RIMAS LUKAS ON

Newly Diagnosed Glioblastoma
Studies, Advances, Strategies

‘A 4-pronged approach is pivotal’

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Stem cell transplantation is used to treat patients with blood cancers and various blood diseases. However, the procedure is most common for blood cancers. ONCOLOGY spoke with David T. Scadden, MD, to discuss which patients are eligible, as well as the latest advances in the field.

Q: Can you describe how a typical autologous stem cell transplant and an allogeneic stem cell transplant are done and how they differ?

DR. SCADDEN: The allogeneic stem cell transplant is the process of receiving stem cells from someone else. This can be a relative or a donor who just happens to be an immunologic match. An autologous stem cell transplant means that you are donating your own stem cells. So, you can imagine that two different groups of people receive these kinds of transplants; however, each patient, whether they are receiving an autologous or an allogeneic stem cell transplant, undergoes a very similar set of steps, meaning that the stem cells are harvested, collected, and usually stored. Then, the patient goes through the process whereby their own stem cells are eliminated with the use of chemotherapy drugs, drugs plus radiation, or radiation alone. This is necessary both because you want to get rid of the abnormal cells, but you also need to make space for plasma cells that can turn into multiple myeloma, then we can give patients their own cells back. In these cases, the stem cells are harvested and put in the freezer, and then the patients are given intensive chemotherapy to wipe out their existing cells. The frozen stem cells are thawed, and when the chemotherapy drugs have cleared from the body, we infuse their stem cells back in and they begin to make new blood cells.

These approaches are also used in nonmalignant settings, often in people who have genetic disorders, including those who have sickle cell anemia or an immune deficiency. In these cases, you obviously have to use someone else’s stem cells. Additionally, patients who develop aplastic anemia receive someone else’s stem cells when theirs have failed. There are dozens and dozens of diseases for which transplant has now been used, but they typically occur in the settings of lymphoma, myeloma, and leukemia.
the new stem cells. The stem cells are given much like a blood transfusion: they go into the blood and find their way to “specialized niches,” where they start to produce new blood cells. These niches need to be empty or the cells won’t find room and move on. This so-called conditioning is a part of what is necessary before a transplant can be done. After the transplant, clinicians try to manage the complications that arise from having someone else’s cells in your body, or from the cells arriving but taking a long time to make the cells that the patient needs.

Q: Are there conditions or disorders that would preclude patients from being eligible for a stem cell transplant?

DR. SCADDEN: A lot of it has to do with the rigors of the transplant, which make the procedure quite difficult. Patients can be excluded if they have other medical problems such as heart, liver, or kidney disease. We do know that transplant is often a curative therapy. We know that it can be useful in a wide range of disorders for which transplants are not currently used, and the reason is because of the complexity of this treatment. The hope is that we can move beyond the current measures and identify new ways to do a transplant, such that additional people can be eligible for what can be a curative and life-saving therapy.

Q: Your lab works on new transplant approaches in which patients may be able to avoid cytotoxic conditioning, which many patients cannot withstand. Can you talk about some recent advances on this front, or novel approaches in development?

DR. SCADDEN: We know that stem cells can be killed by chemotherapy and

Despite the recent approval of multiple targeted agents and immunotherapies for malignant blood disorders, hematopoietic stem cell transplantation (HSCT) remains the only curative option for a significant number of patients. Dr. Scadden gives an excellent review of the types of indications for, and complications arising from HSCT.

When it comes to disorders such as acute leukemia, myelodysplastic syndromes, and multiply relapsed lymphomas, an allogeneic donor is generally the preferred stem cell source. The mechanism by which allogeneic HSCT is curative is twofold. Initial disease control is achieved through administration of conditioning chemotherapy +/- radiation prior to the transplant. Tumor debulking as a result of the conditioning allows disease control that is long enough for the development of the graft-vs-leukemia (GVL) effect, in which the transplanted immune system recognizes and kills residual malignant cells. GVL then provides a sustained mechanism of long-term immunological surveillance and elimination of residual disease that might lead to relapse.

When allogeneic stem cell transplant fails, it is typically due to one of several factors. On the front end, intrinsic chemoresistance and/or inability to deliver fully ablative doses of conditioning due to patient-specific factors allows the disease to progress prior to the development of GVL. Alternatively, the conditioning provides sufficient upfront control, but the disease is subsequently able to escape the GVL effect by various mechanisms, such as human leukocyte antigen loss, tumor antigen downregulation, and induction of donor immune tolerance and exhaustion.

Taking this into account, attempts to improve outcomes from allogeneic HSCT have focused on these factors. By improving conditioning regimens, especially for less fit patients, it increases the likelihood of a progression-free window that is long enough for patients to reap the benefits of GVL. Alternatively, by augmenting the donor’s immune system post-transplant, GVL can be boosted and tumor escape can be prevented. Specifically in regards to improving conditioning regimens, several promising compounds are at various stages of development. As Dr. Scadden points out, conditioning that incorporates antibody-based therapy allows precise delivery of a potent cytotoxin to the cell of interest, while sparing normal healthy tissues. As a result, tumorcidal effects are enhanced and toxicity is minimized.

In a treatment landscape where novel therapies are as promising as ever, the long-validated field of HSCT is not going away. For many patients, this remains their best chance of cure. Research focused on improving conditioning regimens and enhancing post-transplant immune function will hopefully lead to breakthroughs that will benefit patients with difficult-to-treat hematologic malignancies.

**FINANCIAL DISCLOSURE:** Dr. Donnellan has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

**Dr. Donnellan** is Director of Acute Leukemia/Myelodysplastic Syndromes Research at Sarah Cannon Research Institute/Tennessee Oncology in Nashville, Tennessee.
radiation therapy. But we also know that in doing these treatments, there is a lot of collateral damage. Many other tissues are affected, which inevitably can result in genetic damage that affects the whole body. There are methods now where you can get a much more selective delivery of a toxin. In other words, we know that there are proteins on the surface of stem cells and many different cell types that distinguish them and make them different from other cells. Antibodies can recognize these very specific signature proteins on the cells you want to target. In my lab we try to leverage that as a way to reduce this collateral damage. We’ve loaded these antibodies with a toxin, so that they bind to the stem cells, causing the cells to internalize these toxins, meaning that just those cells are exposed to the toxin and only those cells die. This enables us to cause a much more selective but still powerful depletion of cells, so that the transplanted cells have a place to reside and where we can eliminate most or all of the diseased cells. This is something that has been demonstrated in animal models, and we certainly hope to advance that to humans. This strategy has been taken up and we certainly hope to advance that to the diseased cells. This is something that distinguishes them and makes them different from other cells. Antibodies can recognize these very specific signature proteins on the cells you want to target. In my lab we try to leverage that as a way to reduce this collateral damage.

**Q:** Your lab studies the basic biology of hematopoietic stem cells that reside in the bone marrow. What have you learned in the last few years about the biology of these cells that may be useful for translation into novel therapies for those with hematologic malignancies?

**DR. SCADDEN:** One of the reasons I got involved in this is that I am interested in being able to potentially modify the genes in these cells for people who have inherited disorders of the blood and also to be able to make the cells impervious to certain kinds of infections like HIV. However, some of the early studies were complicated because we just didn’t know enough about blood stem cells. I think we have gained a tremendous amount of knowledge about how blood stem cells work and also the ways in which we can genetically modify them. People have heard of CRISPR, this really exciting new way in which we can edit genes, and find ways to modify damaged DNA and genes and correct them. This technology will be tremendously powerful if it can be applied to diseases where we know a lot about the cells that are affected. There are efforts to use this in the eye, for example, but blood will certainly be an area where gene editing will be used. We are starting to see and will see over the course of the next few years that this will really have an impact.

However, for people to be willing to go through this type of therapy, the process needs to be made much less toxic. We need better ways to be able to access patients’ stem cells, better ways to use fewer numbers of patients’ stem cells, and better ways to allow these modified cells to go in to engraft and remake blood. These are all things that we have been working on in the lab and things that are moving forward to clinical applications. I think these will be enabling technologies for all of the very exciting gene editing techniques that are being tested now.

**Q:** Are there clinical trials that you can highlight that are investigating novel stem cell transplant approaches?

**DR. SCADDEN:** The things that are being tested currently run the gamut. Often they are focused on mitigating immune complications such as graft-vs-host disease, which can occur when a patient undergoes an allogeneic transplant. There are lots of ongoing, very interesting studies that are happening now. These include the use of inhibitors of kinases like JAK and BTK, antibodies against immune costimulating molecules like cytotoxic T-lymphocyte–associated antigen 4, antibodies against adhesion molecules like P-selectin, and antibodies against B cells. There are also some studies coming up soon to test new ways in which cells can move into the blood more rapidly and efficiently, so that it is easier to be a donor. There are also some conditioning studies that will be using antibody approaches, which are for a very limited subset of patients, but that we hope will be available for clinical trials over the next year to year and a half. These latter programs include some from Magenta Therapeutics, where I am a founder. Most clinical studies in the area of stem cell transplantation can be found on BeTheMatch.org or on ClinicalTrials.gov.

**FINANCIAL DISCLOSURE:** Dr. Scadden is director, shareholder, and consultant for Clear Creek Bio, Editas Medicine, Fate Therapeutics (co-founder), LifeVaultBio, Magenta Therapeutics (co-founder), and Red Oak Medicines; he is also a director and shareholder of Agios and a consultant for FOG Pharma.
Management of Gastrointestinal Toxicities From Ixazomib

Tips to Curb Nausea, Vomiting, Diarrhea, and Constipation

Kevin H. Hall, PharmD, BCOP

Introduction
Proteasome inhibitors are widely utilized as a backbone in the treatment of multiple myeloma. Ixazomib is the first orally administered proteasome inhibitor approved by the US Food and Drug Administration. Ixazomib is currently indicated in combination with lenalidomide and dexamethasone for relapsed/refractory multiple myeloma, providing patients with an all-oral three-drug regimen.[1] Recent data also demonstrated that ixazomib monotherapy is an acceptable alternative to lenalidomide for post-transplant maintenance therapy.[2] New challenges arise with the transition to all-oral regimens, as fewer physician and infusion appointments likely result in fewer opportunities to address toxicities and adherence.[3-5] While ixazomib is relatively well tolerated, it is essential to appropriately manage toxicities that reduce patient adherence and quality of life, including gastrointestinal toxicities.[1-3]

Clinical Efficacy and Safety
The efficacy and safety of ixazomib combined with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma were evaluated in the phase III TOURMALINE-MM1 study. [1] Patients were randomized to receive ixazomib 4 mg or placebo orally on days 1, 8, and 15; lenalidomide 25 mg orally on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or unacceptable toxicities occurred. The ixazomib-lenalidomide-dexamethasone (IRd) group demonstrated a significant improvement in median progression-free survival (20.6 months vs 14.7 months in the placebo-Rd group; hazard ratio [HR], 0.74; 95% CI, 0.59–0.94; \( P = .01 \)).[1] More recently, the TOURMALINE-MM3 study evaluated ixazomib maintenance following autologous stem cell transplantation in patients with newly diagnosed multiple myeloma.[2] Patients received ixazomib 3 mg or matching placebo orally on days 1, 8, and 15 in 28-day cycles for 2 years. The dose of ixazomib was increased to 4 mg on cycle 5 if tolerated. Compared with placebo, the ixazomib group demonstrated an increase in progression-free survival of 26.5 months vs 21.3 months (HR, 0.72; 95% CI, 0.58–0.89; \( P = .0023 \)).[2] Thrombocytopenia, rash, gastrointestinal toxicity, and peripheral neuropathy were more common in patients taking ixazomib compared with the placebo groups, yet both studies demonstrated the relative tolerability and safety of ixazomib; discontinuation rates due to treatment-related adverse events were similar to placebo.[1,2] In the TOURMALINE-MM1 study, gastrointestinal events that were more common in the IRd group compared with the placebo-Rd group included diarrhea (45% vs 39%), nausea (29% vs 22%), and vomiting (23% vs 12%), most of which were grade 1 or 2. More patients in the IRd group received antiemetic drugs (21% vs 13%).[1] Nausea was more common on the day of or after ixazomib dosing and during the first 3 cycles of treatment.[3] Similarly, nausea (39% vs 15%), diarrhea (35% vs 24%), and vomiting (27% vs 11%) were more common in the ixazomib group compared with the placebo group in the TOURMALINE-MM3 study. Quality-of-life assessments from the TOURMALINE-MM3 study revealed that the only subscales negatively impacted in patients taking ixazomib were those related to nausea/vomiting.

IN PRACTICE
About one-third of patients taking all-oral therapy experience nausea, and over 20% experience vomiting.
and diarrhea. Antiemetics were administered to or required in 19% of patients in the ixazomib group compared with 4% in the placebo group.[2]

**Management of Nausea and Vomiting**

As the number of myeloma patients on all-oral therapy increases, it is important for clinicians to appropriately manage potential toxicities that may decrease adherence and quality of life. Although classified with a low emetogenic potential, it is essential to provide individuals taking these agents with antiemetic medications, such as ondansetron or prochlorperazine, since approximately one-third of patients will experience nausea and over 20% will experience vomiting.[1,2,6] Those with a history of nausea and vomiting or who are more susceptible to nausea and vomiting, such as women < 50 years of age, should be counseled to take antiemetic prophylaxis before each ixazomib dose. [6] This recommendation may be especially important for patients on ixazomib monotherapy, since they experience higher rates of nausea and vomiting compared with combination therapy.[1,2] Although the TOURMALINE-MM1 and -MM3 studies cannot be directly compared, this is potentially due to the antiemetic effect of dexamethasone in the IRd group.[1,2,7] Patients taking ixazomib in combination with lenalidomide and dexamethasone present an additional confounder and patient education point. Per manufacturer recommendations, ixazomib should be taken on an empty stomach at least 1 hour before or 2 hours after a meal. [7] Those with a history of nausea and vomiting or who are more susceptible to nausea and vomiting, such as women < 50 years of age, should be counseled to take antiemetic prophylaxis before each ixazomib dose. [6] This recommendation may be especially important for patients on ixazomib monotherapy, since they experience higher rates of nausea and vomiting compared with combination therapy.[1,2] Although the TOURMALINE-MM1 and -MM3 studies cannot be directly compared, this is potentially due to the antiemetic effect of dexamethasone in the IRd group.[1,2,7] Patients taking ixazomib in combination with lenalidomide and dexamethasone present an additional confounder and patient education point. Per manufacturer recommendations, ixazomib should be taken on an empty stomach at least 1 hour before or 2 hours after a meal, since a high-fat meal dramatically decreases drug concentrations. [7] With IRd, dexamethasone is taken on the same day as ixazomib. However, since gastrointestinal toxicities, such as gastric ulcers and dyspepsia, are a known adverse effect with dexamethasone, it is commonplace to recommend that patients take it with food to reduce such toxicities, thus separating the administration of dexamethasone and ixazomib. [5,7]

**Key Considerations With Ixazomib**

- The starting dose of ixazomib in relapsed/refractory multiple myeloma should be reduced from 4 mg to 3 mg in patients with a creatinine clearance < 30 mL/min or moderate-to-severe hepatic impairment at baseline. [7]
- Ixazomib is metabolized by several CYP enzymes, and concomitant use with strong CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, St. John’s Wort) should be avoided. [7]
- Ixazomib should be taken on an empty stomach (1 hour before or 2 hours after a meal). [7]
- Herpes zoster prophylaxis is recommended, even while patients are receiving ixazomib monotherapy, since herpes zoster occurred in 60% of patients receiving ixazomib in the TOURMALINE-MM3 study before the trial was amended to require prophylaxis. [2]

**Management of Diarrhea and Constipation**

Diarrhea is more common in patient groups receiving ixazomib and is also increased among those receiving ixazomib in combination with lenalidomide and dexamethasone. Diarrhea occurs primarily on the day of or after ixazomib dosing and can usually be managed successfully with loperamide. [1,3,8,9] Persistent diarrhea that does not coincide with the timing of ixazomib is more likely related to lenalidomide treatment. While excluding other causes of diarrhea, colesevelam hydrochloride, a bile acid sequestrant, has demonstrated benefit for patients with lenalidomide-attributed chronic diarrhea due to bile acid malabsorption. [10,11] Stool softeners and laxatives are generally used to relieve constipation, but other causes, such as opioid pain medication utilization and diet, should be investigated as well. [1-3,8]

**Considerations for Adherence**

A recent study in relapsed/refractory multiple myeloma patients demonstrated through surveys that patients prefer the convenience of an all-oral myeloma regimen, even at the expense of efficacy or additional toxicities. [12] Other surveys have demonstrated that better adherence to therapy correlates with higher quality of life. [13] As the treatment of multiple myeloma continues to shift towards chronic management, strategies to aid patient adherence to oral therapies should be utilized. Beyond toxicities, barriers to adherence for ixazomib include its timing of administration without food and cyclic weekly dosing. [14] Weekly reminder alarms on smart devices and patient-specific calendars, which can be printed off the manufacturer’s website, can be beneficial tools in a patient’s understanding of a perceivably complex schedule of administration. [14,15] Counseling patients on the most likely timing of gastrointestinal toxicities, when to take prophylactic antiemetics if necessary, and how to appropriately manage these events are key in promoting patient adherence and improving quality of life.

