

Clinical Cancer Advances 2020: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

Merry Jennifer Markham, MD¹; Kerri Wachter, BS²; Neeraj Agarwal, MD³; Monica M. Bertagnolli, MD⁴; Susan Marina Chang, MD⁵; William Dale, MD, PhD⁶; Catherine S. M. Diefenbach, MD⁷; Carlos Rodriguez-Galindo, MD⁸; Daniel J. George, MD⁹; Timothy D. Gilligan, MD¹⁰; R. Donald Harvey, PharmD¹¹; Melissa L. Johnson, MD¹²; Randall J. Kimple, MD, PhD¹³; Miriam A. Knoll, MD, DABR¹⁴; Noelle LoConte, MD¹³; Robert G. Maki, MD, PhD¹⁵; Jane Lowe Meisel, MD¹¹; Jeffrey A. Meyerhardt, MD, MPH¹⁶; Nathan A. Pennell, MD, PhD¹⁰; Gabrielle B. Rocque, MD, MSPH¹⁷; Michael S. Sabel, MD¹⁸; Richard L. Schilsky, MD²; Bryan James Schneider, MD¹⁸; William D. Tap, MD¹⁹; Robert G. Uzzo, MD, MBA²⁰; and Shannon Neville Westin, MD²¹

Each year *Clinical Cancer Advances: ASCO's Annual Report on Progress Against Cancer* highlights the most important clinical research advances of the past year, including the Advance of the Year, and identifies priority areas where ASCO believes research efforts should be focused moving forward.

In 2020, ASCO names the Refinement of Surgical Treatment of Cancer as the Advance of the Year. Years of progress in developing new systemic cancer therapies has not only improved patient survival and quality of life but is now transforming surgical approaches to cancer treatment. The emergence of novel systemic therapies combined in new and better ways is significantly changing the role of cancer surgery. ASCO's selection of Refinement of Surgical Treatment of Cancer as the 2020 Advance of the Year recognizes recent strides seen in the effectiveness of these treatments in reducing the amount of surgery, and even the need for it, while increasing the number of patients who can undergo surgery when needed.

Other advances highlighted in the report include progress in cancer prevention, molecular diagnostics, and cancer treatment—surgery, radiotherapy, combination therapy, immunotherapy, and other types of therapies.

The report also features ASCO's 2020 list of Research Priorities to Accelerate Progress Against Cancer. These priorities represent promising areas of research that have the potential to significantly improve the knowledge base for clinical decision-making and address vital unmet needs in cancer care.

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 27, 2019 and published at ascopubs.org/journal/jco on February 4, 2020: DOI <https://doi.org/10.1200/JCO.19.03141>

M.J.M., M.M.B., and R.L.S. served as executive editors.

N.A., S.M.C., W.D., C.S.M.D., C.R.-G., T.D.G., R.J.K., M.A.K., N.L., R.G.M., J.L.M., J.A.M., N.A.P., G.B.R., M.S.S., W.D.T., R.G.U., and S.N.W. served as specialty editors.

D.J.G., R.D.H., M.L.J., and B.J.S. served as Research Priority editors.

A MESSAGE FROM ASCO'S PRESIDENT

Shortly before I was elected President of ASCO, I attended the 65th birthday party of a current patient. She had been diagnosed 10 years earlier with metastatic breast cancer and hadn't been sure she wanted to move forward with further treatment. With encouragement, she elected to participate in a clinical trial of an investigational drug that is now widely used to treat breast cancer. Happily, here we were, celebrating with her now-married daughters, their husbands, and three beautiful grandchildren, ages 2, 4, and 8. Such is the importance of clinical trials and promising new therapies.

Clinical research is about saving and improving the lives of individuals with cancer. It's a continuing story that builds on the efforts of untold numbers of researchers, clinicians, caregivers, and patients. ASCO's *Clinical Cancer Advances* report tells part of this story, sharing the most transformative research of the past year. The report also includes our latest thinking on the most urgent research priorities in oncology.

ASCO's 2020 Advance of the Year—Refinement of Surgical Treatment of Cancer—highlights how progress drives more progress. Surgery has played a fundamental role in cancer treatment. It was the only treatment available for many cancers until the advent of radiation and chemotherapy. The explosion in systemic therapies since then has resulted in significant changes to when and how surgery is performed to treat cancer. In this report, we explore how treatment successes have led to less invasive approaches for advanced melanoma, reduced the need for surgery in renal cell carcinoma, and increased the number of patients with pancreatic cancer who can undergo surgery.

Many research advances are made possible by federal funding. With the number of new US cancer cases set to rise by roughly a third over the next decade, continued investment in research at the national level is crucial to continuing critical progress in the prevention, screening, diagnosis, and treatment of cancer.

While clinical research has translated to longer survival and better quality of life for many patients with cancer, we can't rest on our laurels. With ASCO's Research Priorities to Accelerate Progress Against Cancer, introduced last year and updated this year, we've identified the critical gaps in cancer prevention and care that we believe to be most pressing. These priorities are intended to guide the direction of research and speed progress.

Of course, the effectiveness or number of new treatments is meaningless if patients don't have access to them. High-quality cancer care, including clinical trials, is out of reach for too many patients. Creating an infrastructure to support patients is a critical part of the equation, as is creating connections between clinical practices and research programs. We have much work to do before everyone with cancer has equal access to the best treatments and the opportunity to participate in research. I know that ASCO and the cancer community are up for this challenge.

Sincerely,

Howard A. "Skip" Burris III, MD, FACP, FASCO

ASCO President, 2019-2020

J Clin Oncol 38. © 2020 by American Society of Clinical Oncology

CLINICAL CANCER ADVANCES 2020 AT A GLANCE

Clinical Cancer Advances 2020: ASCO's Annual Report on Progress Against Cancer highlights the most important clinical research advances of the past year and identifies priority areas where ASCO believes research efforts should be focused moving forward.

Advance of the Year: Refinement of Surgical Treatment of Cancer

Progress in the development of new systemic cancer therapies has not only improved patient survival and quality of life but is now transforming surgical approaches to cancer treatment. The emergence of novel systemic therapies—those that travel throughout the body and treat cancer cells wherever they are—combined in new and better ways, is significantly changing the role of cancer surgery.

ASCO's selection of Refinement of Surgical Treatment of Cancer as the 2020 Advance of the Year recognizes recent strides seen in the effectiveness of these treatments in reducing the amount of surgery, and even the need for it, while increasing the number of patients who can undergo surgery when needed. In particular, considerable advances have been seen in neoadjuvant therapies—those given before surgery—as reflected in the highlighted studies below. Progress in systemic therapies for pancreatic and kidney, cancers, as well as melanoma, have helped reshape the role of surgical treatment, making them some of this year's most impressive research successes.

- Neoadjuvant combinations of immunotherapies pave the way for more successful less-invasive surgery for patients with advanced melanoma.
- Targeted therapy provides alternative to immediate surgery in treatment of renal cell carcinoma.
- Upfront treatments make surgery possible for more patients with pancreatic cancer.

This progress is possible, in part, thanks to federal funding. With the number of new US cancer cases set to rise by

roughly a third over the next decade, continued investment in research is crucial.

As a cancer survivor and Chair of the Appropriations Subcommittee that funds the National Institutes of Health, I know first-hand that federally funded research can result in breakthroughs that save millions of lives.

—Representative Rosa DeLauro (D-CT)

Additional Major Advances

- Long-term data show that vaccines against human papillomavirus are reducing cervical cancer risk in real-world settings.
- Biomarker-driven treatment approach opens the door to personalized care for metastatic pancreatic cancer.
- Combinations of different types of therapies suggest that survival can be extended without increasing toxicity.
- Growing number of targeted therapies are offering hope for more patients with difficult-to-treat cancers.

ASCO Research Priorities to Accelerate Progress

ASCO's Research Priorities are intended to identify areas on which future research efforts should be focused to help accelerate progress against cancer. The 2020 priorities are listed in no particular order, address unmet needs or help fill a knowledge gap in areas critical to improving patient care and outcomes:

- Identify Strategies That Predict Response and Resistance to Immunotherapies
- Limit Extent of Surgery by Optimizing Systemic Therapy
- Increase Precision Medicine Research and Treatment Approaches in Pediatric and Other Rare Cancers
- Optimize Care for Older Adults With Cancer
- Increase Equitable Access to Cancer Clinical Trials
- Reduce the Adverse Consequences of Cancer Treatment
- Reduce Obesity's Impact on Cancer Incidence and Outcomes
- Better Identify Premalignant Lesions and Predict When Treatment Is Needed

Cancer Research: Why Federal Support Matters

Research funded by the National Institutes of Health (NIH) and US National Cancer Institute (NCI) plays a pivotal role in improving our understanding of how to prevent, diagnose, treat, and even cure cancer. In fact, nearly a quarter of the studies highlighted in this year's *Clinical Cancer Advances* report were supported in part by NIH and NCI.

Due in large part to the nation's investment in cancer research, we have seen tremendous progress over the past few decades:

- 27% decline in cancer death rates (since peak in 1991)¹
- 2.6 million+ cancer deaths have been averted in the United States in the past two decades²
- 150+ new cancer drugs or indications approved by the US Food and Drug Administration (FDA) since 2006³
- 2 out of 3 people with cancer now live at least 5 years after diagnosis⁴

Funding for Cancer Research

Over the past few years, Congress has demonstrated tremendous bipartisan leadership by passing annual consecutive increases for the NIH. In FY 2020, Congress provided a \$2.6 billion funding increase for the NIH.⁸

By continuing to invest in biomedical research, we can give our top-notch researchers across the nation and in West Virginia the support they need to continue their work and provide a new sense of hope and optimism for the future.

—Senator Shelley Moore Capito (R-WV)

But our work is far from over.

- Considering biomedical inflation, the NIH's purchasing power is only now just reaching prerecession levels, and NCI's budget is \$1.1 billion less than it would be if funding had kept pace with biomedical inflation since FY 2003.⁵
- Funding for the NCI has not kept up with overall increases to the NIH. Between FY 2015 and FY 2019, funding for NCI rose 24%, compared with 29% for NIH overall.⁶
- Despite increases, NCI is still only able to fund a small fraction of new research proposals (12% in 2018 v 28% in 1997).⁷

When we invest in cancer research, everyone benefits.

- Research funded by the NIH generates more than 433,000 jobs and nearly \$74 billion in economic activity annually, directly and indirectly.⁹
- 67% of Americans say the US government should spend more money on finding treatments and cures for cancer, even if it means higher taxes or adding to the deficit.¹⁰

As long as cancer continues to be the life-threatening burden it is today, our nation must continue to prioritize investment in cancer research. Recent budget increases represent a promising future of renewed focus on federally funded cancer research.

Contact your members of Congress to urge their continued support for NIH and NCI funding. The ACT Network makes it easy for you to reach them directly. Visit [asco.org/actnetwork](https://www.asco.org/actnetwork) to take action.

About Clinical Cancer Advances

ASCO's Clinical Cancer Advances report highlights current trends in the field and identifies cancer research priorities that have great potential to advance progress against cancer. The report, now in its 15th edition, is developed by a 20+ member editorial board of experts in a range of cancer types, subspecialties, and care issues. The editors reviewed scientific literature published in peer-reviewed journals or presented at major medical conferences, primarily from October 2018 to September 2019, and selected advances that improve meaningful patient outcomes and have a strong scientific impact. The editors also proposed priority areas of research that address vital unmet needs in cancer care and have the potential to improve the knowledge base for clinical decision-making.

About the American Society of Clinical Oncology and the Association for Clinical Oncology

The American Society of Clinical Oncology (the Society) and the Association for Clinical Oncology (the Association) are committed to making a world of difference in cancer care. The Society and the Association represent nearly 45,000 oncology professionals who care for people living with cancer. Through research, education, and promotion of the highest-quality patient care, the Society works to conquer cancer and create a world where cancer is prevented or cured, and every survivor is healthy. The Association works to ensure that all individuals with cancer have access to high-quality, affordable care; that the cancer care delivery system supports oncology providers in their delivery of optimal cancer care; and that our nation supports federal funding for cancer research as well as efforts centered on cancer prevention, drug development, and clinical trials. Learn more at www.ASCO.org, explore patient education resources at www.Cancer.Net, and follow us on Facebook, Twitter, LinkedIn, Instagram, and YouTube. Learn more about the Association at www.ascoassociation.org and follow us on Twitter.

About Conquer Cancer, the ASCO Foundation

Conquer Cancer funds research into every facet of cancer to benefit every patient, everywhere. As ASCO's foundation, Conquer Cancer helps turn science into a sigh of relief for patients around the world by supporting groundbreaking research and education across cancer's full continuum. Nearly a third of the clinical trials included in this report were conducted by researchers who received funding from Conquer Cancer through Young Investigator Awards or Career Development Awards to grantees and have continued their careers in oncology research.

ADVANCE OF THE YEAR: REFINEMENT OF SURGICAL TREATMENT OF CANCER

Years of progress in developing new systemic cancer therapies has not only improved patient survival and quality of life but is now transforming surgical approaches to cancer treatment. The emergence of novel systemic therapies—those that travel throughout the body and treat cancer cells wherever they are—combined in new and better ways, is significantly changing cancer surgery.

ASCO's selection of Refinement of Surgical Treatment of Cancer as the 2020 Advance of the Year recognizes recent strides seen in the effectiveness of these treatments in reducing the amount of surgery, and even the need for it, while increasing the number of patients who can undergo surgery when needed. In particular, considerable advances have been seen in neoadjuvant therapies—those given before surgery—as reflected in the highlighted studies below. Progress in systemic therapies for pancreatic, kidney, and prostate cancers and melanoma have helped reshape surgical treatment, making them some of this year's most impressive research successes.

Neoadjuvant Combinations of Immunotherapies Paves the Way for More Successful, Less Invasive Surgery for Advanced Melanoma

For patients with locally advanced melanoma, surgery to remove the tumor along with radical lymph node dissection—the removal of most of the lymph nodes near the tumor—has long been the standard of care. The success of systemic treatment following lymph node dissection (known as adjuvant therapy) has set the stage for neoadjuvant therapy (therapy before surgery), including strategies using targeted therapies and immunotherapies. Two studies this past year examined the efficacy and safety of presurgery combination immunotherapy treatments. These studies are already changing practice, helping patients with locally advanced melanoma avoid surgery in many cases.

In the NeoCombi trial (ClinicalTrials.gov identifier: [NCT01972347](#)),^{10a} Australian researchers examined the combination of two molecularly targeted drugs—dabrafenib and trametinib—given before surgery in patients with stage IIIC melanoma with the BRAF^{V600} mutation. Not only did the majority of the 35 patients (86%) on the trial respond by the time of resection, but almost half (46%) had a complete response, according to Response Evaluation Criteria in Solid Tumors (RECIST).

