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Review

New anticancer medicines approved by the EMA in 2024

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Abstract

Tumorous diseases are among the leading causes of death in the developed world, therefore there is a constant need for new antineoplastic medicines. In 2024, the EMA approved 28 anticancer drugs, of which 13 contain new active substances. In this review, we briefly summarize the mechanism of action and use of the new drugs approved by the EMA.

1. Introduction

Cancer is a generic term for a wide range of diseases that share the common characteristic of aberrant, excessive cell proliferation. Nowadays, cancer is one of the leading causes of death in the developed world, and the burden of these diseases is expected to increase in the future[1].

In 2024, the European Medicines Agency (EMA) recommended 114 medicines, including 46 new active substances, for marketing authorization. The majority of the approved medicines are antineoplastic agents. Of the 28 approved antitumor medicines,13 contain new active ingredients, and 4 of them are designated as orphan drugs[2].

In this brief review, we summarize the most important pharmaceutical information on the new active substance anticancer therapeutics approved by the EMA in 2024[2].

2. Approved medicines

The 13 approved new pharmacons belong to the following groups: 5 small molecule kinase inhibitors (4 tyrosine kinase inhibitors and 1 serine/threonine kinase inhibitor), 7 monoclonal antibodies (4 checkpoint inhibitors, 1 immunoconjugate, 1 bispecific antibody, and 1 anti-CLDN18.2 antibody) and 1 first in class HIF-2α inhibitor. Among

them, 4 medicines were designated as orphan drugs and 1 (belzutifen) was considered as an “important contribution to public health”[2].

2.1 Kinase inhibitors

2.1.1 Repotrectinib

In 0.9-2.6% of non-small cell lung cancer (NSCLC), mutation of ROS1 tyrosine kinase is a driver mutation, causing a constitutively active enzyme even in the absence of the ligand, leading to cell growth. Resistance to previous ROS1 inhibitors has led to a need for new pharmacons in this field. Repotrectinib is a new, oral inhibitor of ROS1 and tropomyosine receptor kinase A, B, and C (TRKA, TRKB, TRKC). Repotrectinib was designed to be effective against resistance mutations. It acts by binding to the ATP/binding pocket to the enzymes in their active conformation (type I kinase inhibitor), thus inhibiting their activity (kinases use ATP to phosphorylate targets). Repotrectenib was approved by the FDA in 2023 for the treatment of adults with locally advanced or metastatic ROS1-positive NSCLC[3]. The EMA approved it for treating adults with advanced NSCLC with ROS1 gene fusion, and treating adults or children aged 12 years and older with solid tumors with NTRK (neurotrophic tyrosine receptor kinase) gene fusion if other NTRK inhibitors did not work[4].

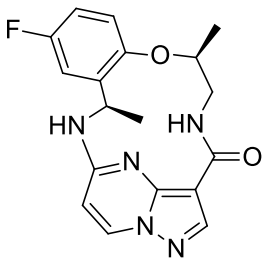


***Figure 1**.:* The structure of repotrectinib.

2.1.2 Lazertinib

Epidermal growth factor receptor (EGFR) is a well-known target for antineoplastic agents. First-generation EGFR inhibitors (erlotinib, gefitinib) were among the first clinically used tyrosine kinase inhibitors. Unfortunately, however, in most patients, resistance develops against first and second-generation (afatinib, dacomitinib) EGFR inhibitors. Lazertinib is an oral, third-generation EGFR inhibitor, developed to target the EGFR T790M resistance-causing mutation (change of threonine 790 to methionine). It is also active against Ex19del (deletion of the exon 19) and exon 21 L858R (exchange of leucine to arginine) mutations, but not against wild-type EGFR[5].

Lazertinib is a type V irreversible inhibitor of EGFR. It binds covalently to cysteine 797 of the enzyme at the ATP binding site[6]. Lazertinib can be combined with amivantamab, a bispecific monoclonal antibody, targeting EGFR and mesenchymal epithelial transition factor[7]. Lazertinib was approved in 2021 in Korea for the treatment of patients with EGFR T790M mutation-positive, locally advanced, or metastatic NSCLC who have previously received other EGFR inhibitor[5]. The EMA approved it in combination with amivantamab for the treatment of adults with advanced NSCLC, who were not treated previously, in the presence of Ex19del or Ex21 L858R mutations[8]. The FDA approved it in 2024 in combination with amivantamab-vmjw as first-line treatment for locally advanced or metastatic NSCLC with EGFR Ex19del or Ex21 L858R mutations[9].

