Improvements in our understanding of the molecular mechanisms of cancer combined with advances in genome sequencing have provided revolutionary new therapeutic options for several hard-to-treat tumors in recent decades. For other challenging tumor types these advances have served only to highlight their significant complexity and, despite the development of novel treatments, there has been limited improvement in prognosis.

Aggressive GBM remains incurable despite FDA approvals

Though rare, glioblastoma (GBM) are the most common malignant primary brain tumors. These highly aggressive tumors have a dismal prognosis (median survival from diagnosis is just over a year) and are notoriously hard to treat for many reasons, including their location, poor response to therapy, and complex and heterogeneous molecular make-up.

Unlike most other tumors, which can often be cured by surgical resection if caught early enough, it is difficult to completely remove GBM safely. Nevertheless, surgery in combination with chemotherapy and radiation therapy (RT) remains standard of care (SOC), reflecting the limited treatment options available.

GBM is among the most highly vascularized solid tumors, characterized by extensive angiogenesis and an abnormal vasculature, and anti-angiogenic therapies targeting the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) have been intensely investigated. Based on the demonstration of improved response rates, bevacizumab received regulatory approval by the US Food and Drug Administration in 2009 for the treatment of recurrent GBM. It remains the only targeted therapy approved by the agency and no agent to date has demonstrated improved survival in this setting.

Meanwhile, the use of bevacizumab in the first-line setting has stirred up significant debate, after contrasting reports from 2 phase 3 trials. Both of the trials evaluated the addition of bevacizumab to SOC and showed similar improvement in progression-free survival (PFS), with no significant effect on overall survival (OS). However, a marked difference was observed in the impact of bevacizumab on quality of life and performance status, with one trial showing an improvement and the other a worsening. It will be an important discrepancy to unravel because it could have an impact on the potential utility of bevacizumab in this setting.

Bevacizumab continues to be evaluated in clinical trials in combination with other agents (Online, Table 1), and other anti-angiogenic therapies have also been tested in GBM. Cediranib is a small molecule inhibitor of VEGFR, which, despite promising activity in early clinical trials, failed to demonstrate a survival benefit in the recent phase 3 REGAL trial, alone or in combination with lomustine. Cilengitide is an integrin inhibitor; integrins mediate communication between GBM cells and the brain microenvironment and play an important role in angiogenesis as well as motility and invasiveness. This agent also reached phase 3 development but failed to improve patient outcomes when combined with temozolomide and RT in the recently reported CENTRIC trial.

A number of other targeted therapies have been evaluated in GBM (Figure 1) and have, likewise, demonstrated only modest therapeutic activity. The most prominent example is epidermal growth factor receptor (EGFR)-targeted drugs; amplification and overexpression of EGFR is observed in more than half of GBM cases and about half of those are caused by a mutant form of the receptor, EGFRvIII, which leads to constitutive activation of kinase activity.

Several novel therapeutic strategies may offer a glimmer of hope. Researchers have created a “cancer hat” that passes low intensity, intermediate frequency alternating electric fields through the brain.
It’s hypothesized that these fields block the formation of the mitotic spindle and prevent proliferation and differentiation of dividing cells. The NovoTTF-100A/Optune device was developed in patients with GBM and, after a phase 3 trial demonstrated comparable efficacy with physician’s choice chemotherapy, it was approved by the FDA in 2011. Numerous clinical trials of NovoTTF-100A are ongoing and preliminary results from a phase 3 trial in combination with temozolomide in patients with newly diagnosed GBM, which were recently reported at the annual meeting of the Society for Neuro-Oncology (SNO), showed improved PFS and OS.

Immunotherapies, which have taken center stage for cancer treatment in recent years following increased appreciation of the intricate relationship between the immune system and cancer, have also emerged as a potentially effective treatment option for GBM. The major focus has been on vaccines (Online, Table 2), representing a promising therapeutic target for both cancer treatment in recent years following increased appreciation of the intricate relationship between the immune system and cancer, have also emerged as a potentially effective treatment option for GBM. The major focus has been on vaccines (Online, Table 2), representing a promising therapeutic target for both cancer and ES, a therapeutic plateau has been reached. A range of novel therapeutic strategies have been evaluated and, to date, none has further improved survival (Online Table 3; Figure 2). This is particularly problematic for the majority of patients who are diagnosed at more advanced stages of disease that are not surgically treatable and who respond poorly to chemotherapy.

The genomic complexity of bone sarcomas is another significant challenge to their treatment. Apart from ES, which is characterized by translocations in the EWSR1 gene, they are extremely heterogeneous and few broadly targetable driver mutations have been identified. This complexity was highlighted in a recent study. Most pediatric cancers have a low somatic mutation rate (around 0.1 mutations/mega-base [Mb]), but in the aforementioned study osteosarcoma was found to have 1.2 mutations/Mb, which is comparable with some adult tumors.

