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Dermatologists in Cancer Care®

Ipilimumab Approved in Europe for Pediatric Melanoma

JASON HARRIS

IPILIMUMAB (YERVOY) has been approved by the European Commission for the treatment of patients aged 12 and older with unresectable or metastatic melanoma.

The expanded indication for ipilimumab is based on data across 2 trials in which objective responses were observed in 2 of 17 patients aged ≥12 years with advanced melanoma. The responses included 1 partial response that lasted for more than 16 months.

The European Medicines Agency's Committee for Medicinal Products for Human Use previously recommended approval based on these results. Bristol-Myers Squibb (BMS), the manufacturer of ipilimumab, noted in a press release that the CTLA-4 inhibitor is the first immunotherapy agent approved in Europe for the treatment of pediatric melanoma.

"While pediatric melanoma is rare, more effective therapeutic approaches

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ALSO IN THIS ISSUE

Expert Highlights Advances in Cutaneous T-Cell Lymphoma

ANGELICA WELCH

CUTANEOUS T-CELL LYMPHOMA (CTCL) is known to be a rare malignancy, with approximately 3000 diagnoses per year. Historically, progress in developing therapies for this form of non-Hodgkin lymphoma (NHL) has been slow, but 2017 brought about the FDA approval of brentuximab vedotin (Adcetris), giving hope to this poor-prognosis population.

Brentuximab vedotin was approved in November 2017 as a treatment for patients with CTCL who have received prior systemic therapy, specifically for patients with primary cutaneous anaplastic large cell lymphoma and CD30-expressing mycosis fungoides—the most common subtypes of CTCL.

The approval was based on findings from the phase III ALCANZA trial, in which brentuximab vedotin induced a response lasting at least 4 months in 56.3% of patients. This is in comparison with the 12.5% response rate seen with the comparator of physician's choice.1

The anti-CCR4 monoclonal antibody mogamulizumab was granted a priority review designation to a biologics license application for the treatment of patients with CTCL who have received at least 1 prior systemic therapy. This application was based on data of the phase III MAVORIC study, which was presented at the 2017 ASH Annual Meeting. Data from this study showed that mogamulizumab reduced the risk of progression or death by 47% compared with vorinostat (Zolinza) in pretreated patients.2

The investigator-assessed median progression-free survival was 7.7 months

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are needed for this patient population," Peter Mohr, MD, chief physician for the Department of Dermatology at Elbe Klinikum Buxtehude, head of Skin Cancer Center Buxtehude, and a member of the research team, said in a press release. "This approval of Yervoy in the EU expands physicians' options for pediatric patients with advanced melanoma to include an immuno-oncology treatment."

The dose-finding trial considered for the approval included 33 relapsed/refractory patients with solid tumors aged 2 to 21 years. The median age was 13 years, and 20 of the patients were at least 12 years old. Patients received ipilimumab intravenously at doses of 1, 3, 5, and 10 mg/kg over 90 minutes every 3 weeks for 4 doses, and then every 12 weeks thereafter until progression or discontinuation.

The second study was an open-label, single-arm trial that included 12 patients with stage III or IV melanoma who were either previously treated or treatment-naïve. Patient ages ranged from 12 to 16 years. Intravenous ipilimumab was administered at 3 mg/kg (n = 4) or 10 mg/kg (n = 8) over 90 minutes every 3 weeks for 4 doses.

When BMS applied for European approval, the company reported that the safety profile of ipilimumab in children and adolescent patients was comparable to the safety profile in adult patients. BMS also reported in a press release that body weight normalized clearance associated with ipilimumab was comparable between adult and pediatric patients based on a population pharmacokinetic analysis using available pooled data from 565 patients from 4 phase II adult studies (N = 521) and 2 pediatric studies (N = 44).

The FDA approved ipilimumab for pediatric melanoma in July 2017, based on the same data. The approved ipilimumab dose for pediatric melanoma patients is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses.

