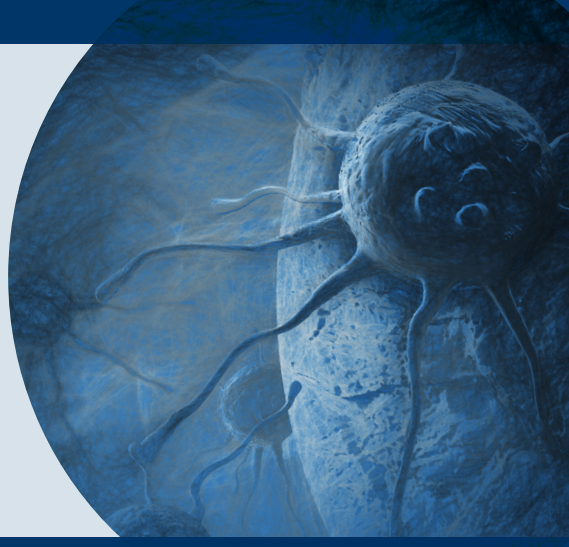
RapidReviews in Oncology®

JULY 2018



NICE Recommends Midostaurin for FLT3+ AML

JASON M. BRODERICK

The National Institute for Health and Care Excellence (NICE) has authorized the use of midostaurin (Rydapt) in combination with standard chemotherapy for the treatment of patients with newly diagnosed *FLT3*-positive acute myeloid leukemia (AML), according to Novartis, the manufacturer of the multikinase inhibitor.

Midostaurin is specifically recommended in the United Kingdom for use in combination with daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy. For patients who achieve a complete response after this initial treatment, NICE also recommended single-agent midostaurin maintenance therapy.

The recommendation is based on the phase III RATIFY trial, in which the addition of midostaurin to standard chemotherapy reduced the risk of death by 22% compared with chemotherapy alone in patients with AML who harbored a *FLT3* mutation.

"As we've come to understand more about the different mutations associated with AML and their effect on prognosis, such as the *FLT3* mutation, it has become essential that clinicians use genetic testing to guide treatment decisions" said Professor Paresh Vyas, MD, PhD, professor of Haematology and Honorary Consultant Haematologist and Group Leader MRC Molecular Haematology Unit, University of Oxford, said in a statement.

"The overall survival advantage that midostaurin plus chemotherapy demonstrated in clinical trials represents a significant advancement for newly diagnosed AML patients with the *FLT3* mutation and helps to establish a new standard of care for these patients with a worse prognosis."

In the phase III RATIFY trial, also known as CALGB 10603, 717 patients with newly diagnosed *FLT3*-mutant AML were randomized to standard induction and consolidation chemotherapy plus midostaurin (n = 360) or placebo (n = 357). Hydroxyurea was allowed for up to 5 days prior to beginning therapy, while *FLT3* test results were obtained.

During induction therapy, daunorubicin was given at 60 mg/m^2 on days 1 to 3 with cytarabine at 200 mg/m^2 on days 1 to 7. Oral midostaurin was administered at 50 mg twice daily on days 8 to 22. If patients achieved a complete remission, consolidation therapy was given with cytarabine at 3 g/m^2 for 3 hours every 12 hours on days 1, 3, and 5 plus either placebo or midostaurin. After 4 cycles of consolidation, maintenance therapy with either midostaurin or placebo was administered for up to 1 year.

The 2 treatment arms were well balanced for age (median, 48 years), race, *FLT3* subtype, and baseline

ALSO IN THIS ISSUE...

complete blood counts. There were more males in the midostaurin arm versus placebo (48.2% vs 40.6%). The primary endpoint of the study was OS, with secondary outcome measures such as event-free survival (EFS) and safety.

In uncensored data, median OS was 74.7 months with midostaurin versus 25.6 months with chemotherapy alone (HR, 0.78; 95% CI, 0.63-0.95; $P = .016$). The 5-year OS rate for patients in the midostaurin arm was 50.9% versus 43.9% with placebo. Median EFS in the midostaurin arm was 8.2 versus 3.0 months with placebo (HR, 0.78; 95% CI, 0.66-0.93; $P = .004$). The 5-year EFS rate with midostaurin was 27.5% versus 19.3% with placebo.