Treatment also made it easier to surgically remove the tumor and surrounding tissue in nearly half of patients (46%). Toxicities were generally similar to those that occur in patients treated with these therapies for metastatic disease. Most patients (80%) experienced fever. Just over half of patients (51%) had serious adverse events. Given the findings, neoadjuvant dabrafenib and trametinib should be considered for patients with stage IIIC melanoma with the BRAF^{V600} mutation.

In a second trial, OpACIN-neo (ClinicalTrials.gov identifier: [NCT02977052](#)),¹¹ researchers evaluated a less-toxic approach to combining two immunotherapies (treatments that help the body's own immune system find and destroy cancer cells)—ipilimumab and nivolumab. Previous work has demonstrated the efficacy of adjuvant ipilimumab plus nivolumab for the treatment of locally advanced melanoma; however, this efficacy came at the cost of increased toxicity.

In OpACIN-neo, researchers evaluated several alternative dosing strategies. Patients with stage III melanoma that was still treatable with surgery who received 1 mg/kg ipilimumab and 3 mg/kg nivolumab every 3 weeks for two cycles had high radiologic objective and pathologic response rates (57% and 77%, respectively). Importantly, these patients were considered high risk, with disease that had spread to at least one lymph node near the tumor. While this regimen was effective, patients experienced fewer grade 3/4 adverse events in the first 12 weeks than standard dosing (ipilimumab 3 mg/kg plus nivolumab 1 mg/kg every 3 weeks for four cycles). Reduced neoadjuvant dosing of ipilimumab and nivolumab could make treatment more tolerable—yet still effective—in patients with advanced melanoma. Long-term outcomes are awaited to determine if this less-toxic approach can be recommended as a standard of care.

Targeted Therapy Provides Alternative to Immediate Surgery in Treatment of Renal Cell Carcinoma

In the absence of effective systemic therapies, surgical resection has traditionally been the primary treatment of many solid tumor cancers, including renal cell carcinoma (RCC). Landmark research from 2001 demonstrated improved survival with removal of the cancerous kidney (primary cytoreductive nephrectomy, or CRNx) followed by immunotherapy compared with immunotherapy alone (interferon alpha-2b). As a result of these data, thousands of individuals have since undergone CRNx. Results from two randomized controlled trials published this past year provide evidence for an alternate treatment approach that might eliminate the need for surgery.

The CARMENA trial (ClinicalTrials.gov identifier: [NCT00930033](#))¹² demonstrated that systemic therapy with sunitinib alone was comparable to cytoreductive nephrectomy followed by sunitinib in patients with metastatic RCC classified as poor or intermediate risk of survival. In this trial, 450 patients with metastatic RCC were randomly assigned to receive either nephrectomy followed by sunitinib or sunitinib alone. Nephrectomy was performed within 28 days of random assignment in the adjuvant treatment arm; sunitinib was started within 21 days of random assignment in the sunitinib-only group.

Sunitinib alone was no worse than surgery followed by sunitinib. Median overall survival was longer for patients receiving only sunitinib—18.4 months compared with 13.9 months. Median overall survival was also longer for patients classified as intermediate or poor risk with sunitinib

only compared with surgery plus sunitinib—23.4 months v 19.0 months and 13.3 v 10.2 months, respectively. Grade 3 or greater adverse events were slightly higher in the sunitinib-only arm (42.7%), compared with nearly a third of patients (32%) in the nephrectomy-sunitinib arm. These included physical weakness/lack of energy, hand-foot syndrome, anemia, and neutropenia.

Results from the SURTIME trial (ClinicalTrials.gov identifier: [NCT01099423](#))¹³ indicate that a surgery-first approach did not improve the progression-free survival rate compared with delaying cytoreduction until after treatment with sunitinib for patients with primary clear cell metastatic RCC. A total of 99 patients were included, with a median follow-up of more than 3 years. At 28 weeks, the progression-free survival was comparable for the two arms (42%-43%). Median overall survival, however, was 32.4 months for those who received sunitinib first and delayed surgery, compared with 15.0 months for those who went immediately to surgery. The results of an exploratory analysis suggest that patients with disease that progressed despite pretreatment with sunitinib had worse prognosis and were less likely to have good results following nephrectomy.

Both studies highlight the evolving role of systemic treatment in patients with metastatic RCC.

Upfront Treatments Make Surgery Possible for More Patients With Pancreatic Cancer

While surgical resection offers the best chance of survival for patients with pancreatic cancer, many either have tumors that are surgically difficult to remove entirely (borderline resectable) or cannot be removed at all (locally advanced). Two preliminary studies suggest that more patients may be eligible for surgery following upfront treatment, though confirmation is needed with randomized trials. One treatment approach, published in the past year, combined a chemotherapy regimen, called FOLFIRINOX for short, with radiotherapy and has already shown promise in making patients eligible for surgery. FOLFIRINOX consists of three chemotherapy drugs: folinic acid (also known as leucovorin), fluorouracil (along with leucovorin), irinotecan, and oxaliplatin. In a similar study published in 2019, the addition of the blood pressure treatment losartan to the FOLFIRINOX/radiotherapy combination showed even better results.

In a single-arm phase II study (ClinicalTrials.gov identifier: [NCT01591733](#)),^{13a} researchers investigated neoadjuvant FOLFIRINOX plus radiotherapy in 48 patients with borderline resectable pancreatic ductal adenocarcinoma. Following FOLFIRINOX, patients were restaged. Those with resolution of vascular involvement received a short course of proton radiation with capecitabine. Patients with persistent vascular involvement received standard radiotherapy with fluorouracil or capecitabine.

Surgery was performed either 1-3 weeks after a short course of radiotherapy or 4-8 weeks after a long course for patients who met the requirements for surgery. Among 31

patients who underwent surgery, more than two-thirds (67%) of the patients had negative margins (no cancer cells seen on pathologic examination). Median progression-free survival for all patients in the trial was 14.7 months, and overall survival was 37.7 months. Among those patients who were able to undergo resection, however, progression-free survival was significantly improved (48.6 months). Median overall survival had not been reached for this group, but overall survival at 2 years was 72% (compared with 56% for all patients). Grade 3 or higher adverse events occurred in 19% of patients, with diarrhea, neutropenia, and peripheral neuropathy being the most common severe events. This study was funded in part by the NCI.

Another study explored the benefit of adding the common blood pressure medicine losartan to neoadjuvant FOLFIRINOX and radiation in adults with locally advanced pancreatic cancer. The renin-angiotensin-aldosterone (RAA) system plays roles in cell proliferation, metabolism, and growth and regulates blood pressure, electrolyte, and fluid levels and cardiac output. Because losartan works by mediating the RAA system, researchers speculated that the therapy could help further reduce the size of pancreatic tumors, allowing more patients to undergo surgery.

In a single-arm phase II study (ClinicalTrials.gov identifier: [NCT01821729](#)),¹⁴ all patients with locally advanced pancreatic cancer received FOLFIRINOX and losartan, and those with radiographically resectable tumors received short-course proton radiotherapy and capecitabine. Patients with persistent vascular involvement received standard long-course radiotherapy with fluorouracil or capecitabine. This approach resulted in more than half of patients (61%) going on to surgery and surgical margins (the tissue surrounding the removed tumor) that were free of cancer cells.

Surgery was performed either 1-3 weeks after a short course of radiotherapy or 4 to 8 weeks after a long course. Overall, median progression-free survival was 17.5 months for the 49 patients in the federally funded study, and overall survival was 31.4 months. In comparison, among the 34 patients who were able to undergo resection, progression-free survival and overall survival were 21.3 and 33.0 months, respectively.

The results with the addition of losartan compared favorably to a similar trial published in 2018. That study was also single-arm, phase II trial and included 48 patients with newly diagnosed, previously untreated, localized pancreatic cancer determined to be borderline resectable. Grade 3 or higher adverse events occurred in 51% of patients, with neutropenia, thrombocytopenia, diarrhea, and nausea/vomiting being the most common severe events. Grade 1/2 peripheral neuropathy was also common. This study was funded in part by the NCI.

ADVANCES IN CANCER PREVENTION

Thanks to research, treatment options are increasing in number and efficacy across multiple types of cancer and for diverse populations of patients, even as side effects are

minimized and better managed to maximize patients' quality of life. Preventing cancer, however, remains a high priority to improve public health.

Cancer prevention encompasses many strategies, including lifestyle changes that can minimize cancer risk, better screening tools to diagnose cancer sooner, and approaches that can prevent cancer by preventing infection by cancer-causing organisms. To advance cancer prevention, however, means not only figuring out which new approaches will work but also implementing those approaches proven to be effective in relevant populations.

Longer Real-World Follow-Up Validates That HPV Vaccines Reduce Cervical Cancer Risk

Vaccines against several forms of human papillomavirus (HPV) were developed and licensed for adolescents and young adults to prevent HPV infection, which can lead to cervical cancer and anogenital warts later in life.¹⁵ Since the first vaccine was licensed in 2006, nearly 100 countries have instituted HPV vaccination programs. Currently in the United States, the vaccine is approved for females and males age 9-45 years.¹⁶ Clinical trials that led to vaccine approvals showed nearly 100% protection against persistent cervical infections with HPV types 16 and 18, which account for 70% of cervical cancers and 86%-95% of all other HPV-associated cancers.¹⁷

In a 2019 analysis of data from 40 trials in 14 high-income countries, researchers reported that the prevalence of HPV 16 and 18 dropped by 83% among females age 13-19 years and by 66% in young women age 20-24 years in the 5-8 years after the introduction of HPV vaccination.¹⁸ The prevalence also decreased for women age 25-29 years (most of whom are unvaccinated in the general population) in the same period. Decreases in prevalence were also seen for HPV 31, 33, and 45 for females age 13-24 years.

The researchers also looked at the population-level impact of vaccination on rates of precancerous cervical lesions (cervical intraepithelial neoplasia grade 2+, or CIN2+). Among those screened for CIN2+, researchers found a decrease of 51% in incidence in females age 15-19 and 31% among women age 20-24 years. The study results not only provide strong evidence that HPV vaccines prevent cervical cancer in real-world settings but also bolster the importance of vaccination programs worldwide.

Large Study Finds No Cancer Protection Benefit From Vitamin D Supplements

By helping the body absorb calcium, vitamin D is important to bone health. This fat-soluble vitamin is also important to the function of muscles, nerves, and the immune system. It is found in a relatively small number of foods, and through sun exposure the body produces some vitamin D for itself.

In recent years, some small observational studies have suggested that low levels of vitamin D in the blood may be associated with greater risks of cancer. Larger studies were

needed, however, to determine if the link could hold up to a more rigorous analysis.

In a large federally funded, randomized, double-blind, placebo-controlled trial published in 2019, the Vitamin D and Omega-3 Trial (VITAL; ClinicalTrials.gov identifier: [NCT01169259](https://clinicaltrials.gov/ct2/show/study/NCT01169259)),¹⁹ researchers could not reproduce the links between low vitamin D and increased risk of cancer. More than 25,000 healthy people were randomly assigned to receive either 2,000 IU per day of vitamin D3 (along with omega-3 fatty acid supplementation) or placebo. Men enrolled in the trial had to be at least 50 years of age, and women had to be at least 55 years.

After a median follow-up of more than 5 years, there were no differences between those who received vitamin D/omega-3 supplements and those who did not in terms of death from cancer, invasive cancer of any type, breast cancer, prostate cancer, or colorectal cancer. These study results mean that otherwise healthy people do not benefit from vitamin D supplementation to prevent cancer. This study was funded in part by the NIH.

ADVANCES IN MOLECULAR DIAGNOSTICS

Molecular diagnostics can be used for early detection of cancer, prognosis, and prediction of therapy efficacy. These tools also help us understand differences between cancers of the same histologic type. Molecular diagnostics are tests that determine the presence of biomarkers—cellular constituents that can be measured from blood, urine, tumor, or other samples. It is hoped that biomarkers will be able to provide information about the presence and prognosis of a cancer. Biomarkers could also help identify cancer earlier, particularly in people at increased risk, leading to improved survival.

Molecular Detection and Treatment of Testicular Germ Cell Tumors Advanced Through the Genomic Revolution

An increasing understanding of the molecular basis of cancer now enables molecular detection using biomarkers, as well as selection of patients likely to benefit from molecularly targeted treatment approaches. Research into genomic biomarkers in testicular germ-cell tumors has ushered in a new era of treatments for patients with these cancers.

Several classic protein-based germ-cell tumor markers have been used for decades in patients with testicular cancer. The tests, however, are not very accurate. In a 2019 study, investigators looked at serum levels of the genomic biomarker microRNA371 (M371) as a strategy to stage testicular germ-cell tumors and assess response to treatment. Prior studies of a test measuring this marker were encouraging, but additional studies were needed.

In a new study conducted this past year, the investigators demonstrated that the M371 test was very accurate (sensitivity of 90%, specificity of 94%) for predicting clinical stage, tumor size, and response to treatment of testicular germ-cell tumors.²⁰ The results of this study mark

a significant advance in the use of molecular biomarkers as effective tools for diagnosis and disease management. They represent an improvement over currently used tests (β -human chorionic gonadotropin and α -fetoprotein [AFP] for testicular cancers) that is expected to affect patient care going forward should M371 receive FDA approval.

First Biomarker-Driven Approach to Treatment of Metastatic Pancreatic Cancer

The *BRCA* gene is associated with DNA damage repair; thus, mutated *BRCA* in which DNA damage repair is hindered can lead to the development of cancer. *BRCA* mutations identified through genetic/molecular testing can serve as biomarkers for cancer. Biomarkers can also inform which therapy may be the most effective treatment. Germ-cell *BRCA* testing is already routinely done to detect families with high risk, as well as to identify patients with breast or ovarian cancer likely to benefit from olaparib.

Olaparib is an oral PARP (poly [ADP-ribose] polymerase) inhibitor. It works by blocking a process that repairs damage to DNA, which ultimately promotes cell death. The federally funded randomized phase III POLO trial (ClinicalTrials.gov identifier: [NCT02184195](https://clinicaltrials.gov/ct2/show/study/NCT02184195))²¹ was designed to test treatment with olaparib as a maintenance strategy after the control of metastatic pancreatic cancer using first-line chemotherapy.

The trial enrolled 154 patients with metastatic pancreatic cancer who were identified as having germline *BRCA* mutation to receive olaparib or placebo following initial platinum-based chemotherapy. In this population of patients, olaparib significantly delayed cancer progression compared with placebo, with a median progression-free survival of 7.4 months compared with 3.8 months for the placebo group. Two years after initiating olaparib, pancreatic cancer in 22.1% of patients had not progressed, compared with 9.6% of those treated with placebo, in whom the cancer had not progressed. This study was funded in part by the NCI.