**FINANCIAL DISCLOSURE:** The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

**For references visit**
cancernetwork.com/ixazomib-toxicities

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Newly Diagnosed Glioblastoma: A Review on Clinical Management

Rimas V. Lukas, MD, Derek A. Wainwright, PhD, Erik Ladomersky, PhD, Sean Sachdev, MD, Adam M. Sonabend, MD, and Roger Stupp, MD

ABSTRACT: Glioblastoma is an aggressive primary tumor of the central nervous system. This review will focus on clinical developments and management of newly diagnosed disease, including a discussion about the incorporation of molecular features into the classification of glioblastoma. Such advances will continue to shape our thinking about the disease and how to best manage it. With regards to treatment, the role of surgical resection, radiotherapy, chemotherapy, and tumor-treating fields will be presented. Pivotal studies defining our current standard of care will be highlighted, as well key ongoing trials that may influence our management of glioblastoma in the near future.

Introduction
Glioblastoma, previously known as glioblastoma multiforme, is the most aggressive among infiltrative gliomas, a group of primary tumors arising from the central nervous system (CNS). Patients with this cancer type face significant morbidity and mortality, with over 13,000 deaths per year in the United States. Recent advances in our biological understanding of gliomas have led to important and substantive changes in their classification, in the identification of prognostic and predictive molecular markers, and in the therapeutic management of newly diagnosed glioma.

Classification
The term ‘glioblastoma multiforme’ was introduced in the 1926 classification system devised by Cushing and Bailey,[1] ‘Multiforme,’ which refers to a heterogenous histologic appearance and proliferation of multiple cell types, was abandoned from the revised nomenclature in the 2007 World Health Organization Classification of Tumors of the Central Nervous System, and is now simply called ‘glioblastoma.’[2] Glioblastoma is histologically defined by neoplastic cells with astrocytic characteristics and the presence of either endothelial proliferation—often in a glomeruloid morphology—and/or necrosis, which may resemble a pseudopalisading pattern (a false fence of neoplastic cells surrounding an area of necrotic tissue).

Due to its aggressive and highly proliferative course, glioblastoma is considered a grade IV astrocytoma. Molecular characterization has allowed for further refinement of the condition’s classification and is now an integral part of the diagnosis of malignant glioma.[3] Patients are classified into one of two distinct categories based on the presence or absence of mutations in the IDH1 or IDH2 genes.

Primary glioblastoma/IDH wild-type glioblastoma
The majority of glioblastomas are IDH wild-type and correspond to the longstanding clinical description of primary glioblastomas, which arise rapidly from non-neoplastic brain cells and progress quickly. In addition, a subgroup of lower-grade gliomas may carry molecular features and signatures similar to glioblastoma, with a similarly aggressive natural course,[4] for which an intensive treatment strategy is advocated. These facts stress that a microscopic histologic diagnosis alone is insufficient to make informed and rational clinical decisions; therefore, it is essential that molecular alterations be integrated when diagnosing and managing glioma. This will potentially be of benefit...
Glioblastoma remains a macabre tumor with only incremental improvement over the last 4 to 5 decades. Fortunately, we practice in a time of remarkable growth in our neuroscience and cancer biology knowledge base. This leads one to hope that innovation in the management of glioblastoma is close at hand.

In the near future, operative methods will continue to trend toward decreased invasiveness, through techniques such as guided laser thermal ablation. Surgical precision will improve through fluorescence-guided resection of tumors. Drug delivery, too, will be optimized with the use of transport vesicles steered by engineered proteins and nanoparticles, used as vehicles to deliver therapeutic agents across the blood-brain barrier. Consequently, many drugs previously thought unsuitable for glioblastoma due to systemic toxicity or blockage by the blood-brain barrier may prove useful.

Moreover, it is expected that big data, next-generation sequencing, and genetic identification algorithms will guide operative intervention, clinical trials, and medication selection. Such methods will also account for the marked heterogeneity in glioblastoma and lead to an era of molecular polytherapy, guided by analysis from numerous tumor samples from the same patient. Such tailored ‘molecular cocktails’ will improve efficacy by targeting upstream initiators, alterations enabling cell growth, and predicted downstream compensation/resistance mechanisms.

Recent advances in sequencing of tumor DNA from circulating tumor markers will make such clinical trials easier to perform and less reliant on operative procedures such as invasive tumor biopsies. Hope, too, remains that combination immunotherapy will play a role in glioblastoma management, whether by tailoring immune cells to target glioblastoma or by reinventing appropriate microglial function.

Insights on stem cell biology will also help to advance our management of glioblastoma. While radiation and traditional chemotherapy may serve a waning role in the future, their efficacy will be improved by simultaneous use of agents targeting tumor stem cell quiescence. Realistically, though, salvage therapy will still be required, and one can envision the use of self-replicating viruses to fight tumor stem cells, finally partially fulfilling the promise inherent in our present knowledge base.

To completely fulfill our promise to our patients, we’ll have to accept that glioblastoma is a disease of information and mixed-up signals among the genome, epigenome, microbiome, proteome, transcriptome, and metabolome, among others. As such, we’ll need a better biobliome of all the expanding information that separates the inessential from the pertinent.

**Financial Disclosure:** Dr. Butowski has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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**Secondary glioblastoma/IDH-mutated glioblastoma**

Up to 10% of patients with glioblastoma harbor a mutation in the IDH1 or IDH2 genes, an early event in gliomagenesis. Since these glioblastomas often arise from a prior lower-grade glioma, they are considered secondary glioblastomas. In the past, both primary and secondary glioblastomas were considered to be the same clinical entity. However, recent studies clearly indicate that IDH-mutated glioblastomas have a more protracted natural course. As such, secondary glioblastomas are to be classified as a distinct biological and molecular entity for which different treatment strategies will ultimately be proposed. Former series of long-term survivors are commonly enriched for patients with IDH-mutated tumors.

**Epidemiology**

Primary CNS tumors represent only 2% of adult cancer diagnoses; however, due to their location and often rapid clinical course, they are associated with high morbidity and mortality. About 50% of primary malignant CNS tumors are glioblastoma, with an incidence rate of 3.20 per 100,000 population for the United States. Incidence is higher in whites than in blacks (3.46 vs 1.79 per 100,000 population, respectively), with a 1.93:1 ratio ($P < .05$), a difference for which no biological explanation exists. Compared with whites, the incidence of glioblastoma is somewhat lower in Asians. The condition occurs more frequently in men than in women, with a 1.58:1 ratio ($P < .05$). Over the last 3 decades, the incidence of glioblastoma in the United States has been relatively stable; however, an aging population and better diagnostic tools may lead to a higher incidence of disease, as has been suggested in other countries. Further study is needed to confirm changes in incidence, and, if present, to determine the causal factors.
Both environmental and patient-intrinsic factors may influence the risk of developing glioblastoma. An established risk factor is prior exposure to ionizing radiation to the CNS. The lag time between radiation and the development of glioblastoma may range from years to decades.[9-11] Unlike other cancers, there is no histologic or molecular signature that is pathognomonic for radiation-induced glioblastoma. The condition is observed in several hereditary cancer syndromes, including Lynch syndrome (with mutations in MSH2, MLH1, MSH6, and PMS2) and Li-Fraumeni syndrome (with mutations in TP53).[7] While mutations in some tumor suppressor genes increase the risk of susceptibility, the presence of an allergic disorder appears to be associated with a decreased incidence of glioma, including glioblastoma, across a number of epidemiologic and preclinical studies.[7,12-14]

Pathophysiology

Despite extensive study, the cellular origin of glioblastoma and the pathophysiologic mechanism of gliomagenesis remain uncertain. Research on the cell of origin for glioblastoma often involves targeting different precursor cell populations in transgenic mouse models and explores the effects of these interventions on the development of glioma. However, contemporary thought favors primitive pluripotent cells, including neural stem cells, glial precursor cells, and oligodendrocyte precursor cells.[15] Numerous preclinical models have been conducted in this area, each with their favorable attributes and drawbacks.[16-19]

Research demonstrates that, amongst IDH wild-type glioblastomas, there are spatial intratumoral differences in the mutational profile and clonality of tumor cells, with approximately half of the mutations being regionally exclusive. Distinct areas found within these tumors can exhibit a hypermutated phenotype. When present, mutations in the TERT gene appeared across all clones.[20] Recent studies utilizing xenografts in murine models have shown that these tumors consist of a slow-cycling population of stem-like cells, which give rise to a rapidly dividing progenitor cell population, a proportion of whose daughter cells develop into terminal differentiated cells, supporting a hierarchical model of gliomagenesis.[21] A minority of the clonal population proves resistant to chemotherapy.[21] In turn, this cell population will require different treatments. When evaluated longitudinally, recurrent glioblastoma can accumulate additional mutations,[22] and can appear similar to the primary tumor or may resemble a distinct subclonal population.[23,24] It is thought that this genomic heterogeneity is driven, at least in part, by the uneven cellular inheritance patterns of extra-chromosomal DNA.[25] As we garner a clearer understanding of the pathophysiology of gliomagenesis, new areas for potential therapeutic intervention will open up.

In addition to the difficulties associated with treating heterogenous tumors, which evolve over the course of the disease and harbor treatment-resistant subpopulations of cells, the blood-brain barrier is another impediment to the effective treatment of these tumors. The blood-brain barrier is a dynamic functional system, which both precludes and modulates the traversing of systemically administered therapies into the CNS, including CNS tumors.[26] Numerous means have been utilized to overcome this obstacle. Thus far, the most successful have included systemically administered drugs with adequate CNS penetration (eg, temozolomide) and locally delivered alternating electrical fields (tumor-treating fields, TTFIELDS). Direct intracranial application of both chemotherapy (eg, biodegradable carmustine-impregnated wafers) and radiation (eg, brachytherapy) has also been explored.

Intratumoral injection of oncolytic viruses and chimeric antigen receptor (CAR) T-cell therapies is a modern example of a similar strategy that is undergoing active investigation.[27,28] Disruption of the blood-brain barrier to facilitate transmission of a systemically administered therapy has been under investigation for many decades. Initial studies utilized intra-arterially–administered agents.[29] A recent strategy being studied includes ultrasound to open up the barrier.[30] Another, which has had varying degrees of success, is avoiding the need to overcome the blood-brain barrier. The utilization of therapeutics whose direct activity occurs on the luminal side of the blood-brain barrier (eg, bevacizumab)[31]—or which act on the luminal side, with a goal of affecting function on the tumoral side of the barrier (eg, immune checkpoint inhibitors)—is another way to attempt to circumvent this obstacle. It is reasonable to surmise that more than one approach may prove to be successful.

Therapeutic Management

The therapeutic management of newly diagnosed glioblastoma typically involves a four-pronged approach. First, surgical resection is completed to the maximal safe extent, thereby reducing the tumor load and establishing a histopathological and molecular diagnosis. Following surgery, adjuvant radiotherapy is given with concomitant and maintenance chemotherapy, as is treatment of alternating electrical fields.

Surgery

Surgery plays an important diagnostic and therapeutic role in the management
of glioblastoma: it offers tissue for histological and molecular diagnosis, immediate relief of the tumor-related mass effect and its associated symptoms, and potential cytoreduction. However, due to the invariably infiltrative nature of the disease, even macroscopically complete resection is not curative. Numerous retrospective studies have evaluated the value of the extent of resection in glioblastoma. While early work suggested a dichotomous picture with a need for a substantial extent of resection of the contrast-enhancing tumor,[32] subsequent studies demonstrated the graded benefit of the extent of resection.[33,34] A more recent meta-analysis also supports a more extensive resection with improved 1- and 2-year survival rates, as well as prolonged progression-free survival.[35] In low-grade glioma, the extent of resection is influenced by the area of increased signal on T2/fluid-attenuated inversion recovery (FLAIR) imaging.[36-39] Similarly, glioblastoma tumors are not limited to the area of enhancement but rather involve the area of increased T2/FLAIR signal. The extent of resection of this non-enhancing glioblastoma may also be of clinical impact, as demonstrated in a recent retrospective study.[40]

Although the association between extent of resection and survival has been reported and consistently confirmed in numerous studies, it is subject to several potential confounders, biases, and occult prognostic factors. While cytoreduction may intuitively delay disease recurrence, the non-linear growth of tumor cells seen in glioblastoma could quickly recover the tumor burden that was removed during surgery, negating the survival benefit of small increments of cytoreduction. The durability of the effect of cytoreduction, and whether it leads to a survival benefit, is likely related to the rate of tumor cell proliferation. On the other hand, patients with neurological deficits have lower functional status, which ultimately impacts their overall survival. Thus, it is possible that relief of mass effect leading to improved functional status from resection might prolong survival in symptomatic patients, irrespective of cytoreduction. Finally, the tumor location may also reflect the underlying biology and dictate the natural history of the disease. Determination of the influence of these previously described variables on overall survival is complicated, since resectable tumors may have an overall better prognosis, regardless of the actual extent of resection.

