

Evidence-Based  
ONCOLOGY™FEBRUARY 2019  
VOL. 25 • NO. 2

## ALSO IN THIS ISSUE



SP43

## NEWS IN NEOADJUVANT THERAPY.

A study at The University of Texas MD Anderson Cancer Center raises new possibilities for this treatment strategy with immunotherapy in locally advanced melanoma, [SP43](#).

COTA

## READY FOR LAUNCH.

A conversation with Andrew Pecora, MD, who reports that COTA's

long-awaited system of analytics to drive decision making in cancer care is ready for implementation, [SP45](#).



PATEL

## TEAMWORK COUNTS.

Authors from Carolina Blood and Cancer Care Associates in South Carolina discuss how team-building strategies helped ensure the successful early foray into the Oncology Care Model, [SP47](#).



## NEW INDICATION.

FDA recently granted accelerated approval for pembrolizumab (Keytruda) for adult and pediatric patients with recurrent locally advanced metastatic Merkel cell carcinoma, [SP50](#).

THE CENTER FOR  
BIOSIMILARS

## BIOSIMILARS NEWS.

FDA approves third trastuzumab biosimilar;

Mylan and Biocon's trastuzumab's biosimilar gets European marketing approval, [SP51](#).

## FRONTIERS IN CARE

## Is Immunotherapy the Future of Glioblastoma Treatment?

Samantha DiGrande

**IMMUNOTHERAPY HAS SEEN GREAT** success in the treatment of numerous cancers, from melanoma to lung, breast, colorectal, kidney, and even some brain cancers.<sup>1</sup> But thus far, despite several attempts, the devastating brain disease glioblastoma has not been among the immunotherapy success stories. In fact, glioblastoma researchers have had few advances in more than a decade.<sup>2,3</sup>

CONTINUED ON SP74

# Is Immunotherapy the Future of Glioblastoma Treatment?

Samantha DiGrande

CONTINUED FROM COVER



**REARDON**  
David Reardon, MD, of Dana-Farber Cancer Center, is the lead author on several key studies in glioblastoma, including the CheckMate 143 trial.

However, the next year may bring a different story for immunotherapy in treatment of glioblastoma. Researchers and physicians are anxiously awaiting the results of a study investigating nivolumab (Opdivo) in patients with glioblastoma. Two current phase 3 randomized trials with nivolumab have completed accrual of patients and are waiting for data to mature.<sup>4,5</sup> According to clinicaltrials.gov, the first, CheckMate 498, has a scheduled completion date of October 2019.

*Evidence-Based Oncology*<sup>TM</sup> (EBO) spoke with David Reardon, MD, a neuro-oncologist at the Dana-Farber Cancer Institute and the lead author on the first phase 3 study of an immune checkpoint inhibitor in glioblastoma, CheckMate 143.<sup>6</sup> Reardon explained that the forthcoming results are “highly anticipated studies that we’re critically waiting on ... we’ll know if the results were successful for 1 or both [studies], and those could be the basis for an FDA approval.”

Glioblastomas are malignant grade 4 tumors that make up about 15% of all brain tumors and are projected to be diagnosed in nearly 210,000 people globally each year.<sup>7</sup> Glioblastomas may present de novo, described as beginning “as a grade 4 tumor with no evidence of a lower grade precursor.”<sup>8</sup> Conversely, a secondary glioblastoma may progress from a lower-grade tumor and evolve over time.

These tumors are notoriously difficult to treat. Traditionally, glioblastomas are diagnosed as either isocitrate dehydrogenase (IDH)-wildtype or IDH-mutant tumors. IDH-wildtype glioblastomas are more common; they are responsible for about 90% of all diagnosed glioblastomas, tend to be more aggressive, and generally have a worse prognosis than IDH-mutant glioblastomas.<sup>9</sup>

In recent years, glioblastoma has claimed the lives of several high-profile individuals, including former Delaware Attorney General Beau Biden, the son of former vice president Joe Biden<sup>10</sup>; Arizona Senator John McCain; and Massachusetts Senator Edward Kennedy.<sup>11</sup> In 2016, Joe Biden spent his final year as vice president leading the Cancer Moonshot initiative, which seeks to rapidly develop vaccine immunotherapies to fight cancer, including glioblastoma.<sup>12</sup>

In 2018, the former vice president and his wife, Jill Biden, EdD, founded the Biden Cancer Initiative to promote data sharing, reduce disparities of care, and bring more patients into the cancer research process.<sup>13</sup> (The Biden Cancer Initiative is a Strategic Alliance Partner of *The American Journal of Managed Care*<sup>®</sup>; this program promotes collaboration in patient education and administration policies for cancer prevention, detection, diagnosis, research, and care approaches.)

