New Molecular Entities

Jaypirca™ (*pirtobrutinib*) – Loxo/Lilly Oncology received approval for its novel BTK inhibitor as treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy (including treatment with another BTK inhibitor). The approval was based on response rates observed among 120 MCL patients who were treated with Jaypirca™ after having previously received a different BTK inhibitor. Among those patients 60 (50 percent) had either a "complete" or "partial response" (15 and 45 patients, respectively). The median duration of response was 8.3 months. While Jaypirca™ joins an increasingly crowded field of small molecules targeting BTK, it is the first non-covalent ("reversible") inhibitor of the protein implicated in B-cell proliferation and, as such, can reestablish inhibition in some MCL patients previously treated with covalent BTK inhibitors (*ibrutinib, acalabrutinib, or zanubrutinib*).

Orserdu™ (*elacestrant*) -- Stemline Therapeutics, a subsidiary of one of the oldest pharma companies in the world, was granted approval to market the first oral therapy that targets a genetic mutation that often arises in breast cancer patients treated with aromatase inhibitors. The approval is for use of the new "selective estrogen receptor downregulatory" as treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. Support for the approval comes from a randomized trial that enrolled 478 postmenopausal women and men with ER+/HER2- advanced or metastatic breast cancer of which 228 patients had *ESR1* mutations, Within the mutation-positive cohort, 46 percent of the 115 patients randomized to treatment with Orserdu™ were event free by the reporting date (with a median progression-free survival of 3.8 months) while that was true for only 31 percent of the patients randomized to treatment with either *fulvestrant* or an aromatase inhibitor (who had a median PFS of 1.9 months). However, the statistically significant difference in PFS observed in the ESR1 mutation-positive patients did not hold for the broader population of patients that were enrolled in the trial. An exploratory analysis in the 250 patients without *ESR1* mutations showed no significant

advantage in PFS conferred by treatment with Orserdu™ (hence the approval being limited to use in mutation-positive patients). An announcement of the approval of a companion diagnostic that identifies ESR1 mutation-positive patients---the Guardant360 CDx assay—accompanied FDA's press release on Orsertu™

Changes in Labeled Indications

Brukinsa® (*zanubrutinib*) **–** Beigene BTK inhibitor—which first came to market in 2019 indicated for use in mantle cell lymphoma and was subsequently approved in Waldenstrom's macroglobulinemia and relapsed/refractory marginal zone lymphoma--is now also approved for treating adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL). Evidence in support of the new indication comes from one randomized study (SEQUOIA) that recruited previously untreated CLL/SLL patients and from a second (ALPINE) that evaluated effectiveness in patients with previously treated relapsed/refractory disease. Most of the patients in the SEQUOIA trial were randomized to treatment with either Brukinsa® (n=241) or a combination of *bendamustine* and *rituximab* (n=238). Efficacy was assessed based on progression free survival (PFS), which was significantly better in the Brukinsa® arm (85 percent without progression or death and median PFS not yet reached) than in the *bendamustine+rituxan* arm (70 percent without progression or death and a median PFS of 33.7 months). Patients recruited to the trial whose disease had a 17p deletion (n=110) were not randomized—rather, all were treated with Brukinsa® and evaluated based on response to therapy (achieved by 88 percent of them). Response to therapy also served as the principal efficacy measure in the ALPINE trial (n=652), which randomized previously treated patients to receive either Brukinsa® or *ibrutinib*. Whereas 80 percent of patients in the Brukinsa® arm responded to therapy, the same was true for 73 percent of patients treated with *ibrutinib*. Median duration of response had not yet been reached in either patient cohort after a median follow-up of 14.1 months

Keytruda® (*pembrolizumab*) – Merck's checkpoint inhibitor had its role in NSCLC expanded to now include use in the adjuvant setting, specifically as adjuvant therapy following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥4 cm), II, or IIIA disease. Evidence supporting the new use comes from a Phase III trial (n=1,177) in which NSCLC patients randomized to receive Keytruda post-resection demonstrated significantly superior disease-free survival (DFS) to that of patients randomized to receive placebo. The magnitude of the improvement is somewhat unclear because the detailed results included in new label are only for the 1,010 patients who also received chemotherapy. Within that group, 65 percent of patients in the Keytruda group remained disease free at study's end (with a median disease-free interval of 58.7 months) while the same was true for 54 percent of patients in the placebo arm (median disease-free interval of 34.9 months). In a

subgroup analysis of the 167 trial patients that did not receive chemotherapy, there was no difference seen in DFS between patients randomized to placebo or Keytruda.

