By Devon Schuyler

Melphalan Approved as Liver-Directed Treatment for Uveal Melanoma

On August 14, the US Food and Drug Administration (FDA) approved the use of the melphalan hepatic delivery system (Hepzato Kit, Delcath Systems) as a liver-directed treatment for adults with uveal melanoma. Eligible patients have either unresectable hepatic metastases that affect less than 50% of the liver and no extrahepatic disease, or extrahepatic disease that is limited to the bone, lymph nodes, subcutaneous tissues, or lung and is amenable to resection or radiation.

Approval was based on the results of the single-arm, multicenter, open-label FOCUS trial. The trial enrolled 91 patients with uveal melanoma and unresectable hepatic metastases. Limited extrahepatic disease in the bone, subcutaneous sites, lymph nodes, or lungs was permitted if the life-threatening component of the uveal melanoma was in the liver, and the extrahepatic disease was amenable to resection or radiation.

Patients received melphalan (3 mg/kg based on ideal body weight, with a maximum dose of 220 mg per single treatment) by infusion into the hepatic artery every 6 to 8 weeks for up to 6 total infusions. The objective response rate (ORR) was 36.3% (95% CI, 26.4-47) and the median duration of response (DOR) was 14 months (95% CI, 8.3-17.7).

The delivery system includes a boxed warning for severe periprocedural complications that include hemorrhage, hepatocellular injury, and thromboembolic events, as well as for myelosuppression with resulting severe infection, bleeding, or symptomatic anemia. It is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

The most common adverse reactions or laboratory abnormalities were thrombocytopenia, fatigue, anemia, nausea, musculoskeletal pain, leukopenia, abdominal pain, neutropenia, vomiting, increased alanine aminotransferase (ALT), prolonged activated partial thromboplastin time, increased aspartate aminotransferase (AST), increased alkaline phosphatase (ALP), and dyspnea.

FDA Grants Accelerated Approval to Elranatamab-bcmm for Relapsed/Refractory Multiple Myeloma

On August 14, the FDA granted accelerated approval to elranatamab-bcmm (Elrexfio, Pfizer) for adults with relapsed or refractory multiple myeloma (RRMM) who have received at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Elranatamab-bcmm is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager.

Approval was based on the results of the open-label, single-arm, multicenter MagnetisMM-3 study. Elranatamab-bcmm was administered to 97 patients with RRMM who were naive to prior BCMA-directed therapy and had received at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The ORR was 57.7% (95% CI, 47.3-67.7) and the median DOR among the responders was not reached (95% CI, 12 months to not reached) after a median follow-up of 11.1 months. The DOR rate was 90.4% at 6 months (95% CI, 78.4-95.9) and 82.3% at 9 months (95% CI, 67.1-90.9).

Elranatamab-bcmm carries a boxed warning for life-threatening or fatal cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity (ICANS). Because of the risks of CRS and neurologic toxicity, including ICANS, elranatamab-bcmm is available only through a restricted program under a REMS.

The most common adverse reactions were CRS, fatigue, injection site reaction, diarrhea, upper respiratory tract infection, musculoskeletal pain, pneumonia, decreased appetite, rash, cough, nausea, and pyrexia. The most common grade 3 to 4 laboratory abnormalities were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased white blood cells, and decreased platelets.

Niraparib/Abiraterone Plus Prednisone Approved for *BRCA*-Mutated Metastatic Castration-Resistant Prostate Cancer

On August 11, the FDA approved the fixed-dose combination of niraparib and abiraterone acetate (Akeega, Janssen Biotech), in conjunction with prednisone, for adults with deleterious or suspected deleterious *BRCA*-mutated castration-resistant prostate cancer (mCRPC). Patients' BRCA status must be determined by an FDA-approved test.

Approval was based on the results of MAGNITUDE, a randomized, double-blind, placebo-controlled trial of patients with mCRPC. A total of 423 patients with homologous recombination repair (HRR) gene-mutated disease and 233 patients with HRR-unmutated disease were randomized in a 1:1 ratio to receive niraparib (Zejula, GSK) at 200 mg and abiraterone acetate at 1000 mg plus prednisone at 10 mg daily, or placebo and abiraterone acetate plus prednisone daily.

Of the 423 patients in the HRR gene-mutated cohort, 225 (53%) had prospectively determined *BRCA* gene mutations. Among these 225 patients, there was a statistically significant improvement in median radiographic progression-free survival (rPFS) with the investigational treatment vs the control treatment, at 16.6 vs

10.9 months, respectively (hazard ratio [HR], 0.53; 95% CI, 0.36-0.79; *P*=.0014). An analysis of the 198 patients (47%) with non-*BRCA* HRR mutations did not find a statistically significant increase in rPFS or OS with the investigational treatment vs the control treatment.