GERMLINE GENETIC TESTING: ASCO PROVISIONAL CLINICAL OPINION

In January 2019, ASCO issued a Provisional Clinical Opinion (PCO) stating that germline genetic testing for cancer susceptibility—including testing for *BRCA* mutations—may be discussed with patients with pancreatic cancer even if there is no clear family history. For more details, view the PCO at <https://ascopubs.org/doi/full/10.1200/JCO.18.01489>.

CANCER TREATMENT ADVANCES

Our understanding of the biology of cancer continues to grow rapidly, leading to new types of targeted treatments and novel therapeutic approaches. In the past year, treatments were combined in new ways, optimal dosing

and scheduling were identified for existing treatments, and adverse events were reduced. Researchers also identified groups of patients more likely to benefit from specific treatments and made strides in surgery and radiotherapy.

SURGERY

Aggressive Treatment Improves Disease Control in Certain Patients With Stage IV Lung Cancer

A growing body of evidence suggests that more aggressive treatment with radiation (known as local consolidative therapy) or surgery extends survival for select patients with stage IV non-small-cell lung cancer (NSCLC) with spread limited to a small number of metastases (oligometastatic) outside of the lungs. The concept behind local consolidative therapy is that oligometastatic disease may represent an intermediate state between locally advanced disease and unequivocally metastatic disease. Small trials have suggested that ablative therapy (surgery or stereotactic radiation) to a few sites of metastatic disease (local consolidative therapy) extends progression-free survival.

In 2016, researchers published early data from a randomized study that examined this approach. The trial was closed early after it demonstrated an 8-month benefit in progression-free survival for patients who received local consolidative therapy compared with maintenance therapy or observation. In 2019, researchers published updated results from the phase II randomized trial (ClinicalTrials.gov identifier: [NCT01725165](https://clinicaltrials.gov/ct2/show/study/NCT01725165))²² of 49 patients with stage IV NSCLC with up to three metastatic sites and stable disease for 3 months after first-line systemic therapy. Patients in the study were randomly assigned to maintenance therapy/observation or local consolidative therapy (surgery or radiotherapy) and observation/maintenance therapy. This study was funded in part by the NCI.

The median progression-free survival was more than three times longer for patients undergoing local consolidative therapy compared with the maintenance/observation group—14.2 months v 4.4 months. Likewise, median overall survival more than doubled in the local consolidative therapy group (41.2 months v 17.0 months). The findings are important because they support the notion that the oligometastatic state represents a unique tumor biology that may be managed effectively with local therapy. No patient reported severe adverse events (grade 3 or greater) beyond those reported in the earlier publication. This approach is now being tested in phase III randomized trials.

Open Surgery Proves Superior to Minimally Invasive Surgery for Early-Stage Cervical Cancer

Minimally invasive surgery has largely been adopted for the surgical treatment of early-stage cervical cancer. Guidelines in the United States and Europe, however, allow for either laparotomy (open surgery) or laparoscopy (minimally invasive surgery performed with either conventional or robotic techniques) to be used for radical hysterectomy in

patients with early-stage (IA1 to IIA) cervical cancer. Two important studies recently showed superior survival for patients who received open surgery to treat cancer.

In the LACC trial (ClinicalTrials.gov identifier: [NCT00614211](#)),²³ researchers reported worse progression-free survival and overall survival with minimally invasive surgery in a randomized controlled trial comparing the approach to open abdominal radical hysterectomy in more than 600 women with early-stage cervical cancer (IA1, IA2, or IB1). At 3 years, progression-free survival was 91.2% v 97.1% and overall survival was 93.8% v 99.0% with minimally invasive surgery and open surgery, respectively. These differences remained statistically significant after adjusting for relevant prognostic factors.

Similar findings were reported in a second study based on retrospective data from the National Cancer Database.²⁴ Half of the more than 2,000 women in the dataset underwent minimally invasive radical hysterectomy and the remainder had open surgery. The 4-year mortality rate was higher among patients treated with minimally invasive radical hysterectomy—9.1% v 5.3%.

Together, these studies call into question whether laparoscopic hysterectomy for early-stage cervical cancer should remain a standard of care. Further research is necessary to determine if there is a patient population for which this approach results in acceptable clinical outcomes.

RADIOTHERAPY

Stereotactic Radiation Prolongs Survival in Patients With a Limited Number of Metastases

Patients with oligometastatic disease and a well-controlled primary tumor may be eligible for a curative treatment approach. The use of radiotherapy and/or surgery, called “local consolidative therapy,” has been suggested as an approach to treat limited cancer metastases with the intention of eradicating disease.

The phase II SABR-COMET trial (ClinicalTrials.gov identifier: [NCT01446744](#)),²⁵ published in 2019, is one of the first randomized trials to compare stereotactic ablative radiotherapy with standard palliative care aimed at minimizing symptoms and preventing complications.

The trial included 99 patients with one to five metastatic lesions. Primary cancers were predominantly breast, colorectal, lung, or prostate. Overall survival in the stereotactic radiotherapy group was more than a year longer, 41 months, v 28 months in the standard of care group. Adverse events with radiotherapy were more common than with standard care. Only 9% of the 33 patients receiving standard care had an adverse event of grade 2 or more compared with 29% of the 66 patients receiving radiotherapy. The most common adverse events were fatigue, trouble breathing, and pain. In addition, three deaths in the radiotherapy group were considered to be treatment related. Phase III trials are needed to validate the findings, determine the number of

metastases to treat, and identify how to balance improved cancer control with increased toxicity.

Trials Confirm Cisplatin Plus Radiotherapy as Standard Care for HPV-Positive Head and Neck Cancer

HPV-positive squamous cell carcinoma has a very good prognosis when treated with cisplatin and radiotherapy; however, cisplatin carries risk of severe acute adverse events and late toxicity. As a result, there has been substantial interest in treatment de-escalation strategies in HPV-driven head and neck cancer. Early trials of the targeted drug cetuximab in combination with radiation suggested both a survival and toxicity advantage for cetuximab.

Two complementary trials evaluated the noninferiority of cetuximab plus radiotherapy compared with cisplatin plus radiotherapy. Data from these trials turned out to be practice-changing: both showed that the combination of radiation and cetuximab led to worse outcomes than the combination of radiation and cisplatin. In addition, toxicities appeared to be similar with cetuximab.

After 2 years of follow-up in the 334-patient De-ESCALaTE trial (ClinicalTrials.gov identifier: [NCT01874171](#)),²⁶ patients who received cisplatin had longer overall survival compared with those who received cetuximab—97.5% v 89.4%. There was no difference between the two patient groups in terms of severe adverse events (grade 3 or greater) that did not last long and/or were chronic.

The second trial (805 patients), RTOG 1016 (ClinicalTrials.gov identifier: [NCT01302834](#)),²⁷ showed similar results, with 5-year estimated survival at 77.9% in the cetuximab group compared with 84.6% for the cisplatin group. The proportions of acute to moderate toxicity and late moderate to severe toxicity were lower for those receiving cisplatin compared with those receiving cetuximab. While surprising, the outcomes of these trials have defined cisplatin plus radiotherapy as the standard of care in patients with HPV-positive squamous cell carcinoma.

TAPUR

ASCO's Targeted Agent and Profiling Utilization Registry Study (TAPUR; ClinicalTrials.gov identifier: [NCT02693535](#)) continues to enroll patients and report findings on patient outcomes. TAPUR evaluates antitumor activity of commercially available, targeted anticancer drugs when used outside of their FDA-approved indications. It aims to identify new uses for existing, effective treatments that target tumor genomic profiles.

More than 2,350 participants have been registered and more than 1,700 treated with a TAPUR study therapy. Based on treatment responses in the first stage of the study, patient cohorts are either expanded to stage II for further study or permanently closed. To see the full list of patient cohort updates, visit tapur.org/news.

COMBINATION THERAPY

Antibody Drug Conjugate Delays Recurrence of HER2-Positive Breast Cancer

Trastuzumab emtansine (T-DM1) was approved by the FDA in 2019 for adjuvant (postoperative) treatment of patients with residual invasive disease after neoadjuvant (preoperative) treatment with a regimen that included a taxane and trastuzumab. T-DM1 only benefits patients with breast cancers that overexpress a protein called human epidermal growth factor receptor 2 (HER2), which promotes the growth of cancer cells. HER2 is overexpressed in roughly 14% of women with breast cancer.²⁸

Trastuzumab, a monoclonal antibody directed against HER2, has been transformative in the care of patients with HER2-positive breast cancer since it was first approved in 1998. T-DM1 links the biologic drug trastuzumab with the chemotherapy drug emtansine. This allows for selective delivery of the chemotherapy drug into HER2-overexpressing cells, resulting in cell cycle arrest and apoptosis.

The 2019 approval of adjuvant T-DM1²⁹ came in response to the phase III KATHERINE trial (ClinicalTrials.gov identifier [NCT01772472](#)),³⁰ which included nearly 1,500 patients. All patients had residual invasive disease following neoadjuvant treatment with taxane- and trastuzumab-based regimens and were randomly assigned in a 1:1 fashion to receive 14 cycles of adjuvant trastuzumab (the current standard of care) or 14 cycles of adjuvant T-DM1. Those who received adjuvant T-DM1 had a 50% lower risk of recurrence of invasive disease or death compared with those who received postoperative trastuzumab.

Immunotherapy Combined With Chemotherapy Delays Cancer Progression in a Group of Patients With Metastatic Triple-Negative Breast Cancer

In triple-negative breast cancer, the three most common types of receptors that drive most breast cancer growth are not expressed—estrogen and progesterone receptors (ER and PR), and HER2. Those patients with cancers that are negative for ER, PR, and HER2, otherwise known as triple-negative breast cancers, have not been able to benefit from hormone-targeted or HER2-targeted therapies, and as a result, chemotherapy has been the only option for systemic therapy. Unfortunately, for patients with metastatic triple-negative breast cancer, prognosis is extremely poor, with average survival rates of 18 months or less from the time of metastatic diagnosis.

This past year, results from IMpassion130 were presented and published, (ClinicalTrials.gov identifier: [NCT02425891](#))³¹ showing that combining the programmed cell death-ligand 1 (PD-L1) targeted therapy atezolizumab with a common chemotherapy (nanoparticle albumin-bound [nab] paclitaxel) improved progression-free survival in patients with triple-negative breast cancer. In the entire study population, patients receiving the combination had a progression-free

survival of 7.2 months, compared with 5.5 months for those who received placebo plus nab-paclitaxel. Patients were stratified by PD-L1 immune cell (IC) status (positive or negative), and authors found that the benefit of atezolizumab was limited to the PD-L1 IC-positive population. In the PD-L1 IC-positive population, progression-free survival was 7.5 months with the combination and 5.0 months with nab-paclitaxel alone. In the PD-L1 IC-positive population, progression-free survival was not markedly different between arms.

Atezolizumab plus nab-paclitaxel was approved by the FDA in March 2019 for this population and is already in widespread use.³² In June 2019, updated survival data from IMpassion130 were made available, showing that for the PD-L1 IC-positive patients, the addition of atezolizumab significantly improved overall survival (25 months v 18 months), whereas for PD-L1 IC-negative patients, there was no difference between arms (19.7 v 19.6 months). The study highlights the importance of continued research into biomarkers of immunotherapy responsiveness and into different subsets of triple-negative disease.^{32a}

Adding Ribociclib to Endocrine Therapy Improves Survival in Young Women With Advanced ER-Positive/HER2-Negative Breast Cancer

Premenopausal women with breast cancer tend to have more aggressive disease with worse survival than those who are postmenopausal, and they are often under-represented in clinical trials compared with older women. Research suggests that breast cancer in premenopausal women may be biologically different. Despite this, the recommended treatment of women with hormone receptor–positive (HR-positive), HER2-negative breast cancer has historically been similar for both groups.

Results from an interim analysis of the MONALEESA-7 (ClinicalTrials.gov identifier: [NCT02278120](#))³³ trial indicate that combining the CDK4/6 inhibitor ribociclib with endocrine therapy provides an overall survival advantage for pre- and perimenopausal women with advanced HR-positive, HER2-negative breast cancer, compared with standard endocrine therapy plus placebo. The trial enrolled 335 patients, and the estimated overall survival with ribociclib at 42 months was 70.2%, compared with 46% for women who received placebo plus standard treatment. Endocrine therapy consisted of goserelin plus either a nonsteroidal aromatase inhibitor (ie, letrozole or anastrozole) or tamoxifen. Overall survival was a prespecified secondary endpoint of this trial (progression-free survival was also improved and had been reported previously). Adverse events with ribociclib were similar to those seen in previous studies. Neutropenia was greater for patients receiving ribociclib (63.5% v 4.5%). Hepatobiliary toxic effects (11% and 6.8%, respectively) and abnormal heart rhythm (in 1.8% and 1.2%, respectively) were also greater for patients who received ribociclib.

While the role of therapies like ribociclib in breast cancer continues to evolve, MONALEESA-7 shows a clear overall

survival benefit in pre- or perimenopausal women with HR-positive, HER2-negative advanced breast cancer. These findings represent an important step forward for the treatment of women with this disease.

More Highly Targeted Drug Combinations Work Together to Improve the Survival for Prostate and Kidney Cancer

The efficacy of single-agent targeted and immune therapies has led researchers to investigate potentially more powerful combinations. The hope is that these multipronged approaches will further extend survival without increasing toxicity. Two studies in RCC published this year have advanced the case for combining immunotherapies with a type of targeted therapy called tyrosine kinase inhibitors in the first-line treatment setting. In the KEYNOTE-426 trial (ClinicalTrials.gov identifier: [NCT02853331](#)),³⁴ investigators demonstrated that treatment with the combination of axitinib and pembrolizumab resulted in significantly longer survival and better response than with standard sunitinib alone in patients with previously untreated metastatic RCC. Axitinib is a tyrosine kinase inhibitor that works by blocking the growth of blood vessels, and thus the flow of blood, to a tumor. Pembrolizumab is a PD-1 targeted immunotherapy, called an immune checkpoint inhibitor, that works by helping the immune system identify and target cancer cells. Axitinib is better tolerated than sunitinib, making it an attractive addition to pembrolizumab.

In the study, the estimated 18-month overall survival was 82.3% and 72.1%, respectively, for the combination of axitinib and pembrolizumab compared with sunitinib (standard therapy). Progression-free survival was also greater for the combination therapy—15.1 v 11.1 months. Grade 3 or greater adverse events from any cause were 75.8% for combination therapy and 70.6% for sunitinib.

In a second trial, called JAVELIN Renal 101 (ClinicalTrials.gov identifier: [NCT02684006](#)),³⁵ investigators demonstrated longer progression-free survival with the combination of avelumab (a PD-L1 targeted immunotherapy) and axitinib compared with standard sunitinib therapy in patients with advanced, newly diagnosed RCC. The median progression-free survival was 13.8 months for the combination v 7.2 months for sunitinib. The rate of any adverse events and those grade 3 or greater were comparable in the two groups (71%).

