ESMO World Congress on Gastrointestinal Cancer And European Post-Chicago Melanoma/Skin Cancer Meeting

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ESMO World Congress on Gastrointestinal Cancer

The European Society for Medical Oncology (ESMO) 18th World Congress on Gastrointestinal Cancer (WCGIC), held this year in Barcelona, Spain, from June 29 to July 2, hosted 3,000 oncologists and other medical professionals. With the concurrent release of ESMO's new consensus guidelines for metastatic colorectal cancer, we focus on related research sessions below.

Analysis of Patients 75 Years of Age And Older in the Open-Label Phase 3b CONSIGN Trial of Regorafenib in Previously Treated Metastatic Colorectal Cancer

- Eric Van Cutsem, MD, Professor of Medicine, University Hospitals Gasthuisberg/Leuven and Katholieke Universiteit, Leuven, Belgium; Chairperson of the ESMO Consensus Conference and Co-Chairperson of WCGIC

The median age at diagnosis for colorectal cancer is 68 years, and one-third of new cases occur in patients 75 years of age or older. Due to concerns about their ability to tolerate anticancer therapies, older patients with colorectal cancer may not receive potentially helpful therapies, Dr. Van Cutsem said. To evaluate the safety of regorafenib in this population, he analyzed a subgroup of patients 75 years of age and older who participated in the international phase 3b CONSIGN study and compared the drug's effects with those that occurred in the patients younger than 75 years old.

Regorafenib, an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in oncogenesis, angiogenesis, and the tumor microenvironment, initially proved its efficacy in the phase 3 CORRECT trial. The study, conducted in treatment-refractory metastatic colorectal cancer (mCRC) patients ages 22 to 85 years, demonstrated improved overall survival (the primary endpoint) for regorafenib versus placebo.

The later CONSIGN trial also evaluated the use of regorafenib in treatment-refractory mCRC patients. While investigator-assessed progression-free survival (PFS) data were collected as the only efficacy endpoint, the primary measure was safety. The study included 2,872 patients with mCRC who progressed after standard therapies and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1. The patients received regorafenib 160 mg daily for the first three weeks of each four-week cycle until disease progression, death, or unacceptable toxicity. Standard therapies included fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab/panitumumab in *KRAS* wild-type patients.

Of the patients assigned to treatment, 268 (9%) were 75 years of age or older (median, 77 years), and 2,604 were younger than 75 years of age (median, 61 years). Compared with the under-75 subgroup, more patients in the 75 years or older subgroup had an ECOG PS of 1; had four or more prior treatment regimens on or after diagnosis of metastatic disease; and had been diagnosed with metastatic disease for 18 months or more.

Treatment duration, median number of cycles, and daily dose were similar in the two subgroups. Most patients had at least one treatment-emergent adverse event (TEAE) (younger than 75 years, 91%; 75 years or older, 91%). Regorafenib-related TEAEs of grade 3 or higher occurred in 56% of the subgroup younger than 75 years versus in 64% of the subgroup older than 75 years. Rates of serious and grade 5 events were similar in the two subgroups. Regorafenib-related TEAEs led to treatment discontinuations in 9% of patients younger than 75 years old and in 12% of patients 75 years of age or older. Grade 3 or higher fatigue and hypertension were numerically higher in the 75 and older subgroup, and the rate of grade 3 or higher hand-foot skin reactions was numerically higher in the younger-than-75 subgroup.

Dr. Van Cutsem said that median PFS was similar in the two groups: 2.7 months for those younger than 75 years old and 2.5 months for those 75 years of age or older.

Summarizing in an interview, he said, "There were no major differences in safety. As long as patients are fit enough, age in itself is not an exclusion criterion for treatment with regorafenib in metastatic colorectal cancer." He noted that dose reductions and dose interruptions in both subgroups highlight the importance of adverse event management and dose modification.

