Since the initial clinical approval in the late 1990s and remarkable anticancer effects for certain types of cancer, molecular targeted therapy utilizing small molecule agents or therapeutic monoclonal antibodies acting as signal transduction inhibitors has served as a fundamental backbone in precision medicine for cancer treatment. These approaches are now used clinically as first-line therapy for various types of human cancers. Compared to conventional chemotherapy, targeted therapeutic agents have efficient anticancer effects with fewer side effects. However, the emergence of drug resistance is a major drawback of molecular targeted therapy, and several strategies have been attempted to improve therapeutic efficacy by overcoming such resistance. Herein, we summarize current knowledge regarding several targeted therapeutic agents, including classification, a brief biology of target kinases, mechanisms of action, examples of clinically used targeted therapy, and perspectives for future development.

**INTRODUCTION**

Cancer is one of the main causes of disease-related death worldwide. According to Global Cancer Observatory (GLOBOCAN) estimates of cancer incidence and mortality, there were approximately 19.3 million new cancer cases and almost 10.0 million cancer deaths in 2020 globally. The cancer-related burden (such as incidence and mortality) is expected to be 28.4 million cases in 2040, which is a 47% increase compared with that in 2020, largely due to increases in risk factors, such as aging, socioeconomic development, overweight status, and smoking. Therefore, it is necessary to develop efficacious treatment strategies for patients with cancer.

Several therapeutic modalities, such as surgery, radiation therapy, and systemic anticancer therapy, have been applied clinically for cancer treatment, either alone, in combination, or sequentially, depending on the stage, resectability, biology, comorbidities, and patient’s overall functional performance. Systemic anticancer therapy, involving a wide range of anticancer drugs for treatment, palliation, symptom alleviation, and quality of life improvement, includes cytotoxic chemotherapy, hormonal agents, targeted therapy, and antitumor immunotherapy.

Cytotoxic chemotherapy inhibits the survival of actively proliferating cells by disrupting the synthesis of DNA and RNA, blocking mitosis, and/or forming covalent bonds with DNA, RNA, and proteins, and it has been extensively used in adjuvant or neoadjuvant therapy as well as in palliative therapy. Due to the disadvantages of chemotherapy, including side effects and toxicity associated with nonselective action against actively proliferating normal cells, there has been innovative development of ‘targeted’ cancer treatment with increased cancer cell specificity. Targeted therapy may include the following: conventional molecular targeted agents, such as small molecule inhibitors or antibodies that specifically inhibit signal transduction pathways involved in growth, proliferation, and survival; hormonal agents such as estrogen receptor (ER) antagonists and aromatase inhibitors, which have been used for treatment of hormone receptor (HR)-dependent breast cancer and male and female reproductive cancers; immune checkpoint inhibitors (e.g., antibodies against programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)), which activate host antitumor immunity in a direct or indirect manner; and even targeted cytotoxic therapy that interferes with a specific cellular target (e.g., methotrexate, a dihydrofolate reductase inhibitor). Despite the anticancer effectiveness of these targeted therapies, these drugs are only applicable for patients harboring targetable driver mutations or aberrations. In addition, side effects or toxicity caused by unexpected cross-reactivity with normal cells and emergence of intrinsic or acquired drug resistance hamper their effectiveness. Notwithstanding some limitations, targeted therapy has resulted in remarkable survival benefits in some types of cancer and has led to a revolution in the fundamental concept of cancer treatment, providing the fundamental backbone for evolution toward precision or personalized medicine in cancer. Herein, we summarize current knowledge with respect to molecular targeted therapy, including the history, types, and mechanism of action, and provide examples of clinically available targeted therapy. In this paper, ‘targeted therapy’ is confined to conventional molecular targeted therapy (signal transduction inhibitors).

**Brief history of molecular targeted therapy**

Paul Ehrlich first proposed the concept of targeted therapy in the 1890s as a “magic bullet” that would be completely specific for the target and thus safe without any additional toxicity. This theory was initially applied to infectious diseases but not to anticancer therapy due to insufficient knowledge of the etiology and biology of cancer; however, this concept has since been expanded to cancer treatment. Trastuzumab, an anti-HER2 monoclonal antibody, and imatinib, a small molecule tyrosine...
kinase inhibitor targeting the BCR-ABL fusion-mediated aberrantly activated ABL kinase, were developed and clinically approved in 1998 and 2001 for treatment of HER2-positive breast cancer and Philadelphia chromosome-positive chronic myelogenous leukemia, respectively\(^{14,17-19}\). The success of imatinib in the clinic has served as the paradigm for extensive use of small molecule kinase inhibitors as anticancer therapy\(^\text{21,26}\), and a number of anticancer molecular targeted therapies have been approved for clinical use in cancer patients\(^\text{21,27}\). The timeline for the development of the main molecular targeted therapy is illustrated in Fig. 1.

### Types, mechanisms of action and resistance, and adverse effects/toxicity of molecular targeted therapy

To date, numerous molecular targeted therapeutic agents have been used clinically for cancer treatment. The classification of molecular targeted therapeutic agents and their targets, mechanism of action, side effects, and toxicity are described below.

#### Types of molecular targeted therapy

The two major types of molecular targeted therapy are monoclonal antibodies (mAbs) and small molecule kinase inhibitors (SMKIs)\(^\text{28}\). mAbs target extracellular ligands (e.g., bevacizumab targets vascular endothelial growth factor [VEGF]), membrane receptors (e.g., trastuzumab targets HER2 and cetuximab; panitumumab targets EGFR), and membrane-bound proteins (e.g., rituximab targets CD20), acting through ligand-binding blockade, ligand–receptor interaction neutralization, or target molecule internalization/degradation\(^\text{14,20}\).

Except for inhibitors targeting nonkinase cellular proteins (e.g., mutated KRAS and proteasome) or epigenetic modulators (e.g., histone deacetylases), most SMKIs suppress protein kinases involved in the transformation, growth, proliferation, and survival of cancer cells. As deregulation of protein kinases (e.g., activation by gain-of-function genetic mutation, gene amplification, autonomous activation, and chromosomal rearrangement) has been associated with cancer development and progression\(^\text{21-24}\), protein kinases have been regarded as important targets for developing molecular targeted therapies. Protein kinases are classified into receptor tyrosine kinases, nonreceptor (cytoplasmic) tyrosine kinases, serine/threonine kinases, and lipid kinases based on their subcellular localization, substrate type, and hallmark roles in cancer\(^\text{23}\) (Fig. 2). A detailed explanation of the signal transduction by receptor tyrosine kinase is described in previous studies\(^\text{25,26}\).

SMKIs block the enzymatic activity of the aforementioned kinases via several modes of action\(^\text{26}\). Type I kinase inhibitors bind to the ATP-binding pocket of the active conformation of the enzyme [DFG (Asp-Phe-Gly)-in and α-helix-in]\(^\text{26}\), whereas type I\(^{1/2}\) or type II inhibitors bind the enzyme in an inactive conformation (type I\(^{2/2}\): DFG-Asp in; type II: DFG-Asp out)\(^\text{21,26}\). Type III and type IV inhibitors allosterically suppress kinase activity by binding either to a site next to the ATP-binding pocket or one remote from the ATP-binding pocket located in the kinase substrate-binding site\(^\text{21,26,27}\). Type V inhibitors act as bivalent inhibitors binding to two different portions of the kinase lobe\(^\text{26}\). Type VI inhibitors covalently bind an enzyme to inhibit kinase activity\(^\text{28}\). A recent paper describes the detailed mode of action of each type of kinase inhibitor\(^\text{26}\), and some examples are listed in Table 1.

#### Mechanisms of the anticancer effects of molecular targeted therapy

Molecular targeted therapies achieve anticancer effects through various mechanisms, such as inhibition of cell proliferation, metastasis, and angiogenesis, induction of apoptosis, and reversal of multidrug resistance\(^\text{2} \) (Fig. 2a). Several molecular targeted therapeutic agents also facilitate host antitumor immunity by potentiating CD8\(^+\) T-cell recruitment and natural killer cell cytotoxicity, downregulating immunosuppressive myeloid cells, and inducing immunogenic cell death, either alone or in combination with chemotherapeutic agents\(^\text{29}\). Therapeutic mAbs create a bridge between tumor cells and immune cells via Fab region-mediated binding to a target protein of tumor cells and recognition of immune cells through the Fc region of antibodies\(^\text{30}\), resulting in opsonization and antibody-dependent cellular cytotoxicity (ADCC) toward tumor cells\(^\text{30}\) (Fig. 2b). A recent study demonstrated that neutrophils mediate trogoptosis (Fig. 2c), the phenomenon of transferring surface molecules of interacting cells onto immune cells\(^\text{31,32}\), which causes lytic/necrotic death of antibody-opsonized cancer cells\(^\text{33}\). mAbs and SMIs also exert immune cell-induced cytotoxic effects on cancer cells by activating complement and complement-dependent cytotoxicity\(^\text{34}\), facilitating antigen processing by increasing expression of major histocompatibility complex molecules\(^\text{30,35,36}\) and regulating cytokine/chemokine expression\(^\text{30,37}\).

#### Mechanisms underlying resistance to molecular targeted therapy

The emergence of drug resistance is a major hurdle of efficacious anticancer treatment. Primary (intrinsic) resistance is defined as a refractory status to initial therapy due to intrinsic cellular, genetic, and/or epigenetic alterations. Hyperactivation of compensatory signaling pathways [e.g., truncated HER2 expression (p95HER2) for resistance to anti-HER2 mAbs\(^\text{38}\); KRAS mutation or MET amplification for resistance to anti-EGFR therapy\(^\text{38,39}\)], mutations in kinase domains (e.g., EGFR exon 20 insertion for resistance to anti-EGFR therapy\(^\text{38}\)), isofrom switching (e.g., BRAF/CRAF switching for resistance to anti-BRAF therapy\(^\text{40}\)), and metabolic reprogramming\(^\text{41}\) during disease development are involved in primary resistance to molecular targeted therapy.

Human cancers often exhibit substantial intratumor heterogeneity, which is a main driver for emerging acquired therapy resistance as a result of expansion of rare preexisting refractory populations during treatment in initial responders\(^\text{39,47,42}\). Various molecular and cellular alterations [e.g., development of secondary mutations [EGFR T790M and C797S\(^\text{38,43,44}\), BCR-ABL T315I\(^\text{44}\), BRAF V600E\(^\text{40,44}\), Bruton’s tyrosine kinase (BTK) C418S\(^\text{44}\), anaplastic lymphoma kinase (ALK) G1202R, and ROS1 G2032R and 2036T\(^\text{44}\)] in noncoding RNAs\(^\text{44}\), activation of bypassing signaling pathways, including MET, HER2, type I insulin-like growth factor receptor (IGF-1R), and AXL\(^\text{43,45}\), mutations in BRAF, PTEN, PIK3CA, and MAP2K1\(^\text{43,45,46}\), interaction with stromal cells in the tumor microenvironment\(^\text{43,46}\), alterations in E3 ubiquitin ligases\(^\text{47}\), reactivation of developmental pathways, such as the epithelial-mesenchymal transition (EMT), acquisition of cancer stem cell (CSC)-associated phenotypes, and transdifferentiation to small-cell lung cancer\(^\text{48}\) have also been shown to induce acquired therapy resistance. The mechanisms...
of resistance to each molecular targeted therapy are summarized in Tables 2–6.