Median OS seen in the midostaurin arm was well beyond investigator expectations of 20.9 months. A possible explanation for this could be the rates of stem cell transplantation or incomplete data. The confidence intervals for OS were not fully attained for the midostaurin arm (95% CI, 31.7 – not attained).

Overall, 57% of patients received an allogeneic stem cell transplant at any time during the trial, more commonly in the midostaurin arm versus placebo (58% vs 54%). Median time to transplant was 5.0 months with midostaurin and 4.5 months with placebo. Twenty-five percent of transplants occurred during the first complete remission. Overall, 59% of patients in the midostaurin arm and 54% in the placebo group experienced a complete remission ($P = .18$).

Median OS data were not obtained in the censored population. Overall, the 4-year censored OS rate with midostaurin was 63.8% versus 55.7% for placebo (HR, 0.75; $P = .04$). In those censored for transplant, median EFS with midostaurin was 8.2 versus 3.0 months with placebo (HR, 0.84; $P = .025$).

Grade ≥3 AEs were similar between the midostaurin and placebo arms. Overall, 37 grade 5 AEs occurred in the study, which were similar between the 2 arms, at 5.3% with midostaurin versus 5.0% with placebo. A statistically significant difference was not observed for treatment-related grade 5 AEs ($P = .82$). ■

FDA Approves Tisagenlecleucel for Large B-Cell Lymphoma

JASON M. BRODERICK

The FDA has approved tisagenlecleucel (Kymriah) for use in adult patients with relapsed/refractory large B-cell lymphoma—including diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma—after 2 or more lines of systemic therapy.

The approval is based on the phase II JULIET study, in which the CD19-directed chimeric antigen receptor (CAR) T-cell therapy reached an overall response rate (ORR) of 50% (95% CI, 38%-62%) in adult patients with relapsed/refractory DLBCL.[1] The complete response (CR) rate was 32% and the partial response rate was 18%. The median duration of response had not been reached.

"The goal of Kymriah is to provide physicians with a therapy that has demonstrated durable response rates in relapsed or refractory DLBCL patients, a patient population that has endured multiple rounds of chemotherapy with many having experienced unsuccessful stem cell transplants," Stephen J. Schuster, MD, the Robert and Margarita Louis-Dreyfus Professor in Chronic Lymphocytic Leukemia and Lymphoma Clinical Care and Research in Penn's Perelman School of Medicine and director of the Lymphoma Program at the Abramson Cancer Center, said in a statement.

"With this approval, physicians now have a meaningful therapeutic option that can achieve and maintain a sustained response without stem cell transplant along with a consistent safety profile," added Schuster.

Patients in the open-label, multicenter, single-arm trial JULIET were enrolled at 27 study centers in 10 countries on 4 continents. Overall the study enrolled 160 patients with relapsed/refractory DLBCL who had received at least 2 lines of prior chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT).

Of the overall population, 106 patients were infused with tisagenlecleucel. The median age was 56 years (range, 22-74) among the 68 patients evaluable for efficacy, with 71% of patients being male and 90% being white.

Seventy-eight percent of patient had DLBCL that was "not otherwise specified," with 22% having DLBCL following transformation from

follicular lymphoma (17% high grade). Prior autologous HSCT had been received by 44% of patients. Patients had received a median number of 3 prior therapies (range, 1-6).

Forty-four percent of patients relapsed after their last therapy and 56% of patients had refractory disease. Ninety percent of patient had been treated with lymphodepleting chemotherapy, including 66% with fludarabine and 24% with bendamustine.

There was a median period of 113 days (range, 47-196) from leukapheresis and cryopreservation to tisagenlecleucel infusion. The median dose in the evaluable patient population was 3.5×10^8 CAR-positive viable T cells (range: 1.0 to 5.2×10^8 cells).

All-grade adverse events occurring in at least 20% of the 106 infused patients included cytokine release syndrome (CRS), infections, pyrexia, diarrhea, nausea, fatigue, hypotension, edema, and headache. Grade 3/4 infections occurred in 25% of patients and there were cases of grade 3/4 thrombocytopenia (40%) and neutropenia (25%) that lasted more than 28 days.

Severe or life-threatening CRS occurred in 23% of the 106 patients who received tisagenlecleucel. Grade 3/4 neurologic events occurred in 18% of treated patients. These neurologic toxicities were managed with supportive care. Eleven percent of patients experienced severe or life-threatening encephalopathy. Neurological adverse events were not linked to any patient deaths and no cases of cerebral edema led to a patient death.