An International, Randomized Noninferiority Trial Comparing Three Versus Six Months of Oxaliplatin-Based Adjuvant Chemotherapy For Colon Cancer: Compliance and Safety Of the Phase 3 Japanese ACHIEVE Trial

- Tetsuya Eto, MD, Tsuchiura Kyodo General Hospital Department of Gastroenterology, Tsuchiura, Japan

While oxaliplatin/fluoropyrimidine chemotherapy (5-fluoropyrimidine and leucovorin [5-FU/LV] or capecitabine) is an established adjuvant treatment for colon cancer, neurotoxicity from oxaliplatin is cumulative, dose limiting, and potentially irreversible. Some research has shown, however, that limiting infusional 5-FU to three months instead of bolus 5-FU/LV for

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six months retains efficacy with significantly lower incidence of adverse events.[1,2]

The International Duration Evaluation of Adjuvant Chemotherapy Collaboration was established to test whether three-month oxaliplatin-based adjuvant treatment is noninferior in terms of disease-free survival to six-month treatment in patients with stage 3 colon cancer, with less toxicity. It includes six ongoing clinical studies worldwide from which data will be pooled. Among them, the ACHIEVE trial is comparing three- versus six-month oxaliplatin-based therapy.

ACHIEVE subjects (N = 1,277) had curatively resected stage 3 colon cancer (including rectosigmoid cancer) and performance status of 0–1. Patients who received prior oxaliplatin chemotherapy were excluded. Patients received either a modified (m) FOLFOX6 or XELOX regimen (25%/75%) for six months (n = 635) or three months (n = 642). Median age was approximately 67 years, and approximately 50% of the patients were men. The tumor site was the colon in about three-quarters of patients, and was rectosigmoid in the remainder.

Treatment completion rates were higher in the three-month treatment arm than in the six-month arm (86% versus 61%). Nonhematological adverse events were more common with the six-month regimen (mFOLFOX6, 48%, versus XELOX, 41%) than with the three-month regimen (mFOLFOX6, 35%, versus XELOX, 27%; $P < 0.0001$). Grade 2 or higher hand-foot syndrome was more common with the six-month regimen (mFOLFOX6, 3%, versus XELOX, 15%) than with the three-month regimen (mFOLFOX6, 1%, versus XELOX, 7%; $P < 0.0002$). Grade 2 or higher neuropathy was reported more frequently with the six-month treatment (mFOLFOX6, 36%, versus XELOX, 37%) than with the three-month treatment (mFOLFOX6, 11%, versus XELOX, 14%; $P < 0.0001$). There was one treatment-related death due to duodenal perforation in the six-month mFOLFOX6 arm.

Among grade 3 or higher hematological adverse events, neutropenia was more frequent with the six-month regimen (mFOLFOX6, 34%, versus XELOX, 15%) than with the three-month regimen (mFOLFOX6, 27%, versus XELOX, 10%; $P < 0.0036$). One case of febrile neutropenia was observed in the six-month arm.

Looking at the two 5-FU backbones, Dr. Eto noted that leukopenia and neutropenia rates (grade 3 or above) were higher for mFOLFOX, and thrombocytopenia and nonhematological adverse events were more common for XELOX. Neuropathy (grade 2 or higher) was similar (approximately 25%) for both mFOLFOX6 and XELOX. Overall, multivariate and univariate analyses showed that adverse events of grade 3 or higher were significantly more common with the six-month regimen, with mFOLFOX6, with older age, with higher body surface area, with lower baseline renal function, and among women.

ACHIEVE results showed that while both mFOLFOX6 and XELOX were safe and well tolerated, treatment-emergent adverse events were significantly lower in the three-month arm than in the six-month arm. Treatment compliance was lower in the standard six-month arm, Dr. Eto added.

Efficacy findings are not expected to be available until the 2017 American Society of Clinical Oncology annual meeting.

