a crucial role in embryonic development and tumorigenesis, contributing to radio- and chemo-resistance in brain tumors and leading to poor prognosis. Advances in understanding the Shh pathway, including signaling and interactions with other pathways, are paving the way for targeted therapies and clinical trials, offering potential treatment options for brain and other cancers.[103] PTCH is a protein that can also be referred to as PTCH1. It is a key regulator of this pathway. PTCH inhibits activity of Smoothened, or SMO, which prevents the pathway's activation, but this happens in the

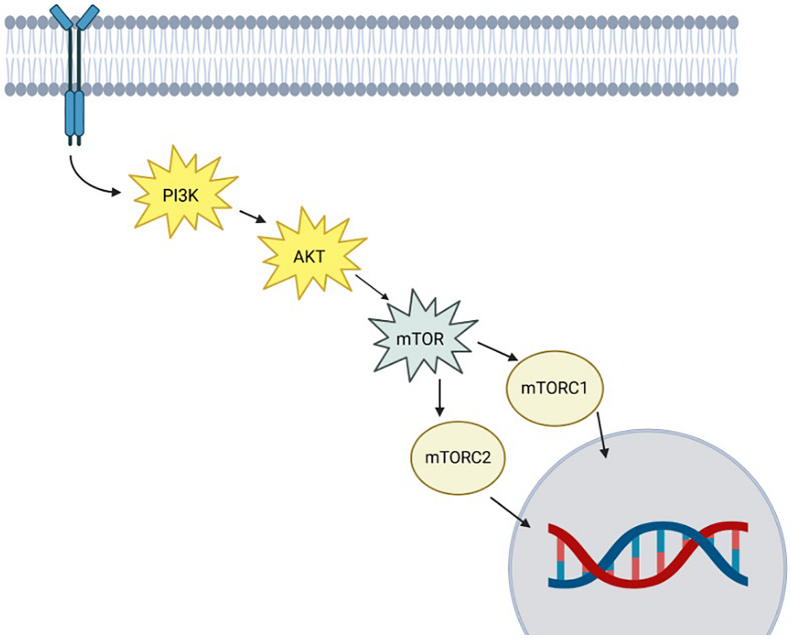

FIG. 3: mTOR works in two complexes, mTORC1 and mTORC2. mTORC1 is activated by growth factors and nutrients and promotes protein synthesis and cell growth. mTORC2 helps with cell survival and organization. The pathway is regulated by signals from AKT. (Figure was generated using www.BioRender.com with an academic license.)

absence of Hh ligands. When the ligands do bind to PTCH, the suppression of SMO is lifted, which means it turns on the pathway signalling, which affects cell growth and differentiation.[104] This signalling pathway is seen in many other types of cancers with other pathways as well, making it clear that it is utilized into tumorigenesis a lot, which is how it is related to cancer.[105,106] Vismodegib (Erivedge) is a small molecule that inhibits the Hh pathway that binds to smoothened (SMO), preventing uncontrolled cell proliferation. It was approved by the FDA in 2012 and by EMA in 2013, but its role in other cancers still under investigation.[25] Sonidegib (Odomzo) is actually the second Hh inhibitor to be approved by the FDA, after Vismodegib.[107] For the most part, this drug is under many drug trials with other drugs. Itraconazole is actually a systemic antifungal, and was identified as a potential antagonist of the Hh signaling pathway, inhibiting Hh activity and medulloblastoma growth SMO through a distinct mechanism from other SMO antagonists,[108] but these are only some inhibitors amongst others in this pathway (Fig. 4).

F. Drugs Inhibiting Angiogenesis

Angiogenesis is the process through which new blood vessels are formed from pre-existing ones. It is essential for various physiological functions such as tissue repair, development, and reproduction, and also plays a pivotal role in pathological conditions such as cancer and chronic respiratory diseases. Key regulators such as VEGF are involved in this process.[109] Angiogenesis contributes significantly to tissue remodeling and progression, making it a critical target for therapeutic interventions.[110] VEGF-driven angiogenesis starts tumor growth and metastasis by creating a blood supply. It also affects tumor microenvironment interactions, influencing immune evasion and cancer cell behavior. Understanding VEGF's role in these processes has led to the development of anti-angiogenic therapies.[111] Drugs targeting the VEGF pathway have shown significant promise in inhibiting angiogenesis. Bevacizumab, an anti-VEGF antibody, is FDA approved for second-line treatment of GBM, where it reduces vascular permeability, though its impact

