Nivolumab Versus Investigator’s Choice (IC) For Recurrent or Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (SCCHN): CheckMate-141

• Maura L. Gillison, MD, PhD, Chair of Cancer Research, Ohio State University Comprehensive Cancer Center, Columbus, Ohio

An estimated 600,000 people worldwide are diagnosed annually with squamous cell carcinoma of the head and neck (SCCHN), Dr. Gillison noted at an AACR press conference. Standard initial treatment includes combinations of surgery, radiation, and platinum-based chemotherapy. Within three to five years of treatment, however, about half of patients experience disease reoccurrence. Average survival when disease recurs within six months of platinum-based chemotherapy is six months or less. No agents have been shown to improve survival in this population, and no new treatments have been approved in more than 10 years. “New treatment options are desperately needed,” she said.

T-cell function, she explained, is regulated by the programmed death-1 (PD-1) checkpoint pathway, and tumors may exploit this pathway to “hide” from the immune system. Human papillomavirus (HPV)-positive and HPV-negative SCCHN both express programmed death ligand-1 (PD-L1). Antitumor activity is reduced when PD-1 on T cells binds to PD-L1/PD-L2 on tumors. Dr. Gillison noted that tumors arising in the oropharynx have been linked with HPV infection. When nivolumab binds to PD-1 on T cells, the antitumor immune response is restored.

The CheckMate-141 study is a randomized, global, phase 3 trial testing nivolumab (3 mg/kg intravenous [IV] every two weeks) in a 2:1 ratio versus investigator’s choice of methotrexate (40 mg/m² IV weekly), docetaxel (30 mg/m² IV weekly), or cetuximab (400 mg/m² IV once, then 250 mg/m² weekly). The primary endpoint is overall survival (OS). Among 361 subjects, the median age at baseline was 60 years, and most had one (45.2%) or two (34.9%) prior lines of systemic cancer therapy. About three-fourths were current or former smokers. One-year median OS was 7.5 months (95% confidence interval [CI], 5.5–9.1) in the nivolumab group and 5.1 months among those receiving investigator’s choice of therapy (95% CI, 4.0–6.0; hazard ratio [HR], 0.70; P = 0.01). In the nivolumab group, one-year OS was 36.0% (28.5%–43.4%) versus 16.6% (8.6%–26.8%) for investigator’s choice. While the benefit versus investigator’s choice was apparent regardless of PD-L1 or p16 status, it was greatest in those who had higher PD-L1 expression (HR, 0.55) or who were p16 positive (HR, 0.56).

The OS effect of nivolumab was also reported in both HPV-positive and HPV-negative disease. Median OS was 9.1 months for patients assigned nivolumab versus 4.4 months for those assigned investigator’s therapy of choice in HPV-positive disease; among patients with HPV-negative disease, median OS was 7.5 months for nivolumab versus 5.8 months for investigator’s choice. Grade 3–4 treatment-related adverse events occurring in 10% or more of subjects were far more common in the investigator’s choice group—35.1% compared with 13.1% in the nivolumab group. “The safety profile for nivolumab was favorable compared to investigator’s choice therapy and consistent with prior studies,” Dr. Gillison said.

“Nivolumab is the first agent to demonstrate a significant improvement in survival in patients with SCCHN who progress after platinum-based therapy in a randomized, phase 3 comparative trial,” she added. “It represents a new standard of care option for patients with refractory/metastatic SCCHN after platinum-based therapy.”

Durable, Long-Term Survival in Previously Treated Patients With Advanced Melanoma Who Received Nivolumab Monotherapy in a Phase I Trial

• F. Stephen Hodi, Director, Melanoma Center, Dana–Farber Cancer Institute, Boston, Massachusetts

The longest clinical trial survival follow-up of patients receiving anti–PD-1 therapy for advanced melanoma suggests that nivolumab monotherapy provides durable, long-term survival. Nivolumab, an immune checkpoint inhibitor that blocks PD-1 to enhance antitumor immune responses, is approved for first-line treatment of advanced melanoma as either monotherapy or in combination with ipilimumab.

The CA2009-003 dose-escalation study evaluated up to 96 weeks of nivolumab treatment (in five arms, with doses from 0.1 mg/kg IV every two weeks to 10 mg/kg IV every two weeks) among 107 patients (median age, 61 years) with advanced melanoma. Patients had between one and five lines of prior systemic therapies. Seventy-eight percent had visceral metastases at baseline.