Evaluation of Depth of Response Within a Volumetric Model in Patients With Metastatic Colorectal Cancer: Results of the SIRFLOX Study

• Volker Heinemann, MD, Krebszentrum München Comprehensive Cancer Center, Munich, Germany

In a prior report of phase 3 SIRFLOX trial data,[3] adding selective internal radiotherapy (SIRT) to first-line modified (m) FOLFOX6 with or without bevacizumab did not improve progression-free survival (PFS) in metastatic colorectal cancer (mCRC). PFS for those with liver metastases, however, was longer with SIRT by 7.9 months (20.5 months with SIRT versus 12.6 months without; 31% risk reduction; $P = 0.002$).

The prospective, open-label SIRFLOX trial included 530 patients with nonresectable liver-only or liver-dominant mCRC who had no prior chemotherapy for advanced disease (performance status 0–1). Patients with limited extrahepatic metastases and/or a single anatomical area of less than 2 cm in diameter lymph node involvement were allowed. Among patients randomized 1:1 to SIRT (n = 267) delivered via yttrium-90 microspheres (SIR-Spheres, Sirtrex), the objective response rate (ORR) in the liver was significantly higher with SIRT added (78.7% versus 68.8%; $P = 0.042$), and in the overall population, the complete response rate (CR) was higher with SIRT added (4.5% versus 1.5%; $P = 0.054$). (Bevacizumab was also administered at the investigator's discretion per institutional practice.)

Based on SIRFLOX data, Dr. Heinemann related SIRT's impact on hepatic depth of response (DpR) versus chemotherapy alone to baseline tumor burden and to effects on ORR and CR. Ultimately, this analysis will test the relationship between DpR and oveall survival (OS). DpR is based on measures of tumor load at baseline and on the tumor load nadir after treatment. DpR, unlike the Response Evaluation Criteria in Solid Tumors (also known as RECIST), captures postprogression survival until the tumor load becomes lethal, he said.

Investigators stratified patients into two groups: those with a baseline tumor load of 12% or less (239 patients) or greater than 12% (245 patients) in the liver. Mean liver involvement was approximately 18%. Extrahepatic disease was present in about 40% of patients and was the primary tumor *in situ* in approximately 45%.

The addition of SIRT in patients with 12% or less baseline tumor burden did not improve DpR ($P = 0.763$, 8.1% difference favoring chemotherapy alone), although time to nadir was 23.5 days longer with SIRT added (243 days; $P = 0.152$). In the greater than 12% tumor burden group, however, DpR was improved by 20.3% ($P = 0.003$) with SIRT added (77.5% with SIRT added versus 57.2% for chemotherapy alone). In addition, time to nadir was 102 days longer in the SIRT-added group (298 days versus 196 days; $P = 0.001$).

PFS in the liver in the 12% or less tumor burden group was extended by 2.9 months with SIRT added (15.1 months versus 12.2 months; $P = 0.112$). In the greater than 12% tumor burden group, PFS with SIRT was 14.1 months longer (27.2 months versus 13.1 months; $P = 0.003$). Hepatic ORRs in the 12% or

less tumor burden group were similar at about 84%, but CRs were significantly more common with SIRT added (11.3% versus 1.7%; $P = 0.003$). In the greater than 12% tumor burden group, ORR was significantly higher with SIRT added (88.2% versus 67.2%; $P = 0.022$). CRs were low and similar (0.8% for chemotherapy alone versus 0% with SIRT added; $P = 0.303$).

Addressing the observation that SIRT has a greater effect in patients with higher tumor burdens, Dr. Heinemann said in an interview, "Without going back to animal studies, we can only speculate about the exact biology, but maybe because the tumor vasculature in larger metastases is well developed, it may be more able to trap the SIRT microspheres than the very small metastases."

He emphasized that this study is the first in mCRC to evaluate the effects of initial tumor burden on treatment outcomes. Asked if SIRT could be recommended for first-line treatment outside of a clinical trial, he said, "We have a very interesting hypothesis and very interesting data, but we don't recommend SIRT for first-line use in the absence of survival data."

"These findings provide additional evidence to support the benefit of SIRT in patients with metastatic colorectal cancer," he concluded.