## Not Well Understood, Difficult to Treat

In an interview with EBO, Michael Lim, MD, director of the brain tumor immunotherapy program at Johns Hopkins Medicine Sidney Kimmel Comprehensive Cancer Center and professor of neurosurgery, explained that 1 reason glioblastomas are so difficult to treat is that knowledge of the disease is so limited. “Part of the answer is that [there is so much] we don’t know. We do know that it’s a very aggressive tumor, and it has many mechanisms to make it aggressive. It suppresses the immune system at a very profound level; it does things like

angiogenesis, where [the tumor] can provide its own blood vessels, and it’s behind the blood–brain barrier,” he said.

Treatment of glioblastoma usually requires the combination of several approaches, including surgery, radiation, and chemotherapy. Although surgery is widely seen as the best way to get a jump-start on treating the disease, complete resection can be difficult—frequently impossible—because the tumor often overlaps with healthy brain tissue. Additional treatments, such as angiogenesis inhibitors, may be used as a second-line agent for recurring tumors or those that have been unresponsive to treatment.

With standard treatment, median survival for adults with glioblastoma IDH-wildtype is around 11 to 15 months. For patients with IDH-mutant glioblastoma, the prognosis is significantly better, with median survival between 27 and 31 months. However, certain factors can contribute to an improved prognosis, such as if a patient is younger than 50 years or if oncologists have been able to accomplish a near-complete surgical removal of the tumor.<sup>8</sup>

Despite continued research to create more effective, novel therapies, none to date have significantly impacted patient mortality. In fact, since 2005 only 3 new treatments have been approved by the FDA to treat glioblastoma: temozolomide, bevacizumab, and tumor-treating fields.<sup>14</sup> Glioblastoma researchers have been hopeful that a significant path to improved prognosis lies within the emerging field of immunotherapy.

## A New Treatment Frontier

Immunotherapy is a treatment designed to stimulate a patient’s own immune system to fight disease, including cancer. In the past few decades, immunotherapy has become an integral part of treating certain kinds of cancer. It works in a number of ways<sup>2</sup>: Some types of immunotherapy boost the body’s immune system in a general way to help it fight against foreign antibodies, while other types, such as chimeric antigen receptor (CAR) T-cell therapies, involve use of individually engineered T-cells to attack cancer cells. Blood cancers have had significant responses to CAR T-cell therapy, although results have not been replicated to a large degree in solid tumors thus far.

To date, much of the research involving the potential of CAR T-cell therapy to treat glioblastoma has focused on modifying T cells to recognize *EGFRvIII*. Although clinical trials studying *EGFRvIII*-targeted CAR T cells have not shown an improvement in patient mortality or shrinking of the tumor, progress was made: The trials have demonstrated that the treatment can elicit an immune response in the brain.<sup>15</sup> Now, researchers’ next step is to figure out how to strengthen this response enough to make it able to kill tumor cells.

Unfortunately, several other immune-based treatments that looked highly effective in early trials proved disappointing in larger, phase 3 studies.<sup>2</sup> (Reardon is also the lead investigator for a trial involving the immunotherapy durvalumab.<sup>16</sup>) An encouraging silver lining, offered Lim, is “just the fact that we have had some phase 3 [immunotherapy] trials in glioblastoma. For years we had a hard time getting past phase 2,” he said in an interview with the National Cancer Institute.

## FRONTIERS IN CARE

However, with glioblastoma comes a whole new realm of challenges unseen in the treatment of other cancers—most significantly, the blood–brain barrier.

### Blood–Brain Barrier Challenges

The blood–brain barrier is a layer of cells that is designed to protect the brain from viruses and toxins circulating in the bloodstream. Consequently, the barrier is unable to make the distinction between a potentially life-saving therapy and a harmful virus. Often, cancer treatments are blocked from reaching their intended destination.

“Most therapeutics used for cancer patients, like chemo, are not able to get into the brain because of the blood–brain barrier,” Reardon told *EBO*. In brain cancer, “90% to 95% of the arsenal of therapies don’t penetrate that barrier, which makes treatment a major challenge.”

Furthermore, researchers are beginning to understand the nuances involved in how the immune system operates within the brain, and particularly, how glioblastoma tumors excel at evading an immune response. In a recent trial,<sup>17</sup> investigators discovered that T-cell exhaustion is particularly prevalent in glioblastoma. Exhaustion, described as the upregulation of multiple immune checkpoints, is “a known contributor to failures amid immune checkpoint blockade,” Woroniecka et al, wrote in *Clinical Cancer Research*, and it is most likely the cause of the failures of immunotherapies in glioblastoma.

