

Novel anticancer drugs approved in 2020

Jing Li, Ruquan Wang, Jianjun Gao*

Department of Pharmacology, School of Pharmacy, Qingdao University Medical College, Qingdao, Shandong, China.

SUMMARY Cancer is still a major factor threatening human life around the world, and anticancer drugs remain a huge unmet clinical need. Here, we reviewed novel drugs including new molecular entities and new therapeutic biologics approved in the US, EU, Japan, and China that represent the main advances in anticancer drug research and development in 2020. Small molecule inhibitors targeting oncogenes, antibodies, and antibody drug conjugates (ADCs) are the main anticancer drugs that were approved in 2020. More novel anticancer drugs that possess target activity and that overcome drug resistance are anticipated in the future.

Keywords anticancer, drugs, US, EU, Japan, China

There were approximately 19.3 million new cases of cancer around the world in 2020, and approximately 10 million people died of that disease that year according to the Global Cancer Statistics Report (1). An important therapeutic strategy, anticancer drugs remain a huge unmet clinical need in this era. Here, we review novel anticancer drugs including new molecular entities and new therapeutic biologics that were approved in the US, EU, Japan, and China in 2020 (Table 1).

Lung cancer is the second most common cancer and the leading cause of death from cancer (2.2 million cases, 1.8 million deaths) worldwide (1). There are two main subtypes of lung cancer, small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), that account for about 76% of all lung cancers (2). In the past year, the US Food and Drug Administration (FDA) has approved three anti-NSCLC drugs including selpercatinib, pralsetinib, and capmatinib (Table 1). Selpercatinib and pralsetinib target the RET (rearranged during transfection). Selpercatinib was approved for treatment of RET fusion-positive NSCLC that has spread in adults (3). It was also approved for treatment of advanced or metastatic medullary thyroid cancer and advanced RET fusion-positive thyroid cancer in patients age 12 and older who require systemic therapy (3). Pralsetinib was approved for adult patients who suffer from metastatic RET fusion-positive NSCLC (4). Capmatinib is a kinase inhibitor that targets the MET (mesenchymal-epithelial transition) (5). Capmatinib is mainly used for adults with locally advanced or metastatic non-small cell lung cancer whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping (METex14) (5). Japan approved another

MET inhibitor, tepotinib, for the treatment of patients with unresectable, advanced, or recurrent NSCLC with METex14 (6). Tepotinib was first approved in Japan in 2020 as a "line-agnostic" drug, which means that the drug has been approved for patients who have not received treatment and patients who failed to respond to previous treatment. In 2020, the National Medical Products Administration (NMPA) of China approved two anti-NSCLC drugs: almonertinib and ensartinib. Almonertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was approved for adult patients with locally advanced or metastatic NSCLC who have been treated with EGFR-TKI and who have a T790M mutation (7). Ensartinib is indicated for anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic NSCLC that has progressed after patients received crizotinib therapy or who developed a tolerance to crizotinib (8). NMPA approved ensartinib as a second-generation ALK inhibitor. Although SCLC accounts for a small percentage of lung cancer, it has a shorter doubling time, higher growth fraction, and earlier development of metastases compared to NSCLC. Lurbinectedin, a cytotoxic drug approved in the US, is used to treat adult patients with metastatic SCLC whose disease has progressed during or after platinum-based chemotherapy (9).

Breast cancer (2.3 million cases) surpassed lung cancer (2.2 million cases) as the most common type of cancer worldwide in 2020 (1). Four anti-breast cancer drugs have been approved by the US and China, including 3 drugs targeting human epidermal growth factor receptor 2 (HER2) - inotuzumab, margetuximab, and tucatinib - and 1 antibody-drug conjugate (ADC),

Table 1. Approved anticancer drugs in the US, EU, Japan, and China in 2020

Drug	Target	Indication	Country/District	Ref.
Selpercatinib	RET	Non-small cell lung cancer, thyroid cancer	U.S.	(3)
Pralsetinib	RET	Non-small cell lung cancer	U.S.	(4)
Capmatinib	MET	Non-small cell lung cancer	U.S./Japan	(5)
Tepotinib	MET	Non-small cell lung cancer	Japan	(6)
Almonertinib	EGFR	Non-small cell lung cancer	China	(7)
Ensartinib	ALK	Non-small cell lung cancer	China	(8)
Lurbinectedin	DNA	Small cell lung cancer	U.S.	(9)
Inetetamab	HER2	Breast cancer	China	(10)
Margetuximab	HER2	Breast cancer	U.S.	(11)
Tucatinib	HER2	Breast cancer	U.S.	(12)
Sacituzumab govitecan	TROP-2	Breast cancer	U.S.	(13)
Cedazuridine/decitabine	Cytidine deaminase/ DNA methyltransferase	Myelodysplastic syndromes and chronic myelomonocytic leukemia	U.S.	(14)
Belantamab mafodotin	BCMA	Multiple myeloma	U.S./EU	(15)
Isatuximab	CD38	Multiple myeloma	U.S./EU/Japan	(16)
Tafasitamab	CD19	Diffuse large B-cell lymphoma	U.S.	(17)
Tirabrutinib	BTK	Primary central nervous system lymphoma	Japan	(18)
Orelabrutinib	BTK	Mantle-cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma	China	(19)
Ripretinib	KIT and PDGFRA	Gastrointestinal stromal tumor	U.S.	(20,21)
Avapritinib	PDGFRA	Gastrointestinal stromal tumor	U.S./EU	(22)
Surufatinib	VEGFR and FGFR1	Neuroendocrine tumors	China	(23)
Naxitamab	GD2	Neuroblastoma	U.S.	(24)
Pemigatinib	FGFR2	Cholangiocarcinoma	U.S.	(25)
Cetuximab saratolacan	EGFR	Head and neck cancer	Japan	(26)
fluzoparib	PARP	Ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	China	(27)
Tazemetostat	EZH2	Epithelioid sarcoma	U.S.	(28)