Resectable tumors often present in “silent areas of the brain” that tolerate injury for a long period of time prior to becoming symptomatic. In addition, resectable tumors, such as fronto-polar tumors, are more likely to harbor IDH1 mutations, which are associated with a better prognosis. In contrast, unresectable tumors, such as midline/diencephalic or brainstem tumors, often bear H3K27 mutations, which indicate an overall more aggressive biology and a worse prognosis.[41] Further dissection of the relationship between the extent of resection and survival requires controlling for tumor resectability. Yet, this complicated variable is difficult to capture by established scales, and is influenced by anatomical considerations, as well as neurosurgeon-related factors.[42]

Maximizing extent of resection. A number of technological advances have been developed to safely maximize the extent of resection, although their availability and usage may vary greatly. These techniques have become more widespread over time because, in addition to maximizing the extent of resection, they also optimize the safety of intra-axial brain tumor surgery. The major technological tools that surgeons use for improving the safety and accuracy of resection can be divided into three groups, as follows.

Intraoperative navigation technology. This technology involves the use of volumetric imaging (eg, MRI or CT scan), which is used as a reference to locate a lesion/anatomical structure within the surgical field. Navigation involves an optical or electromagnetic system that uses a physical reference to register the location and position of a patient’s head in space, and allows real-time visualization of instruments within the images, which are loaded to a computer. These technologies help minimize the extent of the open craniotomy exposure; optimize a trajectory to access lesions that avoids critical neural structures, such as white matter pathways; and provides an anatomical reference during the operation. However, they are limited by the fact that the refer-

### TABLE 1 Clinical Trials Investigating Various Radiation Dosing Regimens

<table>
<thead>
<tr>
<th>Author</th>
<th>Minimum Age</th>
<th>Fractional Dose</th>
<th>Total Dose</th>
<th>Duration</th>
<th>Concurrent Chemotherapy?</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauman et al (1994)[83]</td>
<td>65 yr (or KPS ≤ 50)</td>
<td>3.0 Gy</td>
<td>30.0 Gy</td>
<td>10 d</td>
<td>No</td>
<td>6 mo</td>
</tr>
<tr>
<td>Roa et al (2004)[115]</td>
<td>60 yr</td>
<td>2.67 Gy</td>
<td>40.0 Gy</td>
<td>15 d</td>
<td>No</td>
<td>5.6 mo</td>
</tr>
<tr>
<td>Malmstrom et al (2012)[81]</td>
<td>60 yr</td>
<td>3.4 Gy</td>
<td>34.0 Gy</td>
<td>10 d</td>
<td>No</td>
<td>7.5 mo</td>
</tr>
<tr>
<td>Roa et al (2015)[84]</td>
<td>65 yr (or KPS 50–70)</td>
<td>5.0 Gy</td>
<td>25.0 Gy</td>
<td>5 d</td>
<td>No</td>
<td>7.9 mo</td>
</tr>
<tr>
<td>Perry et al (2017)[82]</td>
<td>65 yr</td>
<td>2.67 Gy</td>
<td>40.0 Gy</td>
<td>15 d</td>
<td>Yes</td>
<td>9.3 mo</td>
</tr>
</tbody>
</table>

KPS = Karnofsky Performance Status.
enced images are not updated as resection progresses, and brain shift in space in relation to the skull makes this information less reliable as the case advances. To address this, several groups have introduced intraoperative MRI, which provides a real-time update of the field for navigation.[43,44] The true utility and cost-effectiveness ratio of intraoperative MRI remains a highly debated topic, since cost and added time during the procedure are not insignificant. The use of intraoperative ultrasound is a dynamic, easy to use, and affordable alternative for real-time imaging during surgery.

**Electrophysiological monitoring and functional brain mapping.** Wilder Penfield and George Ojemann pioneered the use of electrodes to functionally map sensory and motor primary cortical regions and related subcortical circuits as the spinothalamic and corticospinal tracts to avoid postoperative deficits.[45-48] Over the last few decades, work by George Ojemann, Hugues Duffau, Mitchell Berger, and others has incorporated the routine use of awake brain mapping techniques, which have greatly improved the surveillance of motor circuits, language/comprehension, coordination, vision, and some higher cognitive functions by enabling them to be mapped and preserved.[49-53]

**Fluorescent markers to maximize tumor visualization.** Fluorescent dyes—which are either metabolized by tumor cells, or accumulate in areas of blood-brain barrier breakdown—have been incorporated to maximize tumor tissue visualization in the operating room. This is helpful, as gross tumor tissue often has a similar texture or color as the surrounding edematous brain and is not always easy to distinguish under bright light. The use of 5-aminolevulinic acid under blue light allows the neurosurgeon to view residual tumor in real-time during surgery. A phase III trial demonstrated an improved rate of complete resection (65% vs 36%; \( P < .0001 \)) and an improved 6-month progression-free survival rate (41% vs 21%; \( P = .0003 \)) for contrast-enhancing tumor with 5-aminolevulinic acid compared with conventional microsurgery with white light. However, this did not translate into an improvement in overall survival.[54] Fluorescein has also been used to visualize enhancing tumor, as this dye leaks through areas with defective blood-brain barrier.[55,56] Here, no special light source is needed.

**Radiation therapy.** Radiotherapy has been shown to improve survival in glioblastoma and plays a key role in treatment. Modern conformal radiotherapy—which utilizes threedimensional computerized planning and multi-beam modulation—locally treats MRI-evident disease plus margin to a cumulative absorbed dose of 60 Gy. Given in daily doses of 1.8 to 2.0-Gy fractions, total treatment lasts approximately 6 weeks and is usually initiated 3 to 4 weeks after surgery. While some reports have suggested that delayed radiotherapy has a detrimental effect, other investigators have reported better outcomes; this question has yet to be definitively answered.[57,58] Up to 6 to 7 weeks of postoperative recovery is considered acceptable as part of the established standard of care.

Earlier studies have examined doses of more than 60 Gy, some of which incorporated stereotactic radiosurgery. However, they failed to demonstrate improved outcomes with doses of up to 76 Gy.[59] An ongoing randomized phase II study, NRG BN001 (ClinicalTrials.gov identifier: NCT02179086), is evaluating dose escalation to 75 Gy compared with standard 60-Gy radiotherapy.[60] This study includes distinct cohorts utilizing photons or protons, and the primary endpoint is survival.

For elderly patients or those with substantially altered performance status and poor prognosis, an abbreviated course of “hypofractionated” radiotherapy allows for a shortened overall treatment time. Long-term toxicity is of less concern in this population due to a commonly short survival. Hypofractionated radiation, which has been widely investigated, has been utilized to improve tolerability of radiotherapy (Table 1). Tumor volume often guides the selection of a radiation regimen because the risk of toxicity is theoretically greater with high vs low daily doses. Omitting radiotherapy (even less than the standard 60 Gy) leads to significantly worse survival compared with best supportive care alone.[61] Recent prospective data have demonstrated that abbreviated courses can also be safely and effectively combined with concurrent chemotherapy, as covered in the section below regarding treatment strategies for elderly patients.

A direct prospective comparison between full-course radiotherapy with concurrent and adjuvant chemotherapy vs abbreviated-course radiotherapy with concurrent and adjuvant chemotherapy has not been conducted. In addition to an abbreviated course of radiotherapy, the shorter course also employs a shorter course of concomitant chemotherapy. This lack of direct comparison leaves an important question not fully answered. In many clinical practices, the full course of radiotherapy and chemotherapy will be utilized in elderly patients with good performance status.

**Systemic therapy.** We recently reviewed in detail the pivotal late-phase trials that led to the current standard of care for patients with newly diagnosed glioblastoma.[62] These trials are summarized in Table 2. Temozolomide...
<table>
<thead>
<tr>
<th>Trial Designation</th>
<th>Author</th>
<th>Year</th>
<th>Phase</th>
<th>N</th>
<th>Age</th>
<th>Study Design</th>
<th>Median OS</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Walker[116]</td>
<td>1978</td>
<td>III</td>
<td>222</td>
<td>NR</td>
<td>HGG patients</td>
<td>34.5 wk</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCNU/RT + BCNU vs BCNU vs RT vs supportive care</td>
<td>vs 18.5 wk</td>
<td>vs 35 wk vs 14 wk</td>
</tr>
<tr>
<td>N/A</td>
<td>Westphal[117]</td>
<td>2003</td>
<td>III</td>
<td>240</td>
<td>18–65 yr</td>
<td>HGG patients</td>
<td>13.9 mo vs 11.6 mo in HGG patients</td>
<td>5.9 mo vs 5.9 mo in HGG patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCNU-wafers + RT vs placebo-wafers + RT</td>
<td>34.5 wk vs 18.5 wk vs 35 wk vs 14 wk</td>
<td></td>
</tr>
<tr>
<td>EORTC 26981/22981; NCIC CE3</td>
<td>Stupp[63,64]</td>
<td>2005</td>
<td>III</td>
<td>573</td>
<td>18–71 yr</td>
<td>RT/TMZ + TMZ vs RT</td>
<td>16.6 mo vs 14.9 mo</td>
<td>6.9 mo vs 5.1 mo</td>
</tr>
<tr>
<td>N/A</td>
<td>Keime-Guibert[61]</td>
<td>2007</td>
<td>N/A</td>
<td>85</td>
<td>≥ 70 yr</td>
<td>RT/supportive care vs supportive care</td>
<td>29.1 wk vs 16.9 wk</td>
<td>14.9 wk vs 5.4 wk</td>
</tr>
<tr>
<td>RTOG 0525</td>
<td>Gilbert[72]</td>
<td>2013</td>
<td>III</td>
<td>833</td>
<td>≥ 18 yr</td>
<td>RT/TMZ + TMZ (150–200 mg/m²/d for 25/28 d) vs RT/TMZ + TMZ (75 mg/m²/d for 21/28 d)</td>
<td>16.6 mo vs 14.9 mo</td>
<td>5.5 mo vs 6.7 mo</td>
</tr>
<tr>
<td>RTOG 0825</td>
<td>Gilbert[73]</td>
<td>2014</td>
<td>III</td>
<td>637</td>
<td>≥ 18 yr</td>
<td>RT/TMZ/bev + TMZ/bev vs RT/TMZ + TMZ</td>
<td>16.8 mo vs 16.7 mo</td>
<td>10.7 mo vs 10.6 mo</td>
</tr>
<tr>
<td>AVAglio</td>
<td>Chinot[74]</td>
<td>2014</td>
<td>III</td>
<td>921</td>
<td>≥ 18 yr</td>
<td>RT/TMZ/bev + TMZ/bev vs RT/TMZ + TMZ</td>
<td>16.8 mo vs 16.7 mo</td>
<td>10.6 mo vs 6.2 mo</td>
</tr>
<tr>
<td>CENTRIC EORTC 26071-22072</td>
<td>Stupp[118]</td>
<td>2014</td>
<td>III</td>
<td>545</td>
<td>≥ 18 yr</td>
<td>MGMT methylated</td>
<td>26.3 mo vs 26.3 mo</td>
<td>10.6 mo vs 7.9 mo</td>
</tr>
<tr>
<td>GLARIUS</td>
<td>Herrlinger[107]</td>
<td>2016</td>
<td>II</td>
<td>182</td>
<td>NR</td>
<td>RT/bev + bev/CPT11 vs RT/TMZ + TMZ</td>
<td>16.6 mo vs 17.5 mo</td>
<td>9.7 mo vs 9.59 mo</td>
</tr>
<tr>
<td>ACT IV</td>
<td>Weller[110]</td>
<td>2017</td>
<td>III</td>
<td>745</td>
<td>≥ 18 yr</td>
<td>Enrolled after completion of RT/TMZ</td>
<td>21.1 mo vs 20.0 mo</td>
<td>8.0 mo vs 7.4 mo</td>
</tr>
<tr>
<td>EF-14</td>
<td>Stupp[87,88,93]</td>
<td>2017</td>
<td>III</td>
<td>695</td>
<td>≥ 18 yr</td>
<td>Enrolled after completion of RT/TMZ</td>
<td>20.9 mo vs 16.0 mo</td>
<td>6.7 mo vs 4.0 mo</td>
</tr>
<tr>
<td>CCTG CE.6, EORTC 26062-22061, TROG 08.02</td>
<td>Perry[82]</td>
<td>2017</td>
<td>III</td>
<td>562</td>
<td>≥ 65 yr</td>
<td>Short-course RT/TMZ + TMZ vs short-course RT</td>
<td>9.3 mo vs 7.6 mo</td>
<td>5.3 mo vs 3.9 mo</td>
</tr>
<tr>
<td>CeTeG/NOA-09</td>
<td>Herrlinger[119]</td>
<td>2019</td>
<td>III</td>
<td>141</td>
<td>18–70 yr</td>
<td>MGMT methylated</td>
<td>31.4 mo vs 48.1 mo</td>
<td>16.7 mo vs 16.7 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RT/TMZ + TMZ vs RT/CCNU/TMZ + CCNU/TMZ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCNU-wafers = carmustine wafers; bev = bevacizumab; CCNU = lomustine; CCTG = Canadian Cancer Trials Group; CPT11 = irinotecan; EORTC = European Organisation for Research and Treatment of Cancer; GBM = glioblastoma; HGG = high-grade glioma, including glioblastoma; MGMT = O6-methylguanine-DNA methyltransferase; N/A = not available; NCIC = National Cancer Information Center; NR = not reported; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; TMZ = temozolomide; TROG = Trans Tasman Radiation Oncology Group; TTFields = tumor-treating fields.
mide is a DNA-alkylating chemotherapy agent that is designed to readily cross the blood-brain barrier to achieve therapeutic concentrations in the brain. In 2001, a large, international, randomized, phase III trial, the European Organisation for Research and Treatment of Cancer (EORTC) 26981/22981/NCI Canada (NCIC) CE3 trial, demonstrated prolonged survival when daily temozolomide chemotherapy (75 mg/m² daily × 40-49 days) is added concomitantly to radiotherapy followed by 6 cycles of maintenance temozolomide (150–200 mg/m² × 5/28 days). Based on this landmark trial, temozolomide/radiotherapy followed by maintenance temozolomide has become the worldwide standard of care for patients with newly diagnosed glioblastoma.[63,64]

Temozolomide adds a methyl group to the DNA residues at the O6, N3, and N7 positions that, if unrepaired, leads to DNA strand breaks and cytotoxicity. More than one-third of glioblastomas are deficient in O⁶-methylguanine-DNA methyltransferase (MGMT), a repair protein that removes the methyl adduct from the O6 guanine position. This MGMT deficiency is via methylation of the MGMT gene promoter, which leads to downregulated transcription. Glioblastoma patients with a silenced MGMT gene who are treated with an alkylating agent chemotherapy have a longer survival than those with an unmethylated MGMT and those treated with radiotherapy alone.[65] In studies of paired tissue samples, MGMT promoter methylation is relatively conserved from the newly diagnosed to progressive disease settings, with the majority of tumors maintaining an unchanged profile over time.[66,67]

In mismatch repair-deficient conditions, the O6 guanine methyl adduct is tolerated and can be mutagenic. This may be a key mechanism in the development of glioma mutations due to temozolomide, and is described in low-grade glioma progressing to higher-grade tumors, as well as potentially in the development of a hypermutated phenotype.[68,69]

The methyl adducts at N3 and N7 are addressed by the base excision repair mechanism.[70] Inhibition of this mechanism continues to undergo investigation in trials of poly (ADP-ribose) polymerase (PARP) inhibitors.