ESMO Consensus Guidelines for the Management Of Patients With Metastatic Colorectal Cancer

- Eric Van Cutsem, MD, Professor of Medicine, University Hospitals Gasthuisberg/Leuven and Katholieke Universiteit, Leuven, Belgium; Chairperson of the ESMO Consensus Conference, and Co-Chairperson of WCGIC

"Management of metastatic colorectal cancer is becoming more complex. It requires a strategic approach and evidence-based patient selection for the best treatment options," Dr. Van Cutsem said in his introduction to his oral presentation on the updated consensus guidelines for metastatic colorectal cancer (mCRC). While the last decade has seen better outcomes for patients with mCRC, it remains unclear which advances and strategic changes in treatment and management have been responsible for the improvements. Potential factors include changes in patient clinical presentation because of earlier detection of metastatic disease or closer follow-up after primary tumor resection; improvements in efficacy and administration of systemic therapies; increases in treatments aimed at facilitating resection of metastases for cure or durable relapse-free survival, including use of other ablative techniques; and "continuum of care" strategies coupled with early integration of optimal supportive care. The new guidelines aim at combining what is thought to be contributing to recent outcomes gains, and offer strategies and the evidence supporting them.

The previous "ESMO Clinical Practice Guidelines" report, published in 2014, was a nine-page document. The 2016 consensus guidelines now span 37 pages and list 21 specific recommendation areas.

The first eight areas range across tissue handling, selection, and biomarker testing. For example, testing to determine RAS mutational status is recommended for all patients at the time of diagnosis and should include at least *KRAS* exons 2, 3, and 4 (codons 12, 13, 59, 61, 117, and 146) and *NRAS* exons 2, 3, and 4 (codons 12, 13, 59, 61, and 117). In addition, *BRAF* status testing for prognostic assessment (and/or potential selection for clinical trials) is strongly recommended. Microsatellite instability testing, which can assist clinicians in genetic counseling and offers strong predictive value for the use of immune checkpoint inhibitors, is an emerging biomarker, but is not yet mandatory. Testing for biomarkers such as EGFR or HER2, while emerging in use, is not yet recommended as routine for patient management.

The ninth recommendation area covers emerging technologies, such as circulating tumor cell number and liquid circulating tumor DNA biopsies, reserved for research settings.

Specific treatment strategies enter at the 10th recommendation, which covers oligometastatic disease, followed by recommendations regarding perioperative treatment and conversion therapy for potentially resectable patients.

A striking change in the new guidelines is the emphasis given to ablative therapies, which in the 2014 practice guidelines was limited to a short paragraph and a few mentions. In the 2016 consensus paper, ablative techniques are introduced in the 13th guideline on conversion strategies, and are covered in detail throughout the 16th recommendation. The ablation techniques span thermal, chemo, and radiofrequency ablation, and include stereotactic body radiation therapy and selective internal radiation therapy. The radioembolization recommendation for liver-limited disease is expanded beyond yttrium-90 microspheres to include chemoembolization. Under the "local and ablative treatment" heading, the 2016 paper includes cytoreduction surgery and hyperthermic intraperitoneal chemotherapy.

The remaining recommendations encompass first-line (according to targeted agent used), maintenance, second-line, and third-line therapies.

Discussing innovations in pharmacotherapy for third-line therapy, Dr. Van Cutsem said that trifluridine/tipiracil is now recommended for patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and for RAS wild-type patients with EGFR antibodies. Trifluridine/tipiracil was approved in late 2015 in the United States for mCRC patients who have been treated previously with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biologic product, and, if the patient is RAS wild-type, an anti-EGFR monoclonal antibody.

"These recommendations should help us to fine-tune and improve our strategies, and guide treatment options in order to improve outcomes," Dr. Van Cutsem concluded.

The complete guidelines are available at: https://annonc.oxfordjournals.org/content/early/2016/07/07/annonc.mdw235.full.pdf+html.