Adverse effects and toxicity of molecular targeted therapy. Despite improved specificity for cancer cells, epidemiological studies have indicated that cancer patients who receive targeted therapy may experience various side effects and toxicity. The side effects of targeted therapy include asthenia, anorexia, dyspnea, diarrhea, nausea, vomiting, mucositis, skin rash, fever, hand-foot syndrome, fatigue, cardiotoxicity, hypertension, and bleeding.45,50

Table 1. Classes of selected kinase inhibitors26,28.

| Class | Mechanism of action | Examples |
|-------|---------------------|----------|
| Type I | Binding in the ATP-binding pocket of the active conformation of the enzyme (DFG-in and αC-helix-in) | cabozantinib, ceritinib, gefitinib, palbociclib, pazopanib, ponatinib, ruxolitinib, tofacitinib |
| Type I1/2 | Binding in the ATP-binding pocket of the inactive conformation of the enzyme (type I1/2: DFG-Asp in; type II: DFG-Asp out) | dasatinib, imatinib, lapatinib, lenvatinib, nilotinib, regorafenib, sorafenib, sunitinib, vemurafenib |
| Type III | Allosteric inhibitors binding to a site in the kinase domain either next to the ATP-binding pocket or remote from the ATP-binding pocket | trametinib, everolimus, sirolimus, temsirolimus |
| Type IV | Covalent inhibitors | afatinib, ibrutinib |
| Type V | Bivalent inhibitors that bind two different portions of the kinase lobe | lenvatinib28 |
| Type VI | Covalent inhibitors | lenvatinib is classified as a type I1/2 inhibitor. |

In Ref. 26, lenvatinib is classiﬁed as a type I1/2 inhibitor.
| Target | Genetic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|--------|--------------------------|----------------------|---------------------------------|----------------------------------------------------------|-------------------------------|------------|
| EGFR   | Gefitinib (ZD1839)       | Iressa (AstraZeneca)  | Advanced NSCLC after failure of both platinum-based and docetaxel chemotherapy (2003) | EGFR T790M mutation, MET amplification, HER2 amplification | Skin rash, nausea, diarrhea, transaminitis, ILD-like disorders, hematotoxicity | 8,12,195   |
| EGFR   | Erlotinib (OSI-744)       | Tarceva (Roche/Astellas) | Locally advanced or metastatic NSCLC after failure of prior chemotherapy regimen (2004) | Metastatic NSCLC harboring EGFR mutations (first-line therapy, 2013) | Skin rash, diarrhea, mucositis, pneumonitis, cardiac failure | 8,50,52,64,195 – 197 |
| EGFR   | Afatinib (BIBW2992)       | Gilotrif (Boehringer Ingelheim) | Metastatic NSCLC with kinase activating mutations (2013) | Advanced squamous cell carcinoma of the lung after treatment with platinum-based chemotherapy (2016) | Skin rash, diarrhea, ocular toxicity | 196,198,199 |
| EGFR   | Dacomitinib (PF-00299804) | Vizimpro (Pfizer)    | Metastatic NSCLC with kinase activating mutations (2018) | EGFR T790M/C797S mutation | Skin toxicity, dermatitis acneiform, paronychia, diarrhea | 67,200,201 |
| EGFR   | Osimertinib (AZD9291)     | Targrisso (AstraZeneca) | 1st- or 2nd-generation EGFR-TKI-refractory NSCLC (2015) | Advanced NSCLC with mutated EGFR, regardless of T90M mutation (2018) | Skin rash, diarrhea, mucositis/stomatitis, paronychia, pneumonia, cardiac failure | 8,79,195,202 – 204 |
| EGFR   | Lazertinib (YH25448)      | Leclaza (Yuhan/Janssen) | Advanced or metastatic NSCLC (2021) | Loss of EGFR T790M mutation | Skin rash, itchiness, paresthesia, muscle spasm, headache, diarrhea, anorexia | 72 |
| EGFR   | Cetuximab (ImClone)       | Erbitux (ImClone)    | Metastatic CRC (2004) | RAS/BRAF mutation | Infusion reactions, acneform skin rash, nail disorder | 87 – 89,205 – 208 |
| EGFR   | Panitumumab (Abgenix/Amgen) | Vectibix (Abgenix/Amgen) | Metastatic CRC (2006) | MET amplification | Integument toxicity, skin toxicity, diarrhea | 88,89,206,208 |
| EGFR   | Amivantamab (JNJ-61186372) | Rybrevant (Janssen Biotech) | Advanced NSCLC with EGFR exon 20 insertion mutations progressing after platinum-based chemotherapy (2021) | Infusion reactions, ocular toxicity, peripheral edema, hypalbuminemia | Skin rash, diarrhea, nail disorder | 79,80 |
| EGFR   | Mobocertinib (TAK-788)    | Pramlintumab (Pfizer) | Advanced NSCLC with EGFR exon 20 insertion mutations progressing after platinum-based chemotherapy (2021) | Locally advanced or metastatic HER2-expressing or HER2-unresectable gastric or gastroesophageal junction adenocarcinoma in combination with pembrolizumab (2021) | Skin rash, diarrhea, nail disorder | 85,86,90,209 |

Table 2. Receptor tyrosine kinase inhibitors that have been clinically used for cancer treatment.
| Target | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|--------|--------------------------|----------------------|---------------------------------|----------------------|--------------------------------------|----------------------------------|------------|
| HER2   | Pertuzumab               | Perjeta (Genentech/Roche) | HER2+ early breast cancer (EBC) with high risk of recurrence (2017) |  |  | Diarrhea, nausea, alopecia, fatigue, peripheral neuropathy, vomiting | 8,9, 210 |
| HER2   | Zanidatamab (ZW25)       | (Zymeworks)          | Advanced/metastatic HER2-expressing biliary tract cancers |  |  | Diarrhea, infusion-related reactions | 91 |
| HER2   | Lapatinib (GW-572016)    | Tykerb (GliaxOsmithKline/Novartis) | HER2+ metastatic breast cancer progressing with prior therapy (in combination with capecitabine, 2007) |  | Crosstalk with ER HER2 mutation PIK3CA mutation AXL elevation HER2 L755S mutation | Diarrhea, skin rash, asymptomatic cardiotoxicity | 82, 83, 209, 211 |
| HER2   | Neratinib (HKI-272)      | Nerlynx (Puma Biotechnology) | Extended adjuvant therapy for HER2+ breast cancer (2017) | Advanced or metastatic HER2+ breast cancer progressing with prior therapy (in combination with capecitabine, 2020) |  | Diarrhea | 56, 84, 209, 211, 212 |
| HER2   | Tucatinib (ONT-380)      | Tukysa (Seattle Genetics) | Advanced or metastatic HER2+ breast cancer (in combination with trastuzumab and capecitabine, 2020) | HER2 L755S mutation |  | Diarrhea, cardotoxicity | 85, 211 |
| ALK    | Crizotinib (PF-02341066) | Xalkori (Pfizer)     | Locally advanced or metastatic ALK+ NSCLC (2011) | ROS1-positive NSCLC (2016) | ALK mutation (G1269A, C1565V, E1210K, I1171T, S1206C/V, I1151T/N/S, 1174 C/L/V, V1180L, L1196M) | Nausea, vomiting, diarrhoea, visual disturbance, sinus bradycardia, liver enzyme abnormalities | 79, 96, 98, 99, 213 |
| ALK    | Ceritinib (LDK378)       | Zykadia (Novartis)   | ALK+ metastatic NSCLC after failure of crizotinib therapy (2014) | ALK+ metastatic NSCLC (first-line therapy, 2017) | ALK mutation (G1202R, F1174C/L/V, I1151Tins, L1152P, C1156Y) | Diarrhea, nausea, vomiting, fatigue, elevated level of transaminase | 95, 96, 213 |
| ALK    | Alectinib (CH5424802)    | Alecensa (Chugai Pharmaceutical/Roche) | ALK-rearranged advanced/ recurrent NSCLC with crizotinib resistance (2015) | ALK+ metastatic NSCLC (first-line therapy, 2017) | ALK mutation (G1202R, V1180L and I1171T/N/S) | Photosensitivity, dysgeusia, myalgia, upregulated creatinine phosphokinase | 79, 96, 213 |
| ALK    | Brigatinib (AP26113)     | Alunbrig (ARIAD Pharmaceuticals) | ALK-rearranged metastatic NSCLC (2017) | ALK+ metastatic NSCLC (first-line therapy, 2017) | ALK mutation (G1202R, V1180L and I1171T/N/S) | Photosensitivity, dysgeusia, myalgia, upregulated creatinine phosphokinase | 79, 101, 102, 213 |
| ALK    | Lorlatinib (PF-6463922)  | Lorbruna (Pfizer)    | ALK-rearranged metastatic NSCLC (2018) (second/third-line treatment, accelerated approval) | ALK+ metastatic NSCLC (2021) (regular approval) | ALK mutation (G1202R, E1171T, S1206C/Y, I1171T/N/S, 1174 C/L/V, L1198F) | Edema, cholestasis, peripheral neuropathy, hypertriglyceridaemia, CNS effects | 8, 92, 203 |
| MET    | Capmatinib (INC2980)     | Tabrecta (Novartis)  | Metastatic NSCLC harboring MET exon 14 skipping (2020) | Metastatic NSCLC harboring MET exon 14 skipping (2020) | ALK L1257F mutation MET amplification | Nausea, diarrhoea, peripheral edema, hypoalbuminaemia, increased blood creatinine | 79, 99, 214 |
| MET    | Tepotinib (BMD 1214063)  | Tepmetko (Merck)    | Metastatic NSCLC harboring MET exon 14 skipping (2020) | Metastatic NSCLC harboring MET exon 14 skipping (2020) | | Nausea, vomiting, peripheral edema, hypoalbuminaemia, increased blood creatinine | 79, 99, 214 |
| Target | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|---|---|---|---|---|---|---|---|
| TRK | Larotrectinib (LOXO-101) | Vitrakvi (Loxo Oncology/ Bayer) | Locally advanced or metastatic solid tumors with NTRK gene fusion (2018) | TRKA F589L/G595R/G667C, TRKC G623R/G696A mutation | Upregulation of serum AST/ALT, dizziness, fatigue, nausea, constipation | | 106, 107 |
| TRK | Entrectinib (RXDX-101) | Rozlytrek (Genentech) | Solid tumors with NTRK gene fusion and NSCLC harboring ROS1 rearrangement (2019) | TRKA G595R/G667C, TRKC G623R mutation | | | |
| FLT3 c-KIT PDGFRα/β | Midostaurin (PKC412, CGP 41251) | Rydapt (Novartis) | AML harboring FLT3 mutations (2017) | FLT3 N676K, F691L mutation FLT3 ligand overexpression JAK, PI3K/Akt activation | Nausea, febrile neutropenia, mucositis, vomiting, dermatitis, fever | | 106, 107, 215–217 |
| FLT3 AXL | Gilteritinib (ASP2215) | Xospata (Astellas Pharma) | FLT3-mutated refractory AML (2018) | FLT3 F691L mutation JAK, PI3K/Akt activation | Upregulation of hepatic transaminase/creatinine phosphokinase, edema, cytopenia, febrile neutropenia | | 106, 107, 215–217 |
| PDGFRα/β | Sorafenib (BAY 43-9006) | Nexavar (Bayer/Onyx Pharmaceuticals) | Advanced RCC (2005) | HCC (2008) Locally recurrent or metastatic, progressive DTC refractory to radioactive iodine treatment (2013) | Hand-foot syndrome, asthenia, gastrointestinal irritation, cytopenia, infection, diarrhea, cardiovascular toxicity, fatigue | | 106, 107, 215–217 |
| PDGFRα/β | Sunitinib (SU11248) | Suotent (Pfizer) | Advanced RCC (2006) Imatinib-resistant GST (2006) | Pancreatic neuroendocrine tumor (2011) | Angiogenic factor upregulation Autophagy Metabolic adaptation Stromal cell recruitment | Mucositis, diarrhea, skin abnormality, taste alteration | 8, 126, 218, 219 |
| PDGFRα/β | Pazopanib (GW786034) | Votrient (GlaxoSmithKline/ Novartis) | Advanced/metastatic RCC (2009) | Advanced soft-tissue sarcoma previously treated with chemotherapy (2012) | Angiogenic factor upregulation Stromal cell recruitment | Hepatic injury, fatigue, hand-foot syndrome, myelosuppression | 220 |
| PDGFRα/β | Lenvatinib (E7080) | Lenvima (Eisai/Merck) | Progressive radioactive iodine-refractory thyroid cancer (2015) | Advanced RCC (recurrent or metastatic) (2016) Unresectable HCC (2018) Advanced RCC in combination with pembrolizumab (2021) | Angiogenic factor upregulation Stromal cell recruitment | Hypertension, diarrhea, fatigue/asthenia | 220 |
| MET | Cabozantinib (XL184) | Cometriq (capsule) Cabometyx (tablet) (Exelixis) | Cometriq: medullary thyroid cancer (2012) Cabometyx: RCC (2016) | Cabometyx: HCC (second-line, 2019) | Angiogenic factor upregulation Stromal cell recruitment | Diarrhea, palmar-plantar erythrodysesthesia syndrome | 220 |
| VEGFRs | Axitinib (AG 013736) | Inlyta (Pfizer) | Advanced or metastatic RCC (2012) | Angiogenic factor upregulation Stromal cell recruitment | Hypertension, diarrhea, fatigue | | 220 |
| Target | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|--------|--------------------------|----------------------|---------------------------------|----------------------|--------------------------------------|---------------------------------|------------|
| VEGFR2 | Vandetanib (ZD6474)     | Zactima (AstraZeneca) | Medullary thyroid cancer (2011)  | RET V804M/L mutation Activation of RAS/ RAF/ MEK pathway | | Diarrhea, skin rash, folliculitis, nausea, fatigue, hypertension, QT interval prolongation | 221 |
| VEGFR1/2/3 Tie2 PDGFR-α/β FGFR1/2 c-Kit RET RAFs | Regorafenib (BAY 73-4506) | Stivarga (Bayer) | Metastatic CRC (2012) | Advanced GIST (2013) Advanced HCC (2018) | KIT V654A, D816V mutation | Hypertension, hand-foot skin reaction, diarrhea, fatigue | 220, 222 |
| VEGFR1/2/3 Tie2 PDGFR-α/β FGFR1/2 c-Kit RET RAFs | Tivozanib (AV-951, KRN-951) | Fotivda (AVEO Pharmaceuticals/Kyowa Kirin) | Relapsed or refractory RCC (2021) | | Infiltration of myeloid cells | | 223 |
| PDGFR-α c-Kit | Avapritinib (BLU-285) | Ayvakit (Blueprint Medicines) | Unresectable or metastatic GIST harboring PDGFRα exon 18 mutations, including D842V (2020) | | Memory impairment, cognitive disorder, intracranial bleeding | | 222 |
| PDGFR-α c-Kit | Ripretinib (DCC-2618) | Qinlock (Deciphera Pharmaceuticals) | Advanced GIST treated with three or more kinase inhibitors, including imatinib (2020) | | Alopeia | | 222 |
| FGFRs | Erdafitinib (JNJ-42756493) | Balversa (Janssen Pharmaceuticals) | Metastatic urothelial cancer (2018) | Metastatic or locally advanced bladder cancer with an FGFR3 or FGFR2 alteration (2019) | FGFR1 V561M/F mutation FGFR2 N549H mutation p.E565A and p.L617M single-nucleotide variants | Hyperphosphatemia, dry mouth, diarrhea, fatigue, stomatitis | 91, 224, 225 |
| FGFRs | Pemigatinib (INCB054828) | Pemazyre (Incyte Corporation) | Previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with FGFR2 fusion or other rearrangements (2020) | | | Hyperphosphatemia, dry mouth, diarrhea, fatigue, stomatitis | 91, 224, 225 |
| FGFRs | Futibatinib (TAS-120) | (Taiho Pharmaceutical) | Locally advanced/metastatic cholangiocarcinoma with FGFR2 gene rearrangement (2021) | p.E565A and p.L617M single-nucleotide variants FGFR2 V564F mutation | | Hyperphosphatemia, dry mouth, diarrhea, paronychia, | 91, 224, 225 |
| FGFRs | Infigratinib (BGJ398) | Truseltiq (OED Therapeutics/Helsinn) | Locally advanced/metastatic cholangiocarcinoma with FGFR2 gene rearrangement (2021) | | | Hyperphosphatemia, dry mouth, diarrhea, fatigue, stomatitis | 91, 224, 225 |
| FGFRs | Derazantinib (ARQ 087) | (Basilea Pharmaceutica/Merck) | Intrahepatic cholangiocarcinoma (2021) | | | Hyperphosphatemia, dry mouth, diarrhea, fatigue, stomatitis | 91, 224, 225 |
Specifically, acneiform rash, a skin rash with an acne-like appearance, is a common side effect of anti-EGFR therapy, and hypertension is a common side effect of bevacizumab and anti-VEGF receptor (VEGFR) therapy. These common side effects are related to therapy response. Severe toxicities, such as colitis, digestive perforation, toxic cardiomyopathy, pneumonitis/interstitial lung disease, acute respiratory distress syndrome, posterior reversible encephalopathy syndrome, necrotizing fasciitis, acute renal failure, and hypersensitivity, have been observed in patients receiving molecular targeted therapy, such as antiangiogenic agents, anti-EGFR therapy, and anti-HER2 therapy. The side effects and toxicity of each molecular targeted therapy are summarized in Tables 2–6.