In prostate cancer, new research has shown that combining different types of drugs that target the androgen pathway is effective in treating men newly diagnosed with metastatic prostate cancer. In the ENZAMET trial (ClinicalTrials.gov identifier: [NCT02446405](#)),³⁶ investigators demonstrated that combining the targeted androgen receptor inhibitor enzalutamide with standard androgen suppression improved progression-free survival and overall survival over less-specific targeted androgen-receptor therapy (standard nonsteroidal antiandrogen drugs bicalutamide, nilutamide, or flutamide).

Prostate cancer is stimulated to grow by high levels of androgens. The cancer, however, can become resistant, with the ability to survive with even a small amount of androgen. Enzalutamide works by blocking androgen from supporting tumor growth in a more specific way than standard hormone therapies. Overall survival at 3 years was estimated to be 80% for the enzalutamide group, compared with 72% for the standard therapy group. Clinical progression-free survival was 67% and 37% at 3 years, respectively. Serious adverse events were more common with enzalutamide; 1,125 men were randomly assigned, and 563 received enzalutamide; seven patients experienced seizures, and six discontinued treatment as a result.

These studies demonstrate progress in data needed to balance efficacy and toxicity and to gain a more favorable efficacy profile. In April 2019, the FDA approved pembrolizumab plus axitinib for the first-line treatment of patients with advanced RCC.³⁷ Approval was based on KEYNOTE-426. In May 2019, the FDA approved avelumab plus axitinib for first-line treatment of patients with advanced RCC.³⁸ Approval was based on JAVELIN Renal 101. Also in 2019, the FDA granted priority review to enzalutamide for the treatment of men with metastatic hormone-sensitive prostate cancer. Taken together, these trials are changing standard first-line therapy for advanced-stage kidney and prostate cancer.

Addition of Lomustine to Temozolomide Improves Survival in Glioblastoma

Glioblastoma (also known as glioblastoma multiforme, or GBM) is a fast-growing brain tumor. Glioblastoma is challenging to treat for several reasons: many drugs do not cross into the brain easily, or prove toxic to other brain tissues; glioblastomas are generally resistant to conventional therapies; surgery can be difficult depending on the location of the tumor in the brain; and radiation therapy can damage adjacent tissue.

Since its approval in 2005,³⁹ temozolomide has been a mainstay of treatment of adults with newly diagnosed glioblastoma, used concurrently with radiotherapy and also as maintenance therapy after radiotherapy. Temozolomide is especially effective at extending survival among patients with tumors that have a particular marker (methylation of the *MGMT* gene promoter) associated with treatment sensitivity.

Lomustine is an alkylating anticancer drug that alters tumor DNA to prevent replication and hasten cell death. Lomustine is also able to cross the blood-brain barrier, making it an attractive addition to temozolomide for glioblastoma treatment. Based on preclinical research and positive, small phase II study results, researchers conducted an open-label randomized phase III trial to evaluate the combination of lomustine and temozolomide in patients with newly diagnosed glioblastoma positive for methylated *MGMT* gene promoter.

In the CeTeG/NOA-09 trial (ClinicalTrials.gov identifier: [NCT01149109](#)),⁴⁰ 129 patients were randomly assigned to receive temozolomide with radiation or temozolomide plus lomustine with radiation. Patients who received the combination treatment had a significantly improved median overall survival compared with those who received only temozolomide—48.1 months compared with 31.4 months, respectively. There was slightly more toxicity with lomustine/temozolomide, mainly related to myelosuppression. Although these results are exciting, this was a small study, and larger studies will be needed to confirm these results and weigh the benefit of this combination therapy against the increased toxicity.

In First Major Advance in Decades, Immune Checkpoint Inhibitor Prolongs Survival in Extensive Small-Cell Lung Cancer When Added to First-Line Chemotherapy

In extensive-stage small-cell lung cancer (SCLC), where disease has spread throughout both lungs, to the lymph nodes on the opposite side of the chest from the primary tumor, or to other parts of the body, current treatment relies on platinum-based chemotherapy and the drug etoposide. Etoposide was approved in the early 1980s,⁴¹ and there have been no major advances in the treatment of extensive-stage SCLC since that time. A number of phase III trials have been conducted to evaluate other chemotherapy regimens or the addition of targeted therapies. None of these strategies, however, have been successful.

The IMpower 133 study (ClinicalTrials.gov identifier: [NCT02763579](#))⁴² was a double-blinded phase III trial assessing the immunotherapy atezolizumab in combination with chemotherapy. Atezolizumab is an anti-PD-L1 monoclonal antibody. For the study, 403 patients with extensive-stage SCLC received carboplatin and etoposide chemotherapy with or without atezolizumab. Patients who received atezolizumab had significantly longer overall survival and progression-free survival—12.3 and 5.2 months, respectively—compared with carboplatin and etoposide alone (10.3 months and 4.3 months). In general, adverse events were comparable for the two treatment strategies, though immune-related adverse events (eg, rash and hyperthyroidism) were more common among patients who received atezolizumab. The findings led to FDA approval of atezolizumab in combination with chemotherapy in March 2019.⁴³ The combination therapy has become the standard of care for extensive-stage SCLC in the United States.

Double and Triple Combinations of Targeted Therapy for BRAF-Mutated Metastatic Colorectal Cancer Improves Overall Survival

Approximately 8% to 15% of metastatic colorectal cancers (CRCs) carry the BRAF V600E mutation, which is associated with worse survival and poorer response to standard therapy.^{44,45} However, single drugs aimed at inhibiting BRAF have not been effective against BRAF-mutated CRCs.⁴⁶ Inhibition of the BRAF pathway results in

upregulation of the EGFR pathway, which results in lack of effectiveness. Adding the EGFR inhibitor blocks the upregulated pathway so that the treatment becomes effective—with both the EGFR and BRAF portions of the pathway being blocked. Preclinical data suggest inhibition of EGFR and/or MEK is needed to inhibit the BRAF pathway in CRC.⁴⁷ Therefore, multidrug therapy has raised interest as a potentially more potent therapy for these cancers.

Following a pilot study, the BEACON CRC trial (ClinicalTrials.gov identifier: [NCT02928224](#)) was initiated to compare either encorafenib (BRAF inhibitor) plus cetuximab or encorafenib plus cetuximab and binimetinib (MEK inhibitor) to the investigator's choice of cetuximab plus either irinotecan or FOLFIRI (5-fluorouracil, leucovorin, irinotecan).^{48,50} More than 600 patients with BRAF V600E-mutated metastatic colorectal cancer were randomly assigned to one of the three arms. Median overall survival was significantly improved for both the two-drug (8.4 months) and three-drug (9 months) arms, compared with 5.4 months for standard therapy. In addition, the confirmed objective response rate was highest with the trio, at 26%, compared with 2% for the control arm.

Given the poor prognosis of BRAF-mutated CRC, these results are practice changing and represent a significant advance for these patients. The findings suggest that it may be important for patients with metastatic CRC to be tested for BRAF mutations to guide therapy. While the study was not powered to compare the triple and double regimens, future analyses will explore this.

Combination Regimen Improves Survival for Two Common Types of B-Cell Non-Hodgkin Lymphoma

Indolent B-cell non-Hodgkin lymphomas (NHLs), cancers of the immune system, are typically slow growing, with few to no symptoms; however, they may transform into more aggressive lymphomas and require treatment when they grow beyond a certain size or compromise vital organ function. Indolent lymphomas are not curable with conventional therapies; thus, the goal in treating patients is to maximize response while minimizing treatment-related toxicity. The most common indolent types of NHL are follicular lymphoma and marginal zone lymphoma.⁵¹ In 2019, the FDA approved the first combination treatment regimen that does not include chemotherapy—rituximab plus lenalidomide—for patients with these types of NHL.⁵²

Rituximab is an immunotherapy that targets B cells for destruction by the immune system. Lenalidomide is a type of drug that modifies the immune system and is used to treat multiple myeloma. It works by directly inducing tumor cell death, and it works indirectly to inhibit the bone marrow, which is responsible for the production of blood and immune cells.

The AUGMENT trial (ClinicalTrials.gov identifier: [NCT01938001](#))⁵³ provided key data on the efficacy and safety of the

combination for the treatment of patients with follicular lymphoma and marginal zone lymphoma that has relapsed or not responded to prior treatment. AUGMENT was a phase III, randomized placebo-controlled trial of rituximab with or without lenalidomide involving 358 patients with indolent B-cell NHL with a primary endpoint of progression-free survival. Progression-free survival was significantly better with the combination of lenalidomide and rituximab compared with rituximab alone—39.4 v 14.1 months, respectively. The therapy was well tolerated, although infections (63% v 49%), neutropenia (58% v 23%), and cutaneous reactions (32% v 12%) were more common with the combination regimen. Grade 3 or 4 neutropenia (50% v 13%) and leukopenia (7% v 2%) were also higher with lenalidomide plus rituximab.

IMMUNOTHERAPY

Drug Targeting DNA Repair Delays Disease Progression in Women With Advanced Ovarian Cancer

PARP (poly [ADP-ribose] polymerase) inhibitors, such as the drug olaparib, promote cancer cell death by interfering with DNA replication in cancers that have faulty DNA damage repair genes as a result of genetic mutations (ie, *BRCA* 1 and 2). When *BRCA* 1 and/or *BRCA* 2 genes are mutated—and don't repair damaged DNA—PARP enzymes can repair DNA enough to allow cancers to live and multiply. Olaparib blocks PARP. As a result, DNA damage is not repaired, and cancer cell death is accelerated.

Standard treatment of newly diagnosed advanced ovarian cancer consists of cytoreductive surgery along with platinum-based chemotherapy.⁵⁴ While initially effective, approximately 70% of patients relapse within 3 years.⁵⁵ Recurrent disease is often incurable.

In the phase III SOLO1 trial (ClinicalTrials.gov identifier: [NCT01844986](#)),⁵⁶ researchers found that maintenance treatment with olaparib improved progression-free survival compared with placebo for women with advanced (stage III or IV) *BRCA* 1/2 mutated ovarian cancer. PARP inhibitors like olaparib promote cancer cell death by impairing DNA replication in cancers that have faulty DNA repair genes (ie, *BRCA* 1 and 2).

In this trial, patients with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer were randomly assigned to receive either olaparib or placebo until disease progression. All 391 patients included in the study responded to platinum-based treatment following at least an attempt at surgery. Patients who received olaparib were 70% less likely to experience either cancer progression or death compared with those who received placebo after a median follow-up of 42 months. A similar advantage was still seen at 3 years. The most common adverse events were grade 1 or 2 and included nausea, fatigue, vomiting, and diarrhea. Serious adverse events were more likely among patients who received olaparib—21% v 12% for the placebo group, with anemia being the most common.

These findings led to FDA approval of olaparib for this indication and have substantially changed practice for women with advanced (stage III or IV) ovarian cancer with *BRCA* 1/2 mutations.⁵⁷

Bladder Cancer Survival Improves With Targeted Therapies

Advances were also seen with molecular therapies this year. While platinum-based combination therapy approaches are standard of care for patients with bladder cancer, many cancers do not respond. In addition, patients with poor renal function are often unable to safely receive cisplatin chemotherapy, leaving them with even fewer treatment options. Data on two promising new molecular targets (*FGFR*2/3 and Nectin 4) were presented at the 2019 ASCO Annual Meeting.

One study (JNJ-42756493, ClinicalTrials.gov identifier: [NCT02365597](#))⁵⁸ examined erdafitinib for the treatment of locally advanced or metastatic urothelial cancer. Erdafitinib is a pan inhibitor of human fibroblast growth factor receptors (*FGFR*) that works to reduce blood flow to a tumor, causing it to shrink and die. The study reported treatment of 99 patients who previously received at least two courses of therapy, including 22 patients who had received immunotherapy. The overall response rate to erdafitinib was 40% overall and 59% for the patients who had undergone previous immunotherapy. Although there were no treatment-related deaths, 13% of patients discontinued treatment due to adverse events. In April 2019, the FDA granted accelerated approval to erdafitinib for the treatment of patients with locally advanced or metastatic urothelial carcinoma, with susceptible *FGFR*3 or *FGFR*2 genetic alterations, that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.⁵⁹

In a second study, EV-201 (ClinicalTrials.gov identifier: [NCT03219333](#)),⁶⁰ 125 patients with locally advanced or metastatic urothelial bladder cancer received enfortumab vedotin after checkpoint inhibitors and platinum-based chemotherapy failed to control the disease. Enfortumab vedotin is an antibody-drug conjugate that targets Nectin-4, which plays a role in helping cancer cells stick together to form tumors. The researchers reported on the first cohort, and the overall response rate with enfortumab vedotin was 42%. Taken together, these two studies demonstrate a completely new direction in advanced urothelial cancer, moving from multitreatment chemotherapy, to the incorporation of checkpoint inhibition, and now to molecular targeting.

Immunotherapies and Tyrosine Kinase Inhibitor Approved for the Treatment of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) incidence is growing in the United States. It is also one of the most common cancer types diagnosed each year worldwide.⁶¹ More than

a decade ago, sorafenib became the first-approved targeted therapy against HCC.⁶² Progress was then limited until the past year, when several positive studies emerged that led to FDA approvals of three new drugs for this cancer—pembrolizumab, cabozantinib, and ramucirumab.

The KEYNOTE-224 (ClinicalTrials.gov identifier: [NCT02702414](#)) trial demonstrated that pembrolizumab is promising for the treatment of advanced HCC.⁶³ In this nonrandomized open-label study, 104 patients with HCC that had progressed after sorafenib or who were resistant to the therapy received pembrolizumab. Eighteen patients (17%) had an objective response (one complete, 17 partial), and forty-six patients (44%) had stable disease. Almost three-quarters (73%) of patients had adverse events, with nearly a quarter of patients (24%) having a grade 3 event. In November 2018, the FDA granted accelerated approval to pembrolizumab for patients who have been previously treated with sorafenib.⁶⁴

Cabozantinib showed a survival advantage over placebo in the CELESTIAL trial of previously treated patients with advanced HCC (ClinicalTrials.gov identifier: [NCT01908426](#)).⁶⁵ The phase III study included 707 patients who received sorafenib and had disease progression after at least one systemic therapy; the patients were randomly assigned to receive cabozantinib or placebo. Median overall survival was 10.2 months with cabozantinib v 8 months with placebo. Median progression-free survival was 5.2 and 1.9 months, respectively. Grade 3 or 4 adverse events were more common among patients who received cabozantinib—68% v 36%, respectively. The most common high-grade adverse events included hand-foot syndrome (redness, swelling, and pain on the palms and/or the soles of the feet) and hypertension. In January 2019, cabozantinib was approved for patients with advanced HCC who have been previously treated with sorafenib.⁶⁶

In patients with HCC, an elevated concentration of AFP has been associated with poor prognosis. In the REACH-2 trial (ClinicalTrials.gov identifier: [NCT02435433](#)),⁶⁷ patients with HCC and elevated AFP were randomly assigned to receive ramucirumab or placebo. The patients who received ramucirumab had longer median overall survival and progression-free survival than those who received placebo—8.5 v 7.3 months (overall survival) and 2.8 v 1.6 months (progression-free survival), respectively. Grade 3 or worse treatment-emergent adverse events were more common in those receiving ramucirumab than placebo. The most common were hypertension (elevated blood pressure), hyponatremia (low sodium level), and increased aspartate aminotransferase (a measure of liver damage). In May 2019, ramucirumab was approved as a single agent in patients with an AFP of at least 400 ng/mL and who have been previously treated with sorafenib.⁶⁸

Immunotherapy Makes Inroads in Head and Neck Cancer

Following the initial approval of two immunotherapies (nivolumab and pembrolizumab) for the treatment of

patients with recurrent and/or metastatic head and neck cancer that persists after platinum-based therapy, significant interest has arisen to define additional patient populations that may benefit. Two studies represent the first that will help to define the optimal treatment approach for these patients.

