Plenary Studies Answer Long-Standing Questions in Cancer Patient Care, Highlight Major Improvements in Childhood Cancer Survival

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CHICAGO – Findings presented today at the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO) provide long-sought, conclusive answers about the impact of less aggressive therapy on childhood cancer survival; the optimal timing of surgery for oral cancer; and the use of whole-brain radiation for patients with brain metastases. Another study provides a powerful new immunotherapy option for patients with melanoma. All four studies were presented in ASCO’s Plenary Session, which features research that has the greatest potential to impact patient care.

These advances are expected to immediately influence oncology practice in the United States, leading to improved survival and quality of life for patients. In addition, the findings on oral cancer surgery could deliver far-reaching benefits for people in Asia and other regions of the world where the disease is especially common. Two of the trials were supported with federal funding through the National Institutes of Health.

“Despite tremendous advances, physicians still don’t always know when the benefits of aggressive therapy outweigh the possible side effects,” said ASCO Expert Jyoti D. Patel, MD. “With today’s studies, we finally have conclusive answers for patients considering surgery for oral cancer or radiation when cancer spreads to the brain. At the same time, it’s clear that less aggressive therapy is paying major dividends for childhood cancer survivors. Even with recent advances in the treatment of melanoma with immunotherapy, which has transformed our approach to this disease, today’s findings underscore our need for ongoing study. Today’s takeaway reinforces that some patients will do just fine with one treatment, avoiding the additional side effects of a two-drug combination.”
Studies include:

- In patients with previously untreated advanced melanoma, both nivolumab alone and in combination with ipilimumab were significantly more effective at delaying cancer progression than ipilimumab alone. This is the first phase III trial to compare a combination of immune checkpoint inhibitors with ipilimumab alone.
- An analysis of more than 34,000 five-year survivors of childhood cancer treated over three decades finds modern treatments have reduced long-term mortality rates. Such progress is attributed in part to refined treatment approaches that reduced mortality related to second cancers, as well as heart and lung disease.
- A randomized phase III study finds that elective neck lymph node surgery for patients with early oral cancer reduces the risk of cancer recurrence and improves survival. Oral cancer occurs worldwide but is especially common in countries where tobacco use is high.
- Patients with 1-3 small brain metastases who received radiosurgery followed by whole brain radiation therapy were more likely to experience cognitive decline than those who received radiosurgery alone.

Media Resources:

Online Annual Meeting Media Resource Center: Visit ASCO.org/AMMRC for press releases, the press briefing schedule, embargo policies, high-resolution photos, and the Virtual Press Room, an online repository of corporate and institutional press materials from third-party organizations.

CancerProgress.Net: ASCO’s interactive website chronicling the progress achieved in clinical cancer research, including an in-depth timeline that tracks major research milestones in 18 of the most common cancers.

Cancer.Net: ASCO’s cancer information website for patients, providing doctor-approved information on more than 120 cancer types.

PHASE III STUDY FINDS INITIAL NIVOLUMAB-BASED TREATMENT HALTS MELANOMA PROGRESSION

ASCO Perspective

ASCO Expert Steven O'Day, MD

“Immunotherapy drugs have already revolutionized melanoma treatment, and now we’re seeing how they might be even more powerful when they’re combined. But the results also warrant caution – the nivolumab and ipilimumab combination used in this study came with greater side effects, which might offset its benefits for some patients. Physicians and patients will need to weigh these considerations carefully.”

Related Information
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A randomized phase III trial indicates that initial therapy with nivolumab alone or in combination with ipilimumab is significantly more effective than ipilimumab alone. Nivolumab alone
more than doubled the average time to disease progression, compared to ipilimumab (6.9 months vs. 2.9 months), and the benefit was even greater when ipilimumab and nivolumab were combined (11.5 months). The response rates were also substantially higher in patients receiving the combination therapy (57.6%) and nivolumab (43.7%) alone, as compared to ipilimumab (19%).

“We’re very encouraged that the initial observations about the efficacy of this combination held up in this large phase III trial,” said lead study author Jedd Wolchok, MD, PhD, Chief of Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center in New York, NY. “Our study also suggests that patients with a specific tumor marker appear to benefit the most from the combination treatment, whereas other patients may do just as well with nivolumab alone. This will help doctors provide important insight for patients on which treatment is right for them.”