**SMKIs and mAbs in targeted cancer therapy**

By focusing on U.S. Food and Drug Administration (FDA)-approved kinase inhibitors, target kinases and examples of clinically used inhibitors are briefly introduced below.

**Receptor tyrosine kinase inhibitors**

Inhibitors targeting the EGFR family: The human EGFR family comprises four members of the ErbB lineage of proteins (ErbB1/EGFR, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4). Except for HER2, due to its inability to bind ligand, EGFR family members form homo- and heterodimers and are activated via binding of ligands, such as EGF, epiregulin, transforming growth factor-α (TGF-α), and neurengulins. Approximately 25% of all types of breast cancer patients show HER2 gene amplification or overexpression. EGFR kinase-activating mutations (e.g., exon 19 microdeletions and L858R point mutations in the cytoplasmic tyrosine kinase domain, truncation of extracellular domain [EGFRvIII]) as well as overexpression without genetic alterations may occur in solid tumors. These genetic changes cause abnormal EGFR activation in a ligand-independent fashion. Exon 19 microdeletions and L858R point mutations are commonly found in patients with non-small cell lung cancer (NSCLC), particularly in nonsmoking East Asian females, and EGFRvIII is frequently observed in glioblastoma. Additional EGFR mutations, including E884K, D761Y, T854A, and exon 20 insertion, have been detected in NSCLC and found to confer EGFR TKI resistance.

Several EGFR TKIs have been developed over the past decades and are clinically used for treatment of patients with NSCLC harboring kinase-activating mutations (Table 2). Gefitinib and Erlotinib are first-generation EGFR-TKIs that interact with the ATP-binding pocket of EGFR in either the active or inactive conformation. Second-generation EGFR TKIs, such as Afatinib and Dacomitinib, are irreversible EGFR inhibitors that covalently bind to the ATP-binding pocket of EGFR. Despite the great efficacy of first- and second-generation EGFR-TKIs in patients with kinase-activating mutations in EGFR, the EGFR T790M mutation in exon 20 is associated with acquired resistance to these first- and second-generation EGFR-TKIs (e.g., approximately half of NSCLC patients acquire resistance to first-generation EGFR-TKIs). EGFR T790M provides advantages for the growth and survival of cancer cells and limits the therapeutic efficacy of EGFR TKIs through both steric hindrance and potentiated ATP binding. Accordingly, EGFR TKIs targeting the T790M mutation have been developed and clinically utilized. Osimertinib, a third-generation EGFR TKI, inhibits EGFR kinase activity by forming a covalent bond with the cysteine-797 residue in the ATP-binding pocket and shows an approximately 200 times greater inhibitory effect on mutant EGFR [L858R or exon 19 deletion mutations additionally harboring T790M (L858R/T790M or exon19del/T790M)] than on wild-type EGFR. Another third-generation EGFR TKI, Lazertinib, is an orally available, CNS-penetrable, and irreversible EGFR TKI that inhibits EGFR T790M and kinase-activating mutations. Despite the approval of these agents for...
clinical use, clinical trials evaluating recently developed EGFR TKIs, including ceritinib (CI-1033, a pan-ErbB inhibitor), nabatinib (ASP8273, third-generation EGFR TKI), and rociletinib (CO-1686, third-generation EGFR TKI), have been discontinued owing to safety and risk/benefit issues. Nonetheless, EGFR cysteine-797 mutation was found in 14% of NSCLC patients with acquired osimertinib resistance, leading to the development of fourth-generation EGFR TKIs. Several fourth-generation EGFR TKIs (e.g., BLU-945, EIA045, and OBX02-011) that target EGFR T790M and EGFR C797S have been evaluated in preclinical and clinical settings. Additionally, two inhibitors targeting EGFR exon 20 insertions, such as avamitamab and mobocertinib, have been recently approved for the treatment of patients with advanced NSCLC with progression after platinum-based chemotherapy (Table 2). SMKIs approved to date for clinical use in patients with HER2-positive breast cancer include lapatinib, neratinib, and tucatinib. Lapatinib is an orally available TKI that reversibly interacts with the ATP-binding site of EGFR and HER2 and neratinib is an orally available agent that covalently binds to the ATP-binding site of the tyrosine kinase domain of EGFR and HER2, resulting in irreversible EGFR/HER2 inhibition. Tucatinib is an orally available, selective, and reversible HER2 inhibitor that competitively interacts with the ATP-binding site of HER2. Several clinical trials for recently developed HER2-targeting TKIs are also ongoing.

In addition to SMKIs, mAbs targeting EGFR and HER2 have been used in the clinic (Table 2). EGFR mAbs, including cetuximab and panitumumab, have been clinically used for treatment of patients with metastatic colorectal cancer. HER2-targeting mAbs, such as trastuzumab and pertuzumab, are approved for clinical use in patients with HER2-positive breast cancer. Recently, the HER2-bispecific antibody zanidatamab was approved for patients with HER2-expressing biliary tract cancers, and several clinical trials for recently developed HER2-targeting monoclonal antibodies are ongoing.

ALK inhibitors: ALK is an receptor tyrosine kinase (RTK) with structural homology to leukocyte tyrosine kinase (LTK), which belongs to the insulin receptor superfamily. In normal tissues, ALK expression is predominant in the nervous system and is known to play an important role in physiological regulation of nervous system development and function. Chromosomal rearrangements of the ALK gene and consequent generation of a fusion protein with a number of partner proteins, including echinoderm microtubule-associated protein-like 4 (EML4), nucleo-fusion protein with a number of partner proteins, including rearrangement of the ALK gene and consequent generation of a fusion, or ALK mutations lead to increased EGFR expression and activation. ALK mutations have been found in several types of cancer, such as anaplastic lymphoma, neuroblastoma, and NSCLC. ALK alterations have been found in several types of cancer, such as 3–7% of patients with NSCLC, especially for those with the adenocarcinoma subtype, have been reported to harbor ALK rearrangements; ALK mutations are mutually exclusive with KRAS and EGFR mutations.