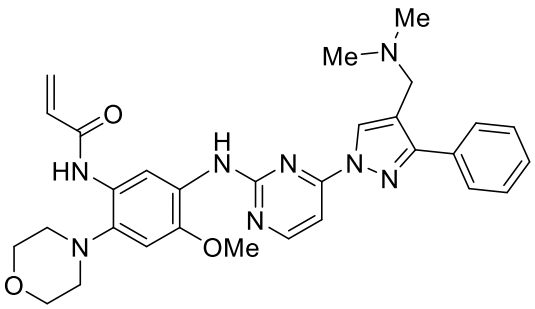


***Figure 2**.:* The structure of lazertinib

2.1.3 Fruquintinib

After reaching a large size, the tumor needs its own blood vessels, to receive sufficient oxygen and nutrients. Vascular endothelial growth factors and their receptors (VEGFRs) play an important role in angiogenesis, and VEGFR deregulation occurs in several diseases, including cancer[10]. Fruquintinib is an oral inhibitor of VEGFR1, 2 and 3. It was approved in 2018 in China for the treatment of metastatic colorectal cancer (mCRC) in patients who have failed at least two prior systemic antineoplastic therapies, including fluoropyrimidine, oxaliplatin, and irinotecan[11]. The FDA approved it in 2023 for the treatment of adult patients with mCRC who received prior fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, as well as for use in anti-VEGF therapy, and, if RAS wild-type and medically appropriate, in anti-EGFR therapy[12]. The EMA approved it to treat adults with mCRC who have already received standard treatment and whose disease has progressed with treatment with trifluridine-tipiracil or regorafenib or who are intolerant to these medicines[13].

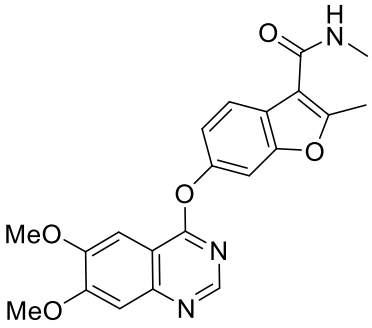


***Figure 3**.:* The structure of fruquintinib

2.1.4 Erdafitinib

Fibroblast growth factor receptors (FGFRs) regulate cell proliferation, migration, survival, and differentiation and can be drivers in several cancers. Erdafitinib is a type I1/2 pan-FGFR inhibitor. It was the first oral FGFR inhibitor approved by the FDA. It was approved in 2019 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have susceptible FGFR3 or 2 mutations and have progressed during or after the treatment of least one line of prior platinum-containing chemotherapy regimen[14, 15]. The EMA approved it for treating unresectable or metastatic urothelial carcinoma in the presence of an FGFR3 mutation[16].

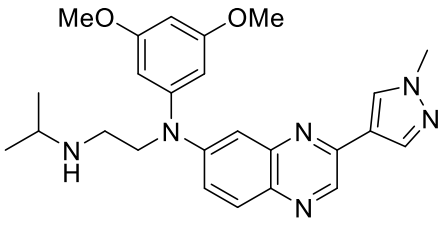
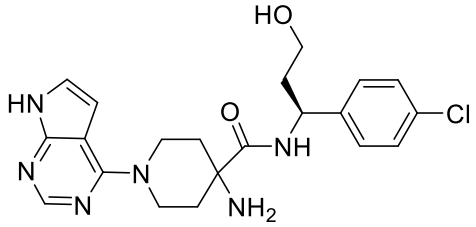


***Figure 4**.:* The structure of erdafitinib

2.1.5 Capivasertib

Akt - also known as protein kinase B (PKB) - is a serine/threonine kinase, playing an important role in cell proliferation and differentiation (among other biological processes), as part of the phosphatidylinositol-3-kinase pathway[17]. Capivasertib inhibits Akt1, 2, and 3, blocking the signaling pathway downstream of the Akt. It was approved by the FDA in 2023, in combination with fulvestrant for treating adult patients with HR-positive, HER2-negative, locally advanced, or metastatic breast cancer with one or more PIK3CA, Akt1, or PTEN mutations[18]. The EMA approved it in the same indication[19].



capivasertib

***Figure 5**.:* The structure of capivasertib

2.2 Monoclonal antibodies (MABs)

2.2.1 Immune checkpoint inhibitors

Immune checkpoints are molecules on the surface of immune cells, which either inhibit or activate immune response. They play an important role in both enabling proper immune response and preventing pathological autoimmune reactions. The function of programmed cell death protein 1 (PD-1, or CD279), located on the surface of immune cells, is to prevent autoimmune reactions and maintain immune tolerance. Programmed cell death ligands 1 and 2 (PD-L1, PD-L2) are found on the surface of several cell types. After binding to PD-L1 or 2, PD-1 inhibits T-cell activation. Blocking the interaction between PD-1 and its ligands can enhance the immune response against tumor cells, making it a significant anticancer strategy[20]. In medicine, monoclonal antibodies are mainly used for this purpose. Serplulimab was approved in 2022 in China for the treatment of adults with advanced unresectable or metastatic microsatellite instability-high (MSI-H) solid tumours[21]. The EMA approved it for the treatment of adults with small cell lung cancer (SCLC) in combination with carboplatin and etoposide. It was designated as an orphan drug[22]. Toripalimab received conditional approval in China in 2018 for the treatment of unresectable or metastatic melanoma[23]. The EMA approved it in combination with gemcitabine and cisplatin for the treatment of recurrent nasopharyngeal cancer and in combination with cisplatin and paclitaxel for treating oesophageal squamous cell cancer if it cannot be treated with surgery or radiotherapy, or is metastatic[24]. Retifanlimab is approved in the USA and in Europe for the treatment of Merkel cell carcinoma (MCC), a rare and aggressive type of skin cancer[25]. It was designated as an orphan medicine[26]. These three molecules are anti-PD-1 antibodies, while sugemalimab represents a different approach. Instead of the receptor, it targets the PD-L1 to block the interaction between the PD-1 and its ligand. Sugemalimab was approved in China for the treatment of ALK-