European Post-Chicago Melanoma/Skin Cancer Meeting

The European Post-Chicago Melanoma/Skin Cancer meetings, under the auspices of the European Association of Dermato–Oncology, aim to provide a comprehensive overview on new developments in melanoma diagnostics and therapy, and to offer insights for choosing the right treatment for the right patient. This year's sixth annual meeting, held in Munich, Germany, from June 30 to July 1, attracted approximately 600 medical professionals.

Melanoma Brain Metastases

- Friedegund Meier, MD, Professor of Dermato–Oncology, University Cancer Center, Dresden, Germany

Dr. Meier began by reviewing a trial examining the effects of adjuvant whole-brain radiotherapy (WBRT) in stereotactic radiosurgery (SRS). SRS has high efficacy for treating brain metastases (90%), but when applied by itself, it is associated with a high rate of new brain metastases development. Research by Paul Brown, MD, Professor of Radiation Oncology at the University of Texas MD Anderson Cancer Center in Houston, examined the survival benefit and acute and late toxicities of WBRT.[4] It showed no impact on survival, but a negative effect on cognitive function. His review of three SRS trials of adjuvant WBRT revealed improvement in local control (81–100% versus 67–73% for SRS alone) and distant brain metastasis control (67–73% versus 36–52% for SRS alone), but no boost in overall survival (OS) (5.7–10.9 months versus 8.0–15.2 months for SRS alone).

Dr. Brown's adjuvant WBRT-N0574 trial showed equivalent OS between SRS and SRS with WBRT after brain tumor resection, but a –22% score after three months for SRS with WBRT in functional well being. The N107C trial of SRS to the surgical bed or WBRT in patients with more than three brain metastases after resection is ongoing. The potential advantages of SRS are less acute toxicity, less delay in systemic therapy, and likely less cognitive impact. The disadvantages of SRS are that it does not address micrometastases and is labor intensive.

The QUARTZ trial of palliative WBRT, which tested WBRT plus supportive care versus supportive care alone in 538 poor-prognosis patients with brain metastases not suitable for resection or SRS, found no WBRT benefit.

Is it possible to decrease WBRT toxicity? The RTOG 0614 trial of WBRT with or without 20-mg once-daily dosing of memantine, an Alzheimer's disease drug, in patients with brain metastases demonstrated a 22% reduction in risk of cognitive deterioration ($P = 0.01$).

Dr. Brown's phase 2 trial (RTOG 0933) of conformal avoidance of the hippocampus revealed memory deficits were reduced from 30% to 7%. A phase 3 trial of WBRT plus memantine versus hippocampal avoidance WBRT plus memantine in 518 patients with brain metastases is ongoing (time to cognitive failure is the outcome measure).

"The role for radiosurgery is growing; the role for WBRT is diminishing," Dr. Meier concluded.

Turning to clinical trials of targeted therapies in 40 or more patients with melanoma brain metastases, Dr. Meier cited phase 2 trials of dabrafenib and vemurafenib, with the former showing intracranial response rates (RRs) of 39.2% and 30.8% in asymptomatic patients with new and recurrent disease, respectively. RRs in symptomatic patients with recurrent and new disease were 18% and 20%, respectively. Progression-free survival was approximately four months in all groups of both trials, and median OS ranged from 6.9 to 8.2 months. Current trials are assessing dabrafenib, dabrafenib and trametinib, vemurafenib and cobimetinib, and buparlisib.

The Eastern Cooperative Oncology Group consensus guidelines warn of potential intracranial neurotoxicity from radiotherapy combined with BRAF inhibitors, but note that rates of radionecrosis, hemorrhage from WBRT or SRS, or both do not appear to be increased with concurrent or sequential administration of BRAF inhibitors, Dr. Meier said. The guidelines recommend refraining from BRAF inhibitors three days before and after fractionated radiotherapy, and for one day before and after SRS.