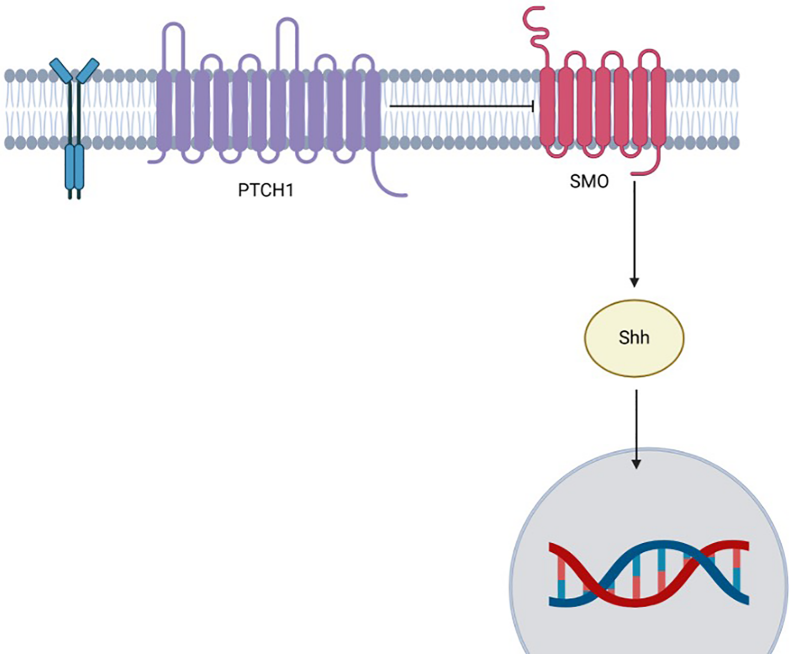

FIG. 4: This diagram shows how the PTCH receptor controls the Hh signaling pathway. When Hh binds to PTCH, it actually removes the inhibition on SMO, allowing SMO to activate signaling. This leads to the activation of transcription factors, which control cell growth and development. (Figure was generated using www.BioRender.com with an academic license.)

on overall survival remains limited.[112] Aflibercept binds VEGF-A, VEGF-B, and placental growth factor to block angiogenesis. While primarily used for ocular diseases, its mechanism has potential applications in GBM.[113] Regorafenib, a multikinase inhibitor, targets VEGFR1-3 and other receptors such as PDGFR and FGFR, offering broader antiangiogenic and tumor inhibition.[114] Although early clinical trials of VEGF inhibitors are facing challenges, continued research holds promise for overcoming limitations in anti-angiogenic therapies for brain tumors[115] (Fig. 5). Current research in neuro-oncology is focused on understanding the molecular mechanisms underlying angiogenesis and resistance to anti-angiogenic therapies. Efforts include identifying novel angiogenic targets, utilizing combination therapies with immunotherapy or molecular inhibitors, and developing biomarkers to predict treatment response. These approaches aim to enhance the durability of angiogenesis inhibition and improve clinical outcomes for patients with malignant brain tumors.[116–118]

IV. CONCLUSIONS

Molecular targets and signaling pathways are crucial in understanding disease mechanisms and advancing personalized therapies, significantly improving diagnostic accuracy, treatment outcomes, and reducing adverse effects. Targeted interventions focusing on key pathways such as MAPK/ERK and PI3K/AKT/mTOR have revolutionized modern healthcare, offering enhanced efficacy and fewer side effects, ultimately improving survival rates and quality of life for patients. Key challenges include tumor heterogeneity, therapeutic resistance, and limited access to comprehensive molecular diagnostics, which can hinder the effective implementation of targeted therapies. Additionally, integrating these therapies into existing protocols requires careful consideration of cost, regulatory approval, and evidence from ongoing clinical trials to guide optimal combination strategies. Future research should prioritize identifying more novel molecular targets and addressing resistance mechanisms to current