The recombinant, human monoclonal antibody ipilimumab binds to CTLA-4, a negative regulator of T-cell activity, and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Research has demonstrated that blocking CTLA-4 enhances T-cell activation and proliferation, including tumor infiltrating T-effector cells. An additional effect of CTLA-4 inhibition is reducing T-regulatory cell function, which potentially enhances T-cell responsiveness, including an immune response against the tumor.

Ipilimumab is approved in more than 50 countries for the treatment of patients with unresectable or metastatic melanoma. ■

European Commission Approves Bristol-Myers Squibb's Yervoy (ipilimumab) for Treatment of Pediatric Patients 12 Years and Older with Unresectable or Metastatic Melanoma. Bristol-Myers Squibb. Published online and accessed January 22, 2018. http://bit.ly/2DVq5K5.

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(95% CI, 5.7-10.3) in the mogamulizumab arm compared with 3.1 months (95% CI, 2.9-4.1) in the vorinostat arm (HR, 0.53; 95% CI, 0.41-0.69; P <.0001), and the overall response rate was 28% with mogamulizumab versus 4.8% with vorinostat (P <.0001).

Wei Z. Ai, MD, an associate clinical professor and hematologist at the University of California, San Francisco (UCSF) Medical Center, gave a presentation on recent developments in T-cell lymphoma during the 2017 OncLive® State of the Science SummitTM on Hematologic Malignancies. In an interview during the meeting, Ai discussed the impact of brentuximab vedotin, as well as the potential with mogamulizumab in CTCL.

OncLive: What recent data have we seen in this space?

AI: In systemic T-cell lymphoma, there were no practice-changing trials presented [at the 2017 ASH Annual Meeting]. However, we are hoping for results from some exciting phase I/II trials in 2018. Phase III trials based on those trials are ongoing, and may be practice changing.

As for CTCL, 2017 was a very exciting year. In the history of this disease, there have only been about 3 randomized studies as it is such a rare disease with only 3000 new cases a year. The first one was in the 1980s, which showed sequential single-agent therapy is as good as combination agents. This is why we treat these patients very differently than the systemic T-cell lymphoma where we almost always use combinations. Two phase III studies were presented at the 2017 ASH Annual Meeting, one of which contributed to the approval of brentuximab vedotin in CTCL about 1 month prior to its presentation at the meeting. The third phase III study of mogamulizumab for CTCL will hopefully lead to an approval very soon; the FDA has granted it a breakthrough designation.

How has the approval of brentuximab vedotin impacted clinical practice thus far?

In my experience, this is a highly active drug, particularly in the advanced-stage disease. CTCL is a very heterogeneous disease; 75% present with early-stage disease and only 25% present with advanced-stage disease. Therefore, as oncologists, we are going to see the patients who are much sicker than the average patients with CTCL.

For early-stage disease, patients receive skin-directed therapy that is often managed by a dermatologist. For advanced-stage disease, patients require system therapy. However, the way that systemic therapy is given to these patients is very different than in systemic T-cell lymphomas. At UCSF, we are very fortunate to have a multidisciplinary clinic where we have dermatologists and radiation oncologists.

Advanced-staged CTCL is a life-threatening disease; the median survival is 2 to 5 years. People don't realize that because

it is so rare. I see brentuximab vedotin in the scenario where this disease is life threatening—in tumor-stage and widespread disease—and I've seen patients with visceral disease respond nicely to this drug. If you look at the randomized trial of brentuximab vedotin and physician's choice very carefully, you can see the dramatic superiority of brentuximab, particularly in the advanced stage of disease.

Can you speak to the data that we have seen with mogamulizumab?

It is an active drug that is pretty well tolerated, particular in Sézary syndrome, as it clears the blood very quickly. Sézary syndrome is a leukemic form of CTCL which, from our historical data, has a median survival of about 5 years. Patients [with Sézary syndrome] quickly grow resistant to chemotherapy.

We have biologic therapies for that disease, but there are a proportion of patients who will progress on that and require a type of chemotherapy. Those patients acquire resistance quite quickly, unfortunately. Therefore, mogamulizumab is very active in this setting and we will use it a lot.