Tisagenlecleucel is approved through the FDA Risk Evaluation and Mitigation Strategy (REMS) program. According to Novartis, the manufacturer of the CAR T-cell therapy, the REMS program will educate healthcare professionals about the risks that may be associated with the treatment.

In August 2017, tisagenlecleucel became the first CAR T-cell therapy approved by the FDA when the agency authorized the treatment's use for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

The approval was based on phase II results from the single-arm ELIANA trial. Data from the study published in the New England Journal of Medicine showed that at a median follow-up of 13.1 months, tisagenlecleucel induced an ORR of 81% in children and young adults with relapsed/refractory B-cell acute lymphoblastic leukemia ALL.[2]

In an analysis of 75 infused patients with 3 or more months of follow-up, 60% of patients achieved CR and 21% of patients achieved CR with incomplete blood count recovery following tisagenlecleucel infusion. ■

REFERENCES

1. Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of Juliet: A global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma. Presented at: ASH Annual Meeting and Exposition; Dec. 9-12, 2017; Atlanta. Abstract 577.
2. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018; 378:439-448.

Managing Thromboembolic Events in Pediatric Cancer

ANGELICA WELCH

Surgical procedures and the administration of chemotherapy by central venous catheter can increase the risk of a thromboembolic events in patients with cancer. To curb this risk, anticoagulants are used in both adults and children undergoing treatment.

Generally, day-to-day traumas that result in bleeding are more likely to occur in children than in adults says Guy Young, MD. This is attributed to the nature of childhood—playing sports, going to the park, or riding a bike.

Anticoagulants increase the risk for bleeding, and for a child undergoing treatment for cancer, a scraped knee could be a more serious situation than it would be in a heathy child. Additionally, anticoagulants such as warfarin come with their own side effects.

In an interview with *OncLive*, Young, director, Hemostasis and Thrombosis Program, attending physician, Hematology, Oncology and Blood and Marrow Transplantation, Children's Hospital Los Angeles, UCLA, discussed the use of anticoagulants in managing thromboembolic events in pediatric cancer.

OncLive: How do you manage thromboembolic events in children with cancer?

Young: Thromboembolic events do occur in children with cancer. They can occur for different reasons. Sometimes they occur simply as a results of the cancer that they have, but more often they occur due to a treatment approach

that is used. Many of the treatments require central venous catheters. These catheters can frequently cause thrombotic events in the vessels in which they are placed.

The treatment for any thromboembolic event is anticoagulation—blood thinners. Children who have cancer who develop blood clots are going to need anticoagulation therapy. There are different anticoagulants that we use these days, however, each one of those carries risk for bleeding. And one of the main problems in treating children with cancer who have blood clots is that often the chemotherapy also puts them at risk for bleeding by lowering their platelet counts. So, treating children who have cancer who also have a thromboembolic event is extra complicated over even other children who have thromboembolic evens who do not have cancer because the risk for bleeding is much higher.

> "All anticoagulants increase the risk for bleeding. Children with cancer are more prone to bleeding partly due to their cancer, and partly as a result of the treatment for their cancers, including surgery and chemotherapy."
>
> —Guy Young, MD

In addition, patients with cancer often have to have invasive procedures done. Particularly, children with leukemia need to have lumbar punctures done frequently, patients with brain tumors need to have surgeries of their brains—so anticoagulation therapy in children with cancer is complicated because of the way we might have to manage it surrounding the events that would occur with any type of surgical or invasive procedure.

How does the treatment being given impact the management of adverse events, and are you worried about drug-to-drug interactions?

All anticoagulants increase the risk for bleeding. Children with cancer are more prone to bleeding partly due to their cancer, and partly as a result of the treatment for their cancers, including surgery and chemotherapy. In addition, there can be drug-drug interaction. Warfarin has many many interactions with a lot of antibiotics and other drugs that patients with cancer may need, therefore it is a very difficult therapy to use in children with cancer. Even newer anticoagulants carry drug interactions.

Children are prone to scrape knees or get hurt. What do you tell parents when it comes to using anticoagulants?

