the dissection can very strongly confer prognostic information.

Earlier studies dating back to the mid-1960s lacked the statistical power needed to resolve this debate over the two alternatives. The studies generated divergent results, and so practice standards varied around the world, with proponents of watch and wait insisting that neck nodes could be removed later without compromising survival.

**Answers From a Definitive Trial**

To produce a definitive answer, D’Cruz launched his study in 2004. A total of 596 patients with T1 or T2 squamous cell oral carcinoma were randomized to either elective dissection or watch and wait. All patients had surgery to remove the primary tumor and adjuvant radiotherapy when indicated. After a median follow-up of 39 months, recurrences in the watch-and-wait arm numbered 146, compared with 81 in the elective dissection arm. Elective dissection also improved survival by a statistically significant 12.5% and reduced risk of death by 36%.

“I think it’s a very good study,” said Hisham Mehanna, Ph.D., chair of head and neck surgery at the University of Birmingham in the United Kingdom, and a discussant at D’Cruz’s ASCO presentation. “It’s well powered, well conducted, and the findings are conclusive.”

Ferris agreed. “The real benefit is that it provides level 1 evidence for what was already standard of care in the United States,” he said. “We’re now required to have level 1 evidence, so this is important. It validates the clinical benefits of elective dissection, and suggests that the procedure is also cost effective.”

The study didn’t address how many neck nodes to remove. However, a different presentation at ASCO showed that the best survival outcomes are obtained by removing 18 nodes or more. Vasu Divi, M.D., an assistant professor at Stanford School of Medicine in Stanford, Calif., and colleagues, reviewed data from 572 patients treated in two clinical trials—RTOG 9501 and 0234—with a median follow-up of 8 years. They concluded that dissecting fewer than 18 nodes results in statistically worse overall survival rates in both HPV-16–positive and HPV-16–negative patients. That finding was consistent with evidence from an April 2014 study in the Annals of Surgical Oncology. Led by Ardalan Ebrahimi, M.D., from the Royal Prince Alfred Hospital in Sydney, Australia, that study also confirmed that no fewer than 18 nodes should be removed during elective dissection in patients with oral squamous cell carcinoma.

**Insights From Ultrasound?**

According to Mehanna, ultrasound imaging might detect occult nodal metastases in the neck and preclude the need for an elective dissection. To investigate that possibility, D’Cruz’s study also randomized patients after surgery to ultrasound-guided surveillance or to standard surveillance based on clinical exam. Those data have yet to be reported, “and until they are, we should continue with the elective procedure,” Mehanna said.

D’Cruz concurred. “Our [unreported] analyses so far show that whether you follow patients with ultrasound, or with clinical exam and ultrasound combined, you still have a survival detriment with watchful waiting.” He added, “We will have better figures to address this issue, but as of now the elective procedure should be the standard of care. We may find a small subset of patients that can be adequately followed on ultrasound, but we can’t jump to any conclusions yet.”

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**ASCO Reveals Additional Promising Results With Immunotherapies**

By Vicki Brower

Patients with advanced, untreated melanoma who took a combination of two immunotherapies, nivolumab and ipilimumab, experienced statistically significantly longer progression-free survival than those who took either drug alone. In this 945-patient phase III randomized, double-blind study, patients taking the combination had a median progression-free survival of 11.5 months, compared with 6.9 months for nivolumab alone, and 2.9 months for patients taking ipilimumab.

Researchers discussed the new phase III trial at a plenary session at the American Society of Clinical Oncology (ASCO) meeting in late May, and results were published simultaneously in the New England Journal of Medicine (online May 31, 2015; doi:10.1056/NEJMoa1504030). The trial, known as CheckMate 067, confirms and strengthens safety and efficacy findings of a recent phase II study that compared the combination with ipilimumab alone (N. Engl. J. Med. 2015;372:2006–2017, May 21, 2015; doi:10.1056/NEJMoa1414428). Nivolumab inhibits PD-1, and ipilimumab inhibits CTLA-4, which are checkpoint molecules that dampen the body’s normal immune response to cancer.