What could the potential impact of mogamulizumab be if approved by the FDA?

When patients with CTCL are in the advanced stage of their disease and require systemic therapy, there is the possibility for acquired resistance. This drug is so well tolerated; it is really going to change the management of advanced-stage disease. The most use will probably be in Sézary syndrome, as it is an advanced stage of disease and is life threatening. The most commonly used therapy at the moment is extracorporeal photopheresis, which is only available in a few academic centers.

Is there anything else you would like to add?

CTCL is an extremely rare form of T-cell lymphoma, and [therapeutic] options would very much benefit the field. We get a lot of referrals from the community, and we feel that the co-management of this population is very important. We would like to continue to do that and, hopefully, we can make the patients' lives better. ■

References

1. Kim YH, Whittaker S, Horwitz SM, et al. Brentuximab vedotin demonstrates significantly superior clinical outcomes in patients with CD30-expressing cutaneous T cell lymphoma versus physician's choice (methotrexate or bexarotene): the phase 3 ALCANZA study. Presented at: 58th Annual ASH Annual Meeting; December 3-6, 2016; San Diego, CA. Abstract 182.
2. Kim YH, MD, Bagot M, Pinter-Brown L et al. Anti-CCR4 monoclonal antibody, mogamulizumab, demonstrates significant improvement in PFS compared to vorinostat in patients with previously treated cutaneous T-Cell lymphoma (CTCL): results from the phase III MAVORIC study. In: Proceedings from the 2017 ASH Annual Meeting; December 9-12, 2017; Atlanta, Georgia. Abstract 817.

Blueprint for Tackling Toxicities From Checkpoint Blockade Agents Is Introduced

ANDREW D. SMITH

IN RECOGNITION OF the variety of immune-related adverse events (irAEs) that patients receiving checkpoint blockade immunotherapy may experience, the National Comprehensive Cancer Network (NCCN) has developed its first set of recommendations to help clinicians manage toxicities.[1] The guidelines provide step-by-step flowcharts for recognizing and responding to 25 toxicities and offer advice on educating patients about irAEs.

Obtaining optimal results from these therapies requires continual vigilance by physicians and patients, said John A. Thompson, MD, codirector of the Seattle Cancer Care Alliance Melanoma Clinic in Washington. He discussed the new guidelines in a presentation at the 2018 NCCN Annual Conference.[2]

"Checkpoint inhibitors haven't been around long enough for the large variety of potential toxicities to become well known, and there is a temptation to think that the absence of immediate toxicities precludes problems down the road," Thompson said in an interview with *OncologyLive*®.

Thompson and his colleagues in Seattle perform physical examinations and blood tests prior to every immunotherapy injection. The NCCN and other medical societies already recommended such procedures, but Thompson warns that they are not sufficient. Providers must also teach patients about the importance of looking for signs of AEs and self-reporting potential problems.

"Education is essential," Thompson said. "Immunotherapy can affect so many different organ systems. Doctors and nurses need to educate patients to detect the symptoms that don't show up on panels or in exams."

Patients often hesitate to report all but the most serious toxicities—even those they recognize as toxicities—because they worry that their doctors will discontinue an effective treatment and allow their tumors to rebound. This is a natural fear, Thompson said, but most clinical trial results suggest that it's misplaced.

"If you look at the trial evidence we have on checkpoint inhibitors, patients who discontinue treatment due to adverse effects fare, statistically speaking, as well as patients who do not discontinue therapy due to [adverse] effects," he said.

That seems counterintuitive to most patients, whose ideas about cancer treatments have been formed by traditional cytotoxic agents that attack tumors directly and stop working when discontinued. There are, however, techniques of explaining the mechanism of immunotherapies.

"Patients are familiar with the idea that the immune system will keep on attacking any foreign cells [cancers] that it learns to recognize because most are familiar with vaccines," Thompson said. "Once we've convinced patients that immunotherapy seems to have the same durable effect in cancer treatment, then patients tend to buy in and report potential toxicities as they arise."