Another issue with using anticoagulants in children is that children are more likely to experience trauma—just the simple day-to-day traumas. They are often playing with their siblings, friends, going to the park, or perhaps participating in sports. So, they are more at risk for traumatic events than a typical adult would be. Patients on anticoagulants are already at increased risk for bleeding, and trauma-associated bleeding is not an uncommon manifestation of patients who are on anticoagulants. Since kids participate in those activities regularly, they are at more risk for bleeding.

Are there any concerns with using vitamin K antagonists in children with cancer?

One of the anticoagulants that we have are vitamin K antagonists, commonly known as warfarin. This is a very difficult drug to use in any child, and especially in children with cancer. Firstly, it has many drug-drug interactions—drugs that many kids with cancer are going to need, such as antibiotics and antiseizure medications. These are drugs that we use to treat these kids, or to deal with the side effects that they develop as a result of chemotherapy.

The other problem with vitamin K antagonists is that they have a long half-life, so they stay in the blood for many days. If a child with cancer suddenly needs to have an unexpected procedure due to a complication of their cancer, it can be very difficult to mange the surgical procedure, due to the fact that it is very hard to reverse the anticoagulant quickly. Vitamin K can reverse vitamin K antagonists, but that process takes 12 to 24 hours. There are drugs that can do it quicker, but they have their own complications, as well.

The combination of the fact that vitamin K antagonists have many drug-drug interactions and have this long half-life, makes it very difficult to use in children with cancer.

Could a treatment like bivalirudin have a place for VTE in children?

There are some newer anticoagulant drugs available for children, one is bivalirudin. Bivalirudin is an IV-direct thrombin inhibitor. For hospitalized children that develop a blood clot, it can be a very good option instead of what we would normally use in that situation, which would be heparin therapy.

Heparin has certain types of complications and side effects that bivalirudin does not have. Furthermore, bivalirudin has some ability to resolve clots quicker than heparin, and so it can be a really good option for children with cancer who are hospitalized and develop blood clots. ■

FDA OKs Tisagenlecleucel in ALL as First Approved CAR T-Cell Therapy

JASON M. BRODERICK

The FDA issued a historic approval of the first chimeric antigen receptor (CAR) T-cell Therapy, authorizing the use of tisagenlecleucel (Kymriah) for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

The approval of the immunocellular therapy follows the advice of the FDA's Oncologic Drugs Advisory Committee, which voted 10-0 in July to recommend approval of tisagenlecleucel for pediatric ALL.

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," FDA Commissioner Scott Gottlieb, MD, said in a statement. "New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses. At the FDA, we're committed to helping expedite the development and review of groundbreaking treatments that have the potential to be life-saving."

The primary efficacy analysis was based on phase II results from the single-arm, international ELIANA trial of 63 patients who received a single dose of tisagenlecleucel. The targeted dose of each tisagenlecleucel infusion was 0.2 to 5.0 x 10^6 transduced viable T cells/kg for patients ≤50 kg and 0.1 to 2.5 x 10^8 transduced viable T cells/kg for those >50 kg.

The overall remission rate was 82.5% (95% CI, 70.9-91.0) in treated subjects. Forty patients (63%) had complete remission (CR) and 12 (19%) had complete remission with incomplete hematologic recovery (CRi).

All patients who had CR or CRi were associated with negative minimal residual disease status in the bone marrow.

Investigators concluded that tisagenlecleucel was associated with clinically meaningful remissions. The estimated relapse-free rate among responders at month 6 was 75.4% (95% CI, 57.2-86.7). The median duration of response was not reached at a median follow-up of 4.8 months.

Eleven patients who had CR or CRi relapsed after tisagenlecleucel prior to data cutoff and before any new cancer therapy. Two other patients relapsed after receiving both tisagenlecleucel and new cancer therapy. Of the 52 patients who had CR or CRi, 29 were still in remission at the last assessment before the data cutoff.

The median event-free survival (EFS) had not been reached at a median follow-up of 5.6 months. Of 63 patients evaluable for efficacy, 20 (31.7%) had an EFS event. At a median follow-up of 6.9 months, overall survival had not been reached.

"This therapy is a significant step forward in individualized cancer treatment that may have a tremendous impact on patients' lives," CAR T-cell therapy pioneer Carl June, MD, the Richard W. Vague Professor of Immunotherapy, Director of the Center for Cellular Immunotherapies in Penn's Perelman School of Medicine, said in a statement. "Through our collaboration with Novartis, we are creating the next wave of immunocellular cancer treatments, and are eager to progress CAR-T therapy in a host of hematologic and other cancer types."