Optimal duration of adjuvant temozolomide chemotherapy. The pivotal EORTC/NCIC study established a regimen of up to 6 adjuvant chemotherapy cycles. However, in the United States, the duration of chemotherapy may still extend for up to 12 cycles or more in non-progressive patients. While early treatment discontinuation is a concern due to the disease’s poor prognosis, cumulative toxicity, impaired bone marrow reserve for subsequent second-line chemotherapy, and increased risk of secondary malignancies are concerns with prolonged treatment. In some trials, treatment was allowed per local practice to be extended to up to 12 cycles.

A pooled meta-analysis of individual patient outcomes data stemming from four randomized trials compared the duration of maintenance temozolomide chemotherapy (6 cycles vs 7+ cycles) among individuals who were non-progressive after 6 cycles.[71] While there was a slight improvement in progression-free survival, no difference in survival was seen for those who received 6 cycles vs more than 6 cycles of chemotherapy. This suggests that prolonged administration and dose intensification do not improve disease control. At this time, the value of temozolomide during radiotherapy, independent of adjuvant temozolomide in the treatment of glioblastoma, is unknown.

Alternative temozolomide dosing schedules. Alternative dosing schedules have been investigated in the newly diagnosed and recurrent disease settings.

However, none of these regimens have been shown to be superior to the standard temozolomide dosing schedule. The randomized Radiation Therapy Oncology Group (RTOG) 0525 study found no benefit with intensified maintenance chemotherapy. Patients were randomized at the end of chemoradiotherapy to either standard maintenance therapy (150–200 mg/m²/day × 5/28 days) or an intensified daily regimen (75 mg/m²/day × 21/28 days), effectively doubling the cumulative dose of chemotherapy. No difference in outcomes was noted, and a higher incidence of grade 3/4 toxicities was observed in the investigational arm.[72]

Hopes and disappointments with bevacizumab. The addition of the anti-angiogenic agent bevacizumab to radiotherapy and temozolomide has been explored in two phase III trials focusing on newly diagnosed glioblastoma[73,74] and one phase III trial focusing on recurrent glioblastoma.[75] The observed and expected improvement in progression-free survival based on imaging did not translate into any improvement in overall survival when bevacizumab was added. Unplanned post-hoc analyses found an association of improved overall survival in a molecularly defined subset of patients.[76] The addition of bevacizumab to hypofractionated radiotherapy demonstrated no improvement in overall survival compared with hypofractionated radiotherapy alone in elderly (≥ 65 years) patients with newly diagnosed glioblastoma.[77] Based on the results of these trials, bevacizumab should not be administered as part of primary treatment of glioblastoma. Of note, some physicians utilize bevacizumab as a corticosteroid-sparing agent to decrease cerebral edema, so that treatment with standard...
Radiotherapy and chemotherapy is feasible without high doses or prolonged use of corticosteroids.

De-escalation of treatment in the elderly. De-escalation of therapeutic interventions has been extensively explored in the elderly and in frail populations with glioblastoma. This interest is driven by the overall brief survival of elderly glioblastoma patients, and thus the desire to shorten the duration of medical intervention. This topic has recently been reviewed in detail. [78,79] Several studies have prospectively evaluated abbreviated courses of radiotherapy in these patients (as covered earlier in the “Radiation Therapy” section).

Two large randomized trials have evaluated the exclusive administration of temozolomide chemotherapy in the elderly. Consistently, both trials demonstrated that withholding radiotherapy and instead treating patients with temozolomide alone may be an option for elderly patients with tumors harboring a methylated MGMT gene promoter, while this strategy is detrimental in the absence of MGMT methylation.[80,81] Monotherapy with temozolomide offers the advantage of an oral treatment regimen without the need for daily radiotherapy. The utilization of a short-course hypofractionated radiotherapy regimen (of 40 Gy in 15 treatments) with concomitant temozolomide, followed by adjuvant temozolomide, was shown to improve outcomes in the elderly, which is consistent with the observed benefi t reported 10 years earlier by the EORTC/NCIC trial in patients up to age 70 years.[82] The clinical circumstances, including chronologic age, performance status, concurrent medical problems, MGMT promoter methylation

### TABLE 3 Ongoing Late-Phase Clinical Trials for Newly Diagnosed Glioblastoma

<table>
<thead>
<tr>
<th>Trial Designation</th>
<th>NCT Number</th>
<th>Phase</th>
<th>Planned N</th>
<th>Novel Treatment</th>
<th>Treatment Regimen</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 3508A (Intellance1)</td>
<td>NCT02573324 [111]</td>
<td>IIb/III</td>
<td>640</td>
<td>ABT-414, an EGFR-targeting antibody-drug conjugate</td>
<td>EGFR amplified or EGFRvIII mutated</td>
<td>RT/TMZ + TMZ vs RT/TMZ/ABT-414 + TMZ/ABT-414</td>
</tr>
<tr>
<td>A071102</td>
<td>NCT02152982 [120]</td>
<td>II/III</td>
<td>440</td>
<td>Veliparib, a PARP inhibitor</td>
<td>MGMT promoter methylated</td>
<td>Post-RT/TMZ enrollment vs TMZ/veliparib +/- TTP</td>
</tr>
<tr>
<td>N/A</td>
<td>NCT00045968 [121,122]</td>
<td>III</td>
<td>348</td>
<td>DCVax®-L, an autologous dendritic cell vaccine</td>
<td>Post-RT/TMZ enrollment</td>
<td>TMZ/placebo vs TMZ/DCVax®-L</td>
</tr>
<tr>
<td>CheckMate-548</td>
<td>NCT02667587 [112]</td>
<td>III</td>
<td>693</td>
<td>Nivolumab, a PD-1 antibody</td>
<td>MGMT promoter methylated</td>
<td>RT/TMZ + TMZ vs RT/TMZ/nivolumab + TMZ/nivolumab</td>
</tr>
<tr>
<td>CheckMate-498</td>
<td>NCT02617589 [111]</td>
<td>III</td>
<td>550</td>
<td>Nivolumab, a PD-1 antibody</td>
<td>MGMT promoter unmethylated</td>
<td>RT/TMZ + TMZ vs RT/nivolumab</td>
</tr>
<tr>
<td>N/A</td>
<td>NCT03345095 [123]</td>
<td>III</td>
<td>750</td>
<td>Marizomib, a proteasome inhibitor</td>
<td>RT/TMZ + TMZ vs RT/TMZ/marizomib + TMZ/marizomib</td>
<td>Open to accrual</td>
</tr>
</tbody>
</table>

* Decision to use TTFields is made prior to enrollment but is then continued throughout study treatment.

* Preliminary results.

DCVax®-L = lysate-pulsed dendritic cell vaccine; EGFR = epidermal growth factor receptor; MGMT = O6-methylguanine-DNA methyltransferase; NCT = National Clinical Trials; PARP = poly (ADP-ribose) polymerase; PD-1 = programmed death 1; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; TMZ = temozolomide; TTP = tumor-treating fields.
status, and logistical concerns should all be weighed during therapeutic decision making for elderly patients with glioblastoma. In healthy MGMT-methylated elderly patients with good performance status, a more aggressive approach, including full-course radiotherapy and temozolomide, can be considered.

**Poor performance status.** Both de-escalation and escalation of care for patients with poor performance status have been considered. Many of these evaluations have been performed specifically in the elderly population, thus potentially limiting their generalizability to younger patients. De-escalation approaches attempt to limit the toxicity of treatment in a patient population that may not tolerate and is less likely to benefit from therapy. These approaches also attempt to shorten treatment duration, as well as the amount of travel to the treatment facility, particularly for patients with limited mobility.

The previously discussed abbreviated radiotherapy courses for elderly patients are also often used in the frail population with a poorer performance status; some prospective studies on abbreviated radiotherapy included patients on the basis of performance status alone.[83,84] The use of temozolomide chemotherapy alone has been studied in patients with poor performance status (Karnofsky Performance Score [KPS] of < 70); it was shown to be associated with an improvement in performance status or an improvement to the level of self-care (KPS ≥ 70) in one-third and one-fourth of patients, respectively.[85] Increasing the number of concomitant therapeutics has been performed with the goals of extending survival and improving functionality. One treatment intensification approach adds bevacizumab to the standard of care, relying on the corticosteroid-sparing effects described earlier. This approach has demonstrated only a transient improvement in performance status, and the data thus far do not justify its routine employment, since median overall survival remained short at 5.6 months (95% CI, 4.4–6.4).[86]

**TTFields**

The addition of TTFields to maintenance temozolomide chemotherapy for newly diagnosed glioblastoma patients has recently been incorporated as a new standard of care.

The effect of TTFields was evaluated in two large, prospective, non-blinded randomized trials. In recurrent disease, TTFields failed to show superiority over best physicians’ choice therapy in patients with recurrent glioblastoma.[93] In a pivotal large, randomized, phase III trial, 695 patients with newly diagnosed glioblastoma were randomized to receive adjuvant temozolomide and TTFields or standard maintenance therapy of temozolomide alone after the end of initial treatment with temozolomide/radiotherapy. Patients who received adjuvant temozolomide and TTFields fared much better than those treated with temozolomide alone. Survival was prolonged, with a hazard ratio of 0.63 (95% CI, 0.52–0.76; P < .001), and durable survival was achieved in some patients.[88] This improvement was observed without a measurable negative impact on health-related quality of life.[94] In the real-world setting, the rate of compliance among patients utilizing TTFields is high.[95] The primary toxicity noted in the trials was mild-to-moderate cutaneous toxicity, which typically resolves with minimal intervention.[96]

**Impact of Other Medications**

It has been hypothesized that certain medications commonly used to treat other conditions may potentially benefit patients with glioblastoma. These range from those prescribed for tumor-related conditions—such as epilepsy,[97,98] and cerebral edema—to those which are independent of the neoplastic disease, including hypertension, hyperlipidemia, and venous thromboembolism.[99,100] Thus far, none have been proven to be beneficial. When thoroughly evaluated, none of the associations observed in several studies could be validated in larger cohorts, underscoring the importance of prospective (rather than retrospective) trials with strong biological hypotheses.

**Corticosteroids**

Corticosteroids are frequently used to decrease cerebral edema. Their off-target effects also lead to the suppression of immune system activity. Recent preclinical and clinical work suggests that these unfavorable effects contribute to shortened survival.[101] This is of particular importance as we evaluate the role of immunotherapeutic approaches for the treatment of glioma.[102] Despite the lack of a clear benefit in survival, bevacizumab has been shown to decrease the utilization of corticosteroids in patients with glioblastoma in numerous trials.[73,74,103-105] In routine clinical practice, functional improvement is often seen in association with radiographic improvement; however, it has not been proven to correlate with improved overall survival.
Future Directions

Efforts are continuously being undertaken to improve outcomes for patients with newly diagnosed glioblastoma. The diminishing return of second- and subsequent-line oncologic therapies supports the testing of promising new therapeutic approaches in the newly diagnosed population. This is underscored by the strong survival benefit seen among patients treated with TTFFields in the newly diagnosed setting compared with those with progressive disease. A number of novel regimens are being studied in the newly diagnosed setting (Table 3). While many contemporary trials for newly diagnosed glioblastoma build upon the standard of care, as previously described, trials for patients with unmethylated MGMT promoter status may omit temozolomide without losing treatment efficacy.[106-108]

Epidermal growth factor receptor (EGFR) remains an attractive therapeutic target, since it is frequently upregulated in glioblastoma, and its expression is associated with a worse prognosis; it is constitutionally activated in 30% of glioblastomas with a VIII variant. However, randomized trials targeting EGFR have repeatedly failed.[109,110] The addition of a novel peptide vaccine, rindopepimut, to the standard of care treatment for patients with EGFR-amplified newly diagnosed glioblastoma is eagerly awaited.[111] Finally, the results of two separate trials evaluating the anti–programmed death 1 monoclonal antibody nivolumab in newly diagnosed glioblastoma patients with unmethylated (CheckMate-498)[112] and methylated (CheckMate-548)[113] MGMT promoter status are anticipated. Biomarkers that may help predict benefit from immunotherapies[114] will require prospective evaluation, but may provide insight into the role of immunotherapeutic approaches in glioblastoma.

Conclusion

The therapeutic management of newly diagnosed glioblastoma is well-defined and includes surgery, radiation, temozolomide, and TTFFields. Nuances to management in the elderly or frail exist; in these populations, treatment de-escalation is often considered on a patient-specific basis. The addition of other systemic therapies—such as antiangiogenic agents or other routinely administered medications, such as anti-epileptic or blood pressure agents—has not been shown to improve survival in newly diagnosed glioblastoma. Concerns exist, substantiated by both preclinical and clinical data, that corticosteroid utilization may negatively impact outcomes of immunotherapeutic approaches for the treatment of these patients. This will need to be carefully considered in the design, administration, and interpretation of clinical trials for this disease. As outcomes in glioblastoma remain poor, continued investigation into promising therapeutics is necessary.

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For references visit cancernetwork.com/newly-dxed-glioblastoma

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**Introduction**

While surgical resection of early-stage lung cancer cures some patients, only a minority remain recurrence-free at 5 years.[1] Multiple trials have shown that the majority of recurrences are in distant sites.[1] The high incidence of distant recurrence suggests that systemic therapies are important to improve cure rates. Systemic chemotherapy with cisplatin-based doublets has been shown to improve survival in advanced metastatic disease,[2] so it was logical to evaluate this therapy following surgical resection. Early trials delivered neoadjuvant, perioperative, and adjuvant chemotherapy with surgical resection. Encouraging results of these early studies led to randomized trials of surgery alone vs surgery plus adjuvant or neoadjuvant chemotherapy, the results of which now inform clinical decision making. More recently, new targets in advanced non–small-cell lung cancer (NSCLC) utilizing molecular therapies or immunotherapies have improved survival in these patients.[3,4] Trials of these therapies in early-stage NSCLC are now underway. In this article, we review the data in support of chemotherapy, molecular therapy, and immunotherapy in early-stage lung cancer.

