New Molecular Entities

- **Epkinly™** (*epcoritamab-bysp*) – The "broad oncology collaboration" announced by Abbvie and Genmab 3 years ago yielded its first "fruits' this month with the accelerated approval of Epkinkly™, a novel bispecific antibody, that binds a protein (CD3) found on T-cells to CD20, a protein that is overexpressed on the surface of lymphoma cells. The approval is for use for treating adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including BLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after 2 or more lines of systemic therapy. Approval was based on 61 percent of patients enrolled in a single-arm trial (N=148) responding to therapy. Of the 90 "responding" patients, 56 had "complete" and 34 had "partial" responses. The median duration of response was 15.9 months. As with all accelerated approvals, continuation my depend on additional evidence confirming the drug's clinical benefit. Epkinly™ comes to market as the first subcutaneously administered therapy for DLBCL, but the administration schedule does state that patients should be hospitalized for 24 hours after administration of their first full 48 mg dose (which occurs on Day 15 of the first cycle).

Changes in Labeled Indications

- **Ayvakit®** (*avapritinib*) -- Blueprint Medicines' kinase inhibitor, which was approved for treating advanced systemic mastocytosis (ASM) in June 2021, has now become the first FDA-approved therapy for indolent systemic mastocytosis (ISM). As with the ASM approval, the limitation that Ayavakit® is not recommended for the treatment of patients with platelet counts of less than 50 X 10^9/L remains in effect for the new indication. Approval is supported by results from a trial (n=212) in which ISM patients with moderate to severe symptoms randomized to receive Ayvakit® (plus best supportive care) had a significantly greater reduction in their self-reported symptom scores (using the ISM-SAF instrument) than did patients receiving placebo and best supportive care (mean change of -15.33 for the Ayvakit® group compared to -9.64 for the placebo group). Differences in the trial were also seen for 3 measures of mast cell burden: percent of patients with ≥ 50 percent reduction in serum tryptase (53.9 versus 0 percent), percent of patients with ≥ 50 percent reduction in peripheral blood KIT D816V allele fraction or undetectable (67.8 versus 6.3 percent), and

percent of patients ≥ 50 percent reduction in bone marrow mast cells or no aggregate (52.8 versus 22.8 percent).

- **Lynparza®** (*olaparib*) -- AZ had the role of its PARP inhibitor in prostate cancer therapy expanded somewhat this month with FDA's approval of its use--in combination with abiraterone and prednisone or prednisolone—in treating adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Data in support of the label expansion come from a large study (n=796) that compared both progression-free and overall survival (PFS and OS) among mCRPC patients randomized to receive Lynparza (with abiraterone) to that of the PFS and OS of patients randomized to receive placebo (with abiraterone). The results were mixed, with the Lynparza arm exhibiting superior PFS but not superior OS when all patients were considered. However, a subsequent analysis, which focused only the subset of 85 patients who were later determined to be BRCA-mutation positive, produced a more positive profile for the AZ drug. Within that group, 70 percent of those treated with Lynparza (compared to only 26 percent of those in the placebo group) remained event free throughout the study period. In addition, being in the Lynparza group reduced the risk of death by 70 percent. Based on these results, and considering toxicities associated with the therapy, FDA decided to limit its approval for use to those mCRPC patients with a demonstrated BRCA mutation.

Accelerated Approvals Reconsidered

- **Imbruvica®** (*imbrutinib*) – The BTK inhibitor developed by Pharmacyclics (and subsequently acquired by Abbvie) first gained market entry in 2013 with an approval for use that was based on responses observed in 73 of 111 mantle cell lymphoma (MCL) patients enrolled in a single arm study. Approval for use in mantle zone lymphoma (MZL) came four years later, again based on response rates in a nonrandomized trial. Because the determinations of "effectiveness" in both MCL and MZL trials was based solely on response to therapy, the approvals were "accelerated" and dependent on the eventual submission of evidence of clinical benefit. The confirmatory randomized trials undertaken to provide such evidence have now been completed and based on FDA's conclusion that primary end-point data from the studies were insufficient to support full approval, Abbvie has decided to voluntarily withdraw both indications from the prescribing information for Imbruvica®**.** Imbruvica remains approved for use in small lymphocytic leukemia/small lymphocytic lymphoma, Waldenström's macroglobulinemia, and in chronic graft-versus-host disease.