The FDA's safety review included 68 patients. The most common (>5%) serious adverse events (AEs) recorded in the study were cytokine release syndrome (CRS), febrile neutropenia, hypotension, acute kidney injury, fever, and hypoxia. Thirty-two patients (47%) experienced grade 3/4 CRS, and median duration was 8 days. There were no deaths associated with CRS.

> "We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer. New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses."
>
> —Scott Gottlieb, MD

Ten patients (15%) experienced grade 3 neurotoxicity, and 18 experienced grade 3/4 infections within 8 days of infusion. Three patients died within 60 days of infusion due to infections.

The FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for tisagenlecleucel. According to Novartis, the manufacturer of the CAR T-cell therapy, the REMS program will educate healthcare professionals about the risks that may be associated with the treatment.

"Kymriah is a first-of-its-kind treatment approach that fills an important unmet need for children and young adults with this serious disease," Peter Marks, MD, PhD, director of the FDA's Center for Biologics Evaluation and Research, said in a statement. "Not

only does Kymriah provide these patients with a new treatment option where very limited options existed, but a treatment option that has shown promising remission and survival rates in clinical trials."

Also acknowledging today's historic approval was the president of the American Society of Hematology, Kenneth C. Anderson, MD, of the Dana-Farber Cancer Institute.

"The approval of CAR T-cell therapy for pediatric leukemia marks an important shift in the blood cancer treatment paradigm. We now have proof that it is possible to eradicate cancer by harnessing the power of a patient's own immune system," said Anderson. "This is a potentially curative therapy in patients whose leukemia is unresponsive to other treatments and represents the latest milestone in the shift away from chemotherapy toward precision medicine. Today's approval is the result of over a decade of hematology research, including research funded by the National Institutes of Health."

In a separate action, the FDA has also expanded the approval of tocilizumab (Actemra) for the treatment of CAR T-cell–induced severe or life-threatening CRS in patients 2 years of age or older. The approval is based on data demonstrating that in clinical trials of CAR T-cell therapy, patients who received tocilizumab had complete resolution of CRS within 2 weeks following 1 or 2 doses of the treatment.

"Until today, there has never been an FDA-approved treatment to manage severe cytokine release syndrome associated with CAR T-cell therapy, which is marked by a rapid onset and can cause life-threatening complications," Sandra Horning, MD, chief medical officer and head of global product development at Genentech (Roche), the manufacturer of tocilizumab, said in a statement. "Today's approval of Actemra/RoActemra for CRS provides physicians with an important tool to help manage this potentially life-threatening side effect." ■

IKZF1 Deletions Predict Poor Prognosis in Pediatric ALL

JASON HARRIS

IKZF1 deletions that co-occurred with deletions in *CDKN2A, CDKN2B, PAX5,* or *PAR1* in the absence of ERG deletion (*IKZF1*^{plus}) were associated with a dramatically reduced prognosis in pediatric patients with B-cell precursor (BCP) acute lymphoblastic leukemia (ALL).

Investigators on the international, multicenter AIEOP-BFM ALL 2000 trial previously established minimal residual disease (MRD) risk as the strongest prognostic factor among this cohort. When investigators categorized patients by MRD status, 5-year event-free survival (EFS) was just 30 ± 14% in high-risk *IKZF1*^{plus}patients compared with 94 ± 5% in those with standard risk and 40 ± 10% in intermediate-risk patients.

The corresponding 5-year cumulative incidences of relapse were 6 ± 6%, 60 ± 10%, and 60 ± 17%, respectively ($P \leq .001$).

Researchers evaluated all 991 children with BCP ALL diagnosed from August 1999 to May 2009 who were enrolled at clinics in Italy and Germany. Patients were stratified into standard-, intermediate-, and high-risk groups based on MRD analysis and required 2 MRD targets with sensitivities of $\leq 1 \times 10^{-4}$.

All patients underwent 7 days of prephase treatment with prednisone and 1 intrathecal dose of methotrexate, followed by induction phase IA and induction consolidation phase IB. From day 8, patients were randomly assigned to continue steroid treatment with either 60 mg/m^2 of prednisone daily or 10 mg/m^2 of dexamethasone daily until day 28 with subsequent tapering of dose in 1 more week.