Toxicity Profiles Differ

Currently, there are 6 FDA-approved immune checkpoint inhibitors: ipilimumab (Yervoy; anti–CTLA-4), nivolumab (Opdivo; anti–PD-1), pembrolizumab (Keytruda; anti–PD-1), atezolizumab (Tecentriq; anti–PD-L1), avelumab (Bavencio; anti–PD-L1), and durvalumab (Imfinzi; anti–PD-L1).

The frequency of toxicities varies among regimens. For example, findings from clinical trials of CTLA-4–targeting antibodies for grade 1 or 2 toxicities indicate that more than 35% of patients experience dermatologic AEs and more than 25% have gastrointestinal (GI) toxicities.2 By comparison, results for PD-1 inhibitors demonstrate irAEs of grade 1 or 2 of approximately 20% for dermatologic toxicities and less than 15% for GI events. Those numbers are lower for PD-L1 inhibitors. The rates of grade 3 to 5 irAEs are highest for those who receive CTLA-4 inhibitors, with GI toxicities topping 10%.

Although numbers like these may seem manageable, a trend toward combination regimens in immunotherapy has resulted in increased toxicities. In the CheckMate-067 trial, 59% of patients treated with a combination of nivolumab and ipilimumab experienced grade 3 or 4 toxicities compared with 21% who received nivolumab and 28% who took ipilimumab.[3]

The new NCCN guidelines describe management of irAEs in these areas:

- Dermatologic: maculopapular rash, pruritis, blistering disorder
- GI: diarrhea, colitis
- Hepatic: transaminitis
- Pancreatic: elevation in amylase and/or lipase, acute pancreatitis
- Endocrine: hyperglycemia, diabetes mellitus, thyroid disease, adrenal and/or pituitary gland failure, hypophysitis
- Pulmonary: pneumonitis
- Renal: elevated serum creatinine, acute renal failure
- Ocular: vision changes
- Nervous system: myasthenia gravis, Guillain-Barré syndrome, peripheral neuropathy, aseptic meningitis, encephalitis, transverse myelitis
- Cardiovascular: myocarditis, pericarditis, arrhythmias, impaired ventricular function
- Musculoskeletal: inflammatory arthritis, myalgias, myositis
- Infusion-related reactions

Strategies for Managing Toxicities

The recommendations for how clinicians should manage toxicities vary with the type and severity of the observed irAE, but many responses share elements. Most immunotherapy-related toxicities stem from an overexcited immune system attacking healthy tissue, so management usually involves medications such as steroids that dampen immune response.

For example, if a patient presents with what appears to be a maculopapular rash, the guidelines advise physicians to perform a full-body skin examination (including mucosa), assess the patient's prior history (if any) of inflammatory dermatological disease, and consider performing a biopsy if there are any unusual features. The recommended treatment for mild cases (grade 1) calls for continuing immunotherapy while starting the patient on an oral antihistamine, a topical emollient, and moderately potent topical steroids. For moderate maculopapular rash (grade 2), the response would entail consideration of an immunotherapy hold while starting the patient on topical steroids and/or prednisone at 0.5 to 1.0 mg/kg daily, an oral antihistamine, and a topical emollient. For severe cases (grade 3 or 4), the recommendations advise holding immunotherapy while starting the patient on a topical steroid and prednisone as well as consulting immediately with a dermatologist.

The step-by-step responses reflect the currently available data on the treatment of immunotherapy- related toxicity, but the relatively recent introduction of such treatments means there are not as much data as the NCCN guideline panel would like.

"At this point, the guidelines are much more a reflection of expert opinion rather than a collection of proven facts," Thompson said. "These guidelines will almost certainly evolve and improve as we get more hard evidence from new trials and new analysis of real-world outcomes, but we are already at the point where we're confident that systematic implementation of these recommendations will improve outcomes for most patients." ■

References

1. National Comprehensive Cancer Network. Management of immunotherapy-related toxicities, version 1.2018. NCCN website. nccn.org/professionals/physician_gls/default.aspx#age. Published February 14, 2018. Accessed May 2, 2018.
2. Thomason JA. New NCCN guidelines: recognition and management of immune checkpoint inhibitor-related toxicity. Presented at: NCCN 23rd Annual Conference; March 22-24, 2018; Orlando, FL.
3. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* 2017;377(14):1345-1356. doi: 10.1056/NEJMoa1709684.