Nivolumab and ipilimumab are monoclonal antibodies that block two different immune checkpoints - PD-1 and CTLA-4, respectively. Both treatments, commonly referred to as checkpoint inhibitors, essentially boost the immune system’s ability to fight cancer.

Prior research has shown that immune checkpoint inhibitors can improve survival for patients with melanoma and lung cancer. Both ipilimumab and nivolumab are FDA-approved for use as single agents in patients with unresectable (cannot be removed by surgery) or metastatic (advanced) melanoma that no longer responds to other drugs.

This study randomly assigned 945 patients with previously untreated, advanced melanoma to receive ipilimumab, nivolumab, or the combination of the two. After a follow-up period of at least nine months, the median progression-free survival was 2.9 months for ipilimumab, 6.9 months for nivolumab, and 11.5 months for the combination. The differences between the combination and ipilimumab groups, and nivolumab and ipilimumab groups were statistically significant.

The response rates for the combination, nivolumab, and ipilimumab groups were 57.6%, 43.7%, and 19%, respectively. The average reductions in tumor burden (depth of response) were 52% with the combination and 34% with nivolumab alone. In contrast, patients who received ipilimumab alone experienced a 5% increase in tumor burden.

As expected, the rate of serious drug-related side effects was the highest in the combination group (55%), and 36% of patients in this group had to stop the therapy due to side effects. Dr. Wolchok remarked that prior studies have shown that many patients who stop immunotherapy early still continue to do well.

This prolonged benefit is explained by the fact that immunotherapy works by activating the immune system rather than targeting the tumor directly. It is not yet clear how long patients need to be treated to fully activate the immune system, and the minimal duration of therapy probably
varies from patient to patient.

Quality of life data were collected on the study, and the analysis of those results will be reported at a later time.

**PD-L1 Status May Help Define Optimal Treatment**

The PD-1 protein on immune cells attaches to another protein called PD-L1, which is sometimes found on the surface of some tumor cells. Prior research suggested that patients who had detectable PD-L1 levels in their tumor (PD-L1-positive tumors) typically had better responses to PD-1 therapy.

In this study, nivolumab alone seemed to be as effective against PD-L1-positive tumors as the combination of nivolumab and ipilimumab. For patients with PD-L1-negative tumors, however, the combination treatment was significantly more beneficial than nivolumab alone.

This study received funding from Bristol-Myers Squibb.

View the full abstract.

**For Your Readers**
- Guide to Melanoma
- What is Immunotherapy?
- Interactive History of Cancer Research Advances

**IMPROVED CARE HAS EXTENDED THE LIFESPAN OF CHILDHOOD CANCER SURVIVORS SINCE THE 1970S**

**ASCO Perspective**

*ASCO Expert Stephen Hunger, MD*

“For decades, we’ve strived to avoid the paradox in which children survive cancer, only to become sick or die years later because of the treatment they received. By carefully refining pediatric cancer treatment, we have improved long-term care and outcomes by leaps and bounds. Cure rates have increased with parallel decreases in death due to complications of cancer treatment. We hope that the positive trends we’re seeing today will continue as our therapeutic approaches continue to improve over time.”

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An analysis of over 34,000 participants in the federally funded Childhood Cancer Survivor Study shows improvement in late mortality achieved over three decades. Among five-year survivors, all-cause mortality at 15 years of diagnosis dropped from 12.4% to 6%. This improvement is attributed in part to changes in care that reduced the risk of mortality related to late effects of pediatric cancer treatment, such as subsequent malignancies and cardiac and lung disease.

“Fifty years ago, only one in five children would survive cancer, and today over 80% are alive five years after diagnosis. Yet, these survivors still grow up with increased risk of dying from late effects, like heart disease and second cancers,” said the lead study author Gregory T. Armstrong, MD, MSCE, a pediatric oncologist at St. Jude Children’s Research Hospital. “Now, we’ve not only helped more children survive their primary cancer, but we’ve also extended their overall lifespan by reducing the overall toxicity of treatment in more modern eras.”

Prior research has shown that up to 18% of five-year childhood cancer survivors die within 30 years of diagnosis. The deaths are due to three major causes: progression or recurrence of the primary cancer, external causes (accidents, suicide), and other health-related causes. The latter category primarily consists of mortality due to late effects of cancer therapy. While the deaths from cancer progression or recurrence plateau over time, mortality from other health-related causes increases with each year survived since diagnosis.