MRD standard-risk patients were MRD negative on treatment days 33 and 78, and MRD high-risk patients had residual disease of $\geq 5 \times 10^{-4}$ on treatment day 78. All remaining patients were considered MRD intermediate risk.

In outcome analysis, *IKZF1*^{plus} was associated with a 5-year EFS of 53 ± 6% compared with 79 ± 5% for patients with *IKZF1*deletion or 87 ± 1% in patients who lacked any *IKZF1* deletion (*IKZF1*^{plus} vs no IKZF1 deletion, $P \leq .001$).

> "We have integrated molecular genetic data with MRD data into a single combined classification that will be used to refine treatment stratification and guide innovative but still costly therapeutic applications in our upcoming trial AIEOP-BFM ALL 2017 for frontline treatment of pediatric ALL."
>
> —Martin Stanulla, MD

Multivariable analyses—including factors such as *IZKF1* deletion, MRD risk status, and slow early MRD

response—showed that *IKZF1*^{plus} had the largest hazard ratio for relapse (HR, 4.00; 95 CI, 1.91-8.37; P <.001), which investigators found underscored the strongest prognostic effect.

"We have integrated molecular genetic data with MRD data into a single combined classification that will be used to refine treatment stratification and guide innovative but still costly therapeutic applications in our upcoming trial AIEOP-BFM ALL 2017 for frontline treatment of pediatric ALL," Martin Stanulla, MD, department of Pediatric Hematology and Oncology, Hannover Medical School, and colleagues wrote.

"To go beyond current risk stratification strategies, additional research on the biologic basis of our observations is needed and will be helpful in guiding the development of more-targeted and less-toxic innovative therapies for children and adolescents with ALL," added Stanulla et al.

Investigators used an independent cohort of 417 patients treated in AIEOP-BFM ALL 2000 who had the necessary genetic information available for confirmation of the negative prognostic effect of *IKZF1*^{plus}. The 5-year EFS observed for *IKZF1*^{plus} was 44 ± 12% compared with 74 ± 7% for *IKZF1* deletions or 85 ± 2% for no *IKZF1* deletions (*IKZF1*^{plus} vs no *IKZF1* deletion, P ≤.001). The respective 5-year cumulative incidences of relapse were 44 ± 12%, 24 ± 7%, and 13 ± 2% (*IKZF1*^{plus} vs no *IKZF1* deletion, P= .001).

"Similar to the observation cohort, multivariable analyses in the validation cohort demonstrated independence of *IKZF1*^{plus}," wrote Stanulla et al. ■

Stanulla M, Dagdan E. Zaliova M, et al. IKZF1plus defines a new minimal residual disease–dependent very-poor prognostic profile in pediatric b-cell precursor acute lymphoblastic leukemia [published online March 2, 2018]. *J Clin Oncol*. doi: 10.1200/JCO.2017.74.3617.

European Panel Backs Carfilzomib Label Update in Myeloma

JASON M. BRODERICK

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended adding final overall survival (OS) data from the phase III ASPIRE trial to the label for carfilzomib (Kyprolis) for the treatment of patients with relapsed/refractory multiple myeloma.

In ASPIRE, the combination of carfilzomib, lenalidomide (Revlimid), and dexamethasone reduced the risk of death by 21% compared with lenalidomide and dexamethasone alone for patients with relapsed multiple myeloma following prior treatment with 1 to 3 regimens.[1] The median OS with the carfilzomib combination was 48.3 months versus 40.4 months with lenalidomide/dexamethasone alone (HR, 0.79, 95% CI, 0.67-0.95; P = .0045).

The OS benefit seen at the final analysis was consistent even in those who received prior treatment with the proteasome inhibitor bortezomib (Velcade). There was a 25% reduction in the risk of death with carfilzomib in those not treated with bortezomib versus a 16% reduction for those treated with the proteasome inhibitor.

The CHMP previously recommended updating carfilzomib's label with OS data from the phase III ENDEAVOR trial, which showed that carfilzomib reduced the risk of death by 21% compared with bortezomib in patients with relapsed/refractory multiple myeloma (median OS, 47.6 vs 40.0 months; HR, 0.791; 95% CI, 0.648-0.964; P = .01).[2] The positive CHMP opinion on the ASPIRE results will now be sent to the European Commission for a final regulatory decision.

