New Molecular Entities

- **Zynyz™** (*retifanlimab-dlwr*) – Incyte became the latest company to bring a PD-1 inhibitor to market with FDA's accelerated approval this month for use of its novel agent as treatment for metastatic or recurrent Merkel cell carcinoma. Support for the approval comes from a single arm study that examined both response to therapy and duration of response in 65 patients (median age 71 years) with metastatic or recurrent, locally advanced disease. Responses were observed in 34 of the enrolled patients (52 percent) with most of those (26 patients) achieving responses that lasted at least 6 months. With the approval, Zynyz™ becomes the third immunotherapy approved for Merkel cell carcinoma, a disease that is diagnosed in about 2,000 patients annually in the US.

Changes in Labeled Indications

- **Mekinist®** (*trametinib*)and **Tafinlar®** (*dabrafenib*) – The novel therapies from Novartis, which target different kinases in the RAS/RAF/MEK/ERK pathway, and which revolutionized treatment of certain BRAF V600E mutated cancers, have now been approved for use (in combination) to treat pediatric patients 1 year of age and older with BRAF V600E-mutated low-grade glioma who require systemic therapy. The approval was supported by the results from a trial (n=110) in which patients randomized to treatment with the two kinase inhibitors had a higher response rate (47 percent) and longer progression-free survival (median PFS of 20.1 months) than did patients randomized to treatment with carboplatin and vincristine (response rate of 10.8 percent and median PFS of 7.4 months). Concurrent with the approval for expanded pediatric use, Novartis is introducing new dosage forms and strengths for each product. Mekinist®, previously available as 0.5 mg and 2 mg tablets, will now also come as a 4.7

mg oral solution and a 10 mg tablet for oral suspension has been added to the 50 mg and 75 mg capsules already available for Tafinlar®.

- **Verzenio®** (*abemaciclib*) -- Lilly's oral CDK4/6 inhibitor, which came to market in 2017 indicated for use in treating advanced or metastatic HR-positive, HER2-negative breast cancer (BC) and subsequently approved as first line therapy for selected patients with high-risk early disease, had its role in BC therapy expanded considerably this month with two new approvals. One was for use (in combination with endocrine therapy) as adjuvant therapy for all HR-positive, HER2-negative, node positive patients at high risk for recurrence and not just for early BC patients with a Ki-67 score ≥ 20 percent (which was the previous requirement). The change was supported by longer term data from the pivotal study supporting the initial approval. Those data show that 85.5 percent of patients receiving Verzenio® (plus endocrine therapy) remained disease-free after 4 years, compared to 78.6 percent of patients randomized to receive endocrine therapy alone—a 35 percent reduction in the risk of death or disease recurrence. The second label expansion approved by FDA was the inclusion of pre- and perimenopausal women with advanced or metastatic HR+, HER2-negative BC as suitable candidates for treatment with Verzenio® in the first line setting. The initial approval for first-line use was restricted to postmenopausal women and men. Estimates are that more than 70 percent of all BC cases are HR-positive and HER2-negative.

Accelerated Approvals Reconsidered

- **Keytruda®** (*pembrolizumab*) **--** When Merck's PD-I inhibitor was first approved for treating patients with MSI-H or mismatch repair deficient solid tumors (in 2017), the approval was based on a trial demonstrating the ability of the novel immunotherapy to elicit a response in heavily pre-treated patients with metastatic disease. However, because of the relatively short follow-up period for that study (the median duration of response had not yet been reached at the time of reporting) the durability of response remained in question, and the approval included the caveat that its continuation was contingent on the provision of additional evidence of clinical benefit at some later time. Such evidence—available now because of the longer follow-up period for patients enrolled in the initial trial—serves as the basis for FDA's decision this month to convert the approval from "accelerated" to "full." Specifically, among the 168 trial patients who responded to Keytruda (out of a total study population of 504), the median duration of response was 63.2 months, with 77 percent of responses lasting of at least 12 months and 39 percent at least 24 months.

New Generics and Biosimilars

Full approvals were granted for:

- *Abiraterone acetate* from Florida Pharmaceutical Products, LLC
- *Carmustine* from Mylan Laboratories
- *Fluorouracil* from Alembic
- *Gemcitabine hydrochloride* from Hikma
- *Nelarabine* from Shorla, and
- *Pemetrexed disodium* from Mylan Laboratories

Tentative approval was granted for:

- *Cabazitaxel* from BPI Labs, LLC, and
- *Ponatinib* from Apotex

Safety-related Changes

- **Ayvakit®** (*avapritinib*) – A new subsection (5.3) was added to the Prescribing Information for Blueprint Medicines' therapy for GIST and advanced systemic mastocytosis warning that the kinase inhibitor may cause *photosensitivity* reactions. The warning is based on the observation that 2.5 percent of clinical trial patients treated with the novel small molecule experienced photosensitive reactions. The updated label suggests clinicians advise their patients to limit UV light exposure during treatment and for one week after discontinuation.

- **Daurismo®** (*glasdegib maleate*) – The Prescribing Information for Pfizer's AML therapy, which is indicated for use in elderly patients (as well as in any patient unable to tolerate the intensive induction chemotherapy) was expanded to include *musculoskeletal* events as adverse events (AE) associated with its use. Changes to the label include instructions (in Table 2.2) for dose modification in the event of a Grade 3 or 4 musculoskeletal AE, a new subsection (5.3) under Warnings and Precautions focused specifically on *musculoskeletal* AEs, and recommended language for communicating the risks of *musculoskeletal* AEs to patients (in Section 17).

