Accelerated Approvals Reconsidered

Blenrep (*belantamab mafodotin-blmf*) - GSK said Tuesday that following a request from FDA, it will withdraw its blood cancer drug from the U.S. market. The decision comes a little more than two years after the BCMA-directed antibody and microtubule inhibitor conjugate was granted an accelerated approval as 5th-line therapy for adult patients with relapsed or refractory multiple myeloma.

Changes in Dosing/Administration

Rylaze® (asparaginase erwinia chrysanthemi) - A new dosage schedule was added for Jazz Pharmaceuticals' therapeutic alternative for leukemia and lymphoma patients with hypersensitivity to E. coli-derived asparaginase. The new schedule calls for 25 mg/m2 on Mondays and Wednesdays and 50 mg/m2 on Fridays. Under the new schedule, clinicians are advised to replace every dose of a calaspargase product with 9 doses of Rylaze® and every dose of a pegaspargase product with 6 doses of Rylaze®

Changes in Labeled Indications

Adcetris® (brentuximab vendotin) – Another ADC, Seattle Genetics' novel agent that combines a CD30-directed antibody with a microtubule inhibitor, had its use in Hodgkin's lymphoma expanded to include use in pediatric patients. The specific indication is for treatment of pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide. Support for its use in cHL comes from differences in progression-free survival observed in a trial (n=600) in which pediatric patients (ages of 2-22) were randomized to receive either Adcetris® with a chemotherapeutic regimen or the chemo regimen alone. While disease recurrence in among all enrolled patients was infrequent (only about 1 in 8 patients overall had an "event" during the study period), it was significantly higher in the control group (17 percent) than among patients in the Adcetris® arm (8 percent)—an overall reduction in risk of 59 percent.

Imfinzi® (durvalumab) and Imjudo® (tremelimumab-actl) – AstraZeneca received its second approval in 2 months for use if its workhorse PD-L1 inhibitor in combination with its recently approved CTLA-4 antibody. The combination regimen, which was approved for use in unresectable hepatocellular carcinoma last month, is now also approved for use in the treatment of

adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. The approval is supported by the results of a large trial (n=675) showing that outcomes for patients randomized to receive the IO combination (in addition to platinum-based chemotherapy) were superior to those of patients randomized to receive only the platinum-based chemo. Specifically, differences were seen in response rates (39 vs 24 percent) progression-free survival (6.2 vs 4.8 months) and overall survival (26 vs 15 percent, with a consequent 23 percent reduction in risk of death).

Libtayo® (cemiplimab-rwlc) – Another immunotherapy that had its role in NSCLC expanded this month is Regeneron's PD-1 inhibitor. Already approved for use (as a single agent) as first-line therapy for patients whose NSCLC tumors have no EGFR, ALK or ROS1 aberrations, are either locally advanced or metastatic, and whose tumors exhibit high PD-L1 expression, the checkpoint inhibitor is now also approved (in combination with platinum-based chemotherapy) for treating those patients irrespective of their PD-L1 status. Approval for the new indication was based on the results of a randomized study (n=466) in which patients treated with Libtayo® and platinum-based chemotherapy had superior outcomes to those of patients receiving placebo and chemotherapy. Significant differences between the Libtayo® and placebo arms were observed for response to therapy (43 vs 23 percent), duration of response (median 15.6 vs. 7.3 months), duration of progression-free survival (median of 8.2 vs. 5.0 months) and overall survival (58 vs 47 percent with an estimated 29 percent reduction in the risk of death).

Udenyca® (pegfilgrastim-cbqv) – The list of approved indications for Coherus Biosciences' pegfilgastim biosimilar was expanded to include use to increase survival in patients acutely exposed to myelosuppressive doses of radiation. The addition brings the list of approved uses in line with those for the reference product (Neulasta®).

New Biosimilars and Genetics

Full Approvals were granted for:

- Cyclophosphamide from Alembic Pharmaceuticals
- Docetaxel from Meridian Laboratories
- Mitomycin from Gland Pharma
- Sorafenib tosylate from Yabao Pharmaceuticals

In addition, Therakind, a British company focused on developing easier dosing for a range of products, received approval for Jylamvo, its branded formulation of an oral methotrexate solution.

New Data

Piqray® (alpelisib) - Initial approval of Novartis' PIK3CA-directed kinase inhibitor (in 2019) was based on evidence from a large, randomized trial (n=572) in which patients with PIK3CA+ advanced/metastatic breast cancer treated with the drug (+ fulvestrant) exhibited superior progression-free survival (PFS) to patients randomized to receive placebo (+ fulvestrant). Data on

overall survival (OS)—which were not yet mature in 2019—have now matured resulting in the following addition to the study description in Section14 of the product label. "At the pre-specified final OS analysis, there was no significant difference in OS between the Piqray plus fulvestrant arm and the placebo plus fulvestrant arm (hazard ratio [HR] = 0.86, 95% CI: 0.64, 1.15)."