“In patients with PD-L1 expression of at least 5%, the median progression-free survival (PFS) was the same in combination and nivolumab-only groups, 14 months, and 3.9 months with ipilimumab,” said Jedd Wolchok, M.D., Ph.D., chief, melanoma and immunotherapeutics service and Lloyd J. Old Chair for clinical investigation at Memorial Sloan-Kettering Cancer Center. “This means that sicker patients could take nivolumab alone with similar outcomes as with combination therapy,” he said.

While about a third of patients stopped treatment because of side effects, there were no drug-related deaths in the combination group, and researchers now know when to stop treatment because of toxic effects, Wolchok said.

At the plenary, researchers hailed the results as a breakthrough in melanoma treatment, and worthy of establishing a new standard of care for advanced disease. At the same time, discussant Leonard Saltz, M.D., chief, gastrointestinal oncology service and head, colorectal cancer section provided some real-world grounding in a discussion on the cost of these new immunotherapies. Commenting on the discussion, he said that “it is clear that these drugs offer substantial benefit to a significant number of patients, but they also carry price tags that are very high. This is a problem we have to confront because as a society...
we can’t afford to spend these amounts on each patient.”

Along with this late-stage trial, researchers at ASCO highlighted other, earlier-stage immunotherapy studies with checkpoint inhibitors in an array of other cancers, including hepatocellular, cervical, gastric, glioblastoma, and head and neck cancer alone and in combination with other drugs. Research also included studies designed to find biomarkers for identifying patients most likely to respond to immunotherapies.

Mismatch Repair–Deficient Tumors

An important phase II study presented by Dung T. Le, M.D., assistant professor of oncology at Johns Hopkins’ Sidney Kimmel Comprehensive Cancer Center in Baltimore, indicates that tumors with mismatch repair (MMR) defects respond well to therapy with the PD-1 inhibitor pembrolizumab, compared with tumors that do not have this genetic defect. DNA MMR is a way that cells can repair some types of DNA damage, including faulty insertion, deletion, and mis-incorporation of bases in replication and recombination. This research simultaneously appeared in the New England Journal of Medicine (online May 30, 2015; doi:10.1056/NEJMoa1500596).

“Mismatch repair–deficient tumors can develop thousands of mutations which are presented as neoantigens that elicit an antitumor response,” Le said. “In our study, we used mismatch repair deficiency as a predictive biomarker to select subsets of tumors that would respond to pembrolizumab,” she said. The average number of mutations in the MMR-deficient tumors was 1,700, Le said.

In this study, three groups received the drug: 25 patients with MMR-deficient colorectal cancer (CRC), 25 with MMR-proficient colorectal cancer, and 21 with MMR deficiency in an array of other cancers. Endpoints were PFS and overall response rate (ORR) at 20 weeks. ORR for MMR-deficient CRC was 62%, 0% for MMR-proficient CRC, and 60% for MMR-deficient non-CRC. The disease control rate was 92%, 16%, and 70% respectively. For patients with MMR-deficient disease, median PFS and overall survival (OS) were not reached, and for the other groups were 2.3 months and 5 months, respectively.

Le’s study supports the theory that tumors with more mutations respond better to immunotherapies than those with fewer mutations, which holds true for lung cancer and melanoma. What the mutational threshold is for response in this cancer is unclear, however. “While mutational burden did predict prolongs PFS, there were responders and nonresponders within the spectrum of tumors with high mutational burden, and a threshold was not determined,” Le said. What is clear is that single-agent PD-1 inhibition is unlikely to play a role in an unselected CCR population, she said. “PD-1 inhibition has activity in non-CRC as well, and other non–MMR-deficient cancers respond to PD-1 inhibition. Some responses may be driven by mutational load, others by viral antigens, and others by yet-to-be-identified antigens or mechanisms,” Le said.

“It is clear that these drugs offer substantial benefit to a significant number of patients, but they also carry price tags that are very high. This is a problem we have to confront because as a society we can’t afford to spend these amounts on each patient.”