Phase 2 research on the use of immune checkpoint inhibitors (anti-programmed cell death protein-1 [PD-1]) included a trial of pembrolizumab in 18 melanoma patients with brain metastases. The RR (complete plus partial response) was 22%. A further brain metastasis trial comparing ipilimumab and anti-PD-1 therapy reported a median OS of 6.64 months for ipilimumab and 11.27 months for anti-PD-1 therapy. Subgroup analysis showed disease control rates (DCRs) with ipilimumab of 32% in asymptomatic patients and 37% in symptomatic patients. With anti-PD-1 therapy, DCRs were 48% in asymptomatic patients and 25% in symptomatic patients.

Dr. Meier commented that ipilimumab efficacy was higher than in published data, explained perhaps by post-ipilimumab treatment with anti-PD-1 therapy in 67% of patients.

Finally, reviewing a trial of SRS with the gamma knife (GK) plus systemic therapy in *BRAF*-mutated patients showed a median OS of approximately three months for GK alone and approximately seven to 13 months for GK plus targeted therapy or immunotherapy.[5] For *BRAF* wild-type patients, the median OS was about two months for GK alone and approximately nine to 14 months for GK plus targeted therapy or immunotherapy. The conclusion was that in patients with melanoma brain metastases, GK followed by new targeted therapies or immunotherapies (especially anti-PD-1) produced limited recurrence, controlled extracerebral disease, and favored prolonged survival.

Dr. Meier suggested future directions, including local therapies (stereotactic radiation, SRS, perhaps WBRT and/or systemic therapy with targeted therapies or immunotherapies) for macroscopic disease; systemic therapy or perhaps WBRT for microscopic disease; and systemic therapies for systemic disease. "With a multidisciplinary approach," she said, "we can make a difference in the lives of our patients."

Highlights of American Society of Clinical Oncology (ASCO) Immunotherapy Findings in Melanoma

• Michael A. Postow, MD, Memorial Sloan Kettering Cancer Center, New York, New York

The progression-free survival (PFS) benefit achieved by adding nivolumab to ipilimumab or with nivolumab alone as compared with ipilimumab alone in patients with treatment-naïve advanced melanoma continued in follow-up out to a median of 18 months. The data were presented in updated Checkmate 067 trial results by Jed D. Wolchok, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, at the 2016 ASCO annual meeting.[6] The combination therapy reduced patients' risk for progression by 58% compared with ipilimumab alone (hazard ratio [HR], 0.42; 99.5% confidence interval [CI], 0.31–0.57; $P < 0.00001$), and nivolumab monotherapy reduced the risk for progression by 45% (HR, 0.55; 99.5% CI, 0.43–0.76; $P < 0.00001$). An exploratory endpoint analysis showed that combination therapy reduced progression risk by 24% compared with nivolumab alone (HR, 0.76; 95% CI, 0.60–0.92).

According to Dr. Postow, what stood out as the highest absolute difference in objective response rate (ORR) between the ipilimumab/nivolumab combination versus nivolumab monotherapy was the one between the two in *BRAF*-mutant patients, with an ORR of 66.7% for the combination and 36.7% for nivolumab alone (Δ30%). In *BRAF* wild-type patients, the difference was only 7% (53.3% for the combination versus 46.8% for nivolumab alone). The import of the 66.7% ORR in *BRAF*-mutant patients, Dr. Postow underscored, is that "we shouldn't just be thinking about targeted therapies for these patients; we should also be thinking about immune therapy. ... The ORR for single-agent nivolumab was very high, as well."

Longer median PFS for nivolumab and the nivolumab/ipilimumab combination continued versus ipilimumab monotherapy at 18 months (nivolumab, 6.9 months; combination, 11.5 months; ipilimumab, 2.9 months), with hazard ratios for the combination of 0.55 versus nivolumab and 0.42 versus ipilimumab. PFS was 44% for the combination, 39% for nivolumab monotherapy, and 14% for ipilimumab monotherapy.