**Advantages of Neoadjuvant Therapy**

Since the majority of recurrences after surgical resection are in distant sites, starting systemic therapy as early as possible maximizes the likelihood of eradicating all micrometastases. Of note, the median age at diagnosis of NSCLC is approximately 70 years, and comorbidities are often present in these patients, particularly those with a history of smoking. This population is best able to tolerate systemic therapy and handle its complications when administered prior to surgery. Neoadjuvant therapy may prevent unnecessary surgery by identifying patients with resistant micrometastatic disease who progress in distant sites despite therapy. The neoadjuvant therapy phase can also be an opportunity to uncover additional comorbid conditions, the management of which can lead to safer surgery or, if not remediable, permit efficient planning of nonoperative therapies.
Pathologic changes in primary tumors at the time of resection provide a reliable way to assess the impact of neoadjuvant treatment on the tumor, and present an opportunity to determine which pathways are involved in allowing cells to persist despite therapy. The presence or absence of residual tumor also presents an opportunity to change or continue the induction regimen after surgery. Objective pathologic responses can be quantitated, and effects on the tumor microenvironment and on the tumor can be assessed.[5-7]

Compared with other types of therapy, neoadjuvant approaches can more rapidly translate clinical research findings into early drug approvals. Compliance with subsequent therapies may also be improved. The neoadjuvant therapy interval can provide additional time to implement and maintain smoking cessation preoperatively, an intervention critical to minimizing risk and allowing for pulmonary “prehabilitation” strategies. Advantages of neoadjuvant therapy are summarized in Table 1.

### TABLE 1 Advantages of Neoadjuvant Therapies for Lung Cancer

- Neoadjuvant therapy attacks micrometastases at the earliest time.
- Therapy may be better tolerated before surgery.
- Sufficient time is available to identify unsuspected metastases and comorbidities before local therapy is initiated.
- Assessment of sensitivity of and resistance to agents used in induction can be completed.
- Determination of pathways contributing to tumor persistence in those without pCR can occur.
- Residual tumor and the surrounding microenvironment can be used to evaluate reasons for lack of benefit and differing responses.
- Potential exists to change the regimen after surgery.
- Accelerated drug approval may be granted if surrogate endpoints are reasonably likely to predict benefit. Longer-term endpoints (EFS, OS) can be assessed for regular approval.
- Major trial endpoints, such as pathologic response, can be determined much faster than time to recurrence after surgery.
- Smoking cessation programs can be implemented before surgery.

EFS = event-free survival; OS = overall survival; pCR = pathologic complete response.

### Neoadjuvant chemotherapy

Past trials evaluating neoadjuvant chemotherapy in early-stage NSCLC were heavily influenced by results from adjuvant chemotherapy trials. Large randomized trials and meta-analyses of these adjuvant trials showed improved survival in the adjuvant chemotherapy arms, with a hazard ratio (HR) of 0.87 and an improved 5-year survival rate of about 5%.[8] Multiple neoadjuvant trials were ongoing at the time that meta-analyses of adjuvant trials were published. Thus, many randomized neoadjuvant trials with a surgery-alone arm were stopped early. However, meta-analyses of these neoadjuvant chemotherapy trials were conducted. A meta-analysis of 15 randomized controlled neoadjuvant trials of 2,385 patients demonstrated that overall survival (OS) was significantly improved with preoperative chemotherapy followed by surgery compared with surgery alone (HR, 0.87; 95% CI, 0.78–0.96; P = .007).[9] Preoperative chemotherapy translated into a 5% absolute improvement in OS at 5 years. Recurrence-free survival (RFS) was also improved with neoadjuvant chemotherapy (HR, 0.85; 95% CI, 0.76–0.94; P = .002). The absolute increase in RFS at 5 years was 6%. Additionally, neoadjuvant chemotherapy decreased the risk of distant recurrence (HR, 0.69; 95% CI, 0.58–0.82; P < .0001). The absolute increase in freedom from distant recurrence at 5 years was 10%. In contrast, adjuvant chemotherapy provided only a 5% absolute improvement in freedom from distant recurrence at 5 years. This meta-analysis of neoadjuvant therapy indicated that the time to locoregional recurrence was not significantly improved with preoperative therapy, suggesting its OS benefit is mainly secondary to decreased rates of distant recurrence.[9]

The magnitude of OS benefit of neoadjuvant chemotherapy was similar to that of adjuvant chemotherapy, although head-to-head comparisons of these two systemic therapy approaches are scarce. One randomized trial, however, did attempt to directly compare neoadjuvant and adjuvant chemotherapy. In this trial, there was no significant difference in 5-year disease-free survival (DFS) or OS.[10]

Thus, current guidelines recommend either neoadjuvant or adjuvant cisplatin doublet chemotherapy for patients with stage IB–IIIA NSCLC.[11] There is still some uncertainty regarding the treatment of patients without nodal involvement. While some studies found that patients with tumors larger than 4 cm without nodal involvement had improved survival with adjuvant chemotherapy,[12] others did not show such an advantage.[9]

Additionally, the large meta-analysis discussed previously suggested that several other variables did not influence the relative OS benefit of neoadjuvant chemotherapy, including the particular chemotherapy regimen used, the number of chemotherapy agents in the regimen, and the type of platinum (cisplatin or carboplatin). Age, sex, histology (squamous vs non-squamous), performance status (0
and number of chemothera-
py cycles (2 vs 3) also did not appear to sig-
taxantly influence the OS benefit of
neoadjuvant chemotherapy.[9] In some
of the neoadjuvant chemotherapy trials,
patients also received subsequent adju-
vant chemotherapy and/or adjuvant ra-
diation. For those receiving neoadjuvant
chemotherapy, the relative OS benefit
when compared with the surgery-alone
group did not appear to differ between
the adjuvant chemotherapy and/or ad-
juvant radiation groups. Because che-
motherapy improved survival by only a
small amount and recurrence occurred
in local sites in some cases, chest radio-
therapy was added to chemotherapy
in both the adjuvant and neoadjuvant
trials. In the adjuvant setting, postop-
erative chest radiotherapy was associ-
ated with decreased survival in stage I
disease, but possible slightly improved
survival in stage IIIAN2 disease.[9,13]

Given controversy in the literature, com-
mon practice in the neoadjuvant stage
IIIAN2 setting has also been variable,
with some patients receiving triple-
modality therapy with chemotherapy and
radiotherapy along with surgery and others receiving chemotherapy alone. It is important that all patients
be presented at multidisciplinary con-
ferences so that a therapeutic strategy is
determined before initiating treatment.

Several concerns with neoadjuvant
chemotherapy are that it could increase
perioperative complications, and that
patients may progress to become un-
resectable prior to potentially cura-
tive surgery. Across several trials and
meta-analyses, the incidence of periop-
erative complications and post-surgical
mortality did not differ significantly
between patients receiving neoadjuvant
chemotherapy prior to surgery and those
proceeding directly to surgery.[9] How-
ever, several other trials, as well as a
large meta-analysis, suggest that the type
of operation does not differ significantly
between patients receiving neoadjuvant
chemotherapy vs those who proceed di-
rectly to surgery. The complete resection
rate has not been shown to be higher in
those receiving neoadjuvant chemother-
apy followed by surgery compared with
patients undergoing surgery alone.[9]

Concurrent neoadjuvant chemother-
apy and radiation also benefits patients
with superior sulcus tumors that are T3
to T4 and N0 to N1, which are a spe-
cial clinical type of NSCLC.[15] With
this treatment approach, 2 cycles of

---

**TABLE 2** Ongoing Randomized Trials of Neoadjuvant Immunotherapy in Early-Stage NSCLC

<table>
<thead>
<tr>
<th>Study Name (Estimated Enrollment)</th>
<th>Treatment Arms Before Surgery</th>
<th>Treatment Arms After Surgery</th>
<th>NCT Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-671 (N = 786) Arm A: pembrolizumab + platinum doublet × 4 cycles</td>
<td>Surgery</td>
<td>Arm A: pembrolizumab</td>
<td>NCT03425643</td>
</tr>
<tr>
<td>Arm B: placebo + platinum doublet × 4 cycles</td>
<td>Surgery</td>
<td>Arm B: placebo</td>
<td></td>
</tr>
<tr>
<td>CheckMate 816 (N = 642) Arm A: nivolumab + ipilimumab × 3 cycles</td>
<td>Surgery</td>
<td>Arm A: CT +/− RT</td>
<td>NCT02998528</td>
</tr>
<tr>
<td>Arm B: platinum doublet × 3 cycles</td>
<td>Surgery</td>
<td>Arm B: CT +/− RT</td>
<td></td>
</tr>
<tr>
<td>Arm C: nivolumab + platinum doublet × 3 cycles</td>
<td>Surgery</td>
<td>Arm C: CT +/− RT</td>
<td></td>
</tr>
<tr>
<td>IMpower030 (N = 302) Arm A: atezolizumab + platinum doublet × 4 cycles</td>
<td>Surgery</td>
<td>Arm A: atezolizumab</td>
<td>NCT03456063</td>
</tr>
<tr>
<td>Arm B: placebo + platinum doublet × 4 cycles</td>
<td>Surgery</td>
<td>Arm B: placebo</td>
<td></td>
</tr>
<tr>
<td>NEOSTAR (N = 66) Arm A: nivolumab + ipilimumab × 3 doses every 2 wks</td>
<td>Surgery</td>
<td>Arm A: CT +/− RT</td>
<td>NCT03158129</td>
</tr>
<tr>
<td>Arm B: nivolumab × 3 doses every 2 wks</td>
<td>Surgery</td>
<td>Arm B: CT +/− RT</td>
<td></td>
</tr>
</tbody>
</table>

CT = chemotherapy; NCT = National Clinical Trials; NSCLC = non–small-cell lung cancer; RT = radiation therapy.

One of the potential benefits of neoad-
juvant chemotherapy is that it may lead
to downstaging of tumors, with resultant
smaller surgeries and more complete
resections. A few studies have suggest-
ed lower rates of pneumonectomy and
higher rates of lobectomy for patients re-
ceiving neoadjuvant chemotherapy com-
pared with those undergoing surgery.[9]
However, several other trials, as well as a
large meta-analysis, suggest that the type
of operation does not differ significantly
between patients receiving neoadjuvant
chemotherapy vs those who proceed di-
rectly to surgery. The complete resection
rate has not been shown to be higher in
those receiving neoadjuvant chemother-
apy followed by surgery compared with
patients undergoing surgery alone.[9]
Neoadjuvant Therapy in Lung Cancer: Does Histology Matter?

Dr. Bunn et al describe the advantages of neoadjuvant therapy in non-small-cell lung cancer: an improved disease-free interval vs adjuvant therapy, potential tumor downstaging, and more time for smoking cessation and patient optimization before surgery. Starting immunotherapy while the tumor is present may enable a more robust immune response in the adjuvant setting.

Learning more about acquired/adaptive resistance and sensitizing and resistance mechanisms is key. The neoadjuvant “window” allows us to delineate the immunologic landscape for sensitivity and resistance to immunotherapy, and to understand differences between histologies. This will aid in developing biomarkers and identifying targets for combinatorial trial design.

Questions remain, however. While major pathologic response (MPR) was validated as a surrogate of survival in those treated with neoadjuvant chemotherapy,[1] a recent study found significant histology-specific (adenocarcinoma vs squamous cell) differences in the MPR needed to correlate with survival.[2] Since immunotherapy’s benefit in the neoadjuvant setting may be in the degree of immune priming, MPR’s usefulness is unclear. The recent International Association for the Study of Lung Cancer[3] workshop may help guide clinical practice.

Since neoadjuvant therapy is for resectable disease, screening is critical. The National Lung Screening Trial[4] and the NELSON study[5] found screening significantly reduces mortality, but only 3% to 4% of the eligible US population has been screened. We expect that the NELSON trial will confirm improved screening rates. The ability to detect more early-stage lung cancers furthers our need to develop optimal treatments.

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cisplatin/etoposide are given concurrently with 45 Gy of radiation; patients with stable disease or better are given 2 more cycles of cisplatin/etoposide after surgery. Among patients receiving neoadjuvant chemoradiation, the 5-year OS rate is superior compared with historical controls receiving only neoadjuvant radiation (44% vs 30%). The OS with concurrent chemoradiation in these patients did not differ by tumor stage at baseline (T3 vs T4). In addition, a progression-free survival (PFS) benefit and fewer local recurrences were seen with neoadjuvant chemoradiation vs radiation in these patients.

Neoadjuvant immunotherapy

Immunotherapy with checkpoint inhibitors that interrupt the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) regulatory axis have revolutionized the treatment of metastatic NSCLC and stage III disease that is not amenable to surgical resection.[4,16-19] By blocking the PD-1/PD-L1 axis, tumor-reactive T cells are better able to recognize and eliminate cancer cells, resulting in improved disease control. These therapies have rapidly become a mainstay of advanced NSCLC treatment due to their improved efficacy and favorable side effect profile compared with chemotherapy. In patients with high PD-L1 expression, the PD-1 inhibitor pembrolizumab alone produced superior survival compared with chemotherapy.[4] On the other hand, in patients with lower levels of PD-L1 expression, the combination of chemotherapy plus an immune checkpoint inhibitor produced superior survival compared with chemotherapy alone.[17-19] With the success seen in the setting of advanced disease, checkpoint inhibitors are starting to be tested in patients with resectable lung cancer as well.

Multiple ongoing clinical trials incorporating checkpoint inhibitors into therapy for early-stage NSCLC are focused on the neoadjuvant setting (Table 2). Preclinical studies and early clinical trials appear to support this neoadjuvant approach. The optimal timing of preoperative checkpoint inhibition was studied in two orthotopic mouse models of breast cancer.[20] Animals were treated with a variety of immune therapies before or after surgical resection. Long-term survivors were observed only in the groups that received neoadjuvant regulatory T-cell ablation or checkpoint inhibitors with a combination of PD1- and CD137-blocking antibodies. The survival advantage was dependent on cytotoxic CD8+ T cells, and, to a lesser extent, on CD4+ T cells; it was also significantly associated with the expansion of tumor-specific CD8+ T cells.

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which was not seen with immune intervention in the adjuvant setting. Similar results were reported in a xenograft mouse model of NSCLC utilizing combined cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and PD-1 blockade. Animals treated in a neoadjuvant fashion followed by surgery experienced improved OS and an increase in tumor-specific T-cell expansion compared with those treated in the adjuvant setting. These results highlight the possibility that the antitumor T-cell repertoire is optimally harnessed by checkpoint inhibitors when a larger amount of antigen is present vs minimal or micrometastatic disease postoperatively.

In the first published trial of neoadjuvant checkpoint therapy, 21 patients with operable stage I to III NSCLC were given nivolumab once every 2 weeks for 2 doses.[22] At the time of surgery, approximately 4 weeks after the first nivolumab dose, 2 patients experienced radiographic disease response, 18 had stable disease, and 1 patient progressed. Remarkably, 9 of the 20 patients who underwent resection experienced a major pathologic response (MPR) with ≤10% viable tumor remaining. The radiographic and pathologic discordance appeared secondary to a dense immune infiltrate, areas of tumor cell death, and tissue repair with fibrosis.[23] Exploratory analyses found an association between higher tumor mutational burden and a decreased degree of residual tumor at the time of surgery. Additionally, one patient with a complete pathologic response demonstrated expansion of tumor-specific T-cell clones in the peripheral blood.[23] Despite these encouraging findings, one patient with MPR experienced a mediastinal lymph node recurrence and received concurrent chemoradiation, and two patients with significant residual tumor at the time of surgery developed metastatic disease.