FDA Approves Adjuvant Dabrafenib/Trametinib for BRAF+ Melanoma

JASON M. BRODERICK

THE FDA HAS APPROVED the combination of dabrafenib (Tafinlar) and trametinib (Mekinist) for the adjuvant treatment of patients with *BRAF* V600E– or V600K–positive stage III melanoma following complete resection.

The approval is based on findings from the phase III COMBI-AD study, in which adjuvant treatment with dabrafenib and trametinib reduced the risk of relapse or death by 53% compared with placebo for patients with BRAF-mutant stage III melanoma.[1,2] After a median follow-up of 2.8 years, the 3-year relapse-free survival (RFS) rate with dabrafenib and trametinib was 58% compared with 39% for placebo (HR, 0.47; 95% CI, 0.39-0.58; *P* <.001).

"The purpose of adjuvant therapy is to improve recurrence-free and overall survival in our patients with melanoma. Adjuvant therapy options are crucial today because more than half of patients have a recurrence after surgery," John M. Kirkwood, MD, Usher Professor of Medicine, Director of Melanoma and Skin Cancer, University of Pittsburgh, said in a statement.

"We developed the first adjuvant therapy approved by the FDA 22 years ago, and now we have the first effective oral targeted therapy combination that prevents relapse among patients with *BRAF*-mutated melanoma that has spread to lymph nodes," added Kirkwood.

The COMBI-AD study randomized 870 patients with *BRAF*V600E/K stage III melanoma to receive dabrafenib plus trametinib (n = 438) or placebo (n = 432). All patients were within 12 weeks of complete surgical resection and had stage IIIa (18%), IIIb (41%), and IIIc (40%) disease. Dabrafenib was given at 150 mg twice daily with trametinib at 2 mg once daily for 12 months. The salvage therapies received following the study were similar in each arm, and, in some cases, included a rechallenge with BRAF/MEK inhibition.

The baseline characteristics were similar between groups. In the combination arm, the median age of patients was 50 years and 91% of tumors had the *BRAF* V600E mutation with the remainder having the V600K alteration. Most patients (92%) had an ECOG performance status of 0. Twelve percent of patients in the combination group had in-transit metastases versus 8% with the placebo. Seventeen percent of patients had ≥4 positive lymph nodes, with the remainder having <4.

The median RFS was not reached with the combination versus 16.6 months for placebo. RFS was improved with dabrafenib/trametinib across all subgroups. Hazard ratios across all subgroups ranged from 0.33 to 0.55 in favor of dabrafenib and trametinib versus placebo.

Early data for overall survival (OS) showed that 86% of patients in the combination arm were alive at 3 years versus 77% with placebo (HR, 0.57; 95% CI, 0.42-0.79; *P* = .0006). At the interim analysis, the OS advantage was not yet deemed statistically significant, according to predefined criteria that required a *P* value of .000019.

The 1-year OS rates were 97% versus 94% and the 2-year OS rates were 91% and 83% for the combination and placebo groups, respectively. The 1-year RFS rates were 88% versus 56% and the 2-year rates were 67% versus 44% for dabrafenib and trametinib versus placebo, respectively. The most common locations of recurrence, for the combination and placebo, respectively, were locoregional (12% vs 25%), distant (22% vs 29%), and both local and distant (2% vs 2%).

The risk of distant metastases or death was reduced by 49% with the combination versus placebo (HR, 0.51; 95% CI, 0.40-0.65). Additionally, there was a 53% improvement in freedom from recurrence with the combination (HR, 0.47; 95% CI, 0.39-0.57).

