Durable responses in metastatic melanoma, improved PFS in advanced colorectal cancer

Two presentations at the 2014 annual meeting of the American Society of Clinical Oncology in Chicago reported encouraging outcomes for patients with metastatic melanoma and colorectal cancer, reports **Neil Osterweil**.

High rate of durable responses to pembrolizumab in metastatic melanoma

Major finding In a phase 1 study of pembrolizumab in patients with advanced melanoma, 1-year overall survival was 69%, and 88% of patients who had a treatment response continued to have a response at 1 year. **Data source** An expansion cohort of 411 patients in a phase 1 trial. **Disclosures** The study was supported by Merck. Dr Ribas disclosed serving as a consultant/adviser to the company. Dr O'Day reported having no relevant financial disclosures.

The investigational targeted agent pembrolizumab induced durable treatment responses in a high percentage of patients with advanced metastatic melanoma, in a phase 1 study. Of 411 patients, 1-year overall survival was 69%, and 88% of patients who had a treatment response continued to have a response at 1 year, according to Dr Antoni Ribas, professor of medicine at the University of California, Los Angeles. "We used to say that melanoma had a median survival of 6-9 months – that wasn't that long ago. Then we said well, maybe it's getting closer to 12 months. Here, we have not reached the median overall survival," he said, noting that at 18 months of follow-up, overall survival is 62% and seems to be plateauing, but longer follow-up will be required to see how long the survival benefit can be maintained.

Dr Steven O'Day of the Beverly Hills Cancer Center in Los Angeles, who moderated the briefing but was not involved in the study said it was remarkable that almost 90% of the patients "are having durable responses with a toxicity profile that is almost unheard of in metastatic cancer." Grade 3 or 4 toxicities occurred in 12% of patients, making pembrolizumab "one of the most benign therapies that I have ever used in my clinic," he said.

New name, same PD-1 antibody

Pembrolizumab, formerly known as lambrolizumab or MK-3475, is a humanized monoclonal antibody targeted against the PD-1 immune system checkpoint. By binding to and inhibiting what Dr Ribas called the "do not kill me" signal, the antibody allows the immune system to recognize and mount a more potent T-cell-mediated defense against melanoma.

The Food and Drug Administration previously granted permbrolizumab a breakthrough therapy designation, and in May 2014 gave it a priority review designation under the agency's accelerated approval program. At the 2013 ASCO annual meeting, Dr Ribas and his colleagues reported a 41% overall response rate (ORR) in the first 135 patients with metastatic melanoma who were treated with the antibody in the phase 1 study KEYNOTE 001.

The data he presented at the 2014 ASCO meeting on the melanoma expansion cohort from that trial support the earlier findings from the study, showing an overall ORR of 34%, with responses seen in 44% of treatment-naive patients, 28% of those who had previously been treated with a different checkpoint inhibitor, ipilimumab, and 40% in patients who had received prior therapies other than ipilimumab.

The current study is an analysis of pooled data on 411 patients, 221 of whom had disease progression on ipilimumab and 190 of whom had never received ipilimumab. All of the patients had melanoma metastatic to the lungs or other organs.

The patients received pembrolizumab in one of three dosing schedules: 10 mg/kg every 2 weeks (57 patients) or every 3 weeks (192), or 2 mg/kg every 3 weeks (162). As noted, the overall survival rate at 1 year was 69% (74% for ipilimumab-naive patients, 65% for ipilimumab-treated patients), with the median overall survival not yet reached.

Dr O'Day said it was encouraging that prior exposure to ipilimumab did not seem to dramatically decrease the benefit from pembrolizumab. "This is critical to us understanding whether to combine or

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sequence these drugs, because there seems to be a lot of cross-resistance between ipilimumab and PD-1 [inhibition]," he said.

The most common adverse event of any grade was fatigue, occurring in 36% of patients, but only 2% of patients had grade 3 or 4 fatigue. Other common events were pruritus (24%), rash (20%), diarrhea (16%), arthralgia (16%), nausea (12%), and vitiligo (11%). The overall rate of any adverse events was 83%, but as noted before, only 12% of patients had a grade 3 or 4 adverse event. These events were manageable across all doses and in both ipilmumab-naive and experienced patients.

Pembrolizumab is currently being investigated in international, randomized controlled clinical trials, Dr Ribas noted.

Maintenance improves PFS in patients with metastatic colorectal cancer

Key clinical point Patients with metastatic colorectal cancer who have at least stable disease after induction chemotherapy may benefit from maintenance therapy with capecitabine and bevacizumab, though further studies on quality of life are needed. **Major finding** The median time to second progression (PFS2) for patients with metastatic colorectal cancer following induction and retreatment was a median of 8.5 months for observation, compared with 11.7 months for maintenance with capecitabine and bevacizumab. **Data source** Randomized controlled trial of 588 patients from 64 hospitals in the Netherlands. **Disclosures** CAIRO3 study was supported by the Dutch Cancer Foundation and by unrestricted scientific grants from Roche and Sanofi-Aventis. Dr Koopman disclosed ties with Roche/Genentech and Sanofi. Dr Saltz disclosed ties with Roche, Genentech, and Sanofi.