While overall survival (OS) analysis is not available yet in the phase 3 trial, Dr. Postow's presentation of the phase 1 Checkmate 069 data at the American Association for Cancer Research annual meeting had shown a 26% median OS benefit for nivolumab plus ipilimumab versus ipilimumab alone in an exploratory analysis, with a 10% advantage in probability of survival (64% versus 54%) at two years in *BRAF* wild-type and *BRAF*-mutant patients.[7]

The OS finding is consistent with the KEYNOTE-006 trial phase 3 finding of 55% OS at two years for both pembrolizumab regimens (every two weeks and every three weeks) and 43% for ipilimumab (HR, 0.68; 95% CI, 0.53–0.87; $P = 0.00085$ for pembrolizumab every two weeks) (HR, 0.68; 95% CI, 0.53–0.86; $P = 0.00083$ for pembrolizumab every three weeks).

While cautioning about cross-trial comparisons, Dr. Postow reviewed several other trials, which all showed programmed cell death protein-1 (PD-1) inhibitor two-year OS in the mid- to upper-mid 50% range (and a phase 1 trial with three-year survival at 68%).

The further concern, he said, is to reduce the side effects of the combination. In the presentation of the phase 1 KEYNOTE-029 data by Georgina Long, MD, with an ipilimumab dose lowered from the standard 3 mg/kg to 1 mg/kg with pembrolizumab (2 mg/kg), the ORR in an expansion cohort was 57% with a six-month PFS of 70% in advanced melanoma.[8] Grade 3 or 4 treatment-emergent adverse events were reported in 42% of patients. Randomized trials are needed, Dr. Postow said, noting that a trial looking at grade 3–5 adverse events comparing ipilimumab 3 mg/kg plus nivolumab 1 mg/kg with ipilimumab 1 mg/kg plus nivolumab 3 mg/kg is upcoming.

The observation of patients who have quickly discontinued ipilimumab dosing because of adverse events and have still had impressive response rates and PFS begs the question of whether it may be feasible to evaluate patients via computerized tomography (CT) scan at week 6 after two doses of ipilimumab/nivolumab, and if they are already responding switch them to nivolumab monotherapy, he said. Furthermore, in Dr. Caroline Robert's presentation of KEYNOTE-001 data on the 61 complete responders who stopped pembrolizumab for observation, only two patients experienced progression.

Summarizing, Dr. Postow said that combination therapy has the highest PFS, response rates, and toxicity. Overall survival data are not yet mature, but combinations with less ipilimumab or none (combining PD-1 with different agents) are of interest. While stopping PD-1 in patients with complete responses has proven successful, stopping PD-1 in patients with partial responses or long-term stability, the role of CT or positron emission tomography scans or biopsy to assess responses, and the efficacy of PD-1 reinduction stand out as themes for future research.

Current Clinical Trials: Soft Tissue And Skin Metastases

• Sanjiv S. Agarwala, MD, Professor of Medicine, Temple University, Bethlehem, Pennsylvania

"Why would anyone be interested in local treatment of a systemic disease?" Dr. Agarwala began. While the new systemic immunotherapies and targeted therapies are exciting and have raised the bar quite high, "we are hitting a toxicity limit. Secondly, let's not forget that melanoma is not just a systemic disease." Three percent to 10% of primary melanomas develop local/in-transit recurrences with a greater than 50% risk of distant disease and death. In addition, the soft tissue and skin metastases that occur frequently in melanoma may be associated with considerable morbidity, which can itself lead to mortality, or the patient can suffer for a long time with local disease that can be very hard to control with the available treatments, including surgery. Furthermore, a significant portion of patients may not be candidates for the aggressive systemic therapies.

Oncolytic immunotherapies can work either directly through cell lysis or indirectly through "bystander responses" through induction of either innate or adaptive immune responses. By making the tumor more visible to the immune system, these oncolytic immunotherapies "make the tumor your friend, your ally."

