Accelerated Approvals Reconsidered

Tabrecta® (*capmatinib hydrochloride*) – Novartis was notified that the accelerated approval it had received for use of its kinase inhibitor for treating adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping (as detected by an FDA-approved test) has been converted to a full approval. The full approval remains based on overall response rates observed in the same open-label trial that served as the basis for the accelerated approval, albeit with a larger number of patients now having been included in the study.

Changes in Dosing/Administration

Calquence® (*acalabrutinib)* – AstraZeneca received approval to introduce a tablet formulation of its kinase inhibitor. As with the capsule, the tablets will be 100 mg.

Imbruvica® (*ibrutinib*) – Pharmacyclics was given approval to market an oral suspension formulation of its kinase inhibitor. The oral suspension bottle is provided in a carton with two 3 mL reusable oral dosing syringes.

Changes in Labeled Indications

Enhertu® (*fam-trastuzumab deruxtecan*) – With two approvals this month, Daiichi Sankyo's HER2-directed antibody drug conjugate gained a wider role in treating breast cancer (BC) as well as a new indication for use in non-small cell lung cancer (NSCLC).

- The BC approval is for the treatment of adult patient with HER2-low unresectable or metastatic disease who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. It was based on a comparative survival for patients randomized to receive Enhertu (n=373) over that of patients randomized to physician's choice of chemotherapy (n=184). The advantage (a 36 percent reduction in the risk of death and an approximate 50 percent reduction in the risk of recurrence) held for patients irrespective of their hormone receptor status.

- The approval for use as second-line therapy for patients with unresectable or metastatic NSCLC whose tumors have activating HER2 mutations was "accelerated" and based on response rather than demonstrated clinical benefit. Supporting data came from a dose-optimization trial (n=52) in which 57.7 percent of patients responded therapy (95 percent CI of 43.2 – 71.3 percent) and had a median duration of response of 8.7 months. HER2 point mutations are estimated to occur in approximately 4 percent of NSCLCs.

Nubeqa® (*darolutamide*) – Bayer's androgen receptor inhibitor, which came to market in mid-2019 approved for non-metastatic hormone-resistant prostate cancer, is now also approved (in combination with *docetaxel*) for adult patients with metastatic hormone-sensitive disease. The expanded role in the second most common U.S. cancer was supported by evidence from a large (n=1,306) multicenter trial in which patients randomized to receive "Nubeqa® + *docetaxel*" demonstrated superior overall survival compared to patients randomized to treatment with "placebo + *docetaxel*." By study's end, 65 percent of the Nubeqa® patients remained alive and the median number of months of survival for them had not yet been reached. By comparison, only 54 percent of patients in the placebo arm remained alive and they had already reached their median survival time (which was 48.9 months). Overall, the risk of death among Nubeqa® treated patients was 68 percent (95 percent CI or 0.57 – 0.80) of that for patients in the placebo group.

Pemazyre® (*pemigatinib*) – Incyte's small molecule targeting fibroblast growth factor receptors (FGFR), which came to market in 2020 approved for treating cholangiocarcinoma with FGFR2 rearrangements, is now approved for treating patients with relapsed or refractory myeloid/lymphoid cancers with FGFR1 rearrangements. The approval, which includes use for patients in both chronic and blast phases, was based on response to therapy observed in a small single-arm study (n=28). Among the study patients who were in chronic phase, 78 percent achieved a complete response, their median time to response was 104 days, and the median duration of response had not yet been reached. A complete cytogenic response was achieved in 79 percent of all patients (95 percent CI of 59-92 percent).

Imbruvica® (*ibrutinib*) – The kinase inhibitor from Pharmacyclics, which was approved in 2017 for treating adults with chronic graft versus host disease (cGVHD), had its role expanded this month to also include use in pediatric patients ≥ 1 year of age. The expansion was supported by results from a dose finding Phase I/II study of 47 children with moderate to severe cGVHD (median age of 13) who required additional treatment after failure of one or more lines of systemic therapy. Efficacy was established based on an overall response rate of 60 percent (95 percent CI of 44-74 percent), and a 5.3-month median duration of response (95 percent CI of 2.8 – 8.8 months). The median time to response in the study was a little less than one month and the median time from first response to death (or the need for new systemic therapy) was 14.8 months.

Lynparza® (*olaparib*) – AstraZeneca announced its intention to voluntarily withdraw approval for use of its PARP inhibitor for treating patients with advanced ovarian cancers that have deleterious (or suspected deleterious) germline BRCA mutations. The decision was accompanied by a letter alerting healthcare professionals of a "potential detrimental effect on overall survival" of Lynparza compared to chemotherapy that was observed in a subgroup analysis of the results of a Phase III

study. Initial approval for the indication had been based on response rates and duration of response observed in a single-arm trial.

New Biosimilars and Generics

Full approvals were granted for:

- *Lenalidomide* from Apotex, Mylan, and Lotus Pharmaceuticals (5, 10, 15, and 25 mg);
- *Lenalidomide* from Dr. Reddy's (2.5 and 20 mg); and
- *Pemetrexed* from both Amneal and Baxter Healthcare

Tentative Approvals granted for:

- *Bendamustine hydrochloride* from Dr. Reddy's and Slayback but the latter is branded as Vivimusta;
- *Dasatinib* from Lupin;
- *Enzalutamide* from Sandoz;
- *Lenalidomide* from Apotex, Mylan and Lotus Pharmaceuticals (2.5 and 20 mg);
- *Midostaurin* from Lotus Pharmaceuticals; and
- *Trabectedin* from Natco Pharma

New Data

Alimta® (*pemetrexed disodium*) – An update—involving the addition of a single case of an event—was made to the overall survival data for the study examining the combination of Alimta®, pembrolizumab and platinum chemotherapy for the initial treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.

New Molecular Entities

None

Safety-Related Changes

Gleevec® (*imatinib*) – '*Panniculitis (including erythema nodosum)*' has been added (in subsection 6.1) to the list of skin and subcutaneous tissue disorders observed during clinical trials with Novartis' breakthrough kinase inhibitor.

Other Changes

Keytruda® (*pembrolizumab*) and **Lenvima®** (*lenvatinib mesylate*) – The prescribing information for both products, which are approved for use in combination to treat advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not microsatellite instability high, has been

revised to reflect the recent approval by FDA of the Ventena MMR RxDx Panel, a test for identifying patients with pMMR advanced endometrial carcinoma.