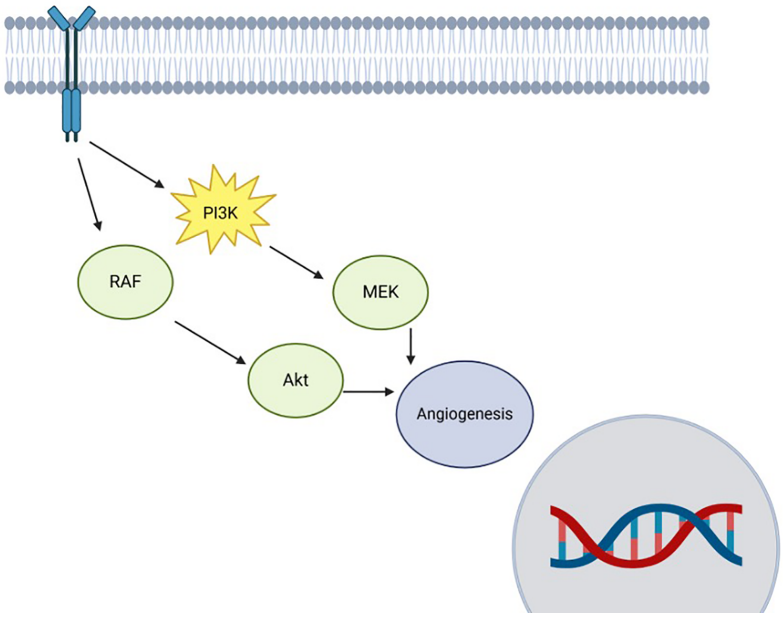

FIG. 5: Angiogenesis is triggered by signals such as VEGF, which binds to receptors on endothelial cells. This activates pathways that promote cell movement and growth, leading to new blood vessel formation. (Figure was generated using www.BioRender.com with an academic license.)

therapies. Promising areas of future research in molecular neuro-oncology include the development of combination therapies to overcome resistance mechanisms, and the identification of novel biomarkers for early diagnosis and treatment stratification. Additionally, developing cost-effective diagnostic tools and ensuring global access to precision medicine remain for maximizing patient benefits and transforming healthcare delivery.

REFERENCES

1. Chamberlain MC. International neurology-neuro-oncology overview. In: Lisak RP, Truong D, Carroll WM, Bhidayasiri R, editors. International neurology. 2nd ed. Hoboken, NJ, USA: John Wiley & Sons, Ltd.; 2016.
2. Afonso M, Brito MA. Therapeutic options in neuro-oncology. Int J Mol Sci. 2022;23(10):5351.
3. Newton HB. Molecular neuro-oncology and development of targeted therapeutic strategies for brain tumors. Part 2: PI3K/Akt/PTEN, mTOR, SHH/PTCH and angiogenesis. Expert Rev Anticancer Ther. 2004;4(1):105–28.
4. Weller M, Pfister SM, Wick W, Hegi ME, Reifenberger G, Stupp R. Molecular neuro-oncology in clinical practice: A new horizon. Lancet Oncol. 2013;14(9):e370–9.
5. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro Oncol. 2021;23(8):1231–51.
6. Smith HL, Wadhwani N, Horbinski C. Major features of the 2021 WHO classification of CNS tumors. Neurotherapeutics. 2022;19(6):1691–704.
7. Polley MYC, Schwartz D, Karrison T, Dignam JJ. Leveraging external control data in the design and analysis of neuro-oncology trials: Pearls and perils. Neuro Oncol. 2024;26(5):796–810.
8. Luger AL, König S, Samp PF, Urban H, Divé I, Burger MC, Voss M, Franz K, Fokas E, Filipski K, Demes MC. Molecular matched targeted therapies for primary brain tumors—A single center retrospective analysis. J Neurooncol. 2022;159(2):243–59.
9. Capper D, Reifenberger G, French PJ, Schweizer L, Weller M, Touat M, Niclou SP, Euskirchen P, Haberler C, Hegi ME, Brandner S. EANO guideline on rational molecular testing of gliomas, glioneuronal, and neuronal tumors in adults for targeted therapy selection. Neuro Oncol. 2023;25(5):813–26.
10. Min H, Lee H. Molecular targeted therapy for anticancer treatment. Exp Mol Med. 2022;54(10):1670–94.
11. Lee YT, Tan YJ, Oon CE. Molecular targeted therapy: Treating cancer with specificity. Eur J Pharmacol. 2018;834:188–96.