The KEYNOTE 040 (ClinicalTrials.gov identifier: [NCT02252042](#))⁶⁹ open-label, phase III trial included patients with head and neck squamous cell carcinoma. The trial enrolled patients with cancer that progressed during or after platinum-containing treatment of recurrent or metastatic disease (or both) or that recurred or progressed within 3–6 months of previous multimodality treatment containing platinum for locally advanced disease. Patients were randomly assigned to receive pembrolizumab (247 patients) or the investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab (standard of care, 248 patients). Median overall survival was 8.4 months with pembrolizumab and 6.9 months with standard of care. Grade 3 or worse treatment-related adverse events occurred in fewer patients treated with pembrolizumab compared with standard of care. The most common treatment-related AE with pembrolizumab was hypothyroidism; with standard care it was fatigue.

In the KEYNOTE-048 trial (ClinicalTrials.gov identifier: [NCT02358031](#)),⁷⁰ patients with recurrent or metastatic squamous cell cancer of the head and neck were randomly assigned to receive pembrolizumab alone or with platinum-based chemotherapy, or cetuximab plus platinum-based chemotherapy. With all patients included in the analysis, pembrolizumab did not significantly improve overall survival over cetuximab/chemotherapy—median overall survival was 11.5 v 10.7 months (pembrolizumab plus chemotherapy was not compared against cetuximab plus chemotherapy in this patient group). However, the median overall survival in the group of patients with higher levels of PD-L1 (a protein that helps tumors hide from the immune system) was better for those who received pembrolizumab plus chemotherapy compared with cetuximab plus chemotherapy: 14.7 months v 11 months (pembrolizumab alone was not compared with cetuximab plus chemotherapy in this group). All-cause grade 3–5 adverse event rates were 54.7% for pembrolizumab alone, 85.1% for pembrolizumab/chemotherapy, and 83.3% for cetuximab/chemotherapy.

Checkpoint Inhibitors Prolong Survival in Locally Advanced NSCLC and in Advanced Squamous NSCLC

An estimated 20% to 30% of all lung cancers are squamous NSCLC, which is associated with poorer survival than nonsquamous NSCLC.⁷¹ Treatment of these patients has been limited to platinum-based chemotherapy. In addition, there have been no major advances in the treatment of unresectable stage III disease since the confirmation that concurrent chemotherapy and radiation improve survival compared with sequential therapy.⁷²

Two phase III randomized trials have suggested that these therapies are effective and safe for patients with NSCLC. In the phase III PACIFIC trial (ClinicalTrials.gov identifier: [NCT02125461](#)),⁷³ the addition of the PD-L1–targeted drug durvalumab significantly prolonged overall survival and progression-free survival, as compared with placebo. Patients in this study had stage III, unresectable NSCLC and did not have disease progression after concurrent chemoradiotherapy. At 2 years of follow-up, median overall survival in the 183 patients who received durvalumab was 66.3%, compared with 55.6% in the 116 patients in the placebo group. Median progression-free survival was 17.2 months for patients receiving durvalumab, compared with 5.6 months for those receiving placebo. Serious adverse events were more common for patients in the durvalumab group—29.1% v 23.1% in the placebo group. Following FDA approval, longer follow-up data showed improved overall survival with the addition of durvalumab. At an update presented at the 2019 ASCO Annual Meeting, researchers reported that at 3 years the overall survival was 57% in the durvalumab arm compared with 43.5% in the placebo arm.

The KEYNOTE 407 trial (ClinicalTrials.gov identifier: [NCT02775435](#))⁷⁴ examined the addition of the PD-1 targeted agent pembrolizumab to carboplatin-based chemotherapy (with paclitaxel or nab-paclitaxel) in patients newly diagnosed with advanced squamous NSCLC. Both overall survival (15.9 months v 11.3 months) and progression-free survival (6.4 v 4.8 months) were longer in patients who received pembrolizumab (278 patients) compared with placebo (271 patients). Adverse events of grade 3 or greater occurred in 69.8% of patients receiving pembrolizumab in combination with chemotherapy compared with 68.2% of patients receiving placebo and chemotherapy. Anemia, alopecia, and neutropenia were the most common adverse events in both groups. The results of this study established this regimen as the new standard of care for patients with advanced squamous NSCLC not previously treated.

Anti-CD47 Plus Rituximab Shows Initial Promise in Relapsed/Resistant Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma originates in the body's lymph system and includes several types (eg, diffuse large B-cell lymphoma [DLBCL] and follicular lymphoma are two common types). For patients with DLBCL that becomes resistant to treatment with rituximab, the prognosis is poor, with a median survival of 6 months.⁷⁵ For patients with follicular lymphoma with disease that has progressed in less than 2 years after diagnosis or is resistant to combination regimens with rituximab, survival is 50%.^{76,77}

CD47 is a protein that protects certain cells from the immune system—a “don't eat me” signal of sorts. While many cells have some CD47 on their surfaces, tumor cells have lots of it. This helps tumors avoid destruction, allowing them to grow and spread. High amounts of CD47 indicate poor prognosis. An investigational drug known as 5F9 (short for

Hu5F9-G4) is thought to block CD47, giving the immune system a chance to identify and destroy cancer cells. Pre-clinical research suggests that adding 5F9 to rituximab (a tumor-fighting monoclonal antibody) may have a synergistic effect (stronger effect than just the two treatments combined).

A first-in-human, phase Ib study (ClinicalTrials.gov identifier: [NCT02953509](#))⁷⁸ published in 2019 assessed both the safety and efficacy of different doses of 5F9 in 22 patients with relapsed or resistant DLBCL or follicular lymphoma. Patients were randomly assigned to receive one of three dosages of 5F9 in combination with rituximab.

The combination showed promising preliminary efficacy: after a median of 22 weeks, half of patients had objective response (shrinkage in the tumors), including 36% with complete response. Responses were ongoing for 91% of patients. The response rates were higher in follicular lymphoma (70%) compared with DLBCL (40%). Adverse events were predominantly grades 1 and 2 headache, anemia, and infusion-related reactions. While the study was small, the results warrant larger and longer studies.

Based on these data, the combination of lenalidomide and rituximab was FDA approved for relapsed indolent B-cell NHL.⁷⁹ Ongoing studies are exploring this combination in earlier lines of relapse and in combination with other novel and targeted therapies for patients with multiply relapsed disease. This study was funded in part by the NIH.

OTHER TREATMENTS

Lower Intensity Methotrexate Treatment of Children, Adolescents, and Young Adults With T-ALL Results in High Cure Rates

Acute lymphoblastic leukemia (ALL) is a malignancy that affects a category of blood cells known as lymphocytes. ALL affects two types of lymphocytes: B cells and T cells. B cells protect the body by making antibodies against invaders, and T cells can directly attack cancer cells as well as help B cells do their job.

T-cell ALL (T-ALL) accounts for about 15% of pediatric patients with ALL, and it is more common in older adolescents and African American children and adolescents. Unfortunately, T-ALL is associated with shorter event-free survival (the time from treatment to disease progression or the development of certain symptoms) and overall survival compared with the more common B-cell disease.

Methotrexate is an anticancer drug that has been a mainstay of treatment of ALL for decades. Nevertheless, the most effective and least toxic schedule and dosing of methotrexate for T-ALL in pediatric patients has been unclear.

Two different approaches are commonly used to reach therapeutic levels (levels high enough to achieve effective treatment) of methotrexate in young patients with ALL; however, these have not been evaluated in the treatment of T-ALL. The first strategy is called Capizzi-style methotrexate

(C-methotrexate, or C-MTX). It involves starting with a lower dose of methotrexate and increasing it over time. C-MTX is often coupled with PEG-asparaginase, another drug used to treat ALL. With high-dose methotrexate (HDMTX) therapy, patients receive the same high dose of methotrexate throughout treatment. HDMTX is often associated with kidney damage and other adverse events. For this reason, leucovorin (folinic acid) is started after initiating treatment with HDMTX to help mitigate toxicity.

The toxicity of HDMTX and the success seen with C-MTX in other cancers (including B-ALL) led researchers to examine which one was optimal in T-ALL. In the phase III AALL0434 trial (ClinicalTrials.gov identifier: [NCT00408005](#))⁸⁰ led by the Children's Oncology Group, 1,000 patients were randomly assigned to receive C-MTX or HDMTX (with or without nelarabine). C-MTX treatment was superior in terms of 5-year disease-free survival and overall survival. Disease-free survival was 91.5% and 85.3% for C-MTX and HDMTX, respectively. Overall survival was 93.7% and 89.4%. Patients assigned to C-MTX had 32 relapses, six involving the central nervous system. Those assigned to HDMTX had 59 relapses, 23 involving the central nervous system. Grade 3 and 4 adverse events during an interim maintenance phase were comparable and included febrile neutropenia and seizures. It is important to note, however, that cranial radiation was administered earlier for patients receiving C-MTX than for those receiving HDMTX, which could have influenced the outcomes.

Thus, the AALL0434 trial established that chemotherapy with C-MTX is superior to HDMTX for T-ALL as administered in the protocol. Furthermore, the trial showed the best outcomes ever reported for children and adolescents with T-ALL. It showed a 5-year disease-free survival rate of 91.5% and overall survival rate of 93.7%. In comparison, the historical overall survival rate for T-ALL was approximately 81% based on earlier clinical trials in this patient population.⁸¹ This study was funded in part by the NCI.

Children With Resected Hepatoblastoma Can Be Cured With Minimal Adjuvant Chemotherapy

Hepatoblastoma is a type of liver cancer composed of cells that resemble embryonic tissue and is the most common type of childhood liver malignancy. Treatment requires surgical resection; however, only about a third of newly diagnosed patients have resectable disease at diagnosis.⁸² These patients typically receive four to six cycles of cisplatin-based adjuvant chemotherapy, which carries increased toxicity.⁸³ New strategies are needed to decrease long-term effects for children with this cancer, particularly hearing damage due to cisplatin.

The phase III AHEP0731 study (ClinicalTrials.gov identifier: [NCT00980460](#))⁸⁴ enrolled children with hepatoblastoma in four risk groups based on several risk factors at diagnosis. Results from children with the lowest risk were reported. Children in this risk group were treated with complete

resection at diagnosis and maintenance therapy consisting of only two cycles of adjuvant cisplatin-based chemotherapy. Eligible patients were younger than 21 years and had histologically confirmed stage I or II hepatoblastoma (excluding those with 100% pure fetal stage I or small-cell undifferentiated histology). Event-free survival was 92% at 4 years and 88% at 5 years, based on 49 evaluable patients. The most common grade 3 to 4 adverse events included febrile neutropenia (14%), decreased neutrophil count (6%), infections (8%), and diarrhea (8%). Ototoxicity (hearing damage) occurred in one patient. One patient, out of the three who relapsed in this cohort, died as a result of the cancer. There were no treatment-related deaths.

Overall survival was maintained with a shorter chemotherapy course, and the results offer the possibility of less-toxic treatment of children with hepatoblastoma who are eligible for upfront resection. This study was funded in part by the NCI.

Promising Results of the Use of the MEK Inhibitor Selumetinib for the Treatment of Children and Adolescents With Refractory Low-Grade Gliomas

Pediatric low-grade glioma is the most common central nervous system tumor in children. While overall survival is generally high, the disease often recurs. No single treatment is universally accepted for these patients. However, standard cytotoxic chemotherapies and radiation therapy are commonly used. In the past 15 years, though, research has shown that nearly all pediatric low-grade gliomas have alterations that activate the RAS-MAP kinase pathway. Selumetinib is part of a new class of drugs called MEK inhibitors that block this process.

The Pediatric Brain Tumor Consortium conducted a phase II trial of selumetinib (ClinicalTrials.gov identifier: [NCT01089101](#))⁸⁵ in children age 3 to 21 years who had varying forms of recurrent, refractory, or progressive pediatric low-grade glioma. The trial was composed of six groups, or strata. This publication included data for strata 1 and 3. The first stratum included 25 patients with a type of glioma called grade I pilocytic astrocytoma. This cancer commonly has mutations that should make it susceptible to selumetinib. The third stratum included 25 patients either with imaging characteristics suggestive of a pediatric low-grade glioma or biopsy-proven low-grade glioma and a clinical or genetic diagnosis of neurofibromatosis type 1. Patients in both strata received 28-day courses of oral selumetinib for up to 26 cycles. More than one-third (36%) of patients in stratum 1 had a partial response; nine had stable disease, and seven had progressive disease. However, more than half of these patients (56%) had progression (nine during treatment and five after completion). All patients in stratum 3 had some evidence of tumor shrinkage with selumetinib, including 10 (40%) partial responses. One patient experienced disease progression while on therapy; seven had progression after therapy completion. Most toxic effects were moderate, although 36% of patients required a dose

reduction of selumetinib. The trial is ongoing, and data for other strata are not yet mature. This study was funded in part by the NCI.

Internet-Based Cognitive Behavioral Therapy Improves Treatment-Induced Menopausal Symptoms in Women With Breast Cancer

Adjuvant breast cancer treatments, including chemotherapy, surgery, and/or endocrine therapy, often cause bothersome side effects that severely alter patients' quality of life. For young women treated for breast cancer, this can mean menopause-like symptoms, with hot flashes and night sweats among the most common. Eighty percent of such women in one study reported hot flashes, and 72% reported night sweats.⁸⁶ Women can also experience problems with sleep quality, sexual functioning, and psychological distress. It has also been shown that these symptoms can lead some women to reduce or even to discontinue endocrine therapy.⁸⁷

Effective treatment of these symptoms is rather limited and many come with side effects. New research, however, suggests that cognitive behavioral therapy (CBT) may be helpful to reduce the burden of hot flashes and night sweats in patients with breast cancer.⁸⁸

In a study (ClinicalTrials.gov identifier: [NCT02672189](#))⁸⁹ published this year, researchers examined the efficacy of a 6-week internet-based CBT program, either self-directed or with support from a therapist, compared with being on a waiting list for help with symptoms. The randomized controlled trial included 254 women no older than 50 years at the time of breast cancer diagnosis who had undergone chemotherapy and/or oophorectomy (surgery to remove one or both ovaries) and/or endocrine treatment. The women were experiencing treatment-induced bothersome hot flashes or night sweats. At 10 weeks, both groups using the internet-based CBT reported significant improvements in hot flashes and night sweats (the primary outcome) and sleep quality compared with women in the waitlist group. Improvements were also seen in frequency of night sweats and menopausal symptoms overall for women in the therapist-guided group. At 24 weeks, the self-guided group reported improved overall menopausal symptoms and the therapist-guided group continued to report improved hot flashes and night sweats. Both CBT groups reported decreased frequency of night sweats with longer follow-up.