Several ALK inhibitors are currently available in the clinical setting (Table 2), and these drugs are approved for the treatment of NSCLC patients. Crizotinib, a first-generation ALK inhibitor, is an orally available ATP-competitive inhibitor that was clinically approved in 2011. Crizotinib was initially developed as a MET inhibitor; however, based on the inhibitory effect of crizotinib on ALK at pharmacologically relevant concentrations and the structural homology of the ATP-binding site between ALK and ROS1, the clinical efficacy of crizotinib has been evaluated in patients carrying alterations in these genes. Consequently, crizotinib has been used as a first- or second-line therapy in patients with NSCLC harboring ALK, ROS1, or MET alterations. However, due to the rapid emergence of resistance to crizotinib and its weak ability to penetrate the central nervous system (CNS), additional ALK inhibitors have been developed. The second-generation ATP-competitive ALK/ROS1 inhibitor ceritinib and the ATP-competitive ALK inhibitor alecinitib have been approved for treatment of patients with crizotinib resistance. In contrast to crizotinib and ceritinib, alecinitib can penetrate the CNS, curing NSCLC patients with brain metastasis and preventing progression of CNS metastasis. Additional blood–brain barrier (BBB)-permeable ATP-competitive ALK TKIs have been developed, including brigatinib, which is effective against FMS-like tyrosine kinase 3 (FLT3), insulin-like growth factor receptor (IGF-1R), EGFR, and several ALK mutations associated with resistance to crizotinib, ceritinib, and alecinitib, and lorlatinib, with inhibitory effects against all recognized ALK mutations except the L1198F mutation.

MET inhibitors: MET is an RTK activated by hepatocyte growth factor (HGF) and mediates several physiological processes, such as embryogenesis and tissue repair; aberrant activation of MET by genetic alterations plays an important role in the proliferation, invasion, and metastasis of tumor cells. Alterations in the MET gene, such as amplification, mutation, and alternative splicing (MET exon 14 skipping), have been detected in NSCLC and other solid tumors. MET overexpression is associated with poor prognosis and resistance to chemotherapy agents, including EGFR targeted therapy. In addition, MET gene exon 14 skipping leads to constitutive activation of the MET signaling pathway and confers sensitivity to MET inhibitors. MET inhibitors, such as orally available ATP-competitive small-molecule TKIs and monoclonal antibodies, have been developed and evaluated in preclinical and clinical trials. Among them, capmatinib and tepotinib are approved for clinical use in treatment of patients with metastatic NSCLC harboring MET exon 14 skipping (Table 2).

TRK and FLT3 inhibitors: Neurotrophic tyrosine receptor kinases (NTRKs) are oncogenes that encode tropomyosin receptor kinase (TRK) proteins, including TRKA, TRKB, and TRKC. TRKs are activated by binding of intrinsic neurotrophin ligands, such as nerve growth factor (NGF) for TRKA, brain-derived neurotrophic factor (BDNF) and neurotrophin 4 (NT-4) for TRKB, and neurotrophin 3 (NT-3) for TRKC. NTRK gene fusion caused by chromosomal rearrangements of NTRK genes with various fusion partners drives ligand-independent, constitutive activation of TRKs, which has been found in a wide range of cancer types, including mammary analog secretory carcinoma, secretory breast carcinoma, and infantile fibrosarcoma. FLT3-CD135, a class III RTK, is exclusively expressed in hematopoietic stem and progenitor cell populations. Constitutive activation of FLT3 kinase through internal tandem duplications (FLT3-ITD) or missense mutations in the FLT3 tyrosine kinase domain has been observed in approximately 30% of patients with acute myeloid leukemia (AML) and a normal karyotype. Several TKIs targeting TRKs (e.g., larotrectinib and entrectinib) or FLT3-ITD (e.g., midostaurin, sorafenib, and gilteritinib) have been developed and approved for clinical use. Examples are listed in Table 2.

Inhibitors targeting PDGF, VEGF, or FGFR family receptors and Ret: Tumor angiogenesis is a hallmark of cancer. Several growth factors and their receptors, such as platelet-derived growth factor (PDGF)/PDGFR, vascular endothelial growth factor (VEGF)/VEGFR, fibroblast growth factor (FGF)/FGFR, stem cell factor (SCF)/c-Kit, glial cell line-derived neurotrophic factor (GDNF)-family ligands/retrograde transduction during transfection (RET), and angiopoietin/Tie regulate the growth, differentiation and migration of cancer cells and angiogenic activities of vascular endothelial cells. PDGFs are members of the ‘cysteine knot’ growth factor superfamily, the members of which contain at least three disulfide bridges and forms homo- or heterodimers. Five types of PDGF dimers...
(PDGF-α, PDGF-β, PDGF-βC, and PDGF-DD) have been identified, and these PDGFs transduce signals by binding to two isotypes of PDGFRs (PDGFRα and PDGFRβ)13. PDGF-α and PDGF-βC, ligands that bind to these PDGFRs with different affinities, have a high affinity for PDGFR-α, whereas PDGF-β and PDGF-DD transduce signaling through PDGFRβ13. PDGFR-α plays both general and specific roles in the development of mesenchymal and fibroblastic cell compartments; PDGFR-β plays an important role in the formation of vascular mural cells, including vascular smooth muscle cells and pericytes13. Alterations in PDGFR-α and PDGFR-β are associated with vascular diseases and mesenchymal-cell/fibroblast-driven pathological conditions, respectively13. Alterations in PDGFR-α, such as point mutations and amplification, exist in approximately 5% of patients with gastrointestinal stromal tumors (GISTs) and 5–10% of patients with glioblastoma multiforme114.

The VEGF family is composed of five glycoproteins, including VEGFA (VEGF), VEGFB, VEGFC, VEGFD (c-fos-induced growth factor, FIGF), and placental growth factor (PIGF or PGF)115. VEGF is expressed as multiple alternative splicing isomers, with pro- or antiangiogenic effects; among them, VEGF165 is the predominant proangiogenic isoform that is overexpressed in various solid tumors115,116. VEGF activates signal transduction by binding to VEGFR family receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4)115,117. VEGFR2 is primarily expressed in vascular endothelial cells, and VEGF/VEGFR2 signaling plays a crucial role in angiogenesis by controlling vascular permeability, proliferation, migration, and survival of vascular endothelial cells115,117. VEGF also stimulates vasculogenesis in tumors by recruiting bone marrow-derived hematopoietic progenitor cells and endothelial progenitor cells115. VEGFC and VEGFD bind VEGFR3 and regulate lymphangiogenesis, contributing to metastatic spread through the lymphatic system118. In addition to these angiogenic effects on vascular endothelial cells, VEGF exerts several tumor-promoting effects, such as increased cancer cell proliferation, migration, invasion, stemness119–121, immune suppression115,122, and premetastatic niche formation122.

The FGF family growth factors, comprising 18 members that are categorized into six subfamilies, activate signal transduction by binding to FGF receptors (FGFRs)123. Five FGFRs (FGFR1–FGFR5) are known123,124. FGFR1–FGFR4 possess tyrosine kinase activity; in contrast, FGFR5 lacks the intracellular tyrosine kinase domain but acts as a coreceptor of FGFR1 and modulates ligand-mediated signaling125. Heparan sulfate glycosaminoglycan (HSGAG) binds to the binding domain, nuclear localization signal motifs, and nuclear translocation135,136. ABL1, but not ABL2, additionally includes a DNA-binding domain, nuclear localization signal motifs, and nuclear translocation135,136. Oncogenic alterations in ABLs, including fusion protein formation caused by chromosome translocations in leukemia (e.g., BCR-ABL1 in Philadelphia chromosome-positive (Ph) chronic myeloid leukemia (CML)) and amplification and somatic mutations in solid tumors, constitutively activate ABL-mediated signaling pathways and promote survival, proliferation, dedifferentiation, migration, and invasion in cancer cells126.

Several kinase inhibitors targeting the BCR-ABL fusion protein have been developed and used clinically (Table 4). Imatinib is an orally active first-generation BCR-ABL inhibitor. Nilotinib is an ATP-competitive type II TKI that binds to the inactive conformation of the BCR kinase (DFG-out conformation137). Mutation in the kinase domain of RET is similar to that of VEGFR2, and PDGFRα/β, c-Kit, CSF-1R, VEGFR2/3, FLT3, Tek, and Tie protein kinases are regulated by a similar autoinhibitory brake mechanism133. Multikinase inhibitors concurrently targeting these kinases have been developed and clinically utilized. Examples are sorafenib, sunitinib, pazopanib, lenvatinib, regorafenib, vandetanib, caboazantinib, axitinib, tivozanib, avapritinib, ripretinib, erdafiitinib, pemigatinib, ingratinitib, derazantinib, futibatinib, selvercatinib, and pralsetinib. Moreover, monoclonal antibodies (e.g., bevacizumab and ramucirumab) or recombinant proteins (e.g., aflibercept) have been used clinically134. Several clinically approved inhibitors targeting these RTKs and additional angiogenesis inhibitors are listed in Tables 2 and 3.

Nonreceptor tyrosine kinase inhibitors

BCR-ABL and SFK inhibitors: Abelson (ABL) family kinases (ABL1 and ABL2) are nonreceptor tyrosine kinases that commonly contain a specific domain cassette consisting of the Src homology 3 (SH3) domain (a protein module that binds to proline-rich sequences), the SH2 domain (a protein module that binds to tyrosine phosphorylated sites), the SH3 domain (SH1 domain, the PXXP motif mediating interaction with SH3 domain-containing proteins, and the C-terminal F-actin binding domain135,136. ABL1, but not ABL2, additionally includes a DNA-binding domain, nuclear localization signal motifs, and nuclear translocation135,136. Activation of ABL kinases is tightly regulated through autoinhibitory intramolecular interactions, intermolecular interactions with other proteins to disrupt or maintain autoinhibitory conformation, and posttranslational modifications such as trans- or Src-mediated tyrosine phosphorylation (e.g., activation of ABL1 by phosphorylation at Y245 and Y412), serine/threonine phosphorylation, acetylation, myristoylation, and polyubiquitination135,136. Oncogenic alterations in ABLs, including fusion protein formation caused by chromosome translocations in leukemia (e.g., BCR-ABL1 in Philadelphia chromosome-positive (Ph) chronic myeloid leukemia (CML)) and amplification and somatic mutations in solid tumors, constitutively activate ABL-mediated signaling pathways and promote survival, proliferation, dedifferentiation, migration, and invasion in cancer cells126.