Patients with metastatic colorectal cancer who had at least stable disease after induction chemotherapy fared better on maintenance therapy with capecitabine and bevacizumab than on observation alone, according to investigators in a phase 3 trial conducted in the Netherlands. They found that patients who were randomly assigned to maintenance therapy after 6 cycles of induction therapy with capecitabine, oxaliplatin, and bevacizumab – the CAPOX-B regimen – had better progression-free survival (PFS) and time to progression (TTP) than did patients assigned to observation alone.

With maintenance therapy, "the quality of life is maintained and clinically not inferior to observation," said lead author Dr Miriam Koopman of the University Medical Center Utrecht Cancer Center, the Netherlands, who presented the final results of the CAIRO3 trial at the ASCO 2014 meeting.

The investigators enrolled 588 patients with metastatic colorectal cancer who had a response of stable-disease or better following 6 cycles of CAPOX-B to either observation or maintenance with oral capecitabine 625 mg/m^2 twice daily and intravenous bevacizumab 7.5 mg/kg on day 1 every 3 weeks. The patients were stratified by prior adjuvant therapy, serum lactate dehydrogenase, response to induction therapy, World Health Organization performance status, and institution.

In both arms, CAPOX-B reintroduction was planned at the time of first progression. The primary endpoint was progression-free survival following reintroduction of CAPOX-B (dubbed PFS2). For patients who for any reason did not receive CAPOX-B after the first PFS, PFS2 was considered to be equal to PFS1, Dr Koopman explained.

Of the 279 patients assigned to observation, 168 (60%) had CAPOX-B reintroduced. Of the remaining 111 patients (40%) in this arm, 7 had ongoing observation, 31 received no treatment, and 73 received treatment other than CAPOX-B. Of the 279 assigned to maintenance, 132 (47%) had CAPOX-B reintroduced. Of the remaining 147 patients (53%) in this arm, 13 continued on maintenance, 45 had no further treatment, 88 had other treatments, and 1 withdrew.

The median PFS from the time of randomization (not including induction) to first progression was 4.1 months in the observation arm and 8.5 months in the maintenance arm (stratified hazard ratio [HR], 0.43; $P \leq .0001$). The benefits of maintenance were also seen with the primary endpoint of PFS2, with a median of 8.5 months for observation, compared with 11.7 months for maintenance (stratified HR, 0.67; $P \leq .0001$). The median time to second progression was 11.1 months in patients randomized to observation, compared with 13. 9 months for those randomized to maintenance (stratified HR, 0.68; $P \leq .0001$).

There were no significant differences in median overall survival (OS) at 18.1 months for the observation arm and 21.6 months for the maintenance arm. There was a small but significant difference in quality of life scores between the groups (3.9-point difference on a 100-point scale, $P = .004$), but this difference was too small to be considered clinically meaningful, Dr Koopman said.

In preplanned subgroup analyses, the authors found evidence to suggest that patients with synchronous metastases who had resection of the primary tumor had a greater OS benefit from maintenance therapy than did patients with metachronous disease, and that those who had complete or partial response as best response to induction therapy seemed to do better than did patients with stable disease after induction. "We do not have a clear-cut explanation for this subgroup analysis," Dr Koopman said.

The investigators hypothesize that the differences between patients with synchronous and metachronous dis-

ease could have been the result of differences in sensitivity to systemic treatment, the prognostic role of resection of the primary tumor, dependence of the angiogenic environment in metastases on the resection status of the primary tumor, or co-option of the local vasculature by the tumor, leading to decreased sensitivity of metachronous metastases to bevacizumab.

The invited discussant, Dr Leonard Saltz, chief of the gastrointestinal oncology service at Memorial Sloan-Kettering Cancer Center, New York, said CAIRO3 results suggest that "treatment breaks for all patients at 4 months may be too many breaks, and too early. Responding patients likely benefit from treatment at least until maximal response, and that's an aspect to consider in terms of figuring out how to utilize a treatment strategy. And treatment-break strategies will need to be individualized, but should not be abandoned."

He also cautioned that the quality of life results reported by the investigators may not accurately reflect how patients feel. "In terms of the quality of life, What we have to conclude is that as our instruments can measure it we do not see a detriment in quality of life. But intuitively, we can conjecture that being on chemotherapy has some negative aspects – just ask any of our patients. So the idea that there is no detriment in quality of life when we're comparing chemotherapy with nonchemotherapy suggests that we need more sensitive and specific tools for the question," he said.