12. Muzyka L, Goff NK, Choudhary N, Koltz MT. Systematic review of molecular targeted therapies for adult-type diffuse glioma: An analysis of clinical and laboratory studies. Int J Mol Sci. 2023;24(13):10456.
13. Asao T, Takahashi F, Takahashi K. Resistance to molecularly targeted therapy in non-small-cell lung cancer. Respir Investig. 2019;57(1):20–6.
14. Zhang Q, Fu Q, Bai X, Liang T. Molecular profiling–based precision medicine in cancer: A review of current evidence and challenges. Front Oncol. 2020;10:532403.
15. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009;27(5):740–5.
16. Westphal M, Heese O, Steinbach JP, Schnell O, Schackert G, Mehdorn M, Schulz D, Simon M, Schlegel U, Senft C, Geletneky K, Braun C, Hartung JG, Reuter D, Metz MW, Bach F, Pietsch T. A randomised, open label phase III trial with nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma. Eur J Cancer. 2015;51(4):522–32.
17. Omuro A, Brandes AA, Carpentier AF, Idbaih A, Reardon DA, Cloughesy T, Sumrall A, Baehring J, van den Bent M, Bähr O, Lombardi G. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: An international randomized phase III trial. Neuro Oncol. 2023;25(1):123–34.
18. Iqbal N, Iqbal N. Imatinib: A breakthrough of targeted therapy in cancer. Chemother Res Pract. 2014;2014:357027.
19. Peters KB, Alford C, Heltemes A, Savelli A, Landi DB, Broadwater G, Desjardins A, Johnson MO, Low JT, Khasraw M, Ashley DM, Friedman HS, Patel MP. Use, access, and initial outcomes of off-label ivosidenib in patients with IDH1 mutant glioma. Neurooncol Pract. 2024;11(2):199–204.
20. Yang Z, Zhang Y, Li R, Yisikandaer A, Ren B, Sun J, Li J, Chen L, Zhao R, Zhang J, Xia X, Liao Z, Carbone DP. Whole-brain radiotherapy with and without concurrent erlotinib in NSCLC with brain metastases: A multicenter, open-label, randomized, controlled phase III trial. Neuro Oncol. 2021;23(6):967–78.
21. Nicolaides T, Nazemi KJ, Crawford J, Kilburn L, Minturn J, Gajjar A, Gauvain K, Leary S, Dhall G, Aboian M, Robinson G, Long-Boyle J, Wang H, Molinaro AM, Mueller S, Prados M. Phase I study of vemurafenib in children with recurrent or progressive BRAFV600E mutant brain tumors: Pacific Pediatric Neuro-Oncology Consortium study (PNOC-002). Oncotarget. 2020;11(21):1942–52.
22. Velasco G, Pineda E, Alameda F, Capellades J, Cruz M, Tovar Ambel E, Foro P, Taus Á, Arumi M, Manuel J. Safety and efficacy of crizotinib in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Phase Ib GEINO 1402 trial. Cancers. 2022;14(10):2393.
23. Brastianos PK, Kim AE, Wang N, Lee EQ, Ligibel J, Cohen JV, Chukwueke UN, Mahar M, Oh K, White MD, Shih HA. Palbociclib demonstrates intracranial activity in progressive brain metastases harboring cyclin-dependent kinase pathway alterations. Nat Cancer. 2021;2(5):498–502.
24. Brown NF, Ng SM, Brooks C, Coutts T, Holmes J, Roberts C, Elhussein L, Hoskin P, Maughan T, Blagden S, Mulholland P. A phase II open label, randomised study of ipilimumab with temozolomide versus temozolomide alone after surgery and chemoradiotherapy in patients with recently diagnosed glioblastoma: The Ipi-Glio trial protocol. BMC Cancer. 2020;20(1):198.
25. DeWire M, Lazow M, Campagne O, Leach J, Fuller C, Senthil Kumar S, Stanek J, De Blank P, Hummel TR, Pillay-Smiley N, Salloum R. Phase I study of ribociclib and everolimus in children with newly diagnosed DIPG and high-grade glioma: A CONNECT pediatric neuro-oncology consortium report. Neurooncol Adv. 2022;4(1):vdac055.
26. Roth P, Pace A, Le Rhun E, Weller M, Ay C, Moyal EC, Coomans M, Giusti R, Jordan K, Nishikawa R, Winkler F. Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO clinical practice guidelines for prophylaxis, diagnosis, treatment and follow-up. Ann Oncol. 2021;32(2):171–82.
27. Patel A. Benign vs. malignant tumors. JAMA Oncol. 2020;6(9):1488.
28. Lapointe S, Perry A, Butowski NA. Primary brain tumours in adults. Lancet. 2018;392(10145):432–46.
29. Van den Bent MJ, Geurts M, French PJ, Smits M, Capper D, Bromberg JE, Chang SM. Primary brain tumours in adults. Lancet. 2023;402(10412):1564–79.
30. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, Pekmezci M, Schwartzbaum JA, Turner MC, Walsh KM, Wrensch MR. The epidemiology of glioma in adults: A "state of the science" review. Neuro Oncol. 2014;16(7):896–913.
31. Sievers P, Bielle F, Göbel K, Schrimpf D, Nichelli L, Mathon B, Appay R, Boldt HB, Dohmen H, Selignow C, Acker T. Identification of a putative molecular subtype of adult-type diffuse astrocytoma with recurrent MAPK pathway alterations. Acta Neuropathol. 2024;148:7.
32. Alshoabi SA, Alareqi AA, Omer AM, Suliman AG, Daqqaq TS. Diffuse astrocytoma and the diagnostic dilemma of an unusual phenotype: A case report. Radiol Case Rep. 2021;16(2):319–26.
33. Gilanie G, Bajwa UI, Waraich MM, Anwar MW. Risk-free WHO grading of astrocytoma using convolutional neural networks from MRI images. Multimed Tools Appl. 2021;80(3):4295–306.
34. Liu S, Liu X, Zhuang W. Prognostic factors associated with survival in patients with diffuse astrocytoma. Front Surg. 2021;8:712350.