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### Table 3. Monoclonal antibodies or recombinant proteins that inhibit angiogenesis modulators.

| Class (Target) | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication (selected) | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|----------------|--------------------------|----------------------|---------------------------------|---------------------------------|-------------------------------------|----------------------------------|------------|
| Monoclonal antibody (VEGF) | Bevacizumab (Genentech/ Roche) | Avastin Avastin (Genentech/Roche) | Metastatic CRC\(^1\) with standard chemotherapy treatment (2004) | Metastatic CRC with 5-FU-based therapy (second-line, 2006) Advanced nonsquamous NSCLC\(^2\) in combination with chemotherapy (2006) Metastatic RCC (2009) Recurrent GBM\(^3\) (2009) Metastatic cervical cancer (2014) Platinum-resistant recurrent ovarian cancer in combination with chemotherapy (2014) | Activation of the proangiogenic pathway Adaptation of an alternative mode of vessel formation | Bleeding, pulmonary hemorrhage, proteinuria, hypertension, wound healing complications, cardiovascular toxicity, hypersensitivity | 229 |
| Monoclonal antibody (VEGFR2) | Ramucirumab (LY3009806, IMC-1121B) | Cyramza Cyramza (Eli Lilly) | Advanced gastric cancer (2014) Aggressive NSCLC (2014) | Metastatic colorectal cancer in combination with FOLFIRI\(^5\) (2015) HCC (2019) EGFR mutated metastatic NSCLC (2020) | | Neutropenia, thrombocytopenia, diarrhea, nausea, vomiting | 230 |
| Recombinant protein (VEGFs, VEGF-trap) | Aflibercept (Regeneron Pharmaceuticals) | Zaltrap, Eylea Zaltrap, Eylea (Regeneron Pharmaceuticals) | Eylea: Wet age-related Macular Degeneration (2011) Zaltrap: previously treated metastatic CRC (2012) | | Endophthalmitis, conjunctivitis, muscle volitantes, headache, arrhythmia | 231 |

\(^1\)CRC: colorectal cancer. 
\(^2\)NSCLC: non-small cell lung cancer. 
\(^3\)GBM: glioblastoma multiforme. 
\(^4\)HCC: hepatocellular carcinoma. 
\(^5\)FOLFIRI: drug combination containing 5-fluorouracil, leucovorin calcium (folic acid), and irinotecan hydrochloride.
| Target    | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|-----------|--------------------------|----------------------|----------------------------------|-----------------------|-------------------------------------|---------------------------------|------------|
| BCR-ABL   | Imatinib (STI-571)       | Gleevec (Novartis)   | Ph⁺ CML (2001)                   | GIST² (2012) Ph⁺ ALL⁴ (2013) | BCR-ABL T315I mutation             | Fatigue, rash, fluid retention, bone pain, diarrhea | 8,135,137,138,145,232 |
| PDGFR c-Kit | Dasatinib (BMS-354825) | Sprycel (Bristol-Myers Squibb) | Ph⁺ ALL (2006)                  | Ph⁺ CML with resistance to or intolerance of prior therapy including imatinib (2009) | BCR-ABL T315I mutation | Neutropenia, thrombocytopenia, diarrhea, rash, fluid retention | 8,137,138,141,232,233 |
| c-Kit PDGFR SFKs⁵ | Nilotinib (AMN107) | Tasigna (Novartis)   | Ph⁻ CML with resistance or intolerance to imatinib (2012) | BCR-ABL T315I mutation | Thrombocytopenia, myalgia, headache | 137–139,141 |
| PDGFR ARGDDR1NQO2EPHB4 | Bosutinib (SKI-606) | Bosulif (Pfizer)    | Ph⁻ CML with resistance or intolerance to existing therapies (2007) | BCR-ABL T315I mutation | Diarrhea, nausea, vomiting | 135,137,138,140 |
| PDGFR | Radotinib⁶ (IY-5511) | Supect (Ilyang Pharmaceutical) | CML (2012)                    | BCR-ABL T315I mutation | Thrombocytopenia, anemia, fatigue, asthenia, nausea, myalgia, pruritis | 8,142,234 |
| FLT3 c-KIT PDGFRET GDNF | Ponatinib (AP24534) | Iclusig (ARIAD Pharmaceuticals) | Resistant or intolerant CML and Ph⁻ ALL (2012) | BCR-ABL compound mutation at T315, E255 | Diarrhea, nausea, vomiting, headache | 135,137,145 |
| BCR-ABL | Asciminib (ABL001) | Scemblix (Novartis) | Ph⁺ CML (2021)                   | BCR-ABL mutation at A337, W464, P465, W468, I502 | Diarrhea, nausea | 143,144,232 |
| JAK | Ruxolitinib (INC424) | Jakafi (Incyste/Novartis) | Myelofibrosis (2011) | BTK C481S, T474I/M mutation | Atrial fibrillation, bleeding, hypertension, diarrhea, nausea, vomiting | 151,152,235,236 |
| | BTK | Ibrutinib (PCI-32765) | Imbruvica (Pharmaceuticalcoffy/AbbVie/Janssen) | MCL (2013)                  | CML (2014) Waldenström's Macroglobulinemia (2015) CLL⁶ (first line) and SLL⁹ (2016) Relapsed/refractory MZL¹⁰ (2017) | Relapsed/refractory CLL (2019) | Atrial fibrillation, bleeding, hypertension, diarrhea, nausea, vomiting | 151,152,235,236 |
| BTK | Acalabrutinib (ACP-196) | Calquence (Acerta Pharma/ AstraZeneca) | Relapsed/refractory MCL (2017) | BTK C481S mutation | Atrial fibrillation, bleeding, hypertension, diarrhea, nausea, vomiting | 151,152,235,236 |
| BTK | Zanubrutinib (BGB-3111) | Brukinsa (BelGene) | MCL (2019)                      | Waldenström's Macroglobulinemia (2021) Relapsed/refractory MZL (2021) | BTK C481S mutation | Diarrhea, nausea, vomiting | 151,152,235,236 |
| JAK | Ruxolitinib (INC424) | Jakafi (Incyste/Novartis) | Myelofibrosis (2011) | BTK C481S, T474I/M mutation | Diarrhea, nausea, vomiting | 151,152,235,236 |
Table 4. continued

| Target | Brand name | Company (Company) | Generic name (Code name) |
|--------|------------|-------------------|-------------------------|
| JAK    | Fedratinib | Inrebic (Celgene/Bristol-Myers Squibb) | SAR102503, TG101348 |

Side effects/toxicity

Diarhea, nausea, vomiting

References

(Selected)

1. Myelo-fibrosis (2019)

Additional indication

Drug resistance mechanism (selected)

References

(Selected)

1. Philadelphia chromosome-positive.
2. CML: chronic myeloid leukemia.
3. GIST: gastrointestinal stromal tumor.
4. ALL: acute lymphocytic leukemia.
5. SFKs: Src-family kinases.
6. Approved in Republic of Korea.
7. MCL: mantle cell lymphoma.
8. CLL: chronic lymphocytic leukemia.
9. SLL: small lymphocytic lymphoma.
10. MZL: marginal zone lymphoma.

BTK and JAK inhibitors: BTK is a nonreceptor tyrosine kinase that plays an essential role in the development and function of B cells. BTK contains five typical domains, including from the N-terminus to the C-terminus the pleckstrin homology (PH) domain required for binding to phosphatidylinositol lipids, the proline-rich Tec homology (TH) domain, a zinc-finger motif for optimal activity and stability of the protein, SH3 and SH2 domains, and the catalytic domain. Antigen engagement by the B-cell receptor causes activation of BTK through phosphorylation at Y551 in the kinase domain by spleen tyrosine kinase (Syk), Lyn, or Src, which leads to downstream signaling pathways, including phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Akt, leading to regulation of B cell survival, proliferation, differentiation, and antibody secretion.

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lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and mantle cell lymphoma (MCL)\textsuperscript{151,152}. The Janus kinase (JAK) family comprises the nonreceptor tyrosine kinases JAK1, JAK2, JAK3, and TYK\textsuperscript{153,154}. Cytokine binding to receptors leads to receptor dimerization and recruitment, trans-autophosphorylation, and activation of JAK, resulting in phosphorylation and activation of downstream signaling cascades such as phosphotyrosylinositol-3-kinase (PI3K)/Akt, MAPK, and signal transducer and activator of transcription (STAT) transcription factors\textsuperscript{153-155}. Deregulation of JAK through hyperactivation and activating mutations (e.g., JAK2 V617F) has been reported in myeloproliferative neoplasms, including myelofibrosis\textsuperscript{156}. Examples of clinically approved inhibitors targeting BTK (e.g., ibrutinib, acalabrutinib, and zanubrutinib) or JAK (e.g., ruxolitinib and fedratinib) are listed in Table 4.

**Inhibitors targeting downstream signaling pathways: RAS Inhibitor and serine/threonine kinase inhibitors.** Activated tyrosine kinases trigger phosphorylation and activation of downstream signaling mediators that are mostly serine/threonine kinases. The main relevant downstream signaling pathways are the PI3K/Akt/mTOR and RAS/RAF/MEK/ERK pathways. Alterations in several components of these pathways (e.g., RAS, RAF, MEK, and PI3K) have been found in various types of cancer and thus considered druggable targets\textsuperscript{156-158}. Cyclins are also downstream effector molecules of these signaling cascades and play an important role in regulating cell cycle progression and various cellular processes, such as gene transcription, DNA damage repair, and metabolism, by associating with cyclin-dependent kinases (CDKs)\textsuperscript{159}. Alterations in cyclins and CDKs have been observed in various cancer types, and several CDK inhibitors have been developed and approved for clinical use\textsuperscript{160}. Examples of these targeted therapeutic drugs are described below.

**RAS/RAF/MEK inhibitors:** RAS is a guanine nucleotide-binding protein that plays an important role in cell proliferation and differentiation, and farnesyltransferase (FTase) is crucial for RAS to associate with membranes and its transforming activity\textsuperscript{161}. Mutations in RAS result in constitutive activation\textsuperscript{162}. Among the three RAS isoforms (KRAS, HRAS, and NRAS), KRAS is the most frequently mutated isoform, and five mutations (G12D, G12V, G12C, G13D, and Q61R) are the most prominent RAS mutations observed in cancer patients\textsuperscript{156}. Based on the important role of RAS FTase in the regulation of RAS transforming activity, several FTase inhibitors have been developed and evaluated, yet none of them have been clinically used because of limited efficacy\textsuperscript{162}. Recently, a small molecule inhibitor targeting mutated KRAS (KRAS\textsuperscript{G12C}) was developed and approved for clinical use. Sotorasib is an orally available inhibitor that binds to inactive guanosine diphosphate (GDP)-bound KRAS via a covalent bond between the C12 residue and the acrylamide warhead and noncovalent bonds between the isoallopyridine substituent and a cryptic pocket comprising H95, Y96, and Q99 residues; this results in inhibition of KRAS\textsuperscript{156,163} without affecting wild-type KRAS\textsuperscript{156,163}. Another KRAS\textsuperscript{G12C} inhibitor, adagrasib (MRTX849), is under clinical trial evaluation\textsuperscript{166}.

Activated RAS in the GTP-bound state leads to association of RAF proteins, causing formation of RAF homo- or heterodimers, RAF phosphorylation, and consequent activation of the downstream signaling mediators MEKs and ERKs\textsuperscript{156,166}. Among the three isoforms of RAF (ARAF, BRAF, and CRAF), mutations in BRAF, especially at the V600 residue (e.g., V600E) in the activation loop, are frequently observed in several types of cancer, including melanoma, papillary thyroid cancer, and colorectal cancer\textsuperscript{157,166,167}. Indeed, the V600E mutation, which causes RAS-independent activation of BRAF, accounts for more than 90% of BRAF mutation cases in cancer\textsuperscript{157,166,167}. Thus far, three RAF inhibitors and three MEK inhibitors have been used for anticancer treatment. Currently available RAF inhibitors target monomeric V600E-mutant BRAF; thus, for dimeric RAF, inhibition of one protomer by the drug paradoxically leads to transactivation of the other protomer and downstream signaling\textsuperscript{157}. Therefore, a combination of MEK inhibitors (e.g., vemurafenib plus cobimetinib, dabrafenib plus trametinib, and encorafenib plus binimetinib) has been clinically utilized\textsuperscript{168}. Examples of clinically approved BRAF and MEK inhibitors are listed in Table 5.

**PI3K/mTOR inhibitors:** The PI3K/Akt/mTOR pathway plays a central role in regulating cell proliferation, survival, growth, and metabolism\textsuperscript{158,159}. Deregulation of the PI3K/Akt/mTOR pathway through mutation or amplification of PIK3CA (encoding the p110α subunit of PI3K), loss or inactivation of phosphatase and tensin homolog (PTEN), and hyperactivation of mTOR have been commonly found in various cancer types\textsuperscript{158,159} and related anticancer drug resistance\textsuperscript{158,170}. Hence, inhibitors targeting PI3K, Akt, and mTOR have been evaluated in preclinical studies and clinical trials, and some inhibitors have been used clinically for cancer treatment.