The study analyzed data from the Childhood Cancer Survivor Study, which evaluates long-term health outcomes in five-year survivors of childhood cancer diagnosed between 1970 and 1999. Thirty-one U.S. and Canadian hospitals currently participate in the study. The cohort, initiated in 1994, is an NIH-funded resource ? any researcher interested in survivorship can request access to the data or banked biologic specimens.

In the current analysis, the National Death Index (a central computerized index of death record information on file in the State vital statistics offices) was used to assess mortality among 34,043 five-year childhood cancer survivors. All were younger than 21 years at diagnosis.

**Major Impact From Scaling Back Treatment for Many Common Pediatric Cancers**

On average, the five-year survivors were followed for 21 years after their diagnosis. The study found that 3,958 (12%) patients had died during that period, and 41% (1,618) of those deaths were from other health-related causes that include death due to late effects of cancer therapy.
Additionally, all-cause mortality was halved over these two decades – 12.4% of patients diagnosed in the early 1970s died within 15 years of diagnosis, compared to only 6% of those diagnosed in the early 1990s.

During the same time period, the cumulative incidence of deaths from other health-related causes decreased from 3.5% to 2.1%. Survivors diagnosed in more recent years had a statistically significant lower risk of dying from other health-related causes (including second cancer, and heart or lung disease).

The study team noted that reductions in mortality were due to fewer deaths related to late effects and were most striking among survivors of Wilms tumor, Hodgkin lymphoma, and acute lymphoblastic leukemia (ALL). Cardiac deaths significantly decreased among survivors of all three cancers. Deaths due to secondary cancer decreased among Wilms tumor survivors only.

These results are driven by doctors’ gradual refinement of treatment by reducing the intensity of therapy for many pediatric cancers with favorable prognosis, without compromising effectiveness. For example, in the 1970s, 86% of patients with ALL received cranial radiotherapy, compared to only 22% in the 1990s. Radiotherapy dose has also been reduced among patients with Hodgkin lymphoma and Wilms tumor. Furthermore, cumulative dose exposure of anthracycline, a chemotherapy drug strongly associated with cardiotoxicity, has been reduced across these three diseases.

"While the modernization of cancer therapy has probably made the most significant difference, improvements in supportive care for survivors, and screening, detection, and treatment of late effects, like new cancers and heart and lung disease, have played an important role in extending their lifespan as well," added Dr. Armstrong.

This study received funding from the National Institutes of Health.

View the full abstract.

For Your Readers
• Survivorship
• Late Effects of Childhood Cancer
• Managing Late Effects of Childhood Cancer
• Interactive History of Cancer Research Advances

PREVENTIVE NECK LYMPH NODE SURGERY IMPROVES EARLY ORAL CANCER SURVIVAL

ASCO Perspective
“This study provides long-awaited answers to a question doctors worldwide have struggled with. We never want to do more surgery than we have to, but for patients with early oral cancer, we now know that more extensive surgery prolongs lives.”

A randomized phase III study resolves long-standing questions about the optimal timing of neck lymph node surgery for patients with early-stage oral cancer. It shows that a preventive approach, known as elective neck dissection (END), both improves survival and lowers recurrence rates compared to therapeutic neck dissection (TND) performed at the time of nodal occurrence.

Oral cancer affects more than 300,000 people worldwide and is especially common in parts of the world where tobacco use is high. Tobacco use and excessive alcohol consumption are estimated to account for 90% of oral cancer diagnoses.

While early oral cancer is often cured with surgery to remove the tumor, it can come back and spread to lymph nodes in the neck. Physicians have long debated whether removing surrounding lymph nodes is essential at the time of the primary oral cancer surgery (END) or if it is optimal to wait until a patient has relapsed (TND).

“Our study is the first to conclusively prove that more lives can be saved with elective neck dissection. This answers a question doctors have been asking for over 50 years, for the treatment of thousands of patients,” said lead study author Anil D’Cruz, MBBS, MS, FRCS, Professor and Chief, Department of Head and Neck Surgery at Tata Memorial Centre in Mumbai, India. “Armed with the results of this study, doctors will be able to confidently counsel patients that adding neck surgery to their initial treatment is worthwhile.”