Adverse events (AEs) were experienced by 97% of those treated with dabrafenib and trametinib versus 88% with placebo. The rates of grade 3/4 AEs were 41% and 14% for the combination and placebo, respectively. Overall, AEs led to discontinuation for 26% of those in the combination arm versus 3% with placebo. The most common all-grade AEs, which were mostly grade 1/2, with the combination were pyrexia (63%), fatigue (47%), and nausea (40%). There were no fatal adverse events with the combination of dabrafenib and trametinib.

"Prevention and early detection are important safeguards from melanoma, but that's only half the picture. Melanoma is an aggressive cancer that can recur, particularly when it shows certain warning signs like increased depth, ulceration, or spread to the lymph nodes," Sancy Leachman, MD, PhD, Chair of the Department of Dermatology at OHSU School of Medicine, said in a statement.

"With proven treatment options for these patients, it is important for dermatologists to assure that appropriate patients are offered adjuvant treatment options—a 'watch and wait' approach is no longer the standard of care. Collaborating with a multidisciplinary care team of surgeons, pathologists and oncologists, and determining the right treatment based on the patient's individual circumstances and mutational status is crucial to our patients' care plans," added Leachman.

The FDA initially granted an accelerated approval to the combination of dabrafenib and trametinib for patients with *BRAF*-mutant metastatic melanoma in January 2014. The combination received a full approval in November 2015, and is now also indicated for the treatment of patients with *BRAF*-mutant non–small cell lung cancer. ■

References

1. Hauschild A, Santinami M, Long GV, et al. COMBI-AD: Adjuvant dabrafenib (D) plus trametinib (T) for resected stage III BRAF V600E/K–mutant melanoma. Presented at: 2017 ESMO Congress; Madrid, Spain; September 8-12, 2017. Abstract LBA6_PR.
2. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *N Engl J Med*. Published online September 10, 2017. DOI: 10.1056/NEJMoa1708539.

Novel Combinations Mark Next Step for Melanoma

DANIELLE BUCCO

IMMUNOTHERAPY HAS LED a transformation for melanoma care but combinations of anti–PD-1 and CTLA-4 agents are toxic and biomarkers are not available to help personalized treatment, calling for further research into less toxic and more effective options, according to a presentation by Caroline Robert, MD, PhD, at the 2017 World Congress of Melanoma.

At this point, the only approved immunotherapy combination remains the PD-1 inhibitor nivolumab (Opdivo) and the CTLA-4 inhibitor ipilimumab (Yervoy). However, research into combination approaches is now focusing on triplets of anti–PD-1 therapies and new checkpoints, such as IDO. Additionally, ongoing research continues to search of a biomarker of response for immunotherapy in melanoma.

"Biomarker research needs to continue to develop to provide the best care for patients," explained Robert, head of the Dermatology Unit at the Institut Gustave Roussy, during her talk at the congress. "Today, there is a lot of interesting data but nothing that we can use for our patients on an individual basis."

When combined nivolumab and ipilimumab was associated with a 12% reduction in the risk of death versus nivolumab monotherapy for patients with treatment-naïve advanced melanoma, according to results from the phase III CheckMate-067 trial.[1] The median overall survival (OS) was not reached with nivolumab/ipilimumab compared with 20 months with ipilimumab alone.

These modest benefits came at the cost of increased adverse events (AEs), Robert noted. Overall, 58.5% of patients experienced treatment-related grade 3/4 AE with the combination compared with 20.8% and 27.7% for nivolumab and ipilimumab alone, respectively.

"There is a slight increase in the progression-free survival and overall survival after longer follow-up," said Robert. "However, it is difficult to give this combination without knowing who will benefit due to the high rate of grade 3/5 toxicities."

In the CheckMate 067 study, of the 314 patients treated with ipilimumab and nivolumab, 176 patients discontinued due to AEs at any time. According to Robert, pooled data from CheckMate 067 and CheckMate 069, which also explored the combination, showed that PFS and OS was not significantly different between the patients who discontinued for adverse events during the induction period and those who did not discontinue, leading to the potential to customize treatment.

"Among physicians we have very different ideas of using this combination for patients who do not have a high burden of disease," said Robert. "We are looking forward to having more indications of when to use this drug combination that gives rise to a higher response rate and longer PFS."