An analysis of all patients with a minimum of 45 months of follow-up showed median OS at 17.3 months, with 34% of patients surviving at five years. The five-year survival rate for metastatic melanoma patients diagnosed between 2005 and 2011 in the National Cancer Institute’s Surveillance, Epidemiology, and End Results database was 16.6%.
Among patients receiving 3 mg/kg of nivolumab (the currently recommended dose), median survival was 20.3 months (95% CI, 7.2–NR). At 12 months, OS in patients who received 3 mg/kg of nivolumab was 64.7%, which fell to 47.1%, 41.2%, and 35.3% at 24, 36, and 48 months, respectively. OS rates appeared to plateau at about 48 months. Dr. Hodi noted that disease control was maintained among five patients who were permitted retreatment with nivolumab at their originally assigned dose after being off treatment for more than 100 days.

The discontinuation rate in patients receiving 3 mg/kg of nivolumab was 5.9% among those with grade 3-4 adverse events (and 5.9% as well for any grade). While fatigue, the most common adverse event for patients receiving 3 mg/kg, was reported among 47.1% of patients, there were no reports of grade 3-4 fatigue. There were no study-drug-related deaths and no new safety signals.

Dr. Hodi concluded, “At a minimum follow-up of 45 months, nivolumab monotherapy resulted in a five-year overall survival rate of 34% in heavily pretreated patients with advanced melanoma.” He added, “These data provide a foundation for establishing anti–PD-1 therapy as another standard for melanoma patients, and hopefully this would translate to other cancer types as well.”

Entrectinib, an Oral Pan-Trk, ROS1, and ALK Inhibitor in TKI-Naïve Patients With Advanced Solid Tumors Harboring Gene Rearrangements
• Alexander Drilon, MD, Medical Oncologist, Memorial Sloan Kettering Cancer Center, New York

Entrectinib is an investigational, highly potent, orally available, ATP-competitive tyrosine kinase inhibitor (TKI) that targets the proteins TrkA/B/C, ROS1, and ALK. Among patients with several types of cancer with NTRK1/2/3, ROS1, or ALK gene alterations, combined analysis of two phase 1 clinical trials showed treatment with entrectinib to be safe and tolerable and to demonstrate clinical activity. The two trials, STARTTRK-1 and STARTTRK-2, enrolled patients who had not received prior treatment with Trk-, ROS1-, or ALK-directed targeted therapeutics.

Dr. Drilon noted that alterations called “fusions,” detected in a variety of types of cancer involving the NTRK1/2/3, ROS1, and ALK genes, cause heightened activity of the TrkA/B/C, ROS1, and ALK proteins coded for by these genes, promoting cancer-cell proliferation and survival. While NTRK1/2/3, ROS1, and ALK fusions are less prevalent in more common cancers, they are highly prevalent (more than 80%) in multiple rare adult and pediatric cancers, such as mammary analogue secretory carcinoma, breast secretory cancer, congenital mesoblastic nephroma, and congenital fibrosarcoma. Also, some primary brain tumors have NTRK fusions (astrocytoma, NTRK2 fusions in 3%; glioblastoma, NTRK1 fusions in 1% to 2%; pediatric gliomas, NTRK3 fusions in 7%). Entrectinib is designed to cross the blood–brain barrier. Brain metastases, Dr. Drilon pointed out, occur in 20% to 40% of all patients with cancer. Preliminary data suggest that tumors with these genetic alterations can be extremely sensitive to entrectinib, Dr. Drilon said. “Optimal therapy would address both systemic and CNS [central nervous system] disease,” he commented. “Entrectinib’s ability to penetrate the blood–brain barrier is a highly valuable characteristic that oncologists look for in a systemic therapy.”

Initial trial analysis among 119 patients established 600 mg as an oral, once-daily, continuous entrectinib dose. In 24 TKI-naïve patients, confirmed responses were high (NTRK1/3, three of three [100%]; ROS1, 12 of 14 [86%]; ALK, four of seven [57%]). An additional response occurred in an NTRK-positive astrocytoma patient. Two responses in patients with ROS1-rearranged cancers were complete responses, and in non–small-cell lung cancer, the objective response rate was 85% (12 of 14). The longest ongoing response has exceeded 27 months, Dr. Drilon said.

AACR press conference moderator Louis M. Weiner, MD, Director of the Georgetown Lombardi Comprehensive Cancer Center, summed up the findings: “The take-home is that gene fusions which are drivers of the malignant property of certain cancers are really good targets.”

Phase 1b Study of Novel Immunotherapy Combination Therapy of Intrallesional Coxsackievirus A21 and Systemic Ipilimumab In Patients With Advanced Melanoma
• Robert Andtbacka, MD, Huntsman Cancer Institute, Salt Lake City, Utah

A very preliminary report on the combination of ipilimumab and Coxsackievirus A21 (CVA21) in patients with advanced melanoma reveals promising responses with low toxicity and a suggestion that activity may be greater than that seen in other ipilimumab combinations. Ancillary studies show activation of CD8+ T cells and support the immune activity of intralesional therapies.