In recent years, however, the discovery of lymphatic vessels in the brain<sup>18</sup> and improved understanding of effector T-cell trafficking into the central nervous system has led to renewed enthusiasm for immunotherapeutic approaches to treat glioblastoma.

### Immune Checkpoint Inhibitors

In CheckMate 143, the investigational drug nivolumab (Opdivo) failed to increase patient survival time compared with patients treated with bevacizumab (Avastin).<sup>6</sup> However, nearly 40% of patients enrolled in the study who received nivolumab were also taking steroids, which may have played a role in the inhibition of an immune response. Reardon explained that the concurrent use of steroids, or their use prior to administering an immunotherapy treatment, could lead to the drug’s lack of efficacy.

“Many brain cancer patients have a fair amount of swelling in the brain from the tumor or a treatment—radiation, for example. That inflammatory reaction can cause symptoms, like headaches. We have traditionally given steroids, such as dexamethasone, to decrease swelling and improve those symptoms,” Reardon described. “Unfortunately, those immunosuppressive anti-inflammatories can blunt the immune system’s [ability] to attack the tumor.”

He offered a note of caution for other physicians: “Become more conscientious about using corticosteroids and come up with other methods that can reduce swelling in the brain, because if we continue to do what we have done,

many patients are just left on them for weeks to months at a time—and that will make it more difficult for the immune system to respond. We are shooting ourselves in the foot when we give patients corticosteroids prior.”

Others believe there is still hope for nivolumab. In a review of the CheckMate 143 results, Filley et al, noted that the patients in the study had already been treated for some time with chemotherapy, which depleted their lymphocytes. Given the hurdles present in glioblastoma, they proposed, this would mean “any PD-1–expressing lymphocytes activated against tumor antigens would be expected to have already migrated to tumor sites, where they are inaccessible to monoclonal antibodies.”<sup>19</sup> Thus, they wrote, nivolumab might be more effective in patients newly diagnosed with glioblastoma, because their activated circulating T cells would have more success interacting with the agent. In patients with recurrent disease, they continued, pairing nivolumab with radiotherapy might be a better strategy, and in fact, these hypotheses are being studied in CheckMate 498<sup>4</sup> and CheckMate 548.<sup>5</sup>

### Vaccines and Viruses

Another form of immunotherapy being studied in glioblastoma is the therapeutic vaccine. Instead of being administered for prevention, as most are, these vaccines are intended to treat an existing disease.

The vaccine DCVax-L is currently being tested in a phase 3 trial involving patients with glioblastoma whose tumors could be removed surgically. It uses dendritic cells (a type of immune cell) that are engineered to provoke an immune response against multiple proteins, or antigens, on tumors.<sup>20</sup>

Additionally, researchers are looking at oncolytic virus therapy as a potential treatment for glioblastoma. Originally, these viruses were developed as therapies to directly infect and kill cancer cells; however, investigators now believe that these viruses work similarly to vaccines and are able to stimulate an immune response against tumors.

“I think that there has been a lot of active, ongoing research, and the fact that we make breakthroughs in other cancers makes us more resolute in our drive and hopes to find help for patients with glioblastoma, and finding a cure,” said Lim.

*Mary Caffrey contributed to this report.*

### REFERENCES

1. Immunotherapy by cancer type. Cancer Research Institute website. cancerresearch.org/immunotherapy/cancer-types. Accessed January 31, 2019.
2. NCI Staff. Can immunotherapy succeed in glioblastoma? National Cancer Institute website. cancer.gov/news-events/cancer-currents-blog/2018/immunotherapy-glioblastoma. Published May 24, 2018. Updated June 6, 2018. Accessed January 28, 2019.
3. Harder BG, Blomquist MR, Wang J, et al. Developments in blood–brain barrier penetrance and drug repurposing for improved treatment of glioblastoma. *Front Oncol*. 2018;8:462. doi: 10.3389/

fonc.2018.00462.