The most common adverse reactions, including laboratory abnormalities, were decreased hemoglobin, decreased lymphocytes, decreased white blood cells, musculoskeletal pain, fatigue, decreased platelets, increased ALP, constipation, hypertension, nausea, decreased neutrophils, increased creatinine, increased potassium, decreased potassium, and increased AST. Among the 423 patients with HRR gene-mutated disease who received the experimental treatment, a total of 27% required a blood transfusion, including 11% who required multiple transfusions.

FDA Grants Accelerated Approval to Talquetamab-tgvs for Relapsed/Refractory Multiple Myeloma

On August 9, the FDA granted accelerated approval to talquetamab-tgvs (Talvey, Janssen Biotech) adults with RRMM who have received at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Approval was based on the results of MonumenTAL-1, a single-arm, open-label, multicenter study of patients with MM who had previously received at least 4 prior systemic therapies. A total of 187 patients in the efficacy population received subcutaneous talquetamab-tgvs at 0.4 mg/kg weekly (following 2 step-up doses in the first week of therapy) or at 0.8 mg/kg biweekly every 2 weeks (following 3 step-up doses) until disease progression or unacceptable toxicity.

Among the 100 patients receiving 0.4 mg/kg, the ORR was 73% (95% CI, 63.2-81.4) and the median DOR was 9.5 months (95% CI, 6.5 to not estimable). Among the 87 patients receiving 0.8 mg/kg, the ORR was 73.6% (95% CI, 63-82.4) and the median DOR was not estimable. An estimated 85% of the responders had their response last for at least 9 months.

The most common adverse reactions in the 339 patients in the safety population were CRS, dysgeusia, nail disorder, musculoskeletal pain, skin disorder, rash, fatigue, decreased weight, dry mouth, pyrexia, xerosis, dysphagia, upper respiratory tract infection, and diarrhea.

Talquetamab-tgvs carries a boxed warning for life-threatening or fatal CRS and neurologic toxicity, including ICANS. Because of these risks, it is available only through a REMS.

Pralsetinib Approved for Non–Small Cell Lung Cancer With *RET* Gene Fusions

On August 9, the FDA granted regular approval to pralsetinib (Gavreto, Blueprint/Genentech) for adults with metastatic rearranged during transfection (RET) fusion-positive non–small cell lung cancer (NSCLC). Patients' RET status must be detected by an FDA-approved test.

Pralsetinib previously received accelerated approval for this indication on September 4, 2020, based on the initial ORR and DOR in 114 patients enrolled in the multicenter, open-label, multicohort ARROW trial. Regular approval was granted based on data from an additional 123 patients and 25 months of additional follow-up, for a total of 237 patients with locally advanced or metastatic RET fusion-positive NSCLC who received pralsetinib until disease progression or unacceptable toxicity.

Among 107 treatment-naive patients, the ORR was 78% (95% CI, 68-85) and the median DOR was 13.4 months (95% CI, 9.4-23.1). Among 130 patients who were previously treated with platinum-based chemotherapy, the ORR was 63% (95% CI, 54-71) and the median DOR was 38.8 months (95% CI, 14.8 to not estimable).

The most common adverse reactions were musculoskeletal pain, constipation, hypertension, diarrhea, fatigue, edema, pyrexia, and cough.

Trifluridine/Tipiracil With Bevacizumab Approved in Previously Treated Metastatic Colorectal Cancer

Trifluridine/tipiracil (Lonsurf, Taiho Oncology) in combination with bevacizumab received approval on August 2 for metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti–vascular endothelial growth factor (VEGF) biologic therapy, and an anti-EGFR therapy if *RAS* wild-type. Trifluridine/tipiracil had previously received approval as a single agent for this indication in September 2015.

The approval was based on the results of the randomized, open-label, multicenter, global SUNLIGHT trial. In this trial, 492 patients with mCRC who had received a maximum of 2 prior chemotherapy regimens and demonstrated progressive disease or intolerance to the last regimen were randomly assigned to trifluridine/tipiracil plus bevacizumab or trifluridine/tipiracil alone.

Patients in the trifluridine/tipiracil plus bevacizumab arm had better outcomes than those in the trifluridine/tipiracil arm, including a longer median OS of 10.8 vs 7.5 months, respectively (HR, 0.61; 95% CI, 0.49-0.77; 1-sided *P*<.001), and a longer median PFS of 5.6 vs 2.4 months, respectively (HR, 0.44; 95% CI, 0.36-0.54; 1-sided *P*<.001).

The most common adverse reactions or laboratory abnormalities for trifluridine/tipiracil with bevacizumab were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased ALP, decreased sodium, diarrhea, abdominal pain, and decreased appetite.