The findings demonstrate that a self-guided internet-based CBT program can significantly alleviate menopausal symptoms for women with breast cancer. If validated in larger studies, internet-based CBT could provide an accessible, effective complement to medications.

FDA APPROVALS

The number of new FDA approvals in oncology continues at a rapid pace. From November 2018 through October 2019, the FDA approved 43 new cancer therapies or new indications of cancer therapies (Appendix [Table A1](#), online only).

RESEARCH PRIORITIES TO ACCELERATE PROGRESS AGAINST CANCER

As the organization that represents and connects the global community of clinicians who discover new treatments for cancer and deliver the latest advances to patients, ASCO first developed a set of Research Priorities to Accelerate Progress Against Cancer in 2019. The priorities for 2020, listed below in no particular order, represent promising areas of research that have the potential to significantly improve the knowledge base for clinical decision-making and address vital unmet needs in cancer care.

Identify Strategies That Predict Response and Resistance to Immunotherapies. Cancer immunotherapy encompasses a broad range of medicines and treatment approaches, including vaccines, immune checkpoint inhibitors, and, most recently, cellular therapies. These interventions have improved the outlook for multiple cancers by producing long-lasting remissions that can last for years in some patients. For others, however, despite initial response to immunotherapy, resistance to treatment can later develop and the cancer can recur. Immunotherapies can also come with substantial adverse effects that can be life-threatening and, in some cases, permanent. The ability to adequately assess, and potentially predict, response and resistance to immunotherapy will lead to better outcomes for patients.

Priority focus areas:

- Identify blood- and tissue-based biomarkers that predict response to immunotherapies and long-term disease control as well as the development of resistance to therapy and adverse events
- Develop predictive models and algorithms that assign risk of severe immune-related toxicities based on readily available patient data

Limit Extent of Surgery by Optimizing Systemic Therapy. A wide range of therapies are recommended to patients around the time of surgery (perioperative) as well as before and after it (neoadjuvant and adjuvant treatment). These therapies aim to reduce the risk of recurrence and cancer-related death associated with microscopic tumor spread. Although such therapy has been associated with dramatic improvements in survival for some patients, studies have shown that the risks can outweigh the benefits for others. It is important to ensure that patients who receive these therapies are the ones most likely to benefit. Eliminating their use in those who are unlikely to benefit will be an important step in optimizing care and eliminating unnecessary adverse effects and costs for patients in whom the benefits are unlikely to outweigh the risks.

Priority focus areas:

- Develop analytically and clinically valid biomarker tests with proven clinical utility to identify recurrence risk after treatment of the primary tumor and determine the best options for patients with different degrees of risk,

including identifying the patients for whom reduced therapy would be beneficial

- Define the patient populations that benefit from peri-operative, neoadjuvant, and adjuvant therapies, including clinical, pathologic, genomic, biochemical, immunologic, and environmental or social factors

Increase Precision Medicine Research and Treatment Approaches in Pediatric and Other Rare Cancers.

Genomic tools have been widely deployed in adult patients with cancer to characterize the tumor mutation profile and guide therapy selection. In certain cancers, the use of these tools has accelerated development of new targeted therapies that have improved and extended patients' lives. Despite this success in adult patients, precision medicine treatment approaches have yet to be widely integrated into the treatment of pediatric cancers, as well as other rare cancers.

Priority focus areas:

- Identify genomic or other molecular alterations in pediatric and rare cancers that can serve as potentially actionable treatment targets
- Develop effective therapeutic agents that can target genomic or other molecular alterations in childhood and rare cancers
- Explore the efficacy of existing targeted therapies in pediatric patients and patients with rare cancers that have mutations shown to be responsive to medicines that work in adult populations

Optimize Care for Older Adults With Cancer. Although adults age 65 years and older represent the majority of people with cancer, few cancer clinical trials focus specifically on this population. Older patients who do participate in clinical trials are generally not representative of the older patients oncologists typically see in daily practice. As a result, clinicians face challenges applying clinical trial data to older patients who may have additional health conditions, varying levels of functional ability, and different goals from clinical trial participants. Researchers must make use of available practice-based, real-world data to study and drive improvements in caring for older adults with cancer. The lack of evidence combined with the inherent diversity of aging populations impedes the delivery of high-quality care for the largest and most rapidly growing segment of patients with cancer.

Priority focus areas:

- Develop standardized methods to characterize physiologic aging, such as geriatric assessment, biomarkers of aging, and clinical pharmacology in older adults, to more reliably predict risk of treatment-related adverse effects in older patients with cancer
- Use practice-based data to better understand the efficacy and toxicities of cancer treatments, including impact on physical function, cognition, and quality of life, particularly among older adults most under-represented in clinical trials, such as those with impaired functional status, comorbidities, or frailty

- Test the role of geriatric assessment-guided management in improving outcomes using personalized care; important focus areas include strategies that minimize undertreatment of fit patients and overtreatment of vulnerable or frail patients, supportive care interventions, and care delivery interventions

Increase Equitable Access to Cancer Clinical Trials. Certain patient populations are consistently under-represented in cancer clinical trials. These include patients from racial and ethnic minorities, rural areas, and lower socioeconomic groups and patients older than 65 years as well as adolescents and young adults age 15 to 39 years. Decreased representation of these groups can limit access to the promising treatments offered through these trials and means that research findings may not fully account for the diversity of biologic, social, and cultural factors that influence outcomes. Additional research is needed to ensure that every patient with cancer, regardless of race, ethnicity, age, geographic location, or socioeconomic status, benefits from research advances.

Priority focus areas:

- Improve understanding of the barriers to trial enrollment among various under-represented groups, taking into consideration patient, practice, community, and trial-specific factors
- Develop and test interventions that enhance clinical trial enrollment among under-represented populations (examples may include use of educational tools, telehealth, and community-based involvement and participatory research)
- Evaluate novel strategies to improve access to clinical research resources in areas with large proportions of under-represented minorities
- Develop mechanisms that improve awareness and education about clinical trials among under-represented groups and the physicians treating them
- Make use of clinical practice data to study differences in cancer incidence, prevalence, natural history of disease, and treatment experience, including efficacy and toxicity, among under-represented populations

MEDICAID ENROLLEES NEED CLINICAL TRIAL ACCESS

Clinical trials often provide the best treatment options for patients with life-threatening conditions. Many patients can't enroll because federal law doesn't require Medicaid to cover the routine costs of participating.

Passage of the bipartisan CLINICAL TREATMENT ACT (H.R. 913) would put clinical trials within reach of millions more patients—including children, people with disabilities, and rural Americans. ASCO supports this important measure to increase access to trials.

Reduce the Adverse Consequences of Cancer Treatment.

Advances in cancer treatment have resulted in a record number of cancer survivors—more than 15.5 million in the United States at present. Many survivors face acute and chronic consequences of cancer, including pain and adverse effects of cancer therapies—such as peripheral neuropathy, cognitive impairment, and cardiotoxicity—that affect quality of life and pose a substantial burden not only to patients but also to the health care system. Identifying strategies to minimize cancer-associated pain and treatment effects is an urgent area of research.

Priority focus areas:

- Develop and test strategies to mitigate and manage chronic toxicities associated with cancer treatment
- Identify genetic variants associated with increased risk of treatment-related toxicities
- Deepen understanding of the underlying mechanisms of toxicities from targeted treatments, determine their contribution to long-term effects, and develop novel strategies to mitigate or eliminate such toxicities
- Expand understanding and use of the range of pain management options for patients with cancer
- Develop new tools to facilitate long-term tracking of patient outcomes that include patient-reported measures

Reduce Obesity's Impact on Cancer Incidence and Outcomes.

The incidence of obesity has dramatically increased over the past several decades.⁹⁰ Despite being the second leading preventable cause of cancer, an ASCO survey found that only 35% of Americans recognize excess body weight as a cancer risk factor.⁹ Obesity is associated with poorer cancer survival and can contribute to increased risk of treatment-related adverse effects. If current trends continue over the next 20 years, it is estimated that obesity will lead to more than 500,000 additional cases of cancer each year in the United States and will surpass smoking as the leading preventable cause of cancer.⁹¹

Priority focus areas:

- Improve the understanding of the mechanisms by which weight and energy balance, including physical

activity and dietary factors, contribute to cancer development and progression

- Investigate how obesity affects response to therapy, risk of cancer recurrence, and long-term cancer outcomes
- Assess the impact of energy balance interventions, such as weight loss, increased physical activity, and improved dietary quality, on cancer risk, recurrence, and mortality
- Identify effective interventions that optimize energy balance in people at risk and who are living with cancer

Better Identify Premalignant Lesions and Predict When Treatment Is Needed.

Many cancers begin as high-risk lesions that invariably progress to invasive cancer, while other premalignant lesions may never require treatment. Currently, little is known about the genetic makeup, heterogeneity, and microenvironment of premalignant lesions, and what causes some to progress to invasive cancer. Increased knowledge will help guide new approaches to intercept and eradicate high-risk lesions before their transformation to malignancy and to spare patients from unnecessary treatments for lesions with a low risk of progression.

Priority focus areas:

- Address barriers to screening and early treatment of premalignant disease
- Identify premalignant lesions with a high risk for progression based on specific features and develop appropriate treatment strategies while also identifying premalignant lesions that do not require intervention
- Identify specific molecular pathways that drive progression of preinvasive lesions to invasive cancer and develop interventions that can delay or prevent progression to malignancy
- Identify features of the microenvironment of premalignant lesions that are associated with progression to invasive disease
- Investigate novel methods for evaluation of premalignant lesions to better inform the risk or likelihood of progression to invasive disease

AFFILIATIONS

¹University of Florida, Gainesville, FL

²American Society of Clinical Oncology, Alexandria, VA

³Huntsman Cancer Institute, Salt Lake City, UT

⁴Dana-Farber/Brigham and Women's Cancer Center, Boston, MA

⁵University of California, San Francisco, CA

⁶City of Hope National Medical Center, Duarte, CA

⁷New York University Cancer Center, New York, NY

⁸St Jude Children's Research Hospital, Memphis, TN

⁹Duke Cancer Center, Durham, NC

¹⁰Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

¹¹Winship Cancer Institute at Emory University, Atlanta, GA

¹²Sarah Cannon Research Institute, Nashville, TN

¹³University of Wisconsin, Madison, WI

¹⁴Hackensack University Medical Center, Hackensack, NJ

¹⁵Northwell Health/Monter Cancer Center and Cold Spring Harbor Laboratory, Lake Success, NY

¹⁶Dana-Farber Cancer Institute, Boston, MA

¹⁷University of Alabama at Birmingham, Birmingham, AL

¹⁸University of Michigan, Ann Arbor, MI

¹⁹Memorial Sloan Kettering Cancer Center, New York, NY

²⁰Fox Chase Cancer Center, Philadelphia, PA

²¹University of Texas MD Anderson Cancer Center, Houston, TX

CORRESPONDING AUTHOR

Kerri Wachter, BS, American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: kerri.wachter@asco.org.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.03141>.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

- American Cancer Society: Cancer facts and figures 2019. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf>
- American Cancer Society: Cancer facts and figures 2019. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf>
- Center Watch: FDA approved drugs for oncology. <https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology>
- National Institutes of Health: Yesterday, today, and tomorrow: NIH research timelines. <https://report.nih.gov/nihfactsheets/viewfactsheet.aspx?csid=75>
- National Institutes of Health: History of Congressional Appropriations. [https://officeofbudget.od.nih.gov/pdfs/FY19/Approp%20History%20by%20IC%20FY%202000%20-%20FY%202019%20\(V3\).pdf](https://officeofbudget.od.nih.gov/pdfs/FY19/Approp%20History%20by%20IC%20FY%202000%20-%20FY%202019%20(V3).pdf)
- National Institutes of Health: History of Congressional Appropriations. [https://officeofbudget.od.nih.gov/pdfs/FY19/Approp%20History%20by%20IC%20FY%202000%20-%20FY%202019%20\(V3\).pdf](https://officeofbudget.od.nih.gov/pdfs/FY19/Approp%20History%20by%20IC%20FY%202000%20-%20FY%202019%20(V3).pdf)
- Bennett LM: Envisioning NCI's Future: Annual Plan and Budget Proposal for FY 2021. <https://www.cancer.gov/grants-training/nci-bottom-line-blog/2019/fy2021-annual-plan-and-budget-proposal>
- US Senate Appropriations Committee: Labor, Health and Human Services, Education, and Related Agencies, 2020. <https://www.appropriations.senate.gov/imo/media/doc/LaborHHS%202020.pdf>
- United for Medical Research: NIH'S Role In Sustaining the US Economy 2019 State-By-State Update. <https://www.unitedformedicalresearch.org/reports/nih-role-in-sustaining-the-u-s-economy/>
- The Harris Poll: ASCO 2018 Cancer Opinions Survey. <https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/2018-NCOS-Results.pdf>
- Long GV, Saw RPM, Lo S, et al: Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB-C, BRAFV600 mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial. *Lancet Oncol*. 20:961-971, 2019
- Rozeman EA, Menzies AM, van Akkooi ACJ, et al: Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): A multicentre, phase 2, randomised, controlled trial. *Lancet Oncol* 20:948-960, 2019
- Méjean A, Ravaud A, Thezenas S, et al: Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med* 379:417-427, 2018
- Bex A, Mulders P, Jewett M, et al: Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: The SURTIME randomized clinical trial. *JAMA Oncol* 5:164-170, 2019
- Murphy JE, Wo JY, Ryan DP, et al: Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: A phase 2 clinical trial. *JAMA Oncol* 4:963-969, 2018
- Murphy JE, Wo JY, Ryan DP, et al: Total Neoadjuvant Therapy With FOLFIRINOX in Combination With Losartan Followed by Chemoradiotherapy for Locally Advanced Pancreatic Cancer: A Phase 2 Clinical Trial. *JAMA Oncol* 5:1020-1027, 2019
- World Health Organization: Human papillomavirus vaccines: WHO position paper, May 2017-recommendations. *Vaccine* 35:5753-5755, 2017
- Murphy JE, Wo JY, Ryan DP, et al: Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: A phase 2 clinical trial. *JAMA Oncol* 5:1020-1027, 2019
- United States Food and Drug Administration: Gardasil. <https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil>
- Gillison ML, Chaturvedi AK, Lowy DR: HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. *Cancer* 113:3036-3046, 2008 (10, suppl)
- Drolet M, Bénard É, Pérez N, et al: Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: Updated systematic review and meta-analysis. *Lancet* 394:497-509, 2019
- Manson JE, Cook NR, Lee I-M, et al: Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 380:33-44, 2019
- Dieckmann KP, Radtke A, Geczi L, et al: Serum levels of microRNA-371a-3p (M371 test) as a new biomarker of testicular germ cell tumors: Results of a prospective multicentric study. *J Clin Oncol* 37:1412-1423, 2019
- Golan T, Hammel P, Reni M, et al: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med* 381:317-327, 2019
- Gomez DR, Tang C, Zhang J, et al: Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol* 37:1558-1565, 2019
- Ramirez PT, Frumovitz M, Pareja R, et al: Minimally invasive versus abdominal radical hysterectomy for cervical cancer. *N Engl J Med* 379:1895-1904, 2018
- Melamed A, Margul DJ, Chen L, et al: Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. *N Engl J Med* 379:1905-1914, 2018
- Palma DA, Olson R, Harrow S, et al: Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. *Lancet* 393:2051-2058, 2019
- Mehanna H, Robinson M, Hartley A, et al: Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCaLATE HPV): An open-label randomised controlled phase 3 trial. *Lancet* 393:51-60, 2019
- Gillison ML, Trotti AM, Harris J, et al: Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): A randomised, multicentre, non-inferiority trial. *Lancet* 393:40-50, 2019
- National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program: Cancer Stat Facts: Female Breast Cancer Subtypes. <https://seer.cancer.gov/statfacts/html/breast-subtypes.html>
- US Food and Drug Administration: FDA approves ado-trastuzumab emtansine for early breast cancer. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ado-trastuzumab-emtansine-early-breast-cancer>
- von Minckwitz G, Huang CS, Mano MS, et al: Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 380:617-628, 2019
- Schmid P, Adams S, Rugo HS, et al: Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med* 379:2108-2121, 2018