35. Ruiz MF, Gennaro MV, Bastone LC, Godoy AR, Torruella M, Perez GR. Molecular biomarkers and integrated pathological diagnosis in the reclassification of gliomas. Mol Clin Oncol. 2021;15:150.
36. Suwala AK, Stichel D, Schrimpf D, Kloor M, Wefers AK, Reinhardt A, Maas SL, Kratz CP, Schweizer L, Hasselblatt M, Snuderl M. Primary mismatch repair deficient IDH-mutant astrocytoma (PMMRDIA) is a distinct type with a poor prognosis. Acta Neuropathol. 2021;141:85–100.
37. Van den Bent MJ, Reni M, Gatta G, Vecht C. Oligodendroglioma. Crit Rev Oncol Hematol. 2008;66(3):262–72.
38. Aboud O, Shah R, Vera E, Burton E, Theeler B, Wu J, Penas-Prado M. Challenges of imaging interpretation to predict oligodendroglioma grade: A report from the Neuro-Oncology Branch. CNS Oncol. 2022;11(1):CNS83.
39. Jenkinson MD, Du Plessis DG, Smith TS, Joyce KA, Warnke PC, Walker C. Histological growth patterns and genotype in oligodendroglial tumours: Correlation with MRI features. Brain. 2006;129(7):1884–91.
40. Van der Vaart T, Wijnenga MM, van Garderen K, Dubbink HJ, French PJ, Smits M, van den Bent MJ. Differences in the prognostic role of age, extent of resection, and tumor grade between astrocytoma IDHmt and oligodendroglioma: A single-center cohort study. Clin Cancer Res. 2024;30(17):3837–44.
41. Cao L, Rong P, Zhu G, Xu A, Chen S. Clinical characteristics and overall survival prognostic nomogram for oligodendroglioma: A surveillance, epidemiology, and end results population-based analysis. World Neurosurg. 2021;151:e810–20.
42. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: A summary. Neuro Oncol. 2021;23(8):1231–51.
43. Mut MELİKE, Guler-Tezel G, Lopes MBS, Bilginer BURÇAK, Ziyal I, Ozcan OE. Challenging diagnosis: Oligodendroglioma versus extraventricular neurocytoma. Clin Neuropathol. 2005;24(5):225.
44. Perry JR, Louis DN, Cairncross JG. Current treatment of oligodendrogliomas. Arch Neurol. 1999;56(4):434–6.
45. Engelhard HH, Stelea A, Mundt A. Oligodendroglioma and anaplastic oligodendroglioma: Clinical features, treatment, and prognosis. Surg Neurol. 2003;60(5):443–56.
46. Van den Bent MJ, Reni M, Gatta G, Vecht C. Oligodendroglioma. Crit Rev Oncol Hematol. 2008;66(3):262–72.
47. Eoli M, Bissola L, Bruzzone MG, Pollo B, Maccagnano C, Simone TD, Valletta L, Silvani A, Bianchessi D, Broggi G, Boiardi A, Finocchiaro G. Reclassification of oligoastrocytomas by loss of heterozygosity studies. Int J Cancer. 2006;119(1):84–90.
48. Van den Bent MJ, Smits M, Kros JM, Chang SM. Diffuse infiltrating oligodendroglioma and astrocytoma. J Clin Oncol. 2017;35(21):2394–401.