- **Erivedge®** (*vismodegib*) **–** Information of *musculoskeletal* AEs was also added to the Prescribing Information for Genentech's hedgehog pathway inhibitor, which was approved in 2012 for use in treating metastatic or locally advanced basal cell carcinoma. As with Daurismo®, the changes include instructions for dose modification in the event of a Grade 3 or 4 *musculoskeletal* AE (in Table 2.3), a new subsection (5.3) under

Warnings and Precautions focused specifically on *musculoskeletal* AEs, and language in the Patient Counseling Information (Section 17) for communicating the risks of *musculoskeletal* AEs to patients.

- **Orgovyx®** (*relugolix*) -- *Angioedema* and *urticaria* were added to the list of adverse events observed during the post marketing phase of the prostate cancer drug. In addition, the Prescribing Information now contains an explicit statement contraindicating use of the hormone receptor agonist in patients with known *hypersensitivity* to its use. Detailed instructions on disposal of unused medication (with a warning not to flush it down the toilet) was added to Section 16.

- **Tabrecta®** (*capmatinib hydrochloride*) – Information on *hypersensitivity* as an adverse event associated with use of Novartis' NSCLC therapy was added to its Prescribing Information. Specifically, a new row focused on *hypersensitivity* was added to the suggestions in Table 2 for dose modifications recommended for adverse events, and a new section (5.4) on *hypersensitivity* was included under Warnings and Precautions for the kinase inhibitor. Clinicians are now advised to withhold Tabrecta® when hypersensitivity is suspected (until resolution of the event) and to permanently discontinue it for serious *hypersensitivity* reactions.

- **Zoladex** (*goserelin acetate*) – A new subsection on the risks of *depression and suicide* associated with use of the gonadotropin-releasing hormone (GnRH) agonist was added to the Warnings and Precautions section of its Prescribing Information. The new subsection (5.10) warns that depression may occur or worsen in women during treatment with GnRH agonists and recommends that clinicians 1) carefully observe women undergoing treatment, especially those with a history of depression, 2) consider whether the risks of continuing therapy outweigh the benefits, and 3) refer women with new or worsening depression to a mental health professional.

Changes in Dosing/Administration

- **Exkivity®** (*mobocertinib succinate*) – Table 1 of the Prescribing Information for Takeda's kinase inhibitor—which shows dosage modifications in the event of adverse reactions--was expanded to include modifications suggested for patients with *increased amylase or lipase*. The new text suggests that for a Grade 3 increase (without signs or symptoms) therapy be withheld until resolution to ≤ Grade 1 is achieved and then be resumed at the same or lower dose; for a Grade 3 increase with signs or symptoms or for a Grade 4 increase, therapy be withheld until resolution to ≤ Grade 1 and then resumed at a lower

dose—but only if resolution occurs within 2 weeks. If resolution is not achieved within 2 weeks, the recommendation is to permanently discontinue the drug.

- **Tepmetko®** (*tepotinib hydrochloride*) – A new subsection (2.3) was added to the Prescribing Information for EMD Serano's NSCLC therapy that advises how to administer the drug to patients who have difficulty swallowing solids. The subsection includes instructions for administration in the event that a naso-gastric tube is required. In addition, the section describing the effects of Tepmetko® on other drugs (7.1) was deleted from the Prescribing Information after findings from pharmacokinetic studies showed little impact of concern.

- **Udenyca®** (*pegfilgrastim-cbqv*) – Coherus Biosciences received approval to market a single- dose, 6 mg/0.6 mL prefilled autoinjector as an additional presentation for its biosimilar formulation of *pegfilgrastim.* With the new formulation comes a warning that the pre-filled autoinjection is not suitable for pediatric patients under 45 kg. The NDC for the new formulation is 70114-201-01

New Data

- **None**

Other

- **Aliqopa®** (*copanlisib*) –Two updates were made to the Clinical Pharmacology section of the Prescribing Information for Bayer's treatment for *follicular lymphoma*. A sentence was added (in Section 12.2) noting that the kinase inhibitor "does not cause a large mean increase in QTc interval > 20 milliseconds" when given at the recommended dose. Also, the conclusion regarding the pharmacokinetics of the drug (in section 12.3) that increases in its "geometric mean unbound AUC" among patients with moderate or severe hepatic impairment had no effect on peak concentrations was changed and now reads "(t)he geometric mean unbound Cmax of *copanlisib* did not increase in patients with moderate hepatic impairment, but increased 1.92-fold in patients with severe hepatic impairment."

- **Balversa®** (*erdafitinib*) – The list of laboratory abnormalities reported in ≥ 10 percent of patients treated with Janssen's kinase inhibitor (shown in Table 4 of the Prescribing Information) was corrected to read "fasting glucose *increased*" rather than "fasting glucose *decreased*".

- **Trelstar®** (*triptorelin pamoate*) **–** Editorial and formatting changes intended to clarify the timing and handling of the injectable suspension were made in Section 2.2. of the Prescribing Information for the hormonal prostate cancer therapy.