Some of the ongoing research of new combinations, Robert explained, includes the exploration of the PD-L1 inhibitor atezolizumab (Tecentriq), which is being explored with cobimetinib (Cotellic) and vemurafenib (Zelboraf) in patients with unresectable *BRAF*-mutant melanoma. Early phase Ib results showed that the overall response rate (ORR) for the triplet combination was 81.6%, with a complete response (CR) of 18.4% after a median follow-up of 10 months. Overall, 41% of patients experienced grade 3/5 AEs.[2]

"This phase I study is attacking more difficult patients who had been treated previously with anti–PD-1 and who have developed resistance," explained Robert.

PD-1 plus an IDO inhibitor has proved to be a synergistic approach, according to results from the phase I KEYNOTE-037 trial, Robert noted. The PD-1 inhibitor pembrolizumab (Keytruda) in combination with the IDO inhibitor epacadostat demonstrated an ORR of 56% with a CR of 13%. The rate of grade 3/5 AEs was much lower with this combination, at just 20%.[3]

Additionally, the 2015 approval of T-VEC (talimogene laherparepvec, Imlygic) was an important advance in the treatment landscape for patients with melanoma, Robert noted. This agent was associated with few AEs, representing an ideal candidate for combinations. To this end, the preliminary findings of the phase I MASTERKEY-265 investigating pembrolizumab plus T-VEC showed an ORR of 62% with a CR rate of 33%. The median PFS for this study has not yet been reached.[4]

The KEYNOTE-034 continues to assess this combination (NCT02263508) along with a phase III expansion cohort of the MASTERKEY-265 trial (NCT02263508). ■

Reference

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Overall survival results from a phase III trial of nivolumab combined with ipilimumab in treatment-naïve patients with advanced melanoma (CheckMate-067): press conference. In: Proceedings from the 2017 American Association for Cancer Research Annual Meeting; April 2 to 5, 2017; Washington DC. Abstract CT075.
2. Sullivan RJ, Hamid O, Gonzalez R, et al. Safety and clinical activity of atezolizumab + cobimetinib + vemurafenib in BRAFV600-mutant metastatic melanoma. In: Proceedings from the 2016 Society for Melanoma Research Annual Meeting, November 6-9, 2016, Boston, MA.
3. Hamid O, Gajewski TF, Frankel AE, et al. Epacadostat plus pembrolizumab in patients with advanced melanoma: Phase 1 and 2 efficacy and safety results from ECHO-202/KEYNOTE-037. n: Proceedings from the 2017 ESMO Congress; September 8-12, 2017; Madrid, Spain. Abstract 1214O.
4. Ribas A, Dummer R, Puzanov I, et al. Oncolytic Virotherapy Promotes Intramoral T Cell Infiltration and Improved Anti-PD-1 Immunotherapy. *Cell.* 2017. doi: http://dx.doi.org/10.1016/j.cell.2017.08.027

Brentuximab Vedotin Approved in Europe for CTCL

JASON HARRIS

BRENTUXIMAB VEDOTIN (Adcetris) has been approved by the European Commission for the treatment of patients with CD30-positive cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

The approval of the antibody-drug conjugate is based on results from the phase III ALCANZA trial, in which brentuximab vedotin induced responses lasting at least 4 months in 56.3% of patients compared with 12.5% in patients receiving physician's choice of standard therapies (P <.0001).[1,2]

The approval follows the recommendation of the European Medicines Agency's Committee for Medicinal Products for Human Use. Takeda Pharmaceuticals issued a press release announcing that brentuximab is now available in the 28 member states of the European Union, Norway, Liechtenstein and Iceland.

"CTCL is a subtype of non-Hodgkin lymphoma that primarily involves the skin; it typically presents with red, scaly patches or thickened plaques of skin that often mimics eczema or psoriasis and can have a substantial impact on patients' self-esteem. There are few approved CTCL treatment options with only limited efficacy, creating a significant unmet need for these patients," Julia Scarisbrick, MD, Department of Dermatology, University Hospital Birmingham, said in a statement.