New Molecular Entities

Elahere (mirvetuximab soravtansin-gynx) – Immunogen, a company devoted to exploring the therapeutic potential of antibody-drug conjugates (ADC) across a set of cancers, received marketing approval this month for a novel ADC that combines an antibody that targets folate receptor alpha (FRα) with a microtubule inhibitor. The approval is for use of the agent in treating adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (who have already received 1-3 systemic treatment regimens). It was supported by a 31.7 percent response rate (and 6.9-month median duration of response) observed in a single-arm study that enrolled 106 FRα-positive, platinum-resistant patients. The approval is accelerated, and its continuation may depend on "verification and description of clinical benefit in a confirmatory trial." The indication includes a recommendation to select patients for treatment based on evidence of overexpression of the FRα protein in their tumors (which occurs in more than half of high-grade serous ovarian cancers). Of note, Roche's Ventana FOLR1 RxDx Assay, which detects such overexpression, was also approved for use this month.

Safety-Related Changes

Darzalex® (daratumumab) and Darzalex Faspro® (daratumumab and hyaluronidase-fihj) – Several changes were approved to the Patient Prescribing Information including some minor edits, the addition of eye pain as a possible infusion-related adverse event and a warning that the decreases in blood cell counts are common with either product but can be severe.

Erleada® (apalutamide) – A new subsection (5.5) on severe cutaneous adverse reactions was added to the Warnings and Precautions portion of the prescribing information for Janssen's androgen receptor inhibitor. The new subsection notes that fatal and life-threatening cases of severe cutaneous adverse reactions (SCARS), including Stevens-Johnson syndrome/toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms, have occurred in patients treated with Erleada.® Clinicians are urged to monitor patients for the development of such reactions, to advise patients of the associated signs and symptoms, to interrupt therapy when an occurrence of SCARS is suspected, and to permanently discontinue Erleada® if SCARS (or any Grade 4 adverse skin reaction) is confirmed.

Lumakras® (sotorasib) – A new subsection on breast cancer resistance protein (BCRP) substrates was added to the discussion of the possible effects of Amgen's RAS inhibitor on other drugs. The new subsection (7.3) warns that because Lumakras® is a BCRP-inhibitor, it may increase the risk of adverse events when co-administered with such drugs. The new language advises clinicians to monitor for adverse reactions of the BCRP substrate and, in the event of an adverse reaction, to decrease the BCRP substrate dosage in accordance with its prescribing information.

Piqray® (alpelisib) -- A recommendation to "consider an alternative drug with no or minimal potential to induce CYP3A4" has been appended to the warning in Section 7.1 regarding concomitant use of Piqray® with strong CYP3A4 inducers. In addition, the language now clarifies that such concomitant use may "reduce alpelisib efficacy."

Vitrakvi ® (larotrectinib sulfate) – The instructions for co-administering Bayer's NTRK-fusion directed kinase inhibitor with CYP3A4 inducers or inhibitors were expanded. Whereas the prescribing information had previously focused only on co-administration with "strong" inducers or inhibitors, the updates—made in section 2.5 on Dosage and Administration and section 7.1 on Effect of Other Drugs--now also includes information on co-administration with "moderate" inducers or inhibitors.

Other Changes

Enhertu® (fam-tastuzumab deruxtecanan) – The phrase "as determined by an FDA-approved test," was added (in section 1.2) to the indication for use of Daichii-Sankyo and AZ's antibody drug conjugate in treating patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer.

Lenvima® (lenvatinib mesylate) – Greater detail was added to section 2.10 on how to prepare Eisai's kinase inhibitor, which comes as 4 and 10 mg capsules, for use as an oral solution. The revised instructions include a recommendation for what to do with any product that is dissolved but not immediately consumed (store under refrigeration for up to 24 hours) and a clarification that the vessel in which the solution is prepared should be cleaned until there is no remaining residue.

Kimmtrak® (tebentafusp-tebn) – The statement in Section 2.1 (Patient Selection) of the prescribing information for Immunosera's novel treatment for uveal melanoma that "(a)n FDA-approved test for the detection of HLA-A*02:01 genotyping is not currently available" has been replaced with a link to a list of FDA-approved companion diagnostics.

Pemetrexed – Actavis Pharma, a generic drug maker acquired by Teva, received FDA approval to update the indications for its formulation of pemetrexed to align them with those for the reference product (Alimta®).

Rybrevant® (amivantamab-vmjw) - The instructions regarding selection of appropriate patients for treatment with Janssen's bi-specific EGF- and MET-directed antibody were updated. Whereas the label had previously recommended selection "based on the presence of EGFR exon 20 insertion mutations" it now specifically recommends that tumor tissue be tested if the mutations are not detected in plasma.