Tukysa®(*tucatinib*) -- Seagen's kinase inhibitor, which came to market approved for use in HER2+ breast cancer, was approved for use in colorectal cancer (CRC) as well, specifically for treating adult patients with RAS wild-type HER2-positive unresectable or metastatic CRC that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The approval was based on evidence of response seen in 32 of 84 patients recruited to a single-arm study in which patients with metastatic or unresectable CRC received the HER2 inhibitor in combination with *trastuzumab*. The median duration of response was 12.4 months and about one third of responders (38 percent) had a response that lasted 12 months or longer. HER2 overexpression is estimated to occur in about 3- 5 percent of metastatic CRC.

Accelerated Approvals Reconsidered

- **None**

New Generics and Biosimilars

Full approvals were granted for:

- *Abiraterone acetate* from Teva Pharmaceuticals
- *Cabazitaxel* from Sandoz, and
- *Nelarabine* from Kindos

Tentative approval was granted for:

- *Acalabrutinib* from Alembic Pharmaceuticals

Safety-related Changes

Jakafi® (*ruxolitinib*) -- A new subsection titled "Monitoring to Assess Safety" was added to the Dosage and Administration portion of the prescribing information for Incyte's kinase inhibitor. The new subsection instructs clinicians to perform a complete blood count (CBC) and inquire about past infections (including tuberculosis, herpes simplex, herpes zoster, and hepatitis B) prior to administering Jakafi and—during treatment--to perform a CBC every 2-4 weeks until doses are stabilized, as well as a lipid parameter assessment every 8-12 weeks. In addition, new language has been added to the warnings section of the label clarifying that *herpes zoster infection* has been reported with use of Jakafi®, that patients should be

monitored for both reactivation and possible transmission, and that physicians should consider treatment interruption if evidence of disease or dissemination occurs.

Marinol® (*dronabinol*) – The guidance in the prescribing information, which had advised female patients with infants and small children not to breastfeed while being treated with the antiemetic and for 9 days after the last dose, has been revised. Citing the beneficial effects of breastfeeding, the new guidance only recommends that "Weight should be monitored in breastfed infants of mothers with nausea and vomiting associated with cancer chemotherapy in whom breastfeeding is appropriate."

Taxotere® (*docetaxel*) -- Revisions were made in the recommended timeframes for contraceptive use by both male and female's patients being treated with the antineoplastic agent. The period for recommended use of contraception post-therapy for females was shortened from 6 to 2 months, while the period for males was extended from 3 to 4 months post-therapy.

Changes in Dosing/Administration

Lumakras® (*sotorasib*) -- Amgen received approval for the introduction of a 320 mg strength tablet of its KRAS inhibitor. The NSCLC drug had previously been available only as a 120mg tablet.

New Data

Darzalex® (*daratumumab*) -- The Clinical Studies section of the prescribing information for Janssen's CD38-directed antibody for multiple myeloma was updated to include a) overall survival results from two studies (MMY3003 and MMY3004) examining Darzalex® use for relapsed/refractory disease, and b) progression-free survival results from a trial evaluating the benefits of adding Darzalex® to a regimen of *lenalidomide* and *low-dose dexamethasone* for newly diagnosed patients (MMY3008). The newly added results show that the advantages in response rates that supported approval of Darzalex® have, with longer study follow-up, translated into advantages in both overall survival (in the two trials conducted in relapsed/refractory patients) and in progression-free survival (in the study of Darzalex® as part of a front-line regimen for newly diagnosed patients).

Other

Balversa® (*erdafitinib*) -- The term *onycholysis* was changed to *nail disorder* in the listing of adverse events associated with use of Janssen's kinase inhibitor.

Ixempra ® (*ixabepilone*) – The first bulleted Indication in the Highlights section of the prescribing information was revised to match verbatim the first indication listed in the full prescribing information