The neoadjuvant immunotherapy NEOSTAR trial at the University of Texas MD Anderson Cancer Center randomized patients to receive nivolumab or nivolumab plus ipilimumab before surgery.[24] Preliminary results in 31 evaluable patients in this trial, a MPR rate of 25% in patients treated with nivolumab and 27% in patients treated with nivolumab plus ipilimumab.

Early-phase clinical trial data on neoadjuvant atezolizumab as monotherapy or in combination with chemotherapy have been reported.[25,26] As monotherapy, 2 doses of atezolizumab induced an MPR in 10 of 45 EGFR/ALK wild-type patients with stage IB to IIIB NSCLC. Patients with EGFR and ALK alterations were excluded from this efficacy analysis.[25] However, 4 patients in the trial had EGFR-activating mutations and 1 patient had an ALK rearrangement. Data are available on 3 of these 5 patients. After neoadjuvant therapy, 1 patient with an EGFR mutation was no longer resectable. At the time of surgery, a second patient with EGFR-positive disease had 90% viable tumor, and the patient with an ALK rearrangement had 60% viable tumor.[25]

In a second early-phase study, 14 patients with stage IB to IIIA NSCLC were administered 4 cycles of neoadjuvant atezolizumab plus carboplatin and nab-paclitaxel.[26] Unlike the reported discordance with neoadjuvant checkpoint inhibitor therapy alone, 8 of the 14 patients who received concurrent atezolizumab and chemotherapy had a radiographic response, and 7 of 14 patients were found to have an MPR. Extended follow-up has yet to be released for neoadjuvant atezolizumab monotherapy; however, after a median of 8.6 months, there have been 4 recurrences following neoadjuvant atezolizumab plus chemotherapy.

As was observed with the neoadjuvant atezolizumab plus chemotherapy study, a phase II trial showed a high MPR with 3 cycles of neoadjuvant nivolumab plus carboplatin and paclitaxel.[27] Of 30 evaluable patients in this trial, a MPR was reported in 24 of them. Similar to the neoadjuvant chemoimmunotherapy trial with atezolizumab plus carboplatin and nab-paclitaxel, there was greater concordance between radiographic and pathologic findings in this trial, in contrast to data from immune checkpoint inhibitor monotherapy. At the time of presentation of these data, no patients had developed recurrence; however, the median follow-up was short, at only 4.1 months.[27]

Three phase III trials—IMpower030,[28] CheckMate 816,[29] and KEYNOTE-671[30]—and multiple phase I and II trials are underway to better define the role of checkpoint inhibitors in neoadjuvant therapy for resectable NSCLC (Table 2). It is worth noting that 2 of the 3 phase III trials (IMpower030 and KEYNOTE-671) will administer subsequent checkpoint inhibitors in the adjuvant setting for 1 year.

### Table 2: Ongoing Trials of Neoadjuvant Molecular Therapies in Early-Stage NSCLC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eligible Patients</th>
<th>Estimated Enrollment</th>
<th>NCT Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>ALK fusion, MET fusion, MET exon 14 skipping mutation, ROS1 fusion</td>
<td>N = 18</td>
<td>NCT03088930</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>EGFR exon 19 deletion, T790M or L858R</td>
<td>N = 27</td>
<td>NCT03433469</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR-activating mutation</td>
<td>N = 40</td>
<td>NCT02804776</td>
</tr>
</tbody>
</table>

NCT = National Clinical Trials; NSCLC = non–small-cell lung cancer.
As we transition to this new era of immunotherapy for NSCLC, multiple questions remain regarding the effective use of checkpoint inhibitors in the neoadjuvant setting. What is the role of chemotherapy, radiation therapy, or concurrent chemotherapy when checkpoint inhibitors are used? Can PD-L1 or tumor mutational burden testing be used to better identify patients who can receive a checkpoint inhibitor alone versus concurrent chemoinmunotherapy, similar to the metastatic setting? Will new biomarkers, such as MPR and clonal T-cell expansion, predict which individuals will have a long-lasting response? Finally, do patients with oncogenic drivers benefit from incorporating checkpoint inhibitors into neoadjuvant therapy? While it may take years before we know how to most effectively incorporate checkpoint inhibitors into neoadjuvant treatment of NSCLC, the progress made thus far represents a major step toward achieving more long-term cures in the early-stage setting.

**Neoadjuvant molecular therapy**

A number of targeted compounds are available for the treatment of metastatic lung cancer harboring activating mutations in oncogenes such as EGFR, ALK, ROS1, BRAF, and MET.[3] In early-stage disease, the RADIANT study evaluated 2 years of adjuvant treatment with erlotinib among patients with stage IB to IIIA tumors and positive EGFR testing by immunohistochemistry or fluorescent in situ hybridization.[31] No benefit in DFS was demonstrated in patients treated with erlotinib vs placebo, although erlotinib prolonged DFS among patients with EGFR mutations (median, 46.4 months vs 28.5 months). This difference was not statistically significant after correcting for multiple comparisons; nevertheless, it generates the hypothesis that EGFR-directed treatment can be useful in the treatment of early-stage NSCLC, either as neoadjuvant or adjuvant therapy in patients with EGFR mutations.

A similar study conducted in China, the ADJUVANT/CTONG1106 trial, evaluated adjuvant gefitinib vs chemotherapy with cisplatin plus vinorelbine in patients with stage II to IIIA NSCLC and EGFR-activating mutations. An improvement in median DFS was seen with gefitinib: the median DFS was 28.7 months with gefitinib vs 18.0 months with chemotherapy (HR, 0.60; 95% CI, 0.42–0.87; *P* = .0054).[32] However, gefitinib was administered for only 24 months on this trial, and the 3-year DFS rates were similar for both regimens. In addition, the DFS curves for the regimens approached each other at 36 months and beyond, suggesting that while targeted therapy may help delay recurrences when given in the adjuvant setting, this benefit may be dependent on continued drug administration and suppression of micrometastases.

The OS data have not yet been reported for the RADIANT or ADJUVANT/CTONG1104 studies, and further follow-up is awaited to determine whether EGFR inhibition can increase the cure rate compared with surgery alone or surgery followed by adjuvant chemotherapy. Additionally, the optimal duration of EGFR inhibition in the adjuvant setting may need to be redefined given the findings on the ADJUVANT/CTONG1104 study after gefitinib was stopped.

Limited clinical trial data are available to guide neoadjuvant targeted therapy in molecularly defined subgroups of lung cancer patients. However, the concept of using small-molecule inhibitors of known oncogenic drivers prior to surgery in patients with earlier stages of disease is intriguing for a number of reasons. First, targeted agents induce tumor shrinkage in 60% to 70% of cases and have disease control rates of about 90%; therefore, delaying surgery poses little risk for tumor progression, a major concern with neoadjuvant treatments. Second, these agents are generally better tolerated than chemotherapy. Third, the high rate of major responses and downstaging is particularly attractive, especially in borderline resectable cases or those in which a pneumonectomy would otherwise be required. Lastly, neoadjuvant clinical trials are unique because they allow access to tissue before and after a systemic therapeutic intervention. This is particularly important for targeted therapies in patients with oncogene-driven lung cancer, where early adaptive events at the protein level are responsible for incomplete molecular inhibition of the driver and residual clinical disease.[33,34] Understanding the biology of residual disease in oncogene-driven lung cancers will help with the design of rational combination treatments in this patient population.

The CTONG1103 study randomized NSCLC patients with activating mutations in exons 19 or 21 of EGFR and stage IIIB or IIIN2 disease to either erlotinib for 42 days both before and 1 year after surgery or gemcitabine plus cisplatin for 2 cycles before and 2 cycles after surgery.[35] Data from this trial were recently presented, and patients in the erlotinib arm achieved a higher response rate (54.1% vs 34.3%; *P* = .092) and longer PFS (median, 21.5 ± 11.9 months; *P* = .003), compared with the chemotherapy arm. Nevertheless, the rates of MPR were generally low (10.7% in the erlotinib arm vs 0% in the chemotherapy arm), and all non-censored patients in both arms had disease progression within 3 years of follow-up. Thus, it is unlikely that neoadjuvant erlotinib will improve the cure rate in this study.

Continued on page 109
A Patient With Pure Teratoma of the Testis Presenting With an Anterior Mediastinal Mass

Alexandria M. Hertz, MD, Timothy C. Brand, MD, and Matthew M. Banti, MD

A 39-year-old man presents with chest pain and shortness of breath. CT scans are ordered, revealing the presence of an anterior mediastinal mass. The patient is sent for a consultation with a cardiothoracic surgeon. Results of cardiovascular, respiratory, and testicular exams completed during this visit are normal. Further evaluation of the mediastinal mass is conducted via MRI (Figure 1), and he is referred to interventional radiology for tissue diagnosis.

Laboratory tests were also performed at this time, which demonstrated the following: beta–human chorionic gonadotropin (beta-HCG), 0.2 mIU/mL (normal, < 5.0 mIU/mL); lactate dehydrogenase (LDH), 226 U/L (normal, 105–333 U/L); and alpha-fetoprotein (AFP), 2.8 ng/mL (normal, < 10.0 ng/mL). Core biopsy of the anterior mediastinal mass demonstrates atypical cells.

A scrotal ultrasound is obtained to assess for a potential germ cell tumor. It reveals a 7-mm mixed cystic and solid hypoechoic mass in the right testicle concerning for a testicular malignancy (Figure 2). PET/CT does not demonstrate lymphadenopathy in the retroperitoneum or elsewhere, or large amounts of increased uptake in the mediastinal mass or testicular lesion. A genital exam by the urologist at that time demonstrates a firm right testicular mass. The patient consents to a right radical inguinal orchectomy.

Final pathology results reveal pure post-pubertal teratoma of the testis consisting of cysts lined by simple epithelium, as well as ciliated cells surrounded by smooth muscle. Stromal hyalinization and calcification are also present, suggesting the possibility of a burned-out germ cell tumor. The seminiferous tubules show spermatogenesis. Germ cell neoplasia in situ was not identified in the hematoxylin and eosin–stained sections or by immunohistochemistry (placental alkaline phosphatase and octamer transcription factor 3/4) (Figure 3).

Which of the following represents the best next step for management?

A. Obtaining additional tissue from the mediastinal mass (ie, resection)
B. Chemotherapy with bleomycin, etoposide, and cisplatin
C. Radiotherapy
D. Surveillance
E. Retroperitoneal lymph node dissection (RPLND)

**FIGURE 1 T2-Weighted MRI of the Mediastinal Mass.** The gadolinium-enhanced images demonstrate the anterior mediastinal mass. Both solid and cystic components are visible in the mass, with a cystic component appearing bright on T2.
Discussion
The most common underlying causes of an anterior mediastinal mass are thymoma, lymphoma, extragonadal germ cell tumors, and teratoma.[1] Anterior mediastinal masses are rarely symptomatic and are usually discovered incidentally via imaging studies. CT imaging is useful in further characterizing the masses, while MRI helps to differentiate cystic lesions.[2] In general, it is recommended that affected patients undergo a laboratory evaluation to test for levels of beta-HCG, AFP, and LDH, as was performed in this patient.[1]

Approximately 1% to 5% of germ cell tumors manifest in extragonadal locations, with the most common being the mediastinum in adult men.[3] Up to 70% of germ cell tumors in the mediastinum contain teratoma.[4] Synchronous teratoma in the testicle should be considered a secondary primary lesion in the setting of mediastinal teratoma.[5] If a diagnosis of a nonseminomatous germ cell tumor (NSGCT) other than pure teratoma is confirmed, neoadjuvant chemotherapy is generally advocated, followed by surgical resection of the mediastinal mass.[4] In this patient’s case, the recommendation for resection of the mediastinal mass (Answer A) was due to concern for a secondary primary lesion, since an isolated metastasis to the mediastinum without retroperitoneal disease on imaging would have been unlikely.[5] When a different lesion type or multiple primary lesions are suspected, an expert pathologic review is recommended to help guide treatment.

Teratoma is composed of multiple germ cell layers, and is typically defined by the maturation of these elements (mature vs immature).[6] Pure teratoma is relatively uncommon, representing only 2% to 6% of all primary testicular tumors. Thorough pathologic review is necessary to rule out other cell types. The prognosis of pure teratoma is favorable. Previous studies have demonstrated that the relapse rate can be as high as 15% to 30% for clinical stage I disease. Additionally, 30% to 40% of men present with metastatic disease.[7,8] Metastatic pure teratoma of the testis may contain other nonseminomatous components, such as embryonal cells.[7-9]

Treatment of stage I lesions consists of radical orchietomy. These patients can then either be followed with surveillance, similar to NSGCTs, or offered RPLND to reduce relapse given the risk of occult retroperitoneal metastasis. [7,10,11] Surveillance is favored given the nonaggressive behavior of teratoma.[7,9,11] In the absence of the mediastinal lesion seen in this case, Answers D and E would also be reasonable choices for management of patients with pure teratoma.

Chemotherapy is not effective against teratoma, and continued growth or persistence of the tumor may occur after treatment.[12] For this reason, Answer B is incorrect in the setting of a pure teratoma tumor. Similarly, radiotherapy has been shown to increase the rate of recurrence when given as a solitary therapy for NSGCT.[13] Therefore, Answer C is not a good option for this patient with pure teratoma of the testis. As pure teratoma is relatively uncommon, no specific surveillance protocol is available. General surveillance principles for NSGCT can be used as a surrogate in these patients after shared decision-making with the patient.[10]

Outcome of This Case
This patient had his mediastinal mass resected robotically; it was found to be ectopic pancreatic tissue associated with a thymic cyst. He is currently being monitored on a surveillance regimen for the nonseminomatous germ cell tumor. Several months later, no signs of recurrence have been seen. ■
A neoadjuvant clinical trial of crizotinib in patients with either ALK, ROS1, or MET alterations is underway.[14] In this study, patients with early-stage NSCLC who are candidates for curative surgical treatment are screened for MET exon 14 skipping mutations, MET fusions, ALK fusions, and ROS1 fusions. If an alteration is identified, crizotinib is given for 6 weeks followed by PET/CT scan and surgical resection. The study has a strong translational rationale, since it will use the resection specimen to evaluate gene expression and changes in the microenvironment that occur with crizotinib treatment. A number of other neoadjuvant studies focusing on the EGFR population are also enrolling patients (Table 3).[14]

**Conclusion**

The high rates of response to targeted therapies and the biology of lung cancers with certain oncogenic drivers offer unique opportunities to explore potentially beneficial treatments in the neoadjuvant setting, as well as to answer specific scientific questions. Further study and proof-of-concept data are needed to determine whether treatment of early-stage lung cancer with effective neoadjuvant targeted therapies can eradicate microscopic disease and improve cure rates. Additionally, genetic and pathway analyses of residual persisting tumor cells should be conducted to identify which pathways to inhibit, which in combination with tyrosine kinase inhibitor therapy, could lead to improved pathologic complete response rates—and perhaps a cure.

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Current Treatment of Esophageal Cancer and Promising Clinical Trials Underway

Dr. Ku discusses considerations in the treatment of esophageal cancer, current treatments, and the emerging role of immunotherapy.

