New Molecular Entities

- **None**

Changes in Labeled Indications

- **Polivy®** (*polatuzumb vedotin*) --Genentech's antibody-drug conjugate (ADC), which came to market with an accelerated approval for use (after at least two prior therapies) for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), has now gained FDA's approval for treating newly diagnosed patients. The CD79-directed ADC is now approved for use--in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone--for the treatment of adult patients with previously untreated DLBCL (not otherwise specified) or high-grade B-cell lymphoma (HGBL) who have an International Prognostic Index score of 2 or greater. The approval is supported by lower rates of disease recurrence or death occurring among 440 previously untreated patients with large B-cell lymphoma randomized them to receive Polivy® in combination with standard first-line therapy than among the 439 patients randomized to receive standard first-line therapy alone. The magnitude of the benefit, while modest—adding Polivy® cut the risks of progression or death by about 25 percent—achieved significance (p = .017) even after a median study follow-up period of more than 2 years. There was no statistically significant difference in overall survival (OS) seen in the prespecified final analysis of all patients with DLBCL, (NOS). However, among the relatively small group of patients in the study with HGBL (n=93), treatment with Polivy® was associated with a 68 percent reduction in their risk of death.

- **Padcev®** (*enfortumab vedotin*) and **Keytruda®** (*pembrolizumab*) **–** Astellas gained approval for use of its novel antibody-drug conjugate (in combination with Merck's PD-1 inhibitor) for treating adult patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy. Approval was based on an overall response rate of 68 percent among the 121 patients enrolled in a

multicohort non-randomized study, as well as on a median duration of response of 22.1 months in the cohort with the longest follow-up (median of 44.1 months). Approval of the combination therapy was accelerated, and its continuation may be contingent on subsequent data demonstrating clinical benefit.

- **Zejula®** (*niraparib*) -- When GSK's PARP inhibitor was first approved for use as maintenance therapy for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (in 2017) it was based on evidence that it was associated with longer *progression-free survival* for all patients irrespective of whether they were BRCA-positive. However, with longer follow-up, the benefits of Zejula® in treating recurrent disease only held for BRCA-positive patients and, in December of this past year, the indication for use in recurrent disease was restricted to patients with "deleterious or suspected deleterious germline BRCA-mutated" disease. In accordance with that change, the instruction to select patients for therapy based on an FDA-approved companion diagnostic has now been added to the prescribing information. Zejula® remains approved as maintenance treatment for patients with advanced disease who respond to platinum-based chemotherapy, irrespective of BRCA status.

Accelerated Approvals Reconsidered

- **Libtayo®** (*cemiplumab*) **--** When first approved (in 2021) for use in basal cell carcinoma (BCC), Regeneron's PD-1 inhibitor was fully approved for locally advanced disease but, because of the small number of patients in the study who had metastatic disease (n=28), was granted an accelerated approval for use in the metastatic setting. Regeneron has since enrolled an additional 26 metastatic patients into the study and based on the response rate across all 54 patients (24 percent) and a median duration of response of 16.7 months, FDA has converted the approval for use in metastatic patients (who have already received or are not candidates for therapy with a hedgehog inhibitor) to full.

- **Polivy®** (*polatuzumb vedotin*) – When Genentech's novel antibody-drug conjugate was first approved for use (in 2019), it was based on evidence from a randomized trial showing that DLBCL patients treated with a combination of Polivy®, *rituximab*, and *bendamustine* (Pola+BR) had a higher percentage of complete responses (40 percent) than did patients randomized to receive *rituximab* and *bendamustine* (BR) alone (18 percent). However, because the study was relatively small (n=80), follow-up was short (ending 6-8 weeks after the final cycle of therapy) and data allowing conclusions about survival benefit were not yet mature, the approval was "accelerated" and remained contingent on the submission of further evidence of clinical benefit. Such evidence has now been assembled--in the form of longer follow-up on the patients in original trial, as well as through the recruitment of 104 additional patients for treatment with the Pola+BR regimen. The newer data show that responses to therapy remained durable and that receipt of Polivy® was associated with longer progression-free survival than BR treatment alone (median PFS of 12.4 versus 4.5 months, respectively). Consequently,

FDA granted full approval for use of Polivy® (in combination with BR) as treatment for adult patients with relapsed/refractory DLBCL after at least two prior therapies.