Because of the specific expression of PI3K, p110δ, and p110β subunits in the hematopoietic system, the association of the PI3K pathway with regulating B-cell receptor (BCR) signaling, and the undesirable toxicity of pan-PI3K or dual PI3K/mTOR inhibitors\textsuperscript{157,158}, PI3K inhibitors that specifically target PI3Kδ or PI3Kγ have been employed for treatment of patients with lymphoma. Some mTOR inhibitors, especially rapamycin analogs (rapalogs) that form a complex with FK506-binding protein 12 (FKBP12) and inhibit mTORC1 (but not mTORC2) activity, have been approved for clinical use\textsuperscript{158}. Additionally, ATP-competitive mTOR inhibitors have been developed and are under preclinical and clinical evaluation\textsuperscript{8}. Examples of clinically utilized PI3K (e.g., idelalisib, duvelisib, copanlisib and alpelisib) and mTOR inhibitors (e.g., sirolimus, temsirolimus, and everolimus) are listed in Table 5.

**CDK inhibitors:** Among more than 20 members of CDK family proteins\textsuperscript{159}, CDK4 and CDK6 (in complex with cyclin D) play a crucial role in promoting cell cycle progression by sequestering CDK inhibitors and inducing various proteins involved in cell cycle progression from G1 to S phase, DNA replication, chromatin structure, chromosome segregation, and the spindle assembly checkpoint through phosphorylation of various targets, including retinoblastoma protein (RB), and activating E2F-mediated transcription\textsuperscript{159}. Hence, CDK4/6 has been considered attractive for targeted anticancer therapy. Three CDK4/6 inhibitors have been used clinically for treatment of patients with HR-positive advanced breast cancer (Table 5). Palbociclib, ribociclib, and abemaciclib are orally available, reversible, and selective CDK4/6 inhibitors that have been used clinically in combination with an aromatase inhibitor for treatment of postmenopausal women with ER-positive and HER2-negative advanced or metastatic breast cancer\textsuperscript{8,173,174}.

**Other targeted anticancer agents.** In addition to PARP inhibitors, other types of clinically used or recently approved targeted therapies, including epigenetic modulators (e.g., DNA methyltransferase inhibitors, histone deacetylase inhibitors, EZH2 inhibitors, and isocitrate dehydrogenase inhibitors), proteasome inhibitors, Bcl-2 inhibitors, and smoothened inhibitors, are summarized in Table 6.

**PARP inhibitors:** The PARP family plays a crucial role in regulating DNA repair processes upon the DNA damage response (DDR) and chromatin modulation\textsuperscript{155,176}. PARP family proteins, especially PARP1 and PARP2, bind to DNA lesions and mediate poly-ADP ribosylation (PARylation) of chromatin and DNA damage response components, resulting in DNA repair by recruiting DNA repair effectors such as XRCC1\textsuperscript{155,176}. After autoPARylation, PARP
Table 5. Serine/threonine kinase inhibitors that have been clinically used for cancer treatment.

| Target | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|--------|--------------------------|----------------------|---------------------------------|----------------------|-------------------------------------|---------------------------------|------------|
| KRAS   | Sotorasib (AMG 510)      | Lumakras (Amgen)     | Locally advanced or metastatic NSCLC harboring G12C-mutant KRAS with at least one prior systemic therapy (2021) | Braf/RAS mutation KRAS G12V, G13D mutation | Nausea, vomiting, diarrhea, elevated aminotransferase level, fatigue, arthralgia | 163, 164, 238 |
| BRAF   | Vemurafenib (PLX4032)    | Zelboraf (Genentech) | Melanoma harboring V600E-mutant BRAF (2011) | Advanced melanoma with BRAF mutation in combination with cobimetinib (2015) | NRAS mutation CRAF overexpression secondary BRAF mutation MEK1/2 mutation | Rash, diarrhea, fatigue, arthralgia | 157, 167, 168, 239–241 |
| BRAF   | Dabrafenib (GSK2118436)  | Tafinlar or Rafinlar (Novartis/GlaxoSmithKline) | Melanoma harboring V600E-mutant BRAF (2013) | Advanced melanoma with BRAF mutation in combination with trametinib (2014) BRAF V600E-mutant metastatic NSCLC in combination with trametinib (2017) BRAF V600E-mutant anaplastic thyroid cancer in combination with trametinib (2018) | NRAS mutation CRAF overexpression secondary BRAF mutation MEK1/2 mutation | Rash, diarrhea, fatigue, arthralgia | 157, 167, 168, 239–241 |
| BRAF   | Encorafenib (LGX818)     | Braftovi (Novartis/Array BioPharma) | Unresectable or metastatic melanoma with BRAF mutations in combination with binimetinib (2018) | BRAF V600E-mutant metastatic CRC in combination with cetuximab (2020) | NRAS mutation CRAF overexpression secondary BRAF mutation MEK1/2 mutation | Rash, diarrhea, fatigue, arthralgia | 157, 167, 168, 239–241 |
| MEK    | Trametinib (GSK1120212, JTP-74057) | Mekinist (GlaxoSmithKline/Novartis) | BRAF V600E-mutant advanced melanoma (2013) | Advanced melanoma with BRAF mutation in combination with dabrafenib (2014) BRAF V600E-mutant metastatic NSCLC in combination with dabrafenib (2017) BRAF V600E-mutant anaplastic thyroid cancer in combination with dabrafenib (2018) | RTK reactivation P13K, STAT3 activation | Rash, diarrhea, fatigue, arthralgia | 157, 167, 168, 239–241 |
| MEK    | Cobimetinib (GDC-0973, RG7420) | Cotellic (Genentech) | Advanced melanoma with BRAF mutation in combination with vemurafenib (2015) | RTK reactivation P13K/STAT3 activation | Rash, diarrhea, fatigue, arthralgia | 157, 167, 168, 239–242 |
Table 5. continued

| Target Gene (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|-------------------------|----------------------|---------------------------------|----------------------|--------------------------------------|---------------------------------|------------|
| MEK                      | Mektinib (Array Biopharma) | Unresectable or metastatic melanoma with BRAF mutations in combination with encorafenib (2018) | | RTK reactivation | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| MEK                      | Selumetinib (AZD6244, ARRY-142886, ARRY-142866) | Neurofibromatosis type 1 plexiform neurofibroma (2020) | | RTK reactivation | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| PI3Kδ                    | Idelalisib (CAL-101, GS-1101) | Relapsed CLL (2014) | | RTK reactivation | Hyperglycemia, rash, stomatitis, fatigue, nausea, diarrhea | 171,172,243-244 |
| PI3Kδ                    | Duvelisib (IP-105, NCK197) | Relapsed or refractory FL (2017) | | Relapsed or refractory FL (2017) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| PI3Kα                    | Alpinib (BAY-90-8266) | Relapsed or refractory FL (2017) | | Relapsed or refractory FL (2017) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| PI3Kα                    | Alpipla (BAY-90-5966) | Relapsed or refractory FL (2017) | | Relapsed or refractory FL (2017) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| PI3Kα                    | Alpinib (BAY-90-5966) | Relapsed or refractory FL (2017) | | Relapsed or refractory FL (2017) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| mTOR                     | Everolimus (CC-200) | Advanced RCC (2007) | | Advanced RCC (2007) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| mTOR                     | Temsirolimus (CCI-797) | RCC after failure of sunitinib or sorafenib (2009) | | RCC after failure of sunitinib or sorafenib (2009) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| mTOR                     | Torisel (CC-797) | High-risk or metastatic breast cancer (2009) | | High-risk or metastatic breast cancer (2009) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| mTOR                     | Everolimus (RAD001) | Advanced or metastatic breast cancer (2015) | | Advanced or metastatic breast cancer (2015) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| CDK4/6                   | Palbociclib (PD-0332991) | HR+ and HER2- metastatic breast cancer (2016) | | HR+ and HER2- metastatic breast cancer (2016) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
| CDK4/6                   | Ribociclib (LDE200) | HR+ and HER2- metastatic breast cancer (2017) | | HR+ and HER2- metastatic breast cancer (2017) | Rash, diarrhea, fatigue, arthralgia | 171,172,243-244 |
dissociates from DNA, and the DNA repair process is completed by recruitment of DNA repair proteins. \cite{176}. BRCA1 and BRCA2 (BRCA1/2) are tumor-suppressor genes that play a key role in repair of double-strand DNA breaks via homologous recombination repair (HRR) process \cite{175,177}. Mutations in BRCA1/2 genes have been found in some cancer types, including breast, ovarian, pancreatic, and prostate cancers \cite{177}. Defects in BRCA function due to BRCA1/2 gene mutations cause loss of the HRR process and mediate the DNA repair process in a nonconservative manner, such as nonhomologous end joining, leading to DNA alteration \cite{175}. As BRCA mutant cancer cells are vulnerable to blockade of the DNA repair process, treatment of BRCA-deficient cells with PARP inhibitors leads to unsustained genomic instability and cancer cell death \cite{175}. This synthetic lethal interaction between PARP blockade and BRCA1/2 mutation suggests a therapeutic strategy targeting PARP for treatment of cancer types harboring BRCA mutations. Based on these findings, some orally available PARP inhibitors, such as olaparib, rucaparib, niraparib, and talazoparib, have been clinically used for treatment of BRCA-mutated cancers, including ovarian, breast, and prostate cancers \cite{178}. Additional investigations to evaluate the effectiveness of combinatorial treatment with chemotherapeutic agents, PI3K inhibitors, and anticancer immunotherapy have been conducted in preclinical and clinical settings \cite{178}.

**Summary and future perspectives in the development of molecular targeted therapy**

Owing to advances in molecular diagnosis, genome-wide analysis, and in-depth understanding of cancer biology, numerous tyrosine kinase inhibitors have recently been developed, tested preclinically and clinically, and utilized for cancer treatment in the clinic. Nevertheless, poor efficacy, toxicity, and tumor relapse due to drug resistance are major obstacles for targeted therapy-based efficacious anticancer treatment. Therefore, further investigation is required to develop efficacious personalized targeted therapies that overcome drug resistance and reduce side effects and toxicity.

To this end, a fundamental template for drug discovery by identifying additional druggable targets through in-depth biochemical, genomic, and molecular studies and structural investigations is needed. Drug discovery with different chemical entities or modes of action is also necessary for the development of molecular targeted therapy. In addition to direct or allosteric modulation of cellular targets, strategies for indirect manipulation of cellular targets [e.g., posttranslational modification] based on biological and functional studies for cancer-specific modulation would be applicable. Furthermore, the development of small molecule inhibitors that concurrently block signaling pathways associated with cancer cell proliferation and drug resistance and design of optimized combinatorial therapeutic strategies using molecular targeted therapy, either alone or in combination with other types of anticancer therapy [e.g., chemotherapy and immune checkpoint inhibitors], would be of importance for increased efficacy, limited toxicity, and minimal drug resistance.

