HEM/ONC News

By Devon Schuyler

FDA Approves Pembrolizumab for Advanced Melanoma

The US Food and Drug Administration (FDA) has granted accelerated approval to pembrolizumab (Keytruda, Merck) for treatment of patients with unresectable or metastatic melanoma that no longer responds to other drugs. Pembrolizumab is for use in patients with disease progression after the use of ipilimumab and (if positive for the *BRAF* V600 mutation) a B-Raf inhibitor.

Pembrolizumab is the first FDA-approved drug that blocks the programmed death receptor 1 protein, which interferes with the ability of the immune system to attack tumor cells. Trials have not established an improvement in survival or disease-related symptoms for pembrolizumab.

The efficacy of pembrolizumab was established in a group of 173 trial participants with advanced melanoma whose disease had progressed despite treatment. Patients received either 2 mg/kg or 10 mg/kg of pembrolizumab every 3 weeks until disease progression, intolerable toxicity, or consent withdrawal. Tumor shrinkage lasting at least 1.4 to 8.5 months occurred in approximately 24% of patients who received the 2 mg/kg dose, and in a similar percentage of patients who received the 10 mg/kg dose.

The safety of pembrolizumab was established in a group of 411 trial participants with advanced melanoma. The most common side effects were fatigue, cough, nausea, pruritis, rash, decreased appetite, constipation, arthralgia, and diarrhea. Pembrolizumab also carries a risk for severe immune-mediated side effects.

AR-V7 Linked to Resistance to Enzalutamide and Abiraterone

Primary resistance to the androgen receptor antagonist enzalutamide (Xtandi, Astellas Pharma/Medivation) and the CYP17A1 inhibitor abiraterone acetate (Zytiga, Janssen Biotech) is common among men with metastatic castration-resistant prostate cancer (mCRPC). Now, a small study in the September 11th issue of the *New England Journal of Medicine* finds that the presence of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells can help predict which patients will not respond to these agents.

For the study, Dr Emmanuel Antonarakis and colleagues identified 62 patients with mCRPC who were initiating treatment with either enzalutamide or abiraterone. Analysis of circulating tumor cells revealed AR-V7 in 39% of the enzalutamide-treated patients and 19% of the abiraterone-treated patients at baseline.

After a median follow-up of 4.6 to 5.4 months, none of the patients with detectable AR-V7 at baseline had responded to either enzalutamide or abiraterone, as defined by a reduction in serum prostate-specific antigen (PSA) levels of 50% or more. By contrast, 53% of the men in the enzalutamide group and 68% of the men in the abiraterone group who were AR-V7–negative responded to the drugs. Men who were AR-V7–positive also had shorter PSA progression-free survival (PFS), clinical or radiographic PFS, and overall survival than those who were AR-V7–negative in both the enzalutamide and abiraterone groups.

The finding that no patients with detectable AR-V7 in circulating tumor cells responded to either enzalutamide or abiraterone was "striking," wrote Dr Peter Nelson in an editorial. He said that although further studies would be required to validate these results, a biomarker with 100% specificity in predicting lack of treatment response would be a "major step forward" in the treatment of patients with mCRPC.

Results Mixed For Pazopanib Maintenance in Ovarian Cancer

Maintenance therapy with pazopanib (Votrient, GlaxoSmithKline) improved PFS in ovarian cancer but was poorly tolerated, according to the results of a recent trial. Pazopanib is a multikinase inhibitor of vascular endothelial growth factor that is approved for the treatment of advanced renal cell carcinoma and soft tissue sarcoma.

The trial, which was published online September 15th in the *Journal of Clinical Oncology* with Dr Andreas du Bois as the first author, included 940 patients with stages II to IV cancer of the ovary, fallopian tube, or peritoneum who had no evidence of disease progression after primary therapy (surgery plus at least 5 cycles of platinum-taxane chemotherapy). Patients were randomly assigned to receive pazopanib 800 mg once per day or placebo for up to 24 months.

The median PFS was significantly higher with pazopanib than with placebo (17.9 vs 12.3 months; hazard ratio, 0.77; 95% CI, 0.64 to 0.91; P=.0021), but an interim survival analysis based on events in one-third of the patients found no effect of pazopanib on overall survival. Grade 3 or 4 adverse events were significantly higher with pazopanib than with placebo, and included hypertension, neutropenia, liver-related toxicity, diarrhea, fatigue, and thrombocytopenia. Patients taking pazopanib were significantly more likely than those taking a placebo to discontinue treatment owing to adverse events (33% vs 5.6%).

Dr Kate Oliver, who wrote an editorial that accompanied the study, said that the "unfavorable benefit-to-risk profile" of pazopanib for maintenance in ovarian cancer was consistent with the results of several previous trials.