Intratumoral injections of Cavatak, a novel oncolytic and immunotherapeutic strain of CVA21, can induce preferential tumor-cell infection, tumor immune-cell infiltration, up-regulation of gamma-interferon response genes, cell lysis, and enhancement of a systemic antitumor immune response. In the phase 2 CALM study, the confirmed response rate among patients with advanced melanoma was 28.1% (16 of 57). Responses were observed in both injected and noninjected metastases.

Preclinical tests of CVA21 combined with the anti–CTLA-4 humanized monoclonal antibody ipilimumab have suggested significantly greater antitumor activity compared with use of either agent alone.

The MITCI (Melanoma Intra-Tumoral Cavatak and Ipilimumab) trial enrolled 26 stage IIIIC and IV melanoma patients with at least one injectable lesion. All received CVA21 intrallesional injections (on days 1, 3, 5, 8, and 22 and subsequently every three weeks until day 358) and ipilimumab (3 mg/kg IV every three weeks for four cycles). Safety was the primary endpoint, with response (immune-related World Health Organization criteria) as the secondary endpoint.

In a preliminary analysis of safety among 11 treated patients, there were no dose-limiting toxicities and only one grade 3 treatment-related adverse event (ipilimumab-related fatigue). Among six patients evaluable for tumor assessment (all ipilimumab-naïve), there were two complete responses and two partial responses (best overall response, 66.7%). Disease control was reported in five of six patients, and immune-related progression-
free survival in four of five (80%) at six months. “This is very early data, but it’s very encouraging,” Dr. Andtbacka said in an interview.

Dr. Andtbacka also reported, in a second poster, on efforts to determine in the tumor microenvironment what distinguished those patients who had responses with CVA21 from those who did not. In a CALM study extension among 13 patients with stage IIC and IV melanoma, investigators performed serial biopsies of at least one lesion before and after treatment with intralesional CVA21, monitoring for evidence of viral-induced changes in immune-cell infiltrates.

Assessment via multispectral imaging revealed notable robust up-regulation of immune-cell infiltrates (CD3+ and CD8+ \( P = 0.044 \)) within lesions in those patients with disease control (responses or stable disease). Dr. Andtbacka added that CVA21 injections up-regulated the interferon-induced genes CXCL10 and CXCL11 and immune checkpoint molecules (CTLA-4, PD-L1, LAG-3, TIM-3, and IDO) within the microenvironment of melanoma lesions, and in general appeared to facilitate more widespread increased expression of immune checkpoint inhibitory molecules than immune checkpoint stimulatory molecules. Up-regulation occurred as early as seven days after the initial viral administration.

“This finding,” Dr. Andtbacka said, “raises the question: Can we do a biopsy after a few injections of CVA21 and then look at the immune profile and then try to determine who will and who will not respond? Also, can we determine through the immune profile who will respond better to an anti–CTLA-4 or PD-L1 drug, for example?” Those responses, he suggested, may occur even among patients who did not respond to ipilimumab or anti–PD-1 agents on their first exposure, because the CVA21 injection may have the effect of “activating the scene” in a way that a systemic agent may not. “The injection is going to up-regulate interferon-gamma, activating immune cells which then enter into the tumor.”

The importance of the presence of CD8+ T cells was echoed in a further poster presentation on intralesional therapies in combination with a checkpoint inhibitor. Shari Pilon-Thomas, PhD, leader of a team of researchers at H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, showed CD8+ T cells to be mediators of delayed tumor growth in an animal model.

Combination therapy with intralesional PV-10 (10% solution of Rose Bengal), a chemo-ablative agent that has been shown to cause regression of cutaneous melanoma lesions in a phase 2 study, and a murine analog of the approved anti–PD-1 antibodies nivolumab and pembrolizumab was shown to delay tumor growth more than injections of either PV-10 or the anti–PD-1 agent alone.

Dr. Pilon-Thomas’ analysis showed high levels of PD-1 expression on the tumors before treatment. Interferon-gamma levels were increased significantly more \( (P < 0.05) \) by the combination than with either PV-10 or anti–PD-1 treatment. The combination of PV-10 and anti–PD-1 therapy induced systemic expansion of tumor-specific CD8+ T cells. A subsequent analysis also showed that depleting CD25 Tregs (cells that shut down CD8 T-cell responses) enhanced antitumor immunity. “This suggests that combination therapy with a co-inhibitor blockade like anti–PD-1 with IL [intralesional] PV-10 and then targeting the suppressor cell population will synergize to induce complete cures,” Dr. Pilon-Thomas said.