"This latest positive CHMP opinion marks the second time Amgen will add overall survival data from a phase III study to the label, further validating the fundamental role of Kyprolis in treating patients with relapsed or refractory multiple myeloma," David M. Reese, MD, senior vice president of Translational Sciences and Oncology at Amgen, said in a statement. "This is a major step towards advancing KYPROLIS-based regimens as standard of care, and we look forward to the European Commission's decision later this year."

The open-label phase III ASPIRE study enrolled 792 patients at a median age of 64 years who had received a median of two prior treatment regimens. Patients were randomized 1:1 to receive the 3-drug carfilzomib regimen or lenalidomide plus low-dose dexamethasone alone. In both groups of the trial, 66% of patients had received prior bortezomib and 20% had prior lenalidomide.

Lenalidomide was administered at 25 mg on days 1 to 21 and dexamethasone was administered at 40 mg on days 1, 8, 15, and 22 of a 28-day cycle.

Intravenous carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 during cycles 1 to 12. On day 1 and 2 of the first cycle, carfilzomib was administered at 20 mg/m^2 followed by 27 mg/m^2 thereafter. Treatment with carfilzomib was not administered on days 8 and 9 during cycles 13 to 18 and was not administered beyond 18 cycles. However, median treatment exposure in the carfilzomib arm was 22 cycles

> "This latest positive CHMP opinion marks the second time Amgen will add overall survival data from a phase III study to the label, further validating the fundamental role of Kyprolis in treating patients with relapsed or refractory multiple myeloma. This is a major step towards advancing KYPROLIS-based regimens as standard of care, and we look forward to the European Commission's decision later this year."
>
> —David M. Reese, MD

The final data analysis for ASPIRE also confirmed findings showing that carfilzomib was associated with a median progression-free survival of of 26.1 months compared with 16.6 months among patients who received lenalidomide and dexamethasone alone (HR, 0.66; 95% CI, 0.55-0.78; P <.0001),

Median duration of therapy in the experimental arm was 72.0 weeks for carfilzomib, 85.0 weeks for lenalidomide, and 80.2 weeks for dexamethasone. In the control arm, patients received lenalidomide for a median duration of 56.7 weeks and dexamethasone for a median of 48.7.

Adverse event (AE) rates were similar between the treatment groups including all-grade AEs (98.0% in both groups), grade ≥3 AEs (87.0% with carfilzomib vs 83.0% for the control group), serious adverse events (65.6% vs 56.8%), discontinuation due to AEs (33.4% vs 30.1%), and grade 5 AEs (11.5% vs 10.5%).

Safety data showed that all-grade nonhematologic events were generally more common in the experimental arm for diarrhea (44.4% vs 37.3%), fatigue (33.4% vs 31.9%), cough (29.6% vs 18.0%), pyrexia (29.8% vs 21.6%), upper respiratory infections (30.1% vs 20.8%), hypokalemia (29.6% vs 14.9%), and muscle spasms (27.0% vs 21.1%). With respect to grade ≥3 adverse events, only hypokalemia in the carfilzomib arm (10.5%) affected as many as 10% of patients in either group.

Hypertension (17.1% vs 8.7%) and venous thrombotic events (10.2% vs 6.2%) occurred more often with carfilzomib. Otherwise, the incidence of acute renal failure, cardiac failure, ischemic heart disease, and peripheral neuropathy occurred in a similar proportion of patients in both groups. The most common grade ≥3 special interest AE was hypertension (6.4% with carfilzomib). No other grade ≥3 special-interest event occurred in as many as 5% of patients. ■

REFERENCES

1. Stewart AK, Siegel D, Ludwig H, et al. Overall survival (OS) of patients with relapsed/refractory multiple myeloma (RRMM) treated with carfilzomib, lenalidomide, and dexamethasone (Krd) versus lenalidomide and dexamethasone (Rd): Final analysis from the randomized phase 3 ASPIRE trial. Presented at: American Society of Hematology 59th Annual meeting; December 9-12, 2017; Atlanta, GA. Abstract 743.
2. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial [published online August 23, 2017]. *Lancet Oncol.* doi: 10.1016/S1470-2045(17)30578-8.