EWSR1/FLI-1 is the most common activating translocation of the EWSR1 gene and plays a significant role in the formation of ES. The insulin-like growth factor receptor (IGF1R) pathway is a major downstream target of activated EWSR1 and is also upregulated in osteosarcoma, thus representing a promising therapeutic target for both cancer types.

Clinical trials of IGF1R inhibitors showed notable responses among a small number of patients with advanced, heavily pretreated disease, but these were short-lived and insufficient to advocate monotherapy. One possible expla-
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FIGURE 2 Signaling pathways targeted by experimental sarcoma therapies. There are currently no FDA-approved targeted therapies for the treatment of bone sarcomas. The IGF1R shown on the left is one of the most promising drug targets, particularly in Ewing sarcoma. A number of monoclonal antibodies targeting this receptor have been evaluated. Responses, though dramatic, are typically short-lived. A number of proteins activated downstream of IGF1R are also being targeted and there is hope for combination therapy. Multi-targeted tyrosine kinase inhibitors have also been heavily investigated, several examples of which are shown on the right. Reproduced with permission from Heymann D, et al.

DNA-PK, DNA-dependent protein kinase; FDA, US Food and Drug Administration; Fli3, fms-related tyrosine kinase 3; Gab2, Grb2-associated binding protein 2; GDP, guanosine diphosphate; Grb2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; IGF1/2, insulin-like growth factor 1/2; IGF1R, insulin-like growth factor receptor 1; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; STAT1/5, signal transducer and activator of transcription 1/5; VEGFR, vascular endothelial growth factor receptor

These studies have also highlighted the importance of understanding patients who seem to have exceptional responses to targeted therapies. Until recently, reports of these “miraculous” outcomes for a select few patients have been largely ignored, and drugs that fail to show improvement for a large number of patients are considered failures. Technological advances have made it possible to unravel the underlying molecular mechanisms of this response.

Studying exceptional responders could prove particularly useful in identifying novel therapies for patients with rare, hard-to-treat tumors such as bone sarcomas. Sequencing studies of exceptional responders from trials of IGF1R and mTOR inhibitor therapy are ongoing and could prove critical to understanding whether further development of these agents should be pursued.

Hepatocellular carcinoma: failure to improve on sorafenib success

Unlike GBM and bone sarcomas, liver cancer is quite common. Hepatocellular carcinoma (HCC), the most prolific subtype, is the sixth most frequently diagnosed cancer and second leading cause of cancer-related mortality globally. Historically, HCC was most common in Asia and Africa, but in recent years the incidence in Western countries has been rising rapidly due to increased rates of hepatitis infection, alcohol abuse, obesity and diabetes, among other factors.

Early-stage HCC can be cured in 30%-40% of cases by surgical resection, transplantation, and ablative techniques. Unfortunately, nearly half of patients are diagnosed at an advanced stage when their tumor is unresectable and can’t be cured by conventional SOC. The prognosis for these patients is especially poor – less than 10% OS at 5 years.

Molecularly targeted therapies have been extensively investigated in HCC (Figure 3), with particular focus on the Ras-Raf-mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)-Akt-mTOR pathways that play a central role in the development of HCC. In 2008, there was a significant advancement in the treatment of advanced stage disease with the approval of sorafenib, following demonstration of improved OS in phase 3 trials. Although sorafenib has become SOC for unresectable, nonablatable, advanced-stage HCC, it merely delays progression of disease and in most cases tumors begin to grow again after less than 6 months. This has created a need for therapies that improve on sorafenib efficacy or that can be used in the second-line setting after sorafenib failure.

A range of other molecularly targeted strategies have been used (Online, Table 4). The success of sorafenib, a multitargeted tyrosine kinase inhibitor (TKI) with anti-angiogenic properties, prompted intensive study of other TKIs with similar mechanism of action. As yet, though many
have reached phase 3 development, none have improved on the efficacy or tolerability of sorafenib in the first-line setting or shown benefit in the second-line setting.

Most recently, the results of the phase 3 REACH trial of VEGFR2 inhibitor ramucirumab were presented at the annual meeting of the European Society of Molecular Oncology and showed no survival benefit. However, an abstract presented at the Gastrointestinal Cancers Symposium in early 2015 described a post hoc analysis of the trial in early 2014 with a lower dose of tivantinib. A data monitoring committee recommended continuation of the trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J Clin Oncol. 2013;31:3212-3218.


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