4. An investigational immuno-therapy study of nivolumab compared to temozolomide, each given with radiation therapy, for newly-diagnosed patients with glioblastoma (GBM, a malignant brain cancer) (CheckMate 498). clinicaltrials.gov/ct2/show/NCT02617589. Updated January 15, 2019. Accessed February 7, 2019.
5. An investigational immuno-therapy study of temozolomide plus radiation therapy with nivolumab or placebo, for newly diagnosed patients with glioblastoma (GBM, a malignant brain cancer) (CheckMate 548). clinicaltrials.gov/ct2/show/NCT02667587. Updated January 15, 2019. Accessed February 7, 2019.
6. Reardon DA, Omuro A, Brandes AA, et al. Randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: CheckMate 143. *Neuro Oncol*. 2017;19(Suppl 3):iii21. doi: 10.1093/neuonc/nox036.071.
7. Reardon DA, Wucherpennig KW, Freeman G, et al. An update of vaccine therapy and other immunotherapeutic approaches for glioblastoma. *Expert Rev Vaccines*. 2013;12(6):597-615. doi: 10.1586/erv.13.41.
8. Glioblastoma (GBM). American Brain Tumor Association website. abta.org/tumor\_types/glioblastoma-gbm/. Accessed February 4, 2019.
9. Tamimi AF, Juweid M. Epidemiology and outcome of glioblastoma. In: De Vleeschouwer S, ed. *Glioblastoma* [Internet]. Brisbane, Australia: Codon Publications; 2017:chapter 8. ncbi.nlm.nih.gov/books/NBK470003/. Accessed February 7, 2019. doi: 10.15586/codon.glioblastoma.2017.ch8.
10. Harding A. The facts about Beau Biden’s cancer. *Health* website. health.com/news/the-facts-about-brain-cancer. Published June 4, 2015. Accessed January 28, 2019.
11. Ducharme J. John McCain and Edward Kennedy died of the same cancer, exactly 9 years apart. *Time* website. time.com/5378429/john-mccain-edward-kennedy-glioblastoma/. Published August 26, 2018. Accessed January 28, 2019.
12. Grimes A. The Cancer Moonshot 2020: then, now & the future. Technology Networks website. technologynetworks.com/cancer-research/articles/the-cancer-moonshot-2020-then-now-later-294966. Published December 8, 2017. Accessed February 5, 2019.
13. Our mission. Biden Cancer Initiative website. bidencancer.org. Accessed January 28, 2019.
14. Bagley SJ, Desai AS, Linette GP, June CH, O’Rourke DM. CAR T-cell therapy for glioblastoma: recent clinical advances and future challenges. *Neuro Oncol*. 2018;20(11):1429-1438. doi: 10.1093/neuonc/noy032.
15. O’Rourke DM, Nasrallah MP, Desai A, et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Sci Transl Med*. 2017;9(399):eaaa0984. doi: 10.1126/scitranslmed.aaa0984.
16. Reardon DA, Kaley TJ, Dietrich J, et al. Phase 2 study to evaluate the safety and efficacy of MEDI4736 (durvalumab [DUR]) in glioblastoma (GBM) patients: an update. *J Clin Oncol*. 2017;35(15 suppl):abstr 2042. doi: 10.1200/JCO.2017.35.15\_suppl.2042.
17. Woroniecka K, Chongsathidkiet P, Rhodin K, et al. T-cell exhaustion signatures vary with tumor type and are severe in glioblastoma. *Clin Cancer Res*. 2018;24(17):4175-4186. doi: 10.1158/1078-0432.CCR-17-1846.
18. Louveau A, Smirnov I, Keyes TJ, et al. Structural and function features of central nervous system lymphatic vessels. *Nature*. 2015;523(7560):337-341. doi: 10.1038/nature14432.
19. Filley AC, Henriquez M, Dey M. Recurrent glioma clinical trial, CheckMate-143: the game is not over yet. *Oncotarget*. 2017;8(53):91779-91794. doi: 10.18632/oncotarget.21586.
20. Liao L, Ashkan K, Tran DD, et al. First results on survival from a large phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma [published correction appears in *J Transl Med*. 2018;16(1):179]. *J Transl Med*. 2018;16(1):142. doi: 10.1186/s12967-018-1507-6.

# MANAGED CARE PERSPECTIVES AT YOUR FINGERTIPS

**AJMC**<sup>®</sup>  
**PEER EXCHANGE**



Participate in a unique opportunity to view lively discussions featuring peer-to-peer exchanges that provide authoritative insights, opinions, and perspectives on important issues facing today's managed care professionals.

## FEATURED 2019 PROGRAMS

- **BONE HEALTH**
- **BREAST CANCER**
- **DIABETES**
- **HEPATIC ENCEPHALOPATHY**
- **MIGRAINE**
- **PRECISION MEDICINE**
- **MULTIPLE MYELOMA**
- **SCHIZOPHRENIA**
- **AND MORE!**

ONLY AT  
[AJMC.COM/PEER-EXCHANGE](https://www.ajmc.com/peer-exchange)