In this trial, conducted at Tata Memorial Centre between 2004 and 2014, 596 patients with early stage oral squamous cancer were randomly assigned to END or TND. An interim analysis of the first 500 patients showed that END resulted in a 37% reduction in risk of death compared to TND. END was associated with a 12.5% absolute increase in three-year overall survival (80% vs. 67.5%), which was statistically significant.

END also resulted in a 56% reduction in the risk of relapse or death with a large 23.6% absolute
increase in three-year disease-free survival (69.5% vs. 45.9%). In essence, there were eight fewer deaths for every 15 fewer relapses with elective neck dissection, firmly establishing it as the standard of care in this disease.

According to the authors, the only downside of neck dissection – a procedure which involves the removal of lymph nodes in the neck – is that it may be associated with some degree of shoulder dysfunction, affecting 5-40% of patients. This is because the nerve that supplies the large muscles associated with shoulder movement traverses the field of surgical dissection. Future research should focus on techniques that could minimize this complication.

As there have been no strong clinical practice recommendations advocating neck dissection with early oral cancers to date, there has been gross variability in practice the world over. This study conclusively shows that elective neck dissection should be the standard of care for patients with early oral cancer.

This study received funding from the institutional research grants of the Tata Memorial Centre.

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• Guide to Oral and Oropharyngeal Cancer
• What is Cancer Surgery
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RISKS OF ADJUVANT WHOLE BRAIN RADIATION THERAPY OUTWEIGH BENEFITS FOR PATIENTS WITH LIMITED BRAIN METASTASES

Summary includes updated data not in the abstract
ASCO Perspective

ASCO Expert Brian Michael Alexander, MD

“This study will help shape treatment decisions for thousands of current and future patients. As doctors, we want the very best for our patients, and sometimes giving less treatment offers the better result. In patients treated with radiosurgery, the benefits of adding whole brain radiation must be weighed against the risks and side effects of treatment, and this study helps us identify the tradeoffs involved.”

A federally funded phase III trial provides additional information regarding a long-standing discussion about the impact of adjuvant whole brain radiation therapy (WBRT) on cognitive function. Patients with 1-3 small brain metastases who received radiosurgery followed by WBRT were more likely to experience cognitive decline than those who received radiosurgery alone. Furthermore, WBRT did not significantly extend patient survival, though it did help control growth of brain metastases.

Up to 650,000 patients newly diagnosed with cancer in the United States every year will develop brain metastases. At least 200,000 of these patients will receive WBRT at some point in the course of their disease (i.e., as adjuvant, salvage, or end-stage therapy).[1]

Patients with limited metastases often receive radiosurgery, a type of radiotherapy that aims beams very precisely at the area of the brain tumor. Brain metastases are removed by conventional surgery in only a select minority of patients.

“We used to offer whole brain radiation early on, but we now know that the toxicities of this therapy are worse for the patient than cancer growth or recurrences in the brain,” said senior study author Jan C. Buckner, MD, a professor of oncology at Mayo Clinic in Rochester, MN. “We expect that practice will shift to reserve the use of whole brain radiation therapy for salvage treatment and end-stage palliative care.”

In the study, 213 patients were randomly assigned to receive radiosurgery or radiosurgery followed by WBRT. All patients had 1-3 brain small brain metastases (up to 3 cm in width). At three months, more patients experienced cognitive decline in the WBRT group (92%) than in the radiosurgery group (64%).
Specifically, patients who received WBRT had a greater decline in immediate recall (30% vs. 8%), delayed recall (51% vs. 20%), and verbal communication (19% vs. 2%). The analysis of quality of life data from this study has not yet been completed. The difference in overall survival was not statistically significant between the two treatment groups.

According to the authors, the findings of this study have broad implications for oncology practice, as brain metastases are a common complication in cancer care. Melanoma and cancers of the lung, breast and colon spread to the brain especially often. Patients with bladder, kidney and gynecologic cancers can also develop brain metastases.

Dr. Buckner remarked that while adjuvant WBRT continues to be an option for patients with resected (surgically removed) brain metastases, the ongoing NCCTG/Alliance trial comparing WBRT to stereotactic radiosurgery to the surgical cavity in patients with resected brain metastasis will eventually determine which treatment approach is better.

This study received funding from the National Institutes of Health.

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View the disclosures for the 2015 ASCO Annual Meeting News Planning Team.
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