While the list of intralesional therapies is growing rapidly, those closest to approval employ electrochemotherapy (cisplatin, bleomycin), chemical ablation (rose bengal disodium 10% [PV-10]), and oncolytic viruses (herpes simplex virus [HSV], coxsackievirus, and reovirus), with talimogene laherparepvec (T-VEC [Imlygic, Amgen]) among them already approved in the U.S. and Europe. Single-agent clinical trials are ongoing with PV-10 (phase 3), electroporation of interleukin (IL)-12, and coxsackievirus type A21 (CVA21) (Cavatak, Viralytics, Ltd.), and combination trials are ongoing with T-VEC, PV-10, and HF10 (an attenuated, replication-competent HSV).

PV-10, a small-molecule fluorescein derivative, causes primary tumor lysis by entering lysosomes, with necrotic tumor cells facilitating antigen presentation leading to regression of distant tumors. The 80-patient phase 2 trial revealed a 51% response rate (26% complete responses [CRs]) in target lesions, and a 33% response rate in nontarget lesions (26% CRs). Progression-free survival was 11.4 months in responders and 4.1 months in nonresponders. Responses were "robust" in stage III subjects, and adverse reactions were mild to moderate.

In the phase 3 trial, 225 patients with locally advanced cutaneous melanoma are receiving PV-10 every four weeks, chemotherapy (dacarbazine or temozolomide) every four weeks, or T-VEC every two weeks.

In electroporation, better tumor cell entry by IL-2, "a fairly strong immune-based cytokine," is induced by application of an electric current to the tumor. It is a commonly used modality in Europe, Dr. Agarwala said. Objective response rates (ORRs) in interim analysis of a 28-patient phase 2 study have been in the 30% to 50% range, with responses in 59% of untreated "bystander" lesions.

In Robert Andtbacka's phase 2 CALM trial of CVA21 in 57 patients with advanced melanoma, the response rate was 36.8% with a disease control rate of 75.4%.

The first trial of an intralesional therapy combined with a systemic therapy was a phase 1b trial of T-VEC or ipilimumab (3 mg/kg) in 18 patients with stage IIIB/C–IVM1c melanoma not suitable for surgical resection, which had ORR as a secondary endpoint. Investigator-assessed responses were observed in 56%, with CRs in 33% of patients.

An evaluation of responses in a phase 1b trial of T-VEC plus pembrolizumab in unresected stage III or IV melanoma found that in 50 injected lesions, there was a 100% reduction in tumor area from baseline in 70% (n = 35). The same 100% reduction was found in 40% of 20 noninjected nonvisceral lesions (n = 8) and in 10.3% of 29 noninjected visceral lesions (n = 3). "Despite the small number of patients, the first combination trials seem to imply a synergy, with the combinations producing a higher response rate than the sums of the rates for the individual agents. But phase 3 trials will be the true test," he said.

The MASTERKEY-265 phase 3 trial of T-VEC and pembrolizumab versus pembrolizumab and a T-VEC placebo will be the first placebo-controlled, randomized trial in melanoma. Further combination trials in melanoma are testing neoadjuvant T-VEC treatment with surgery versus surgery alone, PV-10 with pembrolizumab (1b), and HF10 with ipilimumab (1b/2). The phase 2 portion of the HF10/ipilimumab trial has already reported an ORR of 49% after 24 weeks.

"It is interesting," Dr. Agarwala said, "that we can now combine two agents with different, nonoverlapping toxicities to produce a benefit." The intralesional therapies combined with ipilimumab or pembrolizumab have produced response rates in the 49% to 56% range with grade 3 or higher adverse events in the 24% to 32% range. Combining the available oncolytic therapies in clinical trials with the newer programmed cell death protein-1 (PD-1) inhibitors will potentially avoid the additive adverse effects seen when the PD-1s are combined with the anti-CTLA-4 inhibitor ipilimumab. "The important thing is that you have reasonably good response rates, but the adverse event rates stay the same as with the systemic therapies because adverse events with the intralesional therapies are few and local. So these combination therapies including the intralesional agents are likely to be the future and may be the best way to integrate them into practice."

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