Accelerated Approvals Reconsidered

None

Changes in Dosing/Administration

Turalio® (*pexidartinib*) – Along with the warning regarding fat intake, comes a change in dosage recommendations for Turalio® as well as the introduction of a new strength capsule. Whereas the recommended dosage had been 400 mg twice daily, taken at least an hour before or two hours after meals, the new recommendations are for 250 mg twice daily, taken together with low-fat meals. In accordance with the new recommended dosage, Daiichi Sankyo has received approval to market a 125 mg strength capsule (intended to replace the 200 mg capsules that were available until now).

Changes in Labeled Indications

Cotellic® (*cobimetinib fumarate*) – Genentech's MEK inhibitor, first approved in 2015 for use in combination with the company's BRAF inhibitor (Zelboraf®) for melanoma, was approved for use as a single agent for treating adult patients with histiocytic neoplasms—a diverse set of rare diseases that often have quite poor prognoses. Approval for the new indication was supported by evidence from a small Phase II single-arm study (n=26) that used "response" (measured by both PET and RECIST) as the primary efficacy endpoint. Enrolled patients, 21 of whom had already failed prior systemic therapy, had multi-system disease, recurrent or refractory disease, or single-system disease that was unlikely to benefit from conventional therapies. After a median follow-up of almost a year, 16 of the 24 patients evaluable by PET demonstrated a complete response, with a median time to response of 2 months.

Imfinzi® (*durvalumab*) – The list of indications approved for AZ's immunotherapy was expanded to include use in combination with Imjudo® for *hepatocellular carcinoma* (described above). The approval comes one month after the PD-L1 inhibitor was approved for use, in combination with gemcitabine and cisplatin, as treatment for adult patients with locally advanced or metastatic biliary tract cancer.

New Biosimilars and Generics

Full approvals were granted for:

- *Bortezomib* from both Mylan Labs and Waverley Pharma;
- *Clofarabine* from Eugia Pharma;
- *Cyclophosphamide* from Xellia Pharms APS;
- *Doxorubicin hydrochloride* from Celerity Pharms;
- *Leuprolide acetate* from Amneal; and
- *Paclitaxel* from Alembic Pharms Ltd.

Tentative Approvals granted for:

- *Bendamustine hydrochloride* from Breckenridge Pharmaceuticals; and
- Teva Pharmaceuticals received a tentative "Type-2" approval ("new active ingredient") for Alvaiz, a branded formulation of *eltrombopag choline.*

New Data

Kisqali® (*ribociclib succinate*) – Data on overall survival for post-menopausal women with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled in a randomized study comparing Kisqali® + *letrozole to letrozole* + placebo were added to the prescribing information for Novartis' kinase inhibitor. Those data show that after a median follow-up of 80 months, survival for the Kisqali-treated group remained significantly higher than that for the *letrozole* only cohort of patients ((median of 63.9 and 51.4 months, respectively), resulting in an estimated 24 percent reduction in the risk of death.

Scemblix® (*asciminib*) – Novartis reported longer term follow-up data from the randomized trial that served as the basis for last year's initial approval of its kinase inhibitor for treating Philadelphia-positive CML. That approval was supported by the significantly superior response to therapy (in terms of both "complete cytogenic response" and "major molecular response") observed in Scemblix® patients after a 24-week observation period compared to that seen in patients randomized to be treated with *bosutinib*. The updated data show that the superior response continues after a 96 week follow up, thereby confirming the long-term efficacy and safety of Scemblix® and demonstrating its clinical benefit.

Tagrisso® (*osimertinib*) – The pharmacokinetics section for AstraZeneca's kinase inhibitor was updated with results of a study examining the drug's ability to enter the brain. The study relied on PET brain imaging studies in both healthy volunteers and in NSCLC patients with brain metastases and showed that following intravenous injection of a micro dose of 11C-labeled Osimertinib, the drug is in fact distributed to the brain.

Turalio® (*pexidartinib*) – When the kinase inhibitor was first approved for use (in 2019) it was because, after a 25-week long observation period, patients with symptomatic tenosynovial giant

cell tumor (TGCT) randomized to receive Turalio® exhibited superior outcomes (reductions in tumor volume and improvements in range of motion) to those seen in TGCT patients randomized to placebo. Data from the open-label extension part of that study are now reported in the prescribing information and show that the overall response rate after 96 weeks in the 61 patients originally randomized to the Turalio® arm was 61 percent (95% CI: 48%, 72%) and that the median duration of response had not yet been reached in the 37 responders."