New Generics and Biosimilars

Full approvals were granted for:

- *Arsenic trioxide* from Orbicular Pharmaceutical Technologies,
- *Bendamustine hydrochloride* from Mylan Labs,
- *Nelarabine* from Amneal Pharmaceuticals, and
- *Sorafenib tosylate* from Torrent Pharmaceuticals

Tentative approval was granted for:

- *Palbociclib* from MSN Pharmaceuticals

Safety-related Changes

- **Bosulif®** (*bosutinib*) -- *Interstitial lung disease* (ILD) was added to the list of adverse events seen in clinical trials with the kinase inhibitor. ILD was experienced by more than 0.1 percent but fewer than 1.0 percent of trial patients.

- **Neupogen®** (*filgrastim*) -- *Extramedullary hematopoiesis* (EMH) was added to the list of adverse reactions observed in patients receiving the growth factor after it came to market.

- **Padcev®** (*enfortumab vedotin*) – The discussion of lung-related adverse reactions (ARs) in the Warnings and Precautions portion of Padcev's prescribing information was modified. Specifically, the title of section 5.3 was expanded from "Pneumonitis" to "Pneumonitis/Interstitial Lung Disease (ILD)", the recommendation for withholding treatment in the event of a "persistent or recurrent" Grade 2 reaction was expanded to include any Grade 2 reaction, and a statement was included noting that the incidence of lung-related ARs was particularly high (9 percent) in the 121 study patients who were treated with the newly-approved combination of Padcev® and *pembrolizumab*.

- **Lumakras®** (*sotorasib*) – A new section (8.6) on use in patients with hepatic impairment was added to the prescribing information for Amgen's NSCLC drug. The addition suggests that no dose modification is necessary for patients with mild to moderate impairment and, that while the effect of hepatic impairment on the safety of Lumakras® is not known, patients with hepatic impairment should be monitored more frequently for adverse reactions to the RAS inhibitor.

Changes in Dosing/Administration

- **Libtayo®** (*cemiplumab*) **–** For patients with either *basal cell* or *cutaneous squamous cell carcinomas* the recommended duration of therapy with the IO agent was newly limited to 24 months. No time limit was placed on its use for NSCLC patients for whom treatment was to continue until disease progression or unacceptable toxicity.

- **Zejula®** (*niraparib*) – GSK's PARP inhibitor will now be available in tablet form at strengths of 100, 200 and 300 mgs, each of which will come in bottles of 30 tablets. NDCs for each bottle are 0173-0909-13 (100 mg), 0713-091213 (200 mg) and 0713-0916-13 (300 mg).

New Data

- **Libtayo®** (*cemiplimab*) -- Initial approval of Libtayo® (in 2018) was accompanied by a commitment from Regeneron to enroll some additional patients in its pivotal study of the effectiveness of the IO agent in locally advanced or metastatic squamous cell carcinoma (mSCC) as well as to extend the follow-up period for that study. Those commitments were fulfilled last year, and the resultant data have now been incorporated into the prescribing information for the PD-1 inhibitor (in Table 10, Section 14.2). The expanded table repeats the data included in previous versions but also presents results for the 56 newly recruited mSCC patients (who received 350 mg of Libtayo® every three weeks rather than 3mg/kg every 2 weeks dosing received by the first 136 patients). Both the response rate (46 percent) and the median duration of response among the newly reported cases (41 months with 88 percent or responses extending to 12 months or longer) mirror the results for previously reported cases.

Other

- **Cosela®** (*trilaciclib*) – The description on "distribution" of the kinase inhibitor in the discussion of its pharmacokinetics (in Section 12.3) was bolstered with new data on plasma protein binding and now reads "The in vitro human plasma protein binding of trilaciclib is 69% and appeared independent of *trilaciclib* concentration of 0.75 to 3.0 ug/mL."

- **Retacrit®** (*epoetin alfa*) -- A sentence was added to the prescribing information for Hospira's epoetin alfa biosimilar (Section 2.6) alerting users that the vial stopper is not made with natural rubber latex.