49. Sahm F, Reuss D, Koelsche C, Capper D, Schittenhelm J, Heim S, Jones DT, Pfister SM, Herold-Mende C, Wick W, Mueller W. Farewell to oligoastrocytoma: In situ molecular genetics favor classification as either oligodendroglioma or astrocytoma. Acta Neuropathol. 2014;128:551–9.
50. Forst DA, Nahed BV, Loeffler JS, Batchelor TT. Low-grade gliomas. Oncologist. 2014;19(4):403–13
51. Lanman TA, Compton JN, Carroll KT, Hirshman BR, Ali MA, Lochte B, Carter B, Chen CC. Survival patterns of oligoastrocytoma patients: A surveillance, epidemiology and end results (SEER) based analysis. Interdiscip Neurosurg. 2018;11:70–5.
52. Alther B, Mylius V, Weller M, Gantenbein AR. From first symptoms to diagnosis: Initial clinical presentation of primary brain tumors. Clin Transl Neurosci. 2020;4(2): 2514183X20968368.
53. Reifenberger G, Louis DN. Oligodendroglioma: Toward molecular definitions in diagnostic neuro-oncology. J Neuropathol Exp Neurol. 2003;62(2):111–26.
54. Mohile NA, Messersmith H, Gatson NT, Hottinger AF, Lassman AB, Morton J, Ney D, Nghiemphu PL, Olar A, Olson J, Perry J. Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. J Clin Oncol. 2022;40(4):403–26.
55. Taylor OG, Brzozowski JS, Skelding KA. Glioblastoma multiforme: An overview of emerging therapeutic targets. Front Oncol. 2019;9:486794.
56. Gibbs JB. Anticancer drug targets: Growth factors and growth factor signaling. J Clin Invest. 2000;105(1):9–13.
57. Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR signaling in cancer. Front Oncol. 2014;4:67531.
58. Normanno N, De Luca A, Bianco C, Strizzi L, Mancino M, Maiello MR, Carotenuto A, De Feo G, Caponigro F, Salomon DS. Epidermal growth factor receptor (EGFR) signaling in cancer. Gene. 2006;366(1):2–16.
59. Suh CH, Kim HS, Jung SC, Choi CG, Kim SJ. Imaging prediction of isocitrate dehydrogenase (IDH) mutation in patients with glioma: A systemic review and meta-analysis. Eur Radiol. 2019;29:745–58.
60. Begagić E, Pugonja R, Bečulić H, Čeliković A, Tandir Lihić L, Kadić Vukas S, Čejvan L, Skomorac R, Selimović E, Jaganjac B, Juković-Bihorac F. Molecular targeted therapies in glioblastoma multiforme: A systematic overview of global trends and findings. Brain Sci. 2023;13(11):1602.
61. Miklja Z, Pasternak A, Stallard S, Nicolaides T, Kline-Nunnally C, Cole B, Beroukhim R, Bandopadhayay P, Chi S, Ramkissoon SH, Mullan B, Bruzek AK, Gauthier A, Garcia T, Atchison C, Marini B, Fouladi M, Parsons DW, Leary S, Mueller S, Ligon KL, Koschmann C. Molecular profiling and targeted therapy in pediatric gliomas: Review and consensus recommendations. Neuro Oncol. 2019;21(8):968.
62. Ciardiello F, Tortora G. Epidermal growth factor receptor (EGFR) as a target in cancer therapy: Understanding