"The approval of Adcetris in this setting brings a much needed, effective treatment option to patients living with CTCL and I am looking forward to be able to offer this treatment to CD30-positive patients who have received one prior systemic therapy," added Scarisbrick, who was a member of the research team investigating brentuximab for this indication.

The international, open-label ALCANZA trial included 131 patients with CD30-expressing (≥10% of infiltrate by central review) mycosis fungoides (MF) or primary

cutaneous anaplastic large cell lymphoma (pcALCL), the 2 most common subtypes of CTCL. The intent-to-treat population comprised 128 patients, 97 with MF and 31 with pcALCL. Three patients were excluded because their level of CD30 expression was too low.

Patients with MF had to have received at least 1 prior systemic therapy and those with pcALCL were required to have prior radiation therapy or at least 1 systemic therapy.

Patients were randomly assigned to brentuximab vedotin (n = 64) or physician's choice of the standard treatments methotrexate or bexarotene (n = 64). Brentuximab vedotin was administered intravenously at 1.8 mg/kg once every 3 weeks for up to 48 weeks (16 cycles). Methotrexate was dosed at 5 to 50 mg once weekly and bexarotene was administered orally at 300 mg/m^2 once daily. Treatments were administered until disease progression or unacceptable toxicity.

The objective response rate (ORR) was 67% versus 20% (P<.0001), with complete response (CR) rates of 16% versus 2% (P = .0046), in the brentuximab vedotin and control arms, respectively. The median progression-free survival (PFS) was 16.7 months with brentuximab vedotin versus 3.5 months with physician's choice (hazard ratio, 0.270; 95% CI, 0.169-0.430; P<.0001).

Symptom reduction, as measured by Skindex-29, was significantly better with brentuximab vedotin versus physician's choice (-27.96 vs -8.62; P <.0001).

ORR was 50% Among patients with MF who received brentuximab vedotin versus 10% with physician's choice. The ORR and CR rates were 65% versus 16% and 10% versus 0, respectively. In patients with pcALCL who received brentuximab vedotin, the ORR was 75% versus 20% with physician's choice. The ORR and CR rates were 75% versus 33% and 31% versus 7%, respectively.

In patients with pcALCL in the skin only who received brentuximab vedotin, the ORR4 was 89% versus 27% with physician's choice. The ORR and CR rates were 89% versus 45% and 44% versus 9%, respectively. Among pcALCL patients with extracutaneous disease who received brentuximab vedotin, the ORR4 was 57% versus 0 with physician's choice. The ORR and CR rates were 57% versus 0 and 14% versus 0, respectively.

Patients assigned to brentuximab vedotin were less likely to experience grade ≥3 adverse events (AEs), 41% versus 47%. Patients in both arms were equally likely to experience serious AEs (29%).

Two-thirds of patients in the brentuximab vedotin arm experienced peripheral neuropathy (9%, grade 3) versus 6% in the control arm. Other common all-grade AEs included nausea (36% vs 13%), diarrhea (29% vs 6%), fatigue (29% vs 27%), vomiting (17% vs 5%), alopecia (15% vs 3%), pruritus (17% vs 13%), pyrexia (17% vs 18%), decreased appetite (15% vs 5%), and hypertriglyceridemia (2% vs 18%).

AE-related discontinuations occurred in 24% of patients in the brentuximab vedotin arm and 8% of patients in the physician's choice arm. There were 4 patient deaths in the brentuximab vedotin arm, 3 of which were considered unrelated to treatment. No patients died on-study in the control arm. ■

References

1. Kim YH, Whittaker S, Horwitz SM, et al. Brentuximab vedotin demonstrates significantly superior clinical outcomes in patients with CD30-expressing cutaneous T cell lymphoma versus physician's choice (methotrexate or bexarotene): the phase 3 ALCANZA study. Presented at: 58th Annual ASH Annual Meeting; December 3-6, 2016; San Diego, CA. Abstract 182.
2. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial [published online June 6, 2017]. *Lancet*. 2017 doi: 10.1016/S0140-6736(17)31266-7.