sacituzumab govitecan, which targets tumor-associated calcium signal transducer 2 (TROP-2) (Table 1). Inetetamab combined with vinorelbine was approved in China for patients with HER2-positive metastatic breast cancer who have received one or more chemotherapy regimens (10). In the US, margetuximab combined with chemotherapy is indicated for treatment of adults with metastatic HER2-positive breast cancer who have received two or more anti-HER2 regimens, at least one of which is used for metastatic disease (11). Tucatinib in combination with trastuzumab and capecitabine was approved in the US to treat patients with advanced unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens (12). Sacituzumab govitecan, approved in the US, is a TROP-2-directed antibody and topoisomerase inhibitor drug conjugate for the treatment of adult patients with metastatic triple-negative breast cancer (TNBC) who have previously received at least 2 therapies (13).

Six new drugs to treat hematopoietic malignancies, including cedazuridine/decitabine, belantamab mafodotin, isatuximab, tafasitamab, tirabrutinib and orelabrutinib (Table 1), were approved in the US, EU, Japan, and China in 2020. Decitabine/cedazuridine, which suppresses cytidine deaminase and DNA methyltransferase respectively, was approved as a fixed-dose combination medication for adults with myelodysplastic syndromes (MDS) and chronic

myelomonocytic leukemia (CMML) (14). Belantamab mafodotin and isatuximab are indicated for treatment of multiple myeloma. Belantamab mafodotin, a humanized monoclonal antibody against the B-cell maturation antigen (BCMA) conjugated with the cytotoxic agent maleimidocaproyl monomethyl auristatin F, was approved in the US and EU in 2020 for patients with elapsed or refractory multiple myeloma who have previously received at least four treatments, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulator (15). A CD38-directed cytolytic antibody, isatuximab was approved in the US, EU, and Japan in 2020 for use in combination with pomalidomide and dexamethasone for adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (16). Tafasitamab, tirabrutinib, and orelabrutinib are indicated for treatment of lymphoma. Tafasitamab, a humanized Fc-modified cytolytic CD19 antibody, was approved in the US in combination with lenalidomide, for treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) (17). Both tirabrutinib and orelabrutinib are Bruton's tyrosine kinase (BTK) inhibitors. In Japan, tirabrutinib was approved to treat relapsed or refractory primary central nervous system lymphoma (PCNSL) (18). In China, orelabrutinib was approved for treatment of patients with adult mantle cell lymphoma (MCL) or adult chronic lymphocytic leukemia (CLL)/small

lymphocytic lymphoma (SLL) who have received at least one prior treatment (19).

Other new anticancer drugs approved in the past year include ripretinib for gastrointestinal stromal tumors (GISTs), avapritinib for GISTs, surufatinib for neuroendocrine tumors, naxitamab for neuroblastoma, pemigatinib for cholangiocarcinoma, cetuximab saratolacan for head and neck cancer, fluzoparib for ovarian cancer, and tazemetostat for epithelioid sarcoma. Ripretinib, a kinase inhibitor suppressing KIT and platelet-derived growth factor receptor A (PDGFRA), was approved in the US for treatment of adults with advanced GIST who have received prior three or more kinase inhibitor therapies, including imatinib (20,21). Avapritinib, approved in both the US and EU, is also a PDGFRA inhibitor that is indicated for treatment of adults with unresectable or metastatic GIST harboring the PDGFRA D842V mutation (22). Surufatinib targets the vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor 1 (FGFR1) and was approved in China as a single agent for non-pancreatic and well differentiated neuroendocrine tumors that cannot be surgically removed or are metastatic (23). Naxitamab combined with granulocyte-macrophage colony stimulating factor (GM-CSF) was approved in the US and is indicated for treatment of patients 1 year of age and older with high-risk neuroblastoma in bone or bone marrow (24). Pemigatinib, an inhibitor of fibroblast growth factor receptor 2 (FGFR2), is used to treat patients with locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement who have received previous treatment (25). Cetuximab saratolacan, a chemical conjugate of the photosensitizer IR700 with cetuximab, targets EGFR and was approved in Japan to treat unresectable locally advanced or recurrent head and neck cancer (26). Fluzoparib, a small molecule poly(ADP-ribose) polymerase (PARP) inhibitor, was approved in China to treat patients with platinum-sensitive recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with a germline BRCA mutation (gBRCAm) who have undergone second-line or later chemotherapy (27) (Table 1). Tazemetostat, an inhibitor of enhancer of zeste homolog 2 (EZH2), is indicated for treatment of adults and adolescents age \geq 16 years with metastatic/locally advanced epithelioid sarcoma that is not eligible for complete resection (28).

Although the world struggled with COVID-19 in 2020, significant progress has nonetheless been made in cancer drug research. Small molecule inhibitors targeting oncogenes, antibodies, and antibody drug conjugates (ADCs) were the main anticancer drugs approved in 2020. More novel anticancer drugs that possess target activity and that overcome drug resistance are anticipated in the future.

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- *Address correspondence to:
 Jianjun Gao, Department of Pharmacology, School of Pharmacy, Qingdao University Medical College, #1 Ningde Road, Qingdao 266073, China.
 E-mail: gaojj@qdu.edu.cn