The treatment of squamous esophageal tumors has not changed much over the last 30 to 40 years and consists primarily of chemotherapy. However, newer options such as targeted therapy, anti-vascular endothelial growth factor (VEGF) receptor antibodies, and immunotherapy may have the potential to alter the standard of care. To discuss current and emerging therapy options for esophageal cancer, ONCOLOGY spoke with Geoffrey Y. Ku, MD, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, who specializes in the treatment of malignancies of the gastrointestinal tract, including esophageal tumors.

Q: First, what are the mainstay adjuvant and neoadjuvant therapy options for patients diagnosed with esophageal cancers?

DR. KU: When it comes to esophageal cancers, there are two things to think about. The first is the location of the tumor, and the second is the histology of the cancer. The National Comprehensive Cancer Network (NCCN) guidelines and Memorial Sloan Kettering’s internal guidelines both split the esophagus and the stomach at the gastroesophageal junction. Therefore, we use the Siewert classification system to describe tumors. A Siewert type I tumor is a lower esophageal tumor extending into the gastroesophageal junction; a type II tumor is a true tumor at the gastro-esophageal junction; and a type III tumor is a proximal gastric cancer extending upwards to the gastroesophageal junction.

For the purposes of treatment planning in the localized setting, we consider Siewert type I and type II tumors to be esophageal tumors, and type III tumors and beyond to be gastric tumors. This is the first thing to bear in mind. The second is that there are two histologies in the esophagus. In the

Dr. Ku is a Medical Oncologist who specializes in the treatment of malignancies of the gastrointestinal tract at Memorial Sloan Kettering Cancer Center in New York, New York. His research focuses on the evaluation of novel therapies and combined-modality treatments for esophagogastric cancer. He is a member of the Esophagogastric Task Force of the National Cancer Institute and of the Gastrointestinal (Non–Colorectal Cancer) Committee of the NRG Oncology Cooperative Group.
United States, by far the more common is adenocarcinoma, but we also see squamous cell carcinoma about 25% of the time. Given the overall rarity of esophageal cancers, this means that squamous esophageal carcinoma is extremely uncommon; its incidence is only about 4,000 to 5,000 patients annually.

With regard to adjuvant and neoadjuvant treatment of esophageal and gastro-esophageal adenocarcinomas, we very much continue to administer preoperative chemoradiation. In general, treatment is given preoperatively. It is usually very difficult to give adjuvant treatment, but particularly so after an esophagectomy. The standard of care for esophageal adenocarcinoma remains preoperative chemoradiation. We typically consider surgery to be part of therapy because complete response rates with chemoradiation alone are quite low, between 20% and 25%. For esophageal squamous cell cancer, we consider standard therapy to be definitive chemoradiation with observation. This is due in part to its much higher pathologic complete response rate. The CROSS trial, conducted in the Netherlands, reported a pathologic response rate of almost 50% for patients with squamous cell cancer of the esophagus who received chemoradiation.[1]

In general, most patients who develop squamous cell cancers have comorbidities, since this is a cancer related to smoking and drinking.

Many have cardiopulmonary conditions and generally are not good candidates for surgery. Therefore, if we achieve a complete response clinically with chemoradiation, we typically observe these patients without operating.

A potential alternative for adenocarcinoma tumors at the gastroesophageal junction is perioperative chemotherapy. Studies of perioperative chemotherapy for gastric cancer, such as the MAGIC[2] and FLOT4[3] studies, have also included patients with gastroesophageal junction cancers. We still prefer to give chemoradiation to these individuals. This is mainly because, when the tumor is involving the esophagus and the gastroesophageal junction, a complete or R0 resection is achieved only about 70% of the time. The R0 resection rate is up to 90% with chemoradiation. However, in select patients, perioperative chemotherapy for gastroesophageal junction adenocarcinoma can also be considered, but such a decision should be made following a multidisciplinary review.

In 2017, the accelerated FDA approval of pembrolizumab for patients with gastric and gastroesophageal junction adenocarcinoma first opened the door to immunotherapy for esophageal cancer.

**Q:** What therapy options are available for patients with advanced esophageal tumors?

**DR. KU:** Again, treatment differs for adenocarcinomas vs squamous cell carcinomas. With the exception of the KEYNOTE-181 study (which I will discuss shortly), treatment of squamous esophageal tumors has not really changed over the last 30 to 40 years and primarily consists of chemotherapy. The same chemotherapy drugs are active in both histologies: fluoropyrimidine, platinum agents, taxanes, and irinotecan. The normal sequence, throughout much of the world, is to consider a fluoropyrimidine/platinum doublet in the first-line setting; in the United States, the most widely used regimen is FOLFOX (folinic acid, fluorouracil, and oxaliplatin). We use this to treat patients with both adenocarcinoma and squamous cell cancer. In the second- or third-line setting, we would consider either a taxane or irinotecan.

For adenocarcinomas, several targeted therapies have been approved by the US Food and Drug Administration (FDA). In 2010, based on the results of the Trastuzumab for Gastric Cancer (ToGA) study,[4] trastuzumab was approved as the first targeted therapy for use in gastroesophageal and gastric cancer. Trastuzumab is used to treat tumors that are human epidermal growth factor receptor 2 (HER2)-positive (about 20% to 25% of tumors). The HER2 positivity rate is even higher in distal esophageal and gastroesophageal junction adenocarcinomas than it is in gastric cancer. So, trastuzumab in combination with FOLFOX is the standard of care for all HER2-positive esophageal or gastric adenocarcinomas.

More recently, in 2014, the anti-VEGF receptor antibody ramucirumab was approved in combination with paclitaxel in the second-line setting. Again, the approval was based on a gastric cancer study that also included pa-
tients with gastroesophageal junction adenocarcinomas. Since we now know that adenocarcinomas of the distal esophagus, gastroesophageal junction, and proximal stomach are molecularly the same based on the results of The Cancer Genome Atlas analysis,[5] we extrapolate that same data to distal esophageal adenocarcinomas as well.

Immunotherapy may now also be an option for the treatment of squamous cell esophageal carcinomas. The recent phase III KEYNOTE-181 study,[6] presented at the 2019 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, evaluated the anti–programmed death 1 (PD-1) antibody pembrolizumab. Specifically, researchers studied pembrolizumab vs paclitaxel in the second-line setting for both esophageal adenocarcinomas and squamous cell carcinomas. Patients, particularly those with squamous cell carcinoma, appeared to benefit more from pembrolizumab than from paclitaxel. However, the survival benefits did not meet statistical significance, and that in large part is because of the statistical plan for the study, which comprised three co-primary endpoints. The takeaway point is that pembrolizumab appears to be effective for an unselected population of patients with esophageal squamous cell carcinoma, irrespective of programmed death ligand 1 (PD-L1) status. It remains to be seen whether this agent will ultimately receive FDA approval, or perhaps an NCCN compendium listing, which will allow us to obtain it as a standard-of-care option.

Q: Last year, pembrolizumab also received accelerated FDA approval for patients with gastric and gastroesophageal junction adenocarcinoma. Which patients are most likely to benefit from this therapy?

DR. KU: That particular approval first opened the door to immunotherapy in esophagogastric cancer. In September 2017, the FDA approved pembrolizumab based on the results of the KEYNOTE-059 trial. This single-arm study evaluated almost 260 patients who received pembrolizumab as third-line or greater therapy. In patients with PD-L1–positive tumors, there did appear to be modest benefits; specifically, the response rate in this treatment-refractory patient population was about 12%. There was also durable survival: the 12-month survival rate was approximately 25% in a treatment-refractory population.[7]

I would add that, again, the FDA approval of pembrolizumab is contingent on the tumor cells being PD-L1–positive. This is determined using a specific assay with the 22C3 antibody. PD-L1 positivity is defined as a combined positive score of at least 1, which indicates that there is some staining in either the tumor cells or the peritumoral mononuclear cells. As noted earlier, the KEYNOTE-181 study is one that looked at pembrolizumab as a second-line treatment for esophageal squamous cell cancer.[6] There are now other trials that are studying anti–PD-1 antibodies in the first-line setting.

KEY QUESTION

Are there any other esophageal cancer clinical trials underway that could be practice-changing in the short term?

DR. KU: As I touched on earlier, the KEYNOTE-181 trial, which was just presented, may have implications for treatment in the second-line setting for esophageal squamous cell cancer.[6] The results of another second-line study, KEYNOTE-061, were also reported last year. This was a randomized study of pembrolizumab vs paclitaxel in patients with gastroesophageal junction and gastric adenocarcinomas. Although it was a negative study overall, researchers did find that patients whose tumors have higher PD-L1 positivity (a combined positive score of ≥10), derived more benefit from pembrolizumab vs paclitaxel chemotherapy.[8]

Of course, the study results that I think we are all waiting for are those of KEYNOTE-062, and they may be reported as soon as the 2019 ASCO Annual Meeting in June. The KEYNOTE-062 study is a first-line study with three arms: standard 5-FU/cisplatin chemotherapy, pembrolizumab alone, and pembrolizumab plus 5-FU/cisplatin.[9] The hope is that combination immunotherapy and chemotherapy will be more effective than chemotherapy alone, and we did get a hint of that based on results from an arm of the KEYNOTE-059 trial.[7] Specifically, a small cohort of 25 patients received first-line therapy with a combination of pembrolizumab and 5-FU/cisplatin; although the arm was very small, the outcomes seemed to be slightly improved with the addition of pembrolizumab compared with chemotherapy alone, particularly among patients with PD-L1–positive tumors.[9]

KEYNOTE-062 completed accrual about 2 years ago, so the results will hopefully mature soon. It would certainly be practice-changing if it is a positive study, as it would move pembrolizumab and immunotherapy all the way up from the third-line setting to the first-line setting. If that’s the case, it would represent a significant improvement over everything that’s come before.

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For references visit cancernetwork.com/esophageal-current-ther
Introduction
Prostate cancer is the most common cancer in men in the United States, ranking second to lung cancer among deaths from cancer, with an estimated 29,430 deaths in 2018.[1] The most lethal form of the disease is castration-resistant prostate cancer (CRPC), which occurs with the loss of clinical response to initial androgen deprivation therapy (ADT). The treatment for CRPC has evolved over time, from treatments with a palliative focus to treatments that extend survival. Docetaxel was the first agent found to improve survival in men with CRPC, with a median survival of 19 months.[2,3] There have been five new drugs approved by the US Food and Drug Administration (FDA) for prostate cancer since 2010, which extend survival but are not curative. These new agents include the second-generation hormonal agents abiraterone and enzalutamide, which target the androgen receptor (AR) pathway, as well as non-androgen–targeted therapies, including chemotherapy such as cabazitaxel, DNA-damaging agents such as radium-223, and immunotherapy such as sipuleucel-T.[4] Despite these advances, each class of drugs improves the median survival by only approximately 3 to 4 months, thus stressing the need for novel therapeutic approaches.

Despite the use of ADT in CRPC, cell growth and proliferation continues. The mechanisms that allow cell growth in this clinical state include, but are not limited to, autocrine androgen signaling, AR overexpression, and AR splice variants.[5] Further understanding of these mechanisms has led to the development of the FDA-approved agents (Figure). The aim of this review is to examine the current use and future direction of these novel therapeutic targets.
efit in patients with metastatic CRPC, as demonstrated in two phase III trials, the Southwest Oncology Group 99-16 trial and the TAX 327 trial.[2,3] These two studies established the benefit of taxane chemotherapy and set a new standard of care in the treatment of metastatic CRPC. Despite the survival benefit demonstrated with docetaxel, all patients ultimately progress on treatment due to either innate or acquired taxane resistance.

Cabazitaxel was developed due to its low affinity for MDR1 and superior blood-brain barrier penetration compared with paclitaxel and docetaxel.[6,7] Its efficacy was investigated in the second-line setting in the TROPIC trial, which included men with metastatic CRPC who had progressed during or after docetaxel treatment. This phase III study found an increased overall survival of 15.1 months in patients treated with cabazitaxel, compared with 12.7 months in men treated with mitoxantrone.[8] This was the first agent to demonstrate a survival benefit in docetaxel-refractory patients, and this trial led to the FDA approval of cabazitaxel in 2010.

The FIRSTANA trial investigated the use of cabazitaxel vs docetaxel in the first-line setting for metastatic CRPC. Patients were randomized 1:1:1 to cabazitaxel 20 mg/m² (C20), cabazitaxel 25 mg/m² (C25), or docetaxel 75 mg/m² (D75). The median overall survival was 24.5 months with C20, 25.2 months with C25, and 24.3 months with D75. Adverse events ≥ grade 3 occurred in 41.2% of patients treated with C20, 60.1% of those treated with C25, and 46.0% with D75. Febrile neutropenia was most frequently seen in patients who received C25. Overall, this study showed that cabazitaxel is not superior to docetaxel in the first-line treatment of metastatic CRPC.[9] Despite this finding, there are instances when cabazitaxel could be considered instead of docetaxel. Specifically, cabazitaxel was found to have lower rates of grade 3/4 peripheral neuropathy and may be a better option for certain patients.

### Immunologic targets

Advances in cancer immunology have changed the treatment and prognosis for many advanced malignancies. These immunotherapeutic agents include cancer vaccines, immune checkpoint inhibitors, adoptive T-cell therapy, and viral vectors. Sipuleucel-T, an autologous dendritic cell vaccine, was approved by the FDA in 2010 for prostate cancer. After leukapheresis, harvested antigen-presenting cells are exposed to a fusion protein of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (referred to as PA2024) and infused back into the patient.[10] This process is repeated every 2 weeks for 3 cycles. The phase III IMPACT trial randomized men with metastatic CRPC 2:1 to receive sipuleucel-T or placebo and found no significant difference in time to progression, but found an improved median overall survival in the sipuleucel-T group compared with the placebo group (25.8 months vs 21.7 months).[11] Survival appears to be longer in patients with low-volume disease. The exact mechanism by which these patients experienced improvement in overall survival without a difference in time to progression remains unclear. It is possible that the effect that these immune agents provide is delayed beyond initial progression, in comparison with traditional chemotherapy in which a decrease in time to progression is more closely related to overall survival. This study led to the FDA approval of sipuleucel-T for the treatment of asymptomatic or minimally symptomatic patients with nonvisceral metastatic CRPC in 2010.

The use of cancer vaccines, in an effort...
to stimulate a tumor-directed immune response, is an area of ongoing clinical research and has led to the development of a prostate-specific antigen (PSA)-based vaccine called PSA-TRICOM. This vaccine consists of the vaccinia and fowl-pox viral vectors and contains the PSA gene and the costimulatory molecules B7.1, ICAM-1, and LFA-3, referred to as TRICOM. The proposed mechanism of this vaccine is thought to be through the presentation of PSA to immune cells with costimulatory molecules, which enhances a T-cell cytotoxic response.