New Molecular Entities

Imjudo® (*tremelimumab-actl*) – AstraZeneca was granted marketing approval for its novel CTLA-4 blocking antibody for use, in combination with Imfinzi® (*durvalumab*), for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). Support for the approval comes from a large (N=1,171) trial in which uHCC patients (who had not yet received any systemic therapy) were randomized to receive either the two checkpoint inhibitors in combination, *durvalumab* alone, or *sorafenib* as a single agent. Results showed that the median overall survival among patients receiving both immunotherapies was 16.4 months (95% CI 14.16–19.58), significantly better than the median of 13.8 months seen for patients in the sorafenib group. Additionally, the results supported the non-inferiority of *durvalumab* to *sorafenib* as single agent therapy. The median duration of response for the three patient cohorts (combined IO agents, *durvalumab* alone, and sorafenib) was 22.3, 16.8, and 18.43 months, respectively. The potential of combined use of AZ's two checkpoint inhibitors is currently being explored in Phase III trials for a range of other malignancies, including lung (both small and non-small cell), bladder, and urothelial cancers.

Pedmark® (*sodium thiosulfate*) – Fennec Pharmaceuticals, a late-stage biotech company with a single product, received its first FDA marketing approval late last month (which was not reported in September's newsletter). The approval is for use of Pedmark® to reduce the risk of ototoxicity associated with cisplatin use in pediatric patients 1 month of age and older being treated for localized, non-metastatic solid tumors. Approval was based on results from two randomized, open label studies, one with 114 pediatric patients being treated with cisplatin-based chemotherapy for standard-risk hepatoblastoma and the second with 125 pediatric patients treated with a chemotherapy regimen that included a cumulative cisplatin dose of 200 mg/m2 or higher. The frequency of ototoxicity in patients treated with Pedmark was lower than among patients in the control groups in both studies (39 versus 68 percent and 44 versus 58 percent, respectively) although that difference was only statistically significant in the first study. FDA's approval comes with the limitation that "the safety and efficacy of Pedmark® have not been established when administered following cisplatin infusions longer than 6 hours" because irreversible ototoxicity may have already occurred during longer infusions.

Tecvayli™ (*teclistamab-cqyv*) – Janssen was granted an accelerated approval for use of its novel bi-specific T cell engager as treatment for adult multiple myeloma (MM) patients with relapsed or refractory disease who have received at least four lines of prior therapy (to include a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody). Efficacy of the new molecule—which relies on distinct antibody fragments to simultaneously bind to the CD3 receptor found on T-cells and a protein (BCMA) found on MM cells—was demonstrated by an overall response rate of 61.8 percent a single-arm study that included 110 heavily pretreated MM

patients. Almost half (45.5 percent) of the responders in that study had a complete response. With a median follow-up of 7.4 months, more than 90 percent of initial responders continued to respond at 6 months and two-thirds continued at 9 months. Median duration of response had not yet been reached at the time the study was reported.

Safety-Related Changes

Elzonris® (*tagraxofusp-erzs)* – Information on timing for two of the adverse events observed in the pre-approval clinical trial of Stemline Therapeutics' treatment for blastic plasmacytoid dendritic cell neoplasm—*capillary leak syndrome* and *hepatoxicity*—was added to sections 5.1 and 5.3 of the prescribing information for the CD123-directed cytotoxin. The additions clarify that all but 5 of the 55 patients experiencing CLS in the pre-approval trial did so during the first cycle of therapy, that the incidence of *elevated liver enzymes* (seen in a majority of study patients) also occurred during the first cycle of therapy, and that the elevation of liver enzymes was reversible following dose interruption.

Lynparza® (*olaparib*) – AN explicit statement that some of the thromboembolic events observed in patients enrolled in clinical trials for AZ's PARP inhibitor were "severe or fatal pulmonary embolisms" was added to Subsection 5.4 of the prescribing information. In addition, a recommendation that male patients with female partners of reproductive potential use effective contraception during treatment "and for three months afterward" was modified to now recommend contraception only during active treatment.

Padcev® (*enfortumab vedotin*) – The recommendation for dosage modification in the event of adverse *skin reactions* in patients treated with Astellas Pharmaceuticals' antibody-drug conjugate was modified. Whereas Subsection 2.2 of the prescribing information had previously included recommendations only for more serious reactions (Grade 3 and above), newly inserted language suggests that clinicians "consider withholding" the urothelial cancer therapy even for Grade 2 reactions.

Turalio® (*pexidartinib*) – A warning that Daiichi Sankyo's treatment for symptomatic tenosynovial giant cell tumor should not be taken with a high-fat meal (one that has more than 55 grams of total fat) was added to its prescribing information. The warning, prominently displayed in the Warnings and Precautions highlights, was added because of evidence that fat intake may increase both the incidence and severity of adverse reactions, including hepatoxicity, associated with use of the kinase inhibitor.

Other Changes

Sandostatin® (*octreotide acetate*) – A recommendation to discontinue Sandostatin® injection at least 24 hours before each injection of *lutetium Lu 177 dotatate* when using the radioactive targeted therapy for treating GEP-NET patients was added to the drug interactions section. The addition was made so that guidance is consistent with that currently included (as of March 2021) in the labeling for Sandostatin® LAR depot.