Head and Neck Cancer

Trials with checkpoint inhibitors in advanced squamous cell carcinomas of the head and neck (SCCHN) are booming, evidenced by many trials discussed at ASCO. These cancers represent a huge unmet need, as the only approved drug for this indication is cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, to which very few respond, said Lillian Siu, M.D., senior medical oncologist at Princess Margaret Cancer Centre and professor of medicine at the University of Toronto.

“Applying immunotherapies to advanced head and neck cancer, which will expand to locally recurrent disease soon, is exciting because we are finding that this cancer, which is normally immune suppressed, does respond to these drugs,” Siu said. Their apparent immunogenicity may be due to high mutational burden, to viral antigens present in [human papillomavirus (HPV)]-positive tumors, and to smoking-induced mutations in HPV-negative tumors, she said. This means that both HPV-positive and HPV-negative tumors respond to checkpoint blockers.

Tanguy Seiwert, M.D., assistant professor of medicine, and associate program leader for head and neck cancer at the University of Chicago, presented a series of studies in SCCHN. In an expansion cohort of the KEYNOTE-012 study in 132 patients with recurrent/metastatic SCCHN, pembrolizumab produced an overall response rate (>30% decrease) of 24.8%; 56% of patients experienced any degree of tumor shrinkage. “This was a heavily pretreated population, with 59.1% of patients having received two or more lines of prior therapy,” Seiwert said. Pembrolizumab was well-tolerated, with serious side effects in less than 10% of patients, which compares favorably with chemotherapy.

Overall, when measured by response, pembrolizumab was roughly twice as effective as the only approved targeted therapy for SCCHN, cetuximab, an anti-EGFR antibody. “PD-1 inhibition with pembrolizumab was active in both HPV-positive and HPV-negative patients,” he said. “By contrast, efficacy of EGFR inhibitors in HPV-positive SCCHN remains controversial, with recent data indicating lesser or no activity,” Seiwert said. Pembrolizumab produced objective response rates of 27.2% in HPV-negative and 20.6% in HPV-positive tumors.

“With a 25% response rate, and 25% with stable disease, the disease control rate reaches about 50%, which is remarkable in heavily pretreated SCCHN patients,” Seiwert said. “This holds promise in eventually translating into longer-term survival, as seen in other studies, such as phase III studies in squamous cell lung carcinomas, with a larger fraction of patients experiencing benefit such as disease stabilization,” he said. There are two ongoing phase III studies comparing pembrolizumab with chemotherapy, as well as another phase III study of the anti–PD-1 antibody, nivolumab, with recurrent metastatic disease.
Seiwert’s team also identified a seven-gene expression signature that indicates an inflamed tumor phenotype, based on interferon-γ signaling [abstract 6017]. Patients with this signature were more likely to benefit from pembrolizumab (positive predictive value of 40%), but more important, absence of the signature indicated nonbenefit with high accuracy. The signature was strongly associated with both response and PFS, and researchers are continuing evaluation with the marker.

Finally, in related studies, the team found that patterns of CD8 lymphocyte infiltration vary, and that certain genetic abnormalities, such as mutations or low expression of the histone-methyl-transferase NSD1 gene, EGFR amplification and active Wnt signaling are associated with an inflamed tumor phenotype [abstract 6079]. While more research is needed to validate the biology and usefulness of these biomarkers, Seiwert believes these discoveries will help identify those patients most likely to benefit from anti–PD-1 therapy, as well as potentially identify rational combination strategies that could overcome an inflamed tumor phenotype. “This would expand the pool of SCCHN patients amenable to immunotherapy,” he said.

Combination studies have already begun with SCCHN patients. Siu is conducting a phase I multicenter open-label study combining MEDI4736, a PD-L1 inhibitor, and tremelimumab, a CTLA-4 inhibitor, in 164 patients considered incurable by local therapy. Researchers will determine patients’ PD-L1 status in the trial.