New Generics and Biosimilars

Full approvals were granted for:

- *Carmustine* from MSN,
- *Docetaxel* from Mylan Labs,
- *Fosaprepitant dimeglumine* from Piramal Critical,
- *Gefitinib* from Natco,
- *Lenalidomide* from Hetero Labs Ltd,
- *Levoleucovorin calcium* from Hainan Poly Pharm,
- *Paclitaxel* from Teva pharmaceuticals,
- *Pemetrexed* from Shilpa Medicare Ltd., and
- *Zolpidem tartrate* from Almatica

Tentative approvals were granted for:

- *Dasatinib* from Nanocopoeia LLC. branded as Phyrago,
- *Lenalidomide* from Biocon Pharma,
- *Pazopanib* from Sun Pharm Industries,
- *Plerixafor* from Zydus Pharms USA, and
- *Ribociclib* from MSN Labs PVT Ltd.

Safety-related Changes

- **Inrebic®** (*fedratinib hydrochloride*) -- Data from a recently completed pharmacokinetic study were incorporated into Section 13.1 of the prescribing information for BMS' myelofibrosis drug. Based on those data the recommendations for concomitant use of Inrebic with *dual CYP3A4 and CYP2C19 inhibitors* (in Section 7.1) were changed. Whereas the label had previously stated that concomitant use should be avoided, the new language is less definitive, and suggests that concomitant use is appropriate if accompanied with "more intensive safety monitoring and, if necessary, dose modifications."

- **Mekinist®** (*trametinib*) and **Tafinlar®** (*dabrafenib*) -- The prescribing information for both of Novartis's kinase inhibitors—approved for use in combination for treating a range of malignancies—was updated to include a warning that *hemophagocytic lymphohistiocytosis* (HLH) has been observed in the post-marketing setting when the two drugs are used in combination. The warning is included in the label Highlights as well as in a new subsection (5.12) which recommends "(i)f HLH is suspected, interrupt treatment. If HLH is confirmed, discontinue treatment and initiate appropriate management of HLH."

- **Rydapt®** (*midostaurin*)-- Acute *febrile neutrophilic dermatosis* (Sweet Syndrome) was added (in Section 6.2) to the list of adverse reactions observed during the post-marketing period of Novartis' kinase inhibitor.

- **Sustol®** (*granisetron*) – The sentence "Sustol is not recommended for use in pediatric patients less than 12 years of age because the product administration requires a large gauge needle and an extended administration time" was added to the prescribing information for the anti-emetic.

- **Tecentriq®** (*atezolizumab*) – A recommendation to permanently discontinue use of the IO agent in the event of an adverse reaction involving Grade 2, 3, or 4 *pericarditis* was added to the prescribing information (which had already suggested discontinuation in the event of a > Grade 1 *myocarditis*). Also, a new section (6.2) was added on adverse reactions observed during post marketing period. It includes a set of cardiac related adverse events (pericarditis, pericardial effusion, and cardiac tamponade).

Changes in Dosing/Administration

- **Imbruvica® --** The 560 mg tablet, which was used for the now withdrawn indications of mantle cell and marginal zone lymphomas, has also been withdrawn from the market.

New Data

- **Margenza®** (*margetuximab*) -- Macrogenics' targeted therapy was approved in late 2020 based on results from a randomized trial showing that metastatic breast cancer patients treated with the HER2 agonist (and chemotherapy) enjoyed a 24 percent reduction in the risk of progression compared to patients treated with *trastuzumab* (and chemotherapy). Data of overall survival (OS), which had not yet matured at the time of approval, have now added to the study results contained in the prescribing information. Those data show no difference between the two groups: 72.9 percent of patients in the Margenza® arm had died (after a median survival time of 21.6 months) compared to 70.7 percent of those treated with trastuzumab (whose median survival time was 21.9 months.

Other

- **Cotellic®** (*cobimetinib fumarate*) – A footnote in the table showing the efficacy of Genentech KI in histiocytic neoplasms (Table 8) was corrected to indicate that 19 of the 26 patients in the study of response rates (and not 20 as previously noted) were RECIST evaluable**.**