the role of receptor expression and other molecular determinants that could influence the response to anti-EGFR drugs. Eur J Cancer. 2003;39(10):1348–54.
63. Wykosky J, Fenton T, Furnari F, Cavenee WK. Therapeutic targeting of epidermal growth factor receptor in human cancer: Successes and limitations. Chin J Cancer. 2011;30(1):5.
64. Yewale C, Baradia D, Vhora I, Patil S, Misra A. Epidermal growth factor receptor targeting in cancer: A review of trends and strategies. Biomaterials. 2013;34(34):8690–707.
65. Ono M, Kuwano M. Molecular mechanisms of epidermal growth factor receptor (EGFR) activation and response to gefitinib and other EGFR-targeting drugs. Clin Cancer Res. 2006;12(24):7242–51.
66. Brand TM, Iida M, Wheeler DL. Molecular mechanisms of resistance to the EGFR monoclonal antibody cetuximab. Cancer Biol Ther. 2011;11(9):777–92.
67. Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer. 2003;3(1):11–22.
68. Drosten M, Dhawahir A, Sum EY, Urosevic J, Lechuga CG, Esteban LM, Castellano E, Guerra C, Santos E, Barbacid M. Genetic analysis of Ras signalling pathways in cell proliferation, migration and survival. EMBO J. 2010;29(6):1091–104.
69. Downward J. Ras signalling and apoptosis. Curr Opin Genet Dev. 1998;8(1):49–54.
70. Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. Cancer Res. 2012;72(10):2457–67.
71. Prior IA, Hood FE, Hartley JL. The frequency of Ras mutations in cancer. Cancer Res. 2020;80(14):2969–74.
72. Blum R, Kloog Y. Tailoring Ras-pathway—Inhibitor combinations for cancer therapy. Drug Resist Updates. 2005;8(6):369–80.
73. Sebti SM, Der CJ. Searching for the elusive targets of farnesyltransferase inhibitors. Nat Rev Cancer. 2003;3(12):945–51.
74. Brunner TB, Hahn SM, Gupta AK, Muschel RJ, McKenna WG, Bernhard EJ. Farnesyltransferase inhibitors: An overview of the results of preclinical and clinical investigations. Cancer Res. 2003;63(18):5656–68.
75. Dhillon S. Lonafarnib: First approval. Drugs. 2021;81: 283–9.
76. Widemann BC, Dombi E, Gillespie A, Wolters PL, Belasco J, Goldman S, Korf BR, Solomon J, Martin S, Salzer W, Fox E. Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro Oncol. 2014;16(5):707–18.
77. Sebti SM, Adjei AA. Farnesyltransferase inhibitors. Semin Oncol. 2004;31:28–39.
78. Cheng Y, Tian H. Current development status of MEK inhibitors. Molecules. 2017;22(10):1551.
79. Sullivan RJ, Infante JR, Janku F, Wong DJ, Sosman JA, Keedy V, Patel MR, Shapiro GI, Mier JW, Tolcher AW, Wang-Gillam A. First-in-class ERK1/2 inhibitor ulixertinib (BVD-523) in patients with MAPK mutant advanced solid tumors: Results of a phase I dose-escalation and expansion study. Cancer Discov. 2018;8(2):184–95.
80. Barbosa R, Acevedo LA, Marmorstein R. The MEK/ERK network as a therapeutic target in human cancer. Mol Cancer Res. 2021;19(3):361–74.
81. Hatzivassiliou G, Liu B, O'Brien C, Spoerke JM, Hoeflich KP, Haverty PM, Soriano R, Forrest WF, Heldens S, Chen H, Toy K. ERK inhibition overcomes acquired resistance to MEK inhibitors. Mol Cancer Ther. 2012;11(5):1143–54.
82. Rascio F, Spadaccino F, Rocchetti MT, Castellano G, Stallone G, Netti GS, Ranieri E. The pathogenic role of PI3K/AKT pathway in cancer onset and drug resistance: An updated review. Cancers. 2021;13(16):3949.
83. Alzahrani AS. PI3K/Akt/mTOR inhibitors in cancer: At the bench and bedside. Semin Cancer Biol. 2019;59:125–32.
84. Osaki M, Oshimura M, Ito H. PI3K-Akt pathway: Its functions and alterations in human cancer. Apoptosis. 2004;9:667–76.
85. Jiang N, Dai Q, Su X, Fu J, Feng X, Peng J. Role of PI3K/AKT pathway in cancer: The framework of malignant behavior. Mol Biol Rep. 2020;47(6):4587–629.
86. Serra V, Markman B, Scaltriti M, Eichhorn PJ, Valero V, Guzman M, Botero ML, Llonch E, Atzori F, Di Cosimo S, Maira M. NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. Cancer Res. 2008;68(19):8022–30.
87. Manara MC, Nicoletti G, Zambelli D, Ventura S, Guerzoni C, Landuzzi L, Lollini PL, Maira SM, García-Echeverría C, Mercuri M, Picci P. NVP-BEZ235 as a new therapeutic option for sarcomas. Clin Cancer Res. 2010;16(2):530–40.
88. Dienstmann R, Rodon J, Serra V, Tabernero J. Picking the point of inhibition: A comparative review of PI3K/AKT/mTOR pathway inhibitors. Mol Cancer Ther. 2014;13(5):1021–31.
89. Eckerdt FD, Bell JB, Gonzalez C, Oh MS, Perez RE, Mazewski C, Fischietti M, Goldman S, Nakano I, Platanias LC. Combined PI3Kα-mTOR targeting of glioma stem cells. Sci Rep. 2020;10(1):21873.
90. Zirlik K, Veelken H. Idelalisib. Recent Results Cancer Res. 2018;212:243–64.
91. De Gooijer MC, Zhang P, Buil LC, Çitirikkaya CH, Thota N, Beijnen JH, Van Tellingen O. Buparlisib is a brain penetrable pan-PI3K inhibitor. Sci Rep. 2018;8(1):10784.
92. Nitulescu GM, Margina D, Juzenas P, Peng Q, Olaru OT, Saloustros E, Fenga C, Spandidos DA, Libra M, Tsatsakis AM. Akt inhibitors in cancer treatment: The long journey from drug discovery to clinical use. Int J Oncol. 2015;48(3):869–85.
93. Lopez-Miranda E, Pérez García JM, Gion M, Ribelles N, Cortez P, Alonso Romero JL, Martínez-García M, Gonzalez-Santiago S, Bermejo B, Morales Murillo S, Carañana