Because the side effects and toxicity of targeted therapy are mediated by nonspecific inhibition of the same target in normal cells \cite{179}, strategies for cancer cell-specific targeting are also important. A relevant example is the recent development of KRASG12C inhibitors. Since the clinical failure of farnesyltransferase inhibitors, KRAS has been considered an undruggable target \cite{180}. In a recent study utilizing the high reactivity of cysteine, compounds that covalently bind to KRAS via the mutated cysteine residue and allosterically inhibit GTP binding to KRAS were designed \cite{182}; this approach can inhibit KRAS without occupying the GTP/GDP-binding pocket on the surface and achieve specificity for mutant...
Table 6. Additional targeted therapies that have been clinically used for cancer treatment.

| Target | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|--------|--------------------------|---------------------|----------------------------------|----------------------|--------------------------------------|----------------------------------|------------|
| PARP   | Olaparib (AZD2281)       | Lynparza (AstraZeneca) | Advanced ovarian cancer (2014)   | Maintenance treatment of ovarian cancer (2017, 2018, 2020) BRCA-mutated metastatic breast cancer (2018, 2022) Metastatic pancreatic cancer (2019, 2020) | Restoration of homologous recombination repair and ADP-ribosylation (PARylation) reversion mutations | Ileus, myelodysplastic syndrome, interstitial lung disease | 8,178,247 |
| PARP   | Rubraca (Clovis Oncology) | Rubraca (AstraZeneca) | Advanced ovarian cancer (2016)   | Maintenance treatment of ovarian cancer (2018) | Restoration of homologous recombination repair and ADP-ribosylation (PARylation) reversion mutations | Nausea, vomiting, diarrhea, constipation, red blood cell count decrease, photosensitivity, renal impairment, dysgeusia | 8,178,247 |
| PARP   | Niraparib (MK-4827)      | Zejula (Tesaro)      | Recurrent ovarian cancer (2017) | Maintenance treatment for patients with platinum-resistant ovarian cancer regardless of biomarker status (2020) | Restoration of homologous recombination repair and ADP-ribosylation (PARylation) reversion mutations | Nausea, constipation, platelet/red blood cells count decrease, lymphangioleiomyomatosis | 8,178,247 |
| PARP   | Talazoparib (BMN-673)    | Talzenna (Pfizer)    | BRCA1/2-mutated advanced or metastatic HER2-breast cancer (2018) | Restoration of homologous recombination repair and ADP-ribosylation (PARylation) reversion mutations | Hematopoietic erythropaenia, anaemia, thrombocytopenia, pancytopenia, neutropenia | 8,178,247 |
| DNMT1  | Azacitidine (5-azacytidine) | Vidaza (Pharmion Corporation) | MDS $^2$ (2004) | Adaptive responses of the pyrimidine metabolism network | Fatigue, constipation, mucositis, pneumonia, febrile neutropenia | 8,247,248 |
| DNMT2  | Decitabine (NSC 127716)  | Dacogen (Janssen-Cilag/ Otsuka Pharmaceutical) | Dacogen: MDS (2006) | Adaptive responses of the pyrimidine metabolism network | Fatigue, constipation, mucositis, pneumonia, febrile neutropenia | 8,247,249 |
| HDAC3  | Vorinostat (SAHA)        | Zolinza (Merck)      | Relapse/refractory CTCL$^2$ (2006) | Overexpression of Bcl-2 family proteins JAK/STAT3 pathways HDAC alterations Epigenetic alterations Protection of oxidative stress Alterations in apoptosis/autophagy | Diarrhea, fatigue, nausea, anorexia, dysgeusia, thrombocytopenia, pulmonary embolism, cardiac abnormalities | 250,251 |

References:
8,178,247, 8,247,248, 8,247,249, 250,251
| Target | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|--------|--------------------------|----------------------|----------------------------------|----------------------|--------------------------------------|----------------------------------|------------|
| HDAC   | Romidepsin (FK228, FR901228) | Istodax (Celgene Corp./ Bristol-Myers Squibb) | CTCL (2009) | PTCL $^5$ (2011) | P-glycoprotein-mediated drug efflux HDAC alterations Epigenetic alterations Protection of oxidative stress Alterations in apoptosis/autophagy | Thrombocytopenia, anemia, neutropenia, fatigue, nausea, vomiting, anorexia, tumor lysis syndrome | 250,251 |
| HDAC   | Belinostat (PXD-101) | Beleodaq (Spectrum Pharmaceuticals) | PTCL (2014) | HDAC alterations Epigenetic alterations Alterations in apoptosis/autophagy | Nausea, vomiting, tumor lysis syndrome, hepatic failure, cardiac abnormalities | 250,251 |
| HDAC   | Panobinostat (LBH-589) | Farydak (Novartis/ Secura Bio) | MM$^7$ (2015) | HDAC alterations Epigenetic alterations Protection of oxidative stress Alterations in apoptosis/autophagy | Severe diarrhea, nausea, vomiting, cardiac abnormalities | 250,251 |
| EZH2$^6$ | Tazemetostat (E7438/ EPZ6438) | Tazverik (Epizyme) | Relapsed/refractory follicular lymphoma (2020) | Metastatic or locally advanced epithelioid sarcoma (2020) | EZH2 Y726F, C663Y mutation | Nausea, asthenia, fatigue, alopecia, dry skin, diarrhea, neutropenia, thrombocytopenia | 252 |
| IDH1$^8$ | Ivosidenib (AG-120) | Tibsovo (Servier Pharmaceuticals) | Relapse/refractory AML$^9$ with an IDH1 mutation (2018) | Frontline in AML patients with comorbidities (2019) IDH1-mutated cholangiocarcinoma (2021) | Elevated 2-hydroxyglutarate Hypermethylation | QT interval prolongation, IDH differentiation syndrome, anemia, thrombocytopenia | 8,9,216,253 |
| IDH2   | Enasidenib (AG-221) | Idhifa (Agios Pharmaceuticals) | Relapse/refractory AML with an IDH2 mutation (2017) | Elevated 2-hydroxyglutarate Hypermethylation | Hyperbilirubinemia, thrombocytopenia, IDH differentiation syndrome | 216,253 |
| Proteasome | Bortezomib (PS-341) | Velcade (Millennium/ Takeda/Janssen Pharmaceutical) | Relapse/refractory MM (2003) | | Proteasome mutation/ overexpression Heat shock protein upregulation Autophagy Increased drug efflux Alterations in glutathione metabolism | Peripheral neuropathy, hematologic toxicities, diarrhea, fatigue, dyspnea, zoster reactivation | 254,255 |
| Proteasome | Carfilzomib (PR-171) | Kyprolis (Onyx Pharmaceuticals) | Advanced MM (2012) | | Proteasome mutation Autophagy Increased drug efflux | Hematologic toxicities, pneumonia, hyponatremia, fatigue, hypophosphatemia, infusion reactions, chest pain, heart failure | 254,255 |
| Proteasome | Ixazomib (MLN2238) | Ninlaro (Takeda) | MM (2015) | | Proteasome mutation Autophagy | Hematologic toxicities, fatigue, rash, decreased appetite, diarrhea, vomiting | 254,255 |
| Target | Generic name (Code name) | Brand name (Company) | First approved indication (Year) | Additional indication | Drug resistance mechanism (selected) | Side effects/toxicity (selected) | References |
|--------|--------------------------|----------------------|----------------------------------|----------------------|-------------------------------------|----------------------------------|------------|
| Bcl-2  | Venetoclax (ABT-199)     | Venclexta (AbbVie/ Genentech) | CLL\(^{10}\) (2016)             | AML (2018)            | BCL2 mutation                      | Bone marrow suppression, nausea, vomiting, diarrhea | R,256      |
|        |                          |                      |                                  |                      | Activation of the MAPK/Akt pathway |                                  |            |
|        |                          |                      |                                  |                      | Deregulation of energy metabolism  |                                  |            |
|        |                          |                      |                                  |                      | Interaction with stromal cells     |                                  |            |
|        |                          |                      |                                  |                      |                                     |                                  |            |
|        |                          |                      |                                  |                      |                                     |                                  |            |
|        |                          |                      |                                  |                      |                                     |                                  |            |
| Smoothed | Vismodegib (GDC-0449) | Erivedge (Genentech/ Roche) | BCC\(^{11}\) (2012)             |                      | SMO mutations (e.g., D473H)         | Muscle spasm, weight loss, alopecia, dysgeusia | R,257      |
|        |                          |                      |                                  |                      | SUFU/GLI2 copy number variation/ mutation |                                  |            |
|        |                          |                      |                                  |                      |                                     |                                  |            |
| Smoothed | Sonidegib (NVP-LDE225) | Odomzo (Novartis)    | Locally advanced BCC (2015)      |                      | SMO mutations SUFU/GLI2 copy number variation/mutation | Nausea, dysgeusia, anorexia, muscle spasm, fatigue, creatine kinase elevation | R,257      |
|        |                          |                      |                                  |                      |                                     |                                  |            |
| Smoothed | Glasdegib (PF-04449913) | Daurismo (Pfizer)    | AML (2018)                        |                      | SMO mutations SUFU/GLI2 copy number variation/mutation | Thrombocytopenia, anorexia, peripheral edema, fatigue, neutropenia | R,257      |

\(^{1}\)DNMT: DNA methyltransferase.  
\(^{2}\)MDS: myelodysplastic syndrome.  
\(^{3}\)HDAC: histone deacetylase.  
\(^{4}\)CTCL: cutaneous T-cell lymphoma.  
\(^{5}\)PTCL: peripheral T-cell lymphoma.  
\(^{6}\)EZH2: enhancer of zeste homolog 2.  
\(^{7}\)MM: multiple myeloma.  
\(^{8}\)IDH: isocitrate dehydrogenase.  
\(^{9}\)AML: acute myeloid leukemia.  
\(^{10}\)CLL: chronic lymphocytic leukemia.  
\(^{11}\)BCC: basal cell carcinoma.  
\(^{12}\)ALCL: anaplastic large cell lymphoma.
KRAS beyond wild-type KRAS, thus avoiding the unfavorable effects caused by inhibition of wild-type KRAS\textsuperscript{182,183}. Based on this innovative study and a better understanding of the crystal structure of mutant KRAS, several potent KRAS\textsuperscript{G12C} inhibitors have been developed and approved for clinical use\textsuperscript{183,184}. Agents targeting other types of mutant KRAS, such as KRAS\textsuperscript{G12D}, have also been developed and evaluated in preclinical settings\textsuperscript{185,186}. Studies on molecular diagnosis and discovery of predictive biomarkers are necessary to properly select eligible populations for better efficacy and reduced toxicity\textsuperscript{187}. Several newly developed approaches, such as next-generation sequencing technology\textsuperscript{188}, whole-genome sequencing\textsuperscript{189} and machine learning\textsuperscript{190}, can be applied to this end. In fact, artificial intelligence (AI)-based strategies\textsuperscript{190} are expected to be extensively utilized for the design of the structure and chemical synthetic procedures, identification of potential hits, prediction of pharmacokinetic profiles, assessment of side effects and toxicity, and drug repurposing.

Finally, emerging evidence has shown the role of the host microbiome in cancer development and progression, drug responsiveness, and therapy-induced side effects\textsuperscript{191,192}. For example, the gut microbiome promotes the function of mutant p53 toward oncogenicity\textsuperscript{193} and modulates responsiveness to antitumor therapy such as anti-CD-1 immunotherapy\textsuperscript{194}. A number of investigations into the influence of the gut microbiome on chemotherapy and anticancer immunotherapy are ongoing; however, the effect of the host microbiome on molecular targeted therapy remains elusive. Further studies are necessary to investigate the role of the host microbiome in the efficacy and toxicity of molecular targeted therapy and to identify key factors to develop safer and more efficacious therapeutic strategies based on microbiome-targeted therapy.

In summary, the present paper briefly reviews the current status of molecular targeted therapy and discusses future directions, providing novel therapeutic strategies with better efficacy and safety to improve the prognosis of cancer patients.