This was first investigated in a phase II trial of men with minimally symptomatic metastatic CRPC randomized 2:1 to PSA-TRICOM and GM-CSF or placebo with an empty vector and GM-CSF. Although this study did not show any difference in progression-free survival, it did show an increase of 25.1 months in median overall survival with PSA-TRICOM compared with 16.6 months with placebo.[13] These findings led to a phase III study; unfortunately, no survival benefit was demonstrated with PSA-TRICOM.[14,15]

Chimeric antigen receptor (CAR) T cells are autologous T cells that are engineered ex vivo to express a recombinant AR.[16] The goal of CAR T-cell therapy is to direct immune activation against the target antigen. CAR T-cell therapy has had recent success in the treatment of hematologic malignancies, with FDA approval for the treatment of refractory diffuse large B-cell lymphoma and refractory B-cell acute lymphoblastic leukemia. Prostate cancer is a viable candidate for CAR T-cell development, since it has specific tumor-associated antigens, including prostate-specific membrane antigen and prostate stem cell antigen.

A phase I study using PSA-MA-directed CAR T cells reported that 2 of 5 patients treated obtained a PSA response.[18] A second phase I study using a PSMA-directed CAR T cell is ongoing (ClinicalTrials.gov identifier: NCT01140373). One of the challenges identified in treating metastatic prostate cancer with CAR T-cell therapy is related to the high prevalence of bony disease and the difficulty of recruiting CAR T cells to these lesions, overcoming the immunosuppressive environment.[19]

The success of checkpoint inhibitors that target either cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) axis has changed the way we treat many advanced malignancies, and they continue to gain additional indications from the FDA. The potential promise of immunotherapy in the treatment of prostate cancer is based on findings that show a significant T-cell infiltration in prostate tissue.[20] Phase I/II studies of ipilimumab in metastatic CRPC showed efficacy, leading to the phase III CA184-043 trial, which included patients with bony metastases who had progressed on docetaxel therapy. In this study, patients received 8 Gy of radiation to at least one bony site, followed by either ipilimumab 10 mg/kg or placebo every 3 weeks for a maximum of 4 cycles, with the option of maintenance therapy every 3 months in non-progressing patients tolerating treatment. The median overall survival did not meet statistical significance between the ipilimumab and placebo groups (11.2 vs 10.0 months).[21]

However, a subgroup analysis observed an improved overall survival with ipilimumab in patients with more favorable prognostic features, including those without visceral metastasis, those with no increase or a minimal increase in alkaline phosphatase levels, and those without anemia.[21] The phase III CA184-095 trial investigated the safety and efficacy of ipilimumab vs placebo in chemotherapy-naive patients, and found no significant difference in survival between the groups.[22]

PD-1 has been shown to be a target in prostate cancer, since tumor-infiltrating lymphocytes found in prostate cancer have been shown to express PD-1 and PD-L1, albeit at a lower rate than other solid tumors.[23,24] However, in an early study with the anti–PD-1 agent nivolumab, though tumor responses were demonstrated among patients with solid tumors, there were no responses seen in the 17 patients with CRPC.[25] Tumor samples from only two of these patients were tested for PD-L1 expression and were negative. None of these patients received prior treatment with either abiraterone or enzalutamide, which may change the tumor microenvironment. The combination of ipilimumab and nivolumab is currently being investigated in the phase II CheckMate 630 trial (ClinicalTrials.gov identifier: NCT02985957).

Despite this lack of response to immune checkpoint inhibition, Graff et al
One in 8 men will develop prostate cancer in his lifetime, and most will progress to metastatic castration-resistant prostate cancer (mCRPC), the most aggressive form of this disease. In this review, Considine and Petrylak summarize effective systemic therapies for mCRPC associated with improved survival and highlight promising investigational approaches to treatment.

As a community oncologist who treats multiple types of malignancies, it is exciting to see the evolution of immunotherapy trials in prostate cancer. Checkpoint inhibitors have the ability to produce deep and durable responses and to extend survival in the frontline setting; they can also be effective in treatment-refractory patients. What has eluded us, however, is the ability to precisely identify predictive biomarkers for responders.

We know that programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) expression, microsatellite instability (MSI) status or its correlate mismatch repair protein expression, and tumor mutational burden (TMB) can predict for response to checkpoint inhibitors. However, more practical questions arise as we accrue more experience with these agents and biomarkers. In lung cancer, we have learned that patients with high PD-L1 expression are unlikely to respond to checkpoint inhibitors in the presence of other oncogenic drivers, such as EGFR, ALK, and ROS1. However, TMB has been reported to be an independent predictor of response despite the presence of other oncogenic drivers.

Earlier trials of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor ipilimumab and the PD-1 inhibitor nivolumab were disappointing. The authors highlight the phase III CA184-095 trial, which illustrated no survival advantage for ipilimumab vs placebo in chemotherapy-naive patients. No improvement in outcomes was seen in the phase III CA184-043 trial, either, which evaluated radiation plus ipilimumab vs placebo in the post-docetaxel setting. Disappointingly, none of the 17 CRPC patients responded to treatment in an early nivolumab trial.

As responsible oncologists, we must be careful not to oversell the promise of immunotherapy…or to gloss over the many serious side effects associated with these treatments.

Drawing from other malignancies, the outcomes may be more promising with combination immunotherapy, and by enriching for a population that is more likely to respond. In KEYNOTE-199, de Bono reported on the activity of pembrolizumab in patients with docetaxel-refractory mCRPC and noted increased response rates in patients with somatic BRCA1/2 or ATM mutations. A multitude of trials evaluating combination therapy and enriching for special mCRPC populations are underway. Pembrolizumab is being studied in combination with radium-223 (ClinicalTrials.gov identifier: NCT03093428). KEYNOTE-365 is a four-arm trial evaluating the combination of pembrolizumab with either olaparib, docetaxel and prednisone, enzalutamide, or abiraterone and prednisone (NCT02861573). Nivolumab is currently being evaluated in patients with mCRPC with DNA repair defects (NCT03040791) or CDK12 mutation (NCT03570619), as well as in combination with rucaparib, docetaxel, or enzalutamide (NCT0338790). As reported, a phase III trial of atezolizumab and enzalutamide vs enzalutamide is also underway (NCT03016312).

As responsible oncologists, we must be careful not to oversell the promise of immunotherapy to the majority of patients, who are unlikely to benefit, or to gloss over the many serious side effects associated with these treatments. It will also be important to incorporate clinical value and cost into immunotherapy trials given the number of patients that will ultimately be eligible for this type of therapy. The authors report on other promising agents in mCRPC, including prostate-specific membrane antigen conjugates, including lutetium-177, as well as phosphoinositide 3-kinase inhibitors. Until more is known about the efficacy of these investigational approaches, I encourage my patients with mCRPC to undergo genetic testing, consider clinical trials, and undergo comprehensive genomic profiling to evaluate for a personalized approach.

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identified two exceptional responders, raising the hypothesis that AR blockade may enhance response to immunotherapy, perhaps through upregulation of PD-L1.[26,27] A phase II trial evaluated patients who had progressed on enzalutamide; they were given pembrolizumab every 3 weeks for 4 doses in addition to enzalutamide. Three of the first 10 patients enrolled had a remarkable decrease in PSA levels; of the 2 patients with measurable disease, both had a partial response.[28] This unexpected finding may be explained by a study that demonstrated that patients who had progressed on enzalutamide have a significantly increased number of PD-1/2 dendritic cells in their blood compared with treatment-naive patients responding to enzalutamide.[29] Pembrolizumab may also have activity in prostate cancer patients with microsatellite instability, for which it is FDA approved. It should be noted that only about 2% of CRPC patients are microsatellite instability–high.

Other checkpoint inhibitors are currently being evaluated in CRPC. A phase I study of atezolizumab in patients with metastatic CRPC who had progressed on prior therapy with either enzalutamide and/or sipuleucel-T was recently performed. Of 15 patients, 1 patient had a partial response, 5 patients had stable disease, and 2 experienced a ≥ 50% decrease in PSA and a 12-month overall survival rate of 55.6%. Only 9 of the patients experienced ≤ grade 3 adverse events, and there were no grade 4 or 5 events, demonstrating that atezolizumab was well tolerated and provided long-term disease control in this heavily pretreated population.[30] Currently, a phase III randomized multicenter trial is investigating the combination of atezolizumab with enzalutamide compared with enzalutamide alone in patients who have received prior abiraterone therapy and have either progressed on, are ineligible for, or refused taxane therapy. (ClinicalTrials.gov identifier: NCT03016312).

Membrane and Cellular Targets

PSMA

PSMA is a transmembrane protein that is highly specific for both benign and malignant prostate epithelial cells.[31,32] PSMA is also expressed on vascular endothelium, as well as other epithelial tissues, including salivary glands. PSMA is an ideal therapeutic target, since it is membrane bound, and ligand binding leads to internalization of the molecule.[33] This has led to the development of multiple PSMA-directed therapies, including antibody-drug conjugates. This directed therapy aims to deliver the drug molecules to PSMA expression cells, sparing normal tissues and potential associated side effects. MLN2704 is an antibody-drug conjugate comprised of HuJ591, a humanized anti-PSMA monoclonal antibody, and the microtubule inhibitor DM1. In early-phase studies, a low rate of clinical activity was seen, which was attributed to poor drug delivery secondary to deconjugation of MLN2704. [34] A phase II trial with monomethyl auristatin E, a synthetic antimitotic agent, conjugated with a PSMA monoclonal antibody demonstrated a PSA response > 30% in 30% of patients. Treatment toxicities were common, with 25% of previously taxane-exposed patients developing ≥ grade 3 neutropenia.[35,36]

BIND-014 is a docetaxel-containing PSMA-targeted nanoparticle. These nanoparticles are designed to accumulate in prostate tissue and release docetaxel in a controlled manner.[32,37,38] A phase II study was completed that included 42 docetaxel-naive patients with metastatic CRPC who had previously been treated with abiraterone, enzalutamide, or both. The median radiographic progression–free survival was 7.1 months, with a PSA decline of ≥ 50% seen in 30% of patients. Unfortunately, rates of toxicity were high; the most frequently seen adverse events were fatigue (69%), nausea (55%), and diarrhea (45%), followed by neuropathy, lymphopenia, and anemia. Overall, the toxicity profile and clinical activity of BIND-014 was similar to systemic docetaxel administration, which raised concerns for drug deconjugation and target affinity.[37,38]

Conjugates with radioisotopes allow for targeted delivery of alpha and beta particles to the PSMA-expressing site. Lutetium-177 (177Lu)-PSMA-617 complexes have shown preliminary activity. In retrospective studies, the percentage of patients who experienced a > 50% reduction in PSA levels has been reported to be 30% to 70%. Common side effects included hematologic and salivary gland toxicities.[39] In a phase II trial of 47 heavily pretreated men with metastatic CRPC, patients were given 177Lu conjugated with HuJ591; 36.2% had a > 30% PSA response and a median overall survival of 17.6 months. All patients experienced transient hematologic toxicity, with 46.8% of patients having grade 4 thrombocytopenia.[40] These responses seen in heavily pretreated patients are exciting and have provided the foundation for ongoing prospective clinical trials.

Phosphoinositide 3-kinase (PI3K)

The PI3K signaling pathway regulates cellular processes essential for cell proliferation and growth. The PI3K signaling cascade leads to AKT activation by phosphorylation of pyruvate dehydrogenase kinase 1 (PDK1) and mammalian target of rapamycin (mTOR). Both the AR and PI3K pathways are implicated in prostate cancer, with the PI3K pathway shown to have a role in the development of prostate cancer. Activation of the PI3K signaling
cascade is associated with advanced disease and poor outcomes in patients with prostate cancer.[41-47] Carver et al and Mulholland et al independently demonstrated the relationship between the AR and PI3K signaling pathways. With PTEN loss, the PI3K/AKT pathway is activated, leading to prostate cancer cell growth independent of AR signaling. With potent second-generation AR blockade, there may be selection for tumor cells that are able to grow independent of the AR in a castration-resistant manner. [41,48] Loss of PTEN, which has been identified in 60% of CRPCs, leads to continued activation of PI3K and has been identified as a factor leading to prostate cancer development.[49]

Due to the implications of the PI3K pathway in cancer development and pathogenesis, it has been a popular pharmacologic target for drug development. Multiple classes of drugs have been developed targeting PI3K, as well as downstream targets such as mTOR and AKT.[46] Despite these efforts, early studies of PI3K inhibitors have shown limited efficacy in prostate cancer. A phase II study looking at PX-866, a pan-isoform inhibitor of PI3K, included 43 docetaxel-naive patients with metastatic CRPC. Eleven patients were progression-free at 12 weeks, with only 1 patient having a confirmed PSA response.[50] Burris et al investigated the pan-AKT inhibitor GSK2141795 in 9 patients with prostate cancer, 2 of whom had a partial or complete loss of PTEN and stable disease for over 6 months.[51]

Rathkopf et al investigated the concurrent blockade of mTOR with everolimus and epidermal growth factor receptor inhibition with gefitinib in patients with CRPC.[52] The combination of gefitinib and everolimus did not result in antitumor activity; however, it was found that 13 of 37 patients experienced a rapid increase in PSA, which decreased upon stopping this medication. This finding suggests that the PI3K signaling pathway inhibits the AR and that blockade of the PI3K signaling pathway promotes AR activity. The increase in PSA observed may be a marker of AR reactivation in these patients.[46] This study led to investigations testing concurrent PI3K inhibitors and androgen blockade.[52]

In part B of the phase II study of the PI3K inhibitor PX-866 by Hotte et al, the addition of androgen blockade with abiraterone was investigated in an attempt to reverse acquired androgen resistance. Twenty-five patients with metastatic CRPC who had progressed on abiraterone/prednisone were included in the study and received PX-866. Unfortunately, the addition of PX-866 to abiraterone and prednisone did not result in any antitumor effect. This raised the question of whether this combination should be used earlier in the disease course, prior to the development of castration resistance.[53]

A phase II study of concurrent AKT inhibition with AR blockade with ipatasertib and abiraterone found evidence for both improved progression-free survival and overall survival in patients with metastatic CRPC. In this study, 253 patients with metastatic CRPC who had previously been treated with docetaxel were included and randomized 1:1:1 to either ipatasertib 400 mg, ipatasertib 200 mg, or placebo, all in combination with abiraterone/prednisone. When comparing ipatasertib 400 mg vs placebo, the progression-free survival was 8.2 vs 6.4 months, and overall survival was 18.9 vs 15.6 months. In addition, patients with loss of PTEN were found to have superior progression-free survival when treated with ipatasertib 400 mg vs placebo.[54] Within this study, only 23 of the 253 patients had received novel anti-androgen therapy prior to investigation. It is possible that this combination of AKT and AR inhibition may have clinical benefit if used earlier in the disease course, prior to the development of castration resistance; this is the focus of an ongoing phase III clinical trial.[55]

**Conclusion**

There have been significant advances in the treatment of CRPC; however, options remain limited, and complete eradication of disease has yet to be achieved. Clinical trials have evolved to incorporate molecular targets, such as PSMA, PI3K, and PD-L1. Identification of patients who are likely to respond to these targeted therapies based upon their molecular profiles has the potential to improve efficacy, prolong survival, and reduce unnecessary exposure to drug toxicities.

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For references visit cancernetwork.com/CRPC-part-1