Liver and Esophageal Cancers

At least two other malignancies appear sensitive to checkpoint blockade, as seen in the presentation of the first studies in liver and esophageal cancer. Data from a phase I/II safety study presented by Anthony El-Khoueiry, M.D., assistant professor of clinical medicine in the division of medical oncology at the University of Southern California Norris Comprehensive Cancer Center in Los Angeles, showed safety and efficacy. Safety is of particular concern in liver cancer patients, who often have cirrhosis and viral hepatitis, and who have no options after sorafenib, a tyrosine kinase inhibitor. The response rate for that drug is only 2% in this patient population.

In his study, 47 advanced cancer patients with relatively good liver function received escalating doses of nivolumab for up to 24 months, divided into cohorts with hepatitis B, hepatitis C, or noninfected. Twenty had stable disease, and the longest lasted 17 months. OS rate at 12 months was 62%, whereas OS is about 30% with sorafenib at 1 year.

Two patients had complete responses, and six had partial responses, for an objective response rate of 19%. Seventeen remain in the study, and 30 have stopped treatment: 26 due to disease progression, two because of side effects, and two because of complete responses. Sixty-eight percent had side effects, which include elevation in liver enzymes and itching.

In advanced esophageal cancer, 90 patients’ tumors were tested for PD-L1 status because expression of PD-1 and PD-L1 is associated with poor prognosis. Thirty-seven had PD-L1–positive tumors, and of these, 23 were treated with pembrolizumab. The overall response rate was 23%, and the best response was stable disease in 18%, and progressive disease in 59%. Six patients, including all responders, continue to receive the drug. No grade 4 side effects occurred, nor did any deaths or discontinuation of drug due to side effects. Researchers recommend further study with the drug in these cancers.

**IDO: A New Checkpoint Target**

Researchers presented early results with a checkpoint inhibitor of a new target, indoleamine 2, 3-dioxygenase, or IDO, that is involved, like CTLA-4 and PD-1, in tumor immune escape. To produce an immunosuppressive environment, in cancer, dendritic cells and macrophages activate this enzymewhich inhibits CD8+ cells. Conversely, blocking IDO activates T cells. Numerous companies are developing IDO inhibitors, which are in relatively early-stage development compared to PD-1- and CTLA-4 inhibitors.

IDO is expressed in many solid tumors, including 50%–90% of glioblastomas, and high expression of the enzyme statistically correlates with poor prognosis in glioblastoma. In a phase Ib/II study 12 patients refractory to temozolomide, a standard chemotherapy in this cancer, took this drug plus indoximod, an IDO inhibitor developed by NewLink Genetics of Ames, Iowa. From the phase Ib section, four patients remain on the study, nine are alive, and one is showing an ongoing response after experiencing stable disease for 10 months, said investigator Howard Colman, M.D., Ph.D., director of medical neurooncology at the Huntsman Cancer Center in Salt Lake City. Four others have had stable disease for 4–11 months. No patients have had serious IDO-related treatment-related side effects or reduction of temozolomide dose.

The phase II study is enrolling patients into three cohorts of 20–40 each. In the first group patients will take indoximod and temozolomide; in the second, patients who have progressed on bevacizumab, an angiogenesis inhibitor, will take the two drugs with bevacizumab. The third cohort, whose tumors are amenable to focal radiation, will take indoximod and temozolomide and will receive stereotactic radiosurgery. The primary endpoint is 6-month PFS. “One advantage of this approach is that in addition to the possible ability of drugs to pass through the blood–brain barrier, activated immune cells—T cells, dendritic cells, macrophages, and microglia can pass through it,” Colman said.

In a phase I trial, Wilmington, Del.–based Incyte Corp.’s IDO1 inhibitor, INCB024360, showed a greater than 90% inhibition of the enzyme in patients with an array of solid tumors, including bladder, colorectal, and breast. IDO1, an isomer of IDO, is highly expressed in these tumors. Patients tolerated the oral drug well, and the most common effects were fatigue. In another study, researchers from the National Cancer Institute investigated the effects of the drug on dendritic cells’ maturation and antigen presentation, activation of a tumor antigen-specific cytotoxic T cells, and lysis of tumor cells and regulatory T cells. They found high levels of tumor lysis in human breast cancer cells and statistically significant decrease of regulatory T-cell proliferation induced by IDO production.

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