REFERENCES

1. Sung, H. et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 71, 209–249 (2021).
2. Ke, X. & Shen, L. Molecular targeted therapy of cancer: the progress and future prospects. Br. J. Med. Bull. 125, 143–53 (2017).
3. Jemal, A. et al. Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. J. Natl Cancer Inst. 100, 1672–1694 (2008).
4. Sains, K. S. & Tewhbes, C. Determining lines of therapy in patients with solid cancers: a proposed new systematic and comprehensive framework. Br. J. Cancer 125, 155–163 (2021).
5. Osborne, C. M. & Mullard, A. P. A review of systemic anticancer therapy in disease palliation. Br. Med. Bull. 125, 43–53 (2017).
6. Lind, M. J. Principles of systemic anticancer therapy. Medicine 44, 20–24 (2016).
7. Jones, R. Cytotoxic chemotherapy: clinical aspects. Medicine 44, 25–29 (2016).
8. Zhong, L. et al. Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. Signal Transduct. Target. Ther. 6, 201 (2021).
9. Charlton, P. & Spicer, J. Targeted therapy in cancer. Medicine 44, 34–38 (2016).
10. Peters, G. J. From ‘targeted therapy’ to targeted therapy. Anticancer Res. 39, 3341–3345 (2019).
11. Abraham, J. & Staffurth, J. Hormonal therapy for cancer. Medicine 44, 30–33 (2016).
12. Waldman, A. D., Fritz, J. M. & Lenardo, M. J. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat. Rev. Immunol. 20, 651–658 (2020).
13. Keefe, D. M. K. & Bateman, E. H. Potential successes and challenges of targeted cancer therapies. J. Natl Cancer Inst. Manogr. 2019, lgz008 (2019).
14. Lee, Y. T., Tan, Y. J. & Oon, C. E. Molecular targeted therapy: treating cancer with specificity. Eur. J. Pharmacol. 834, 188–196 (2018).
15. Habeeb, N. W.-A. et al. The use of targeted therapies for precision medicine in oncology. Clin. Chem. 62, 1556–1564 (2016).
16. Valent, P. et al. Paul Ehrlich (1854–1915) and his contributions to the foundation and birth of translational medicine. J. Innuite Medic. 8, 111–120 (2016).

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112. Chen, P. H., Chen, X. & He, X. Platelet-derived growth factors and their recep-
tors: structural and functional integration. Biochim. Biophys. Acta 1834, 2176–2186 (2013).

113. Andrae, J., Gallini, R. & Betsholtz, C. Role of platelet-derived growth factors in
physiology and medicine. Genes Dev. 22, 1276–1312 (2008).

114. Heldin, C. H. Targeting the PDGF signaling pathway in tumor treatment. Cell
Commun. Signal. 11, 97 (2013).

115. Ellis, L. M. & Hicklin, D. J. VEGF-targeted therapy: mechanisms of anti-tumour
activity. Nat. Rev. Cancer 8, 579–591 (2008).

116. Harper, S. J. & Bates, D. O. VEGF-A splicing: the key to anti-angiogenic ther-
apeutics? Nat. Rev. Cancer 8, 880–887 (2008).

117. El-Kenawi, A. E. & El-Remessy, A. B. Angiogenesis inhibitors in cancer therapy:
mechanistic perspective on classification and treatment rationales. Br. J. Med.
Pharmacol. 170, 712–729 (2013).

118. Scavelli, C., Vacca, A., Di Pietro, G., Dammacco, F. & Ribatti, D. Crosstalk across
angiogenesis and lymphangiogenesis in tumor progression. Leukemia 18, 1054–1058 (2004).

119. Liang, Y., Brekken, R. A. & Hyder, S. M. Vascular endothelial growth factor
induces proliferation of breast cancer cells and inhibits the anti-proliferative
activity of anti-hormones. Endocr. Relat. Cancer 13, 905–919 (2006).

120. Kong, D. et al. VEGF-C mediates tumor growth and metastasis at고 프로미토 알레르기 to pro-
progressing EMT epithelial breast cancer cell crosstalk. Oncogene 40, 964–979
(2021).

121. Zhao, D. et al. VEGF drives cancer-initiating stem cell through VEGFR-2/
Stat3 crosstalk. J. Hematol. Oncol. 11, re6 (2018).

122. Xie, Y. et al. FGF/FGFR signaling in health and disease. Cell Death Dis. 327
(2018).

123. Beenken, A. & Mohammadi, M. The FGF family: biology, pathophysiology and
therapy. Nat. Rev. Drug Discov. 8, 235–253 (2009).

124. Babina, I. S. & Turner, N. C. Advances and challenges in targeting FGF signaling
in cancer. Nat. Rev. Cancer 17, 318–332 (2017).

125. Regeenes, R. et al. Fibroblast growth factor receptor 5 (FGFR5) is a co-receptor
for FGFR1 that is up-regulated in beta-cells by cytokine-induced in
flammation. J. Med. Chem. 68, 678–683 (2005).

126. Otto, T. & Scinski, P. Cell cycle proteins as promising targets in cancer therapy.
Nat. Rev. Cancer 17, 93–115 (2017).

127. Cho, K. N. & Lee, K. I. Chemistry and biology of Ras farnesyltransferase. Arch.
Pharmacol. Res. 25, 759–762 (2002).

128. Wang, J., Yao, X. & Huang, J. New tricks for human farnesyltransferase inhibitor:
cancer and beyond. Medchemcomm 8, 841–854 (2017).

129. Zhang, S. S. & Nagasaka, M. Spotlight on Sotorasib (AMG 510) for KRAS (G12C)
positive non-small-cell lung cancer. Lung Cancer 62, 151–155 (2021).

130. Pal Singh, S., Dammenger, F. & Hendriks, R. W. Role of Bruton's tyrosine kinase in
B cells and malignancies. Mol. Cancer 17, 57 (2018).

131. Seavoy, M. M. & Dobrzanski, P. The many faces of Janus kinase. Biochem.
Pharmacol. 83, 1136–1143 (2012).

132. Lee, H. J., Daver, N., Kantarjian, H. M., Verstovsek, S. & Ravandi, F. The role of JAK
pathway dysregulation in the pathogenesis and treatment of acute myeloid
leukemia. Clin. Cancer Res. 19, 327–335 (2013).

133. Quintas-Cardama, A. & Verstovsek, S. Molecular pathways: Jak/STAT pathway:
mutations, inhibitors, and resistance. Clin. Cancer Res. 19, 1933–1940 (2013).

134. Prat, A., Jänne, P. A. & Martella, E. Treatment of cancer patients with
JAK/STAT signal inhibitors. Nat. Rev. Drug Discov. 12, 154–166 (2013).

135. Janne, P. A. et al. Adagrasib in non-small-cell lung cancer harboring a
KRAS(G12C) mutation. N. Engl. J. Med. 370, 130–142 (2018).

136. Bullock, C., Karasidès, M. & Marais, R. The RAF proteins take centre stage.
Nat. Rev. Mol. Cell Biol. 5, 875–885 (2004).

137. Yuan, J., Dong, X., Yap, J. & Hu, J. The MAPK and AMPK signalings: interplay and
implication in targeted cancer therapy. J. Hematol. Oncol. 9, 51 (2016).

138. Boeltinger, P., Thuerigen, O. & Dummer, R. Development of encorafenib for
BRAF-mutated advanced melanoma. Curr. Opin. Oncol. 30, 157–159 (2018).

139. Blair, H. A. & Sotorasib: first approval. Drugs 81, 1573–1579 (2021).

140. Janne, P. A. et al. Adagrasib in non-small-cell lung cancer harboring a
KRAS(G12C) mutation. N. Engl. J. Med. 370, 130–142 (2018).

141. Cheah, C. Y. & Fowler, N. H. Idelalisib in the management of lymphoma.
Blood 128, 331–336 (2016).

142. Ulu, I. Falbocibib: a first-in-class CDK4/CDK6 inhibitor for the treatment of
hormone-receptor positive advanced breast cancer. J. Hematol. Oncol. 8, 98 (2015).

143. Horticabig, G. N. Ribociclib for the first-line treatment of advanced hormone
receptor-positive breast cancer: a review of subgroup analyses from the
MONALEESA-2 trial. Breast Cancer Res 20, 123 (2018).

144. Lord, C. J. & Ashworth, A. PARP inhibitors: Synthetic lethality in the clinic. Science
355, 1152–1158 (2017).
238. Zhao, Y. et al. Diverse alterations associated with resistance to KRAS(G12C) inhibition. *Nature* **599**, 679–683 (2021).

239. Proietti, I. et al. Mechanisms of acquired BRAF inhibitor resistance in melanoma: a systematic review. *Cancers* **12**, 2801 (2020).

240. Sanchez, J. N., Wang, T. & Cohen, M. S. BRAF and MEK inhibitors: use and resistance in BRAF-mutated cancers. *Drugs* **78**, 549–566 (2018).

241. Welsh, S. J. & Corrie, P. G. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther. Adv. Med. Oncol.* **7**, 122–136 (2015).

242. Kun, E., Tsang, Y. T. M., Ng, C. W., Gershenson, D. M. & Wong, K. K. MEK inhibitor resistance mechanisms and recent developments in combination trials. *Cancer Treat. Rev.* **92**, 102137 (2021).

243. Armaghani, A. J. & Han, H. S. Alpelisib in the treatment of breast cancer: a short review on the emerging clinical data. *Breast Cancer* **12**, 251–258 (2020).

244. Wright, S. C. E., Vasilevski, N., Serra, V., Rodon, J. & Eichhorn, P. J. A. Mechanisms of resistance to PI3K inhibitors in cancer: adaptive responses, drug tolerance and cellular plasticity. *Cancers* **13**, 1538 (2021).

245. Li, Z. et al. Mechanisms of CDK4/6 inhibitor resistance in luminal breast cancer. *Front. Pharmacol.* **11**, 500251 (2020).

246. Royce, M. et al. FDA approval summary: abemaciclib with endocrine therapy for high-risk early breast cancer. *J. Clin. Oncol.* **40**, 1155–1162 (2022).

247. Awad, M. M. et al. Acquired resistance to KRAS(G12C) inhibition in cancer. *N. Engl. J. Med.* **384**, 2382–2393 (2021).

248. Kaminskas, E., Farrell, A. T., Wang, Y. C., Sridhara, R. & Pazdur, R. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Cancer Treat. Rev.* **10**, 176–182 (2003).

249. Yuan, K. et al. FDA approval summary: decitabine and cedazuridine tablets for myelodysplastic syndromes. *Clin. Cancer Res.* **28**, 3411–3416 (2022).

250. Bondarev, A. D. et al. Recent developments of HDAC inhibitors: emerging indications and novel molecules. *Br. J. Clin. Pharmacol.* **87**, 4577–4597 (2021).

251. Fantin, V. R. & Richon, V. M. Mechanisms of resistance to histone deacetylase inhibitors and their therapeutic implications. *Clin. Cancer Res.* **13**, 7237–7242 (2007).

252. Julia, E. & Salles, G. EZH2 inhibition by tazemetostat: mechanisms of action, safety and efficacy in relapsed/refractory follicular lymphoma. *Future Oncol.* **17**, 2127–2140 (2021).

253. McMurry, H., Fletcher, L. & Traer, E. IDH inhibitors in AML—promise and pitfalls. *Curr. Hematol. Malig. Rep.* **16**, 207–217 (2021).

254. Merin, N. M. & Kelly, K. R. Clinical use of proteasome inhibitors in the treatment of multiple myeloma. *Pharmaceuticals* **8**, 1–20 (2014).

255. Bennett, M. K., Pitson, S. M. & Wallington-Beddoe, C. T. In Resistance to Targeted Therapies in Multiple Myeloma (eds S. C. W. Ling & S. Trieu) 39–59 (Springer International Publishing, 2021).

256. Yue, X., Chen, Q. & He, J. Combination strategies to overcome resistance to the BCL2 inhibitor venetoclax in hematologic malignancies. *Cancer Cell Int.* **20**, 524 (2020).

257. Xie, H., Paradise, B. D., Ma, W. W. & Fernandez-Zapico, M. E. Recent advances in the clinical targeting of hedgehog/GLI signaling in cancer. *Cell* **8**, 394 (2019).

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**COMPETING INTERESTS**

The authors declare no competing interests.

**ADDITIONAL INFORMATION**

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