32. US Food and Drug Administration: FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-locally-advanced-or-metastatic-triple-negative>
- 32a. Stenger M. Atezolizumab for PD-L1 -Positive Locally Advanced or Metastatic Triple-Negative Breast Cancer. *The ASCO Post*. Oct. 10, 2019
33. Im S-A, Lu YS, Bardia A, et al: Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med* 381:307-316, 2019
34. Rini BI, Plimack ER, Stus V, et al: Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 380:1116-1127, 2019
35. Motzer RJ, Penkov K, Haanen J, et al: Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 380:1103-1115, 2019
36. Davis ID, Martin AJ, Stockler MR, et al: Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med* 381:121-131, 2019
37. US Food and Drug Administration: FDA approves pembrolizumab plus axitinib for advanced renal cell carcinoma. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-plus-axitinib-advanced-renal-cell-carcinoma>
38. US Food and Drug Administration: FDA approves avelumab plus axitinib for renal cell carcinoma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-avelumab-plus-axitinib-renal-cell-carcinoma>
39. Cohen MH, Johnson JR, Pazdur R: Food and Drug Administration Drug approval summary: Temozolomide plus radiation therapy for the treatment of newly diagnosed glioblastoma multiforme. *Clin Cancer Res* 11:6767-6771, 2005
40. Herrlinger U, Tzaridis T, Mack F, et al: Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): A randomised, open-label, phase 3 trial. *Lancet* 393:678-688, 2019
41. Hande KR: Etoposide: Four decades of development of a topoisomerase II inhibitor. *Eur J Cancer* 34:1514-1521, 1998
42. Horn L, Mansfield AS, Szczesna A, et al: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 379:2220-2229, 2018
43. US Food and Drug Administration: FDA approves atezolizumab for extensive-stage small cell lung cancer. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-extensive-stage-small-cell-lung-cancer>
44. Davies H, Bignell GR, Cox C, et al: Mutations of the BRAF gene in human cancer. *Nature* 417:949-954, 2002
45. Van Cutsem E, Cervantes A, Adam R, et al: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27:1386-1422, 2016
46. Clarke CN, Kopetz ES: BRAF mutant colorectal cancer as a distinct subset of colorectal cancer: Clinical characteristics, clinical behavior, and response to targeted therapies. *J Gastrointest Oncol* 6:660-667, 2015
47. Corcoran RB, André T, Atreya CE, et al: Combined BRAF, EGFR, and MEK inhibition in patients with *BRAF*^{V600E}-mutant colorectal cancer. *Cancer Discov* 8:428-443, 2018
48. Van Cutsem E, Huijberts S, Grothey A, et al: Binimetinib, encorafenib, and cetuximab triplet therapy for patients with *BRAF* V600E-mutant metastatic colorectal cancer: Safety lead-in results from the phase III BEACON colorectal cancer study. *J Clin Oncol* 37:1460-1469, 2019
49. ESMO: Targeted Therapy Combination Improves Survival in Patients with Advanced Bowel Cancer [ESMO World GI Press Release]. <https://www.esmo.org/Press-Office/Press-Releases/ESMO-World-Congress-Gastrointestinal-Cancer-Encorafenib-Binimetinib-Cetuximab-Colorectal-BRAFV600E-Beacon-Kopetz>
50. Kopetz S, Grothey A, Yaeger R, et al: Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. *N Engl J Med* 381:1632-1643; 2019
51. American Cancer Society: Types of B-cell lymphoma. <https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/b-cell-lymphoma.html>
52. Celgene: FDA approves REVLMID (lenalidomide) in combination with rituximab for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma. <https://ir.celgene.com/press-releases/press-release-details/2019/FDA-Approves-REVLMID-Lenalidomide-In-Combination-With-Rituximab-For-the-Treatment-of-Adult-Patients-with-Previously-Treated-Follicular-Lymphoma-or-Marginal-Zone-Lymphoma/default.aspx>
53. Leonard JP, Trneny M, Izutsu K, et al: AUGMENT: A phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol* 37:1188-1199, 2019
54. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al: NCCN Guidelines Insights: Ovarian cancer, version 1.2019. *J Natl Compr Canc Netw* 17:896-909, 2019
55. Ledermann JA, Raja FA, Fotopoulou C, et al: Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 24:vi24-vi32, 2013 (suppl 6)
56. Moore K, Colombo N, Scambia G, et al: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 379:2495-2505, 2018
57. Merck: LYNPARZA (olaparib) approved by FDA for first-line maintenance therapy in BRCA-mutated advanced ovarian cancer. <https://investors.merck.com/news/press-release-details/2018/LYNPARZA-olaparib-Approved-by-FDA-for-First-Line-Maintenance-Therapy-in-BRCA-Mutated-Advanced-Ovarian-Cancer/default.aspx>
58. Liorit Y, Necchi A, Park SH, et al: Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med* 381:338-348, 2019
59. US Food and Drug Administration: FDA grants accelerated approval to erdafitinib for metastatic urothelial carcinoma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-erdafitinib-metastatic-urothelial-carcinoma>
60. Petrylak DP, Balar AV, O'Donnell PH, et al: EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors (LBA 4505). *J Clin Oncol* 37, 2019 (suppl 18; abstr 4505)
61. Llovet JM, Montal R, Sia D, et al: Molecular therapies and precision medicine for hepatocellular carcinoma. *Nat Rev Clin Oncol* 15:599-616, 2018
62. Department of Health and Human Services: FDA approval of sorafenib for treatment of patients with advanced renal cell carcinoma. https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2007/021923s004,s005,s006,s007.pdf
63. Zhu AX, Finn RS, Edeline J, et al: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. *Lancet Oncol* 19:940-952, 2018
64. US Food and Drug Administration: FDA grants accelerated approval to pembrolizumab for hepatocellular carcinoma <https://www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma>
65. Abou-Alfa GK, Meyer T, Cheng AL, et al: Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med* 379:54-63, 2018
66. US Food and Drug Administration: FDA approves cabozantinib for hepatocellular carcinoma <https://www.fda.gov/drugs/fda-approves-cabozantinib-hepatocellular-carcinoma>
67. Zhu AX, Kang YK, Yen CJ, et al: Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α -fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 20:282-296, 2019
68. US Food and Drug Administration: FDA approves ramucirumab for hepatocellular carcinoma <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ramucirumab-hepatocellular-carcinoma>

69. Cohen EEW, Soulières D, Le Tourneau C, et al: Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): A randomised, open-label, phase 3 study. *Lancet* 393:156-167, 2019
70. Rischin D, Harrington KJ, Greil R, et al: Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *J Clin Oncol* 37, 2019 (suppl; abstr 6000)
71. Lortet-Tieulent J, Soerjomataram I, Ferlay J, et al: International trends in lung cancer incidence by histological subtype: Adenocarcinoma stabilizing in men but still increasing in women. *Lung Cancer* 84:13-22, 2014
72. Curran WJ Jr, Paulus R, Langer CJ, et al: Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: Randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 103:1452-1460, 2011
73. Antonia SJ, Villegas A, Daniel D, et al: Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 379:2342-2350, 2018
74. Paz-Ares L, Luft A, Vicente D, et al: Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 379:2040-2051, 2018
75. Crump M, Neelapu SS, Farooq U, et al: Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood* 130:1800-1808, 2017 [Erratum: *Blood* 131:587-588, 2018]
76. Casulo C, Byrtek M, Dawson KL, et al: Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the National LymphoCare Study. *J Clin Oncol* 33:2516-2522, 2015
77. Solal-Céligny P, Leconte P, Bardet A, et al: A retrospective study on the management of patients with rituximab refractory follicular lymphoma. *Br J Haematol* 180:217-223, 2018
78. Advani R, Flinn I, Popplewell L, et al: CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. *N Engl J Med* 379:1711-1721, 2018
79. US Food and Drug Administration: FDA approves lenalidomide for follicular and marginal zone lymphoma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenalidomide-follicular-and-marginal-zone-lymphoma>
80. Winter SS, Dunsmore KP, Devidas M, et al: Improved survival for children and young adults with T-lineage acute lymphoblastic leukemia: Results from the Children's Oncology Group AALL0434 methotrexate randomization. *J Clin Oncol* 36:2926-2934, 2018
81. Hunger SP, Lu X, Devidas M, et al: Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the children's oncology group. *J Clin Oncol* 30:1663-1669, 2012
82. Hunger SP, Lu X, Devidas M: Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the Children's Oncology Group. *J Clin Oncol* 30:1663-1669, 2012
- 82a. Trobaugh-Lotrario AD, Katzenstein HM: Chemotherapeutic approaches for newly diagnosed hepatoblastoma: Past, present, and future strategies. *Pediatr Blood Cancer* 59:809-812, 2012
83. Ortega JA, Douglass EC, Feusner JH, et al: Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. *J Clin Oncol* 18:2665-2675, 2000
84. Katzenstein HM, Langham MR, Malogolowkin MH, et al: Minimal adjuvant chemotherapy for children with hepatoblastoma resected at diagnosis (AHEP0731): A Children's Oncology Group, multicentre, phase 3 trial. *Lancet Oncol* 20:719-727, 2019
85. Fangusaro J, Onar-Thomas A, Young Poussaint T, et al: Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: A multicentre, phase 2 trial. *Lancet Oncol* 20:1011-1022, 2019
86. Hunter MS, Grunfeld EA, Mittal S, et al: Menopausal symptoms in women with breast cancer: Prevalence and treatment preferences. *Psychooncology* 13:769-778, 2004
87. Murphy CC, Bartholomew LK, Carpentier MY, et al: Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: A systematic review. *Breast Cancer Res Treat* 134:459-478, 2012
88. Duijts SFA, van Beurden M, Oldenburg HS, et al: Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized, controlled, multicenter trial. *J Clin Oncol* 30:4124-4133, 2012
89. Atema V, van Leeuwen M, Kieffer JM, et al: Efficacy of internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors: Results of a randomized controlled trial. *J Clin Oncol* 37:809-822, 2019
90. Whiteman DC, Wilson LF: The fractions of cancer attributable to modifiable factors: A global review. *Cancer Epidemiol* 44:203-221, 2016
91. National Cancer Institute: Take action to decrease your cancer risk: Obesity and its role in cancer health disparities. <https://www.cancer.gov/about-nci/organization/crchd/blog/2015/nmhm15-spotlight>



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Clinical Cancer Advances 2020: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/journal/jco/site/ifc.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Merry Jennifer Markham

Research Funding: Aduro Biotech (Inst), Lilly (Inst), Tesaro (Inst), Novartis (Inst), VBL Therapeutics (Inst)

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/890992/summary>

Neeraj Agarwal

Consulting or Advisory Role: Pfizer, Medivation/Astellas, Bristol-Myers Squibb, AstraZeneca, Nektar, Lilly, Bayer, Foundation One, Pharmacyclics, Foundation Medicine, Astellas Pharma, Lilly, Exelixis, AstraZeneca, Janssen Oncology

Research Funding: Bayer (Inst), Bristol-Myers Squibb (Inst), GlaxoSmithKline (Inst), Takeda (Inst), Novartis (Inst), Pfizer (Inst), BN ImmunoTherapeutics (Inst), Exelixis (Inst), TRACON Pharma (Inst), Rexahn Pharmaceuticals (Inst), Amgen (Inst), AstraZeneca (Inst), Active Biotech (Inst), Bavarian Nordic (Inst), Calithera Biosciences (Inst), Celldex (Inst), Eisai (Inst), Genentech (Inst), Immunomedics (Inst), Janssen (Inst), Merck (Inst), Newlink Genetics (Inst), Prometheus (Inst), Sanofi (Inst)

Monica M. Bertagnoli

Research Funding: AbbVie (Inst), Agenus (Inst), Astellas Pharma (Inst), AstraZeneca (Inst), Breast Cancer Research Foundation (Inst), Bristol-Myers Squibb (Inst), Celgene (Inst), Complion (Inst), Exelixis (Inst), Genentech (Inst), GHI Pharma (Inst), Gilead Sciences (Inst), GlaxoSmithKline (Inst), Incyte (Inst), Jazz Pharmaceuticals (Inst), Leidos (Inst), Lilly (Inst), Matrex (Inst), Mayo Clinic (Inst), MGH (Inst), Millenium Pharmaceuticals (Inst), Novartis (Inst), Patient-Centered Outcomes Research Institute (PCORI) (Inst), Pfizer (Inst), Robert Wood Johnson Foundation (Inst), Sagerock Advisors (Inst), Taiho Pharmaceutical (Inst), Bayer Health (Inst), Eisai (Inst), Lexicon (Inst), Merck (Inst), Pharmacyclics (Inst), Takeda (Inst), Tesaro (Inst), Baxalta (Inst), Sanofi (Inst), Teva (Inst), Janssen (Inst)