V. Ipatasertib (IPA) combined with non-taxane chemotherapy (CT) for patients (pts) with previously treated advanced triple-negative breast cancer (aTNBC): The PATHFINDER phase IIa trial. 2024:1098.
94. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168(6):960–76.
95. Laplante M, Sabatini DM. mTOR signaling at a glance. J Cell Sci. 2009;122(20):3589–94.
96. Wang X, Proud CG. MTORC1 signaling: What we still don't know. J Mol Cell Biol. 2011;3(4):206–20.
97. Ballesteros-Álvarez J, Andersen JK. MTORC2: The other mTOR in autophagy regulation. Aging Cell. 2021;20(8):e13431.
98. Fu W, Hall MN. Regulation of mTORC2 signaling. Genes. 2020;11(9):1045.
99. Anandappa G, Hollingdale A, Eisen T. Everolimus—A new approach in the treatment of renal cell carcinoma. Cancer Manag Res. 2010;2:61–70.
100. Rini BI. Temsirolimus, an inhibitor of mammalian target of rapamycin. Clin Cancer Res. 2008;14(5):1286–90.
101. Sehgal S. Sirolimus: Its discovery, biological properties, and mechanism of action. Transplant Proc. 2003;35(3):S7–14.
102. Rivera VM, Squillace RM, Miller D, Berk L, Wardwell SD, Ning Y, Pollock R, Narasimhan NI, Iuliucci JD, Wang F, Clackson T. Ridaforolimus (AP23573; MK-8669), a potent mTOR inhibitor, has broad antitumor activity and can be optimally administered using intermittent dosing regimens. Mol Cancer Ther. 2011;10(6):1059–71.
103. Carballo GB, Honorato JR, de Lopes GP, Spohr TC. A highlight on Sonic hedgehog pathway. Cell Commun Signal. 2018;16(1):11.
104. Lindström E, Shimokawa T, Toftgård R, Zaphiropoulos PG. PTCH mutations: Distribution and analyses. Hum Mutat. 2006;27(3):215–9.
105. Rubin LL, De Sauvage FJ. Targeting the Hedgehog pathway in cancer. Nat Rev Drug Discov. 2006;5(12):1026–33
106. Meiss F, Andrlová H, Zeiser R. Vismodegib. Recent Results Cancer Res. 2018;211:125–39.
107. Jain S, Song R, Xie J. Sonidegib: Mechanism of action, pharmacology, and clinical utility for advanced basal cell carcinomas. Onco Targets Ther. 2017;1645–53.
108. Kim J, Tang JY, Gong R, Kim J, Lee JJ, Clemons KV, Chong CR, Chang KS, Fereshteh M, Gardner D, Reya T. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. Cancer Cell. 2010;17(4):388–99.
109. Huveneers S, Phng L. Endothelial cell mechanics and dynamics in angiogenesis. Curr Opin Cell Biol. 2024;91:102441.
110. Ackermann M, Werlein C, Plucinski E, Leypold S, Kühnel MP, Verleden SE, Khalil HA, Länger F, Welte T, Mentzer SJ, Jonigk DD. The role of vasculature and angiogenesis in respiratory diseases. Angiogenesis. 2024;27(3):293–310.
111. Shaw P, Dwivedi SKD, Bhattacharya R, Mukherjee P, Rao G. VEGF signaling: Role in angiogenesis and beyond. Biochim Biophys Acta Rev Cancer. 2024;1879(2):189079.
112. Laviv Y, Regev O, Kanner AA, Fichman S, Limon D, Siegal T, Yust-Katz S, Benouaich-Amiel A. Stem the blood flow: Beneficial impact of bevacizumab on survival of subventricular zone glioblastoma patients. J Neurooncol. 2025 Jan;171(1):201–11.
113. Bressler SB, Barve A, Ganapathi PC, Beckmann K, Apte RS, Marcus DM, Baumane K, Agarwal S, Oleksy P, Reichstein DA, Patel SS. Aflibercept biosimilar myl-1701p vs reference aflibercept in diabetic macular edema: The INSIGHT randomized clinical trial. JAMA Ophthalmol. 2024;142(10):952–60.
114. Mongiardi MP, Pallini R, D'Alessandris QG, Levi A, Falchetti ML. Regorafenib and glioblastoma: A literature review of preclinical studies, molecular mechanisms and clinical effectiveness. Expert Rev Mol Med. 2024;26:e5.
115. Purow B, Fine HA. Progress report on the potential of angiogenesis inhibitors for neuro-oncology. Cancer Invest. 2004;22(4):577–87.
116. Zhang AB, Mozaffari K, Aguirre B, Li V, Kubba R, Desai NC, Wei D, Yang I, Wadehra M. Exploring the past, present, and future of anti-angiogenic therapy in glioblastoma. Cancers. 2023;15(3):830.
117. Nowacka A, Śniegocki M, Smuczyński W, Bożiłow D, Ziółkowska E. Angiogenesis in glioblastoma—Treatment approaches. Cells. 2025;14(6):407.
118. Pellerino A, Bruno F, Soffietti R, Rudà R. Antiangiogenic therapy for malignant brain tumors: Does it still matter? Curr Oncol Rep. 2023;25(7):777–85.