Uncompensated Relationships: Leap Therapeutics, Syntimmune, Syntalogic
Open Payments Link: <https://openpaymentsdata.cms.gov/physician/114497/summary>

Susan Marina Chang

Research Funding: Novartis (Inst), Agios (Inst)

Catherine S. M. Diefenbach

Stock and Other Ownership Interests: Gilead Sciences

Consulting or Advisory Role: Seattle Genetics, Bayer, Bristol-Myers Squibb, Genentech/Roche, Merck, Janssen

Research Funding: Seattle Genetics (Inst), Genentech (Inst), Incyte (Inst), LAM Therapeutics (Inst), Merck (Inst), Bristol-Myers Squibb (Inst), Millennium (Inst), MEI Pharma (Inst), Roche/Genentech (Inst), Janssen (Inst)

Patents, Royalties, Other Intellectual Property: Roche (Inst)

Daniel J. George

Leadership: Capio BioSciences

Honoraria: Sanofi, Bayer, Exelixis, EMD Serono, OncLive, Pfizer, UroToday, Acceleron Pharma, American Association for Cancer Research, Axess Oncology, Janssen Oncology, Millennium Medical Publishing

Consulting or Advisory Role: Bayer, Exelixis, Pfizer, Sanofi, Astellas Pharma, Innocrin Pharma, Bristol-Myers Squibb, Genentech, Janssen, Merck Sharp & Dohme, Myovant Sciences, AstraZeneca

Speakers' Bureau: Sanofi, Bayer, Exelixis

Research Funding: Exelixis (Inst), Janssen Oncology (Inst), Novartis (Inst), Pfizer (Inst), Astellas Pharma (Inst), Bristol-Myers Squibb (Inst), Acerta Pharma (Inst), Bayer (Inst), Dendreon (Inst), Innocrin Pharma (Inst), Calithera Biosciences (Inst), Sanofi/Aventis (Inst)

Travel, Accommodations, Expenses: Bayer, Exelixis, Merck, Pfizer, Sanofi, Janssen Oncology

Timothy D. Gilligan

Travel, Accommodations, Expenses: Dendreon

R. Donald Harvey

Consulting or Advisory Role: Bristol-Myers Squibb, Takeda, GSK

Research Funding: Celgene (Inst), AstraZeneca (Inst), Calithera Biosciences (Inst), ArQule (Inst), Pfizer (Inst), AbbVie (Inst), Boston Biomedical (Inst), Corvus Pharmaceuticals (Inst), Lilly (Inst), Five Prime Therapeutics (Inst), Genmab (Inst), Halozyme (Inst), Incyte (Inst), Nektar (Inst), Rgenix (Inst), Tesaro (Inst), Xencor (Inst), Meryx (Inst)

Melissa L. Johnson

Consulting or Advisory Role: Otsuka (I), Genentech/Roche (Inst), Celgene (Inst), Boehringer Ingelheim (Inst), AstraZeneca (Inst), Calithera Biosciences (Inst), Merck (Inst), Loxo (Inst), Sanofi (Inst), Mirati Therapeutics (Inst), Astellas Pharma (I), Araxes Pharma (Inst), Mersana (Inst), BeiGene (Inst), Incyte (Inst), Pfizer (Inst), Guardant Health (Inst), Bristol-Myers Squibb (Inst), Ribon Therapeutics (Inst)

Research Funding: OncoMed (Inst), BerGenBio (Inst), Lilly (Inst), EMD Serono (Inst), Kadmon (Inst), Janssen (Inst), Mirati Therapeutics (Inst), Genmab (Inst), Pfizer (Inst), AstraZeneca (Inst), Stem CentRx (Inst), Novartis (Inst), Checkpoint Therapeutics (Inst), Array BioPharma (Inst), Regeneron (Inst), Merck (Inst), Hengrui Pharmaceutical (Inst), Lycera (Inst), BeiGene (Inst), Tarveda Therapeutics (Inst), Loxo (Inst), AbbVie (Inst), Boehringer Ingelheim (Inst), Guardant Health (Inst), Foundation Medicine (Inst), Daiichi Sankyo (Inst), Sanofi (Inst), Mersana (Inst), CytomX Therapeutics (Inst), Dynavax (Inst), Birdie (Inst), Corvus Pharmaceuticals (Inst), Incyte (Inst), Genocoe Biosciences (Inst), Gritstone Oncology (Inst), Amgen (Inst), Genentech/Roche (Inst), Adaptimmune (Inst), Syndax (Inst), Neovia Oncology (Inst), G1 Therapeutics (Inst), Bristol-Myers Squibb (Inst), Clovis Oncology (Inst), Acerta Pharma (Inst), Takeda (Inst), Shattuck Labs (Inst), GlaxoSmithKline (Inst)

Travel, Accommodations, Expenses: AbbVie, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Daiichi Sankyo, EMD Serono, Bristol-Myers Squibb, Exelixis, Genentech, Incyte, Merck, Pfizer, Sysmex, Vapotherm

Randall J. Kimple

Honoraria: Galera Therapeutics

Consulting or Advisory Role: Ascension Ventures

Research Funding: Peloton Therapeutics, Igynta

Patents, Royalties, Other Intellectual Property: Patent licensed through the University of North Carolina (I), Patent licensed through the Wisconsin Alumni Research Fund (I)

Other Relationship: International Journal of Radiation Oncology Biology and Physics

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/372678/summary>

Miriam A. Knoll

Consulting or Advisory Role: Bristol-Myers Squibb

Noelle LoConte

Consulting or Advisory Role: Celgene, Bayer, AstraZeneca, AbbVie

Robert G. Maki

Consulting or Advisory Role: Bayer, AADi, Karyopharm Therapeutics, American Board of Internal Medicine (ABIM), Deciphera, TRACON Pharma, Pfizer

Research Funding: Presage Biosciences (Inst), Regeneron (Inst), Daiichi (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate: I write and edit chapters for their online text book; Springer and Wiley: Books for contributions I have made to the published texts

Travel, Accommodations, Expenses: TRACON Pharma, Bayer

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/205679/summary>

Jane Lowe Meisel

Honoraria: Total Health Conferencing

Consulting or Advisory Role: Puma Biotechnology, Pfizer

Research Funding: Seattle Genetics, Pfizer, Lilly

Travel, Accommodations, Expenses: Pfizer, Total Health Conferencing, Puma Biotechnology

Jeffrey A. Meyerhardt

Honoraria: Igynta, Cota Healthcare, Taiho Pharmaceutical

Consulting or Advisory Role: Array BioPharma

Research Funding: Boston Biomedical (Inst)

Nathan A. Pennell

Consulting or Advisory Role: AstraZeneca, Lilly, Regeneron, Cota Healthcare, Merck, Bristol-Myers Squibb, Inivata

Research Funding: Genentech (Inst), Celgene (Inst), AstraZeneca (Inst), Pfizer (Inst), Merck (Inst), Loxo (Inst), Altor BioScience (Inst), Spectrum Pharmaceuticals (Inst), Bristol-Myers Squibb (Inst)

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/204570/summary>

Gabrielle B. Rocque

Consulting or Advisory Role: Pfizer, Genentech/Roche
Research Funding: Carevive Systems, Genentech, Pfizer
Travel, Accommodations, Expenses: Genentech, Carevive (I)

Michael S. Sabel

Patents, Royalties, Other Intellectual Property: Breast Cancer Ally and Melanoma Ally mobile technologies.

Richard L. Schilsky

Research Funding: AstraZeneca (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Genentech/Roche (Inst), Lilly (Inst), Merck (Inst), Pfizer (Inst), Boehringer Ingelheim (Inst)

Travel, Accommodations, Expenses: Varian

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/1138818/summary>

Bryan James Schneider

Research Funding: MedImmune (Inst), Genentech/Roche (Inst), OncoMed (Inst), Bristol-Myers Squibb (Inst), MacroGenics (Inst)

William D. Tap

Leadership: Certis Oncology Solutions, Atropos Pharmaceuticals
Stock and Other Ownership Interests: Certis Oncology Solutions, Atropos
Consulting or Advisory Role: EMD Serono, Lilly, Daiichi Sankyo, Eisai, Blueprint Medicines, Agios, GlaxoSmithKline, NanoCarrier, Deciphera
Research Funding: Novartis, Lilly, Plexxikon, Daiichi Sankyo, TRACON Pharma, Blueprint Medicines, Immune Design, BioAtla, Deciphera
Patents, Royalties, Other Intellectual Property: Companion Diagnostic for CDK4 inhibitors - 14/854329

Robert G. Uzzo

Consulting or Advisory Role: Pfizer, Genentech/Roche, UroGen pharma
Speakers' Bureau: Janssen Oncology
Research Funding: Novartis

Shannon Neville Westin

Consulting or Advisory Role: Roche, AstraZeneca, Genentech, Casdin Capital, Medscape, Clovis Oncology, Watermark Research Partners, Gerson Lehrman Group, Vaniam Group, Tesaro, Merck, Pfizer, Bioascend, Curio Science, Novartis, OncoLive, Circulogene Theranostics, Targeted Oncology, Curio Sciences

Research Funding: AstraZeneca, Novartis, Karyopharm Therapeutics (I), Celgene (I), Bayer, Tesaro, Kite Pharma (I), Cotinga Pharmaceuticals, Clovis Oncology, Roche/Genentech, ArQule, GOG Foundation (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. FDA Approvals of Anticancer Therapies (November 2018 to October 2019)

New Approvals	Comments
New therapies or tests	
October 2019	
Niraparib (Zejula)	For patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status.
August 2019	
Fedratinib (Inrebic)	For adults with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).
Entrectinib (RoZlytrek)	For adult and pediatric patients (≥ 12 years of age) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma that requires systemic anticancer therapy.
July 2019	
Pembrolizumab (Keytruda)	For advanced esophageal squamous cell cancer.
Darolutamide (Nubeqa)	For nonmetastatic castration-resistant prostate cancer.
May 2019	
Gilteritinib (Xospata)	Indicated for adult patients who have relapsed or refractory acute myeloid leukemia (AML) with an FLT3 mutation as detected by an FDA-approved test.
Venetoclax (Venclexta)	For adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
Ado-trastuzumab emtansine (Kadcyla)	For the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.
Ivosidenib (Tibsovo)	For newly diagnosed acute myeloid leukemia (AML) with a susceptible IDH1 mutation, as detected by an FDA-approved test, in patients who are at least 75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy.
December 2018	
Tagraxofusp-erzs (Elzonris)	A CD123-directed cytotoxin, for blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.
Calaspargase pegol-mknl (Asparlas)	An asparagine-specific enzyme, as a component of a multiagent chemotherapeutic regimen for acute lymphoblastic leukemia (ALL) in pediatric and young adult patients age 1 month to 21 years.
Olaparib (Lynparza)	For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
November 2018	
Gilteritinib (Xospata)	For treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with an FLT3 mutation as detected by an FDA-approved test.
Truxima (rituximab-abbs)	The first biosimilar to Rituxan (rituximab) for patients with CD20-positive, B-cell non-Hodgkin lymphoma (NHL) to be used as a single agent or in combination with chemotherapy.
Larotrectinib (Vitrakvi)	For adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or in whom the cancer has progressed following treatment.

(continued on following page)

TABLE A1. FDA Approvals of Anticancer Therapies (November 2018 to October 2019) (continued)

New Approvals	Comments
New indications	
September 2019	
Daratumumab (DARZALEX)	For adult patients with multiple myeloma in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant.
Apalutamide (ERLEADA)	For patients with metastatic castration-sensitive prostate cancer.
Pembrolizumab (KEYTRUDA) and lenvatinib (LENVIMA)	For the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.
July 2019	
Selinexor (XPOVIOs)	In combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and in whom the disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
June 2019	
Pembrolizumab (KEYTRUDA)	For patients with metastatic small-cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.
Daratumumab (DARZALEX)	In combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
Polatuzumab vedotin-piiq (POLIVY)	A CD79b-directed antibody-drug conjugate indicated in combination with bendamustine and a rituximab product for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies.
May 2019	
Lenalidomide (REVLIMID)	In combination with a rituximab product for previously treated follicular lymphoma and previously treated marginal zone lymphoma.
Alpelisib (PIQRAY)	In combination with fulvestrant for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.
Avelumab (BAVENCIO)	In combination with axitinib for first-line treatment of patients with advanced renal cell carcinoma (RCC).
Ramucirumab (CYRAMZA)	A single agent for hepatocellular carcinoma (HCC) in patients who have an α -fetoprotein (AFP) of ≥ 400 ng/mL and have been previously treated with sorafenib.
April 2019	
Pembrolizumab (KEYTRUDA)	In combination with axitinib for the first-line treatment of patients with advanced renal cell carcinoma (RCC).
Pembrolizumab (KEYTRUDA)	For the first-line treatment of patients with stage III non-small-cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC. Patients' tumors must have no EGFR or ALK genomic aberrations and express PD-L1 (Tumor Proportion Score [TPS] $\geq 1\%$) determined by an FDA-approved test.
March 2019	
Atezolizumab (TECENTRIQ)	In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small-cell lung cancer.
Atezolizumab	For PD-L1-positive unresectable locally advanced or metastatic triple-negative breast cancer.
February 2019	
Trastuzumab and hyaluronidase-oyks injection (Herceptin HYLECTA)	For subcutaneous use for the treatment of HER2-overexpressing breast cancer, injection is a combination of trastuzumab, a HER2/neu receptor antagonist, and hyaluronidase, an endoglycosidase.
Trifluridine/tipiracil tablets (LONSURF)	A fixed combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor—for adult patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and, if appropriate, HER2/neu-targeted therapy.

(continued on following page)

TABLE A1. FDA Approvals of Anticancer Therapies (November 2018 to October 2019) (continued)

New Approvals	Comments
Pembrolizumab (KEYTRUDA)	For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
January 2019	
Cabozantinib (CABOMETYX)	For patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.
December 2018	
Pembrolizumab (KEYTRUDA)	For adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.
Herzuma (trastuzumab-pkrb)	Approved as a biosimilar to trastuzumab for patients with HER2-overexpressing breast cancer.
Atezolizumab (TECENTRIQ)	In combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic nonsquamous, non–small-cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations.
November 2018	
Venetoclax (VENCLEXTA)	In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Glasdegib (DAURISMO)	In combination with low-dose cytarabine (LDAC), for newly diagnosed acute myeloid leukemia (AML) in patients who are 75 years old or older or who have comorbidities that preclude intensive induction chemotherapy.
Brentuximab vedotin (ADCETRIS)	In combination with chemotherapy for previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas.
Pembrolizumab (KEYTRUDA)	For patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.
Lorlatinib (LORBRENA)	For patients with anaplastic lymphoma kinase (ALK)-positive metastatic non–small-cell lung cancer (NSCLC) with disease that has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease or with disease that has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease.

NOTE. Data from US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. <https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications>.