negative, EGFR-mutant metastatic NSCLC in combination with pemetrexed and carboplatin (for non-squamous NSCLC) or with paclitaxel and carboplatin (for squamous NSCLC)[27]. The EMA approved it for the treatment of metastatic NSCLC in combination with platinum-based therapy[28].

2.2.2 Immunoconjugates

The concept behind the immunoconjugates is to simultaneously exploit the anticancer activity of a cytotoxic agent and the selectivity of a monoclonal antibody. Immunoconjugates consist of three main parts: the antibody (which targets a molecule overexpressed in the tumor cells), the linker (which can be cleavable or non-cleavable), and the cytotoxic agent. The cytotoxic molecule must be potent, chemically stable, water-soluble, targeting intracellular molecules, and modifiable to be able to conjugate to the antibody[29].

Maytansinoids are anza macrolide derivatives, chemically related to the natural product maytansine I. They act as antimitotic agents, binding to the β-tubuline in a similar manner to the vinca alkaloids, but more potently. Thus they cause depolymerization of microtubuli, blocking cell division. Despite their effectiveness, their clinical application is hindered by their high toxicity and narrow therapeutic window. This, however, can be overcome by conjugating the derivatives to monoclonal antibodies for better targeting and improved selectivity. Antibody-linked maytansinoids were among the first immunoconjugates[29, 30].

Mirvetuximab soravtansine consists of an anti-folate receptor α monoclonal antibody, and a maytansinoid derivative DM4 (ravtansine), linked together via a cleavable disulfide linker. The antibody component targets folate receptor α (FRα), which is often overexpressed in tumor cells. After binding to the receptor, the medicine is internalized and the cytotoxic agent is released from the conjugate. Due to bystander killing, the active catabolites also kill tumor cells surrounding the target cells, ensuring the destruction of nearby tumor cells without FRα receptors. Mirvetuximab soravtansine was approved in 2022 by the FDA for the treatment of FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer[31]. The EMA approved it for the same indication and it was designated as an orphan drug[32].

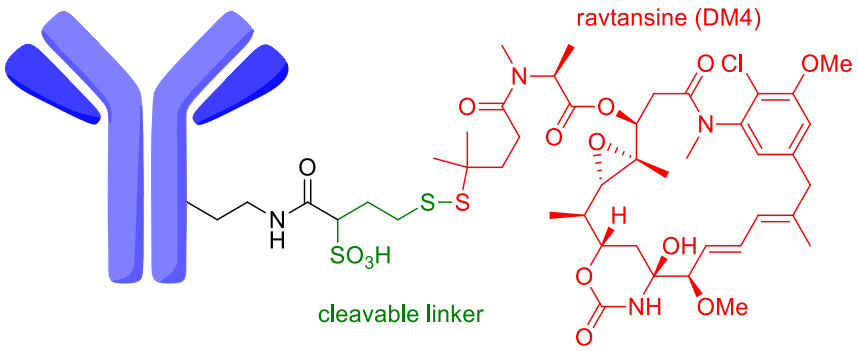


***Figure 6**.:* The structure of mirvetuximab soravtansine

2.2.3 Bispecific antibodies (bsAbs)

Bispecific antibodies represent a relatively new but rapidly expanding approach in medicine. In the last 4 years, 9 new bispecific antibodies have been approved, mostly for anticancer therapy. Their main advantage over their classic, monospecific counterparts is that they can mediate new therapeutic effects. A significant portion of approved bsAbs are T cell engagers (bispecific T cell engager = BiTe). Besides binding to their target on tumor cells, BiTes also bind to CD3 on the surface of T cells, thus coupling immune cells to tumor cells, inducing their destruction[33].

Odronextamab is a bispecific antibody, targeting CD3 and CD20 on the surface of the B cells. The EMA approved it for the treatment of relapsed or refractory follicular lymphoma and diffuse large B cell lymphoma[34].

2.2.4 Other antibodies

Claudin 18.2 (CLDN18.2) is a transmembrane protein, and an important component of the tight junction. It can be found in the stomach and plays a role in acid resistance and ion permeability. CDLN 18.2 has tumor suppressor and tumor promoter roles, too. Gastric or gastroesophageal tumors often remain CLDN18.2 positive, and unlike in healthy cells, CLDN18.2 is exposed on their surface, making them targetable with antibodies[35, 36]. Zolbetuximab is an anti-CLDN18.2, chimeric antibody, approved in Japan and in the US in 2024 for the treatment of HER2 negative, CLDN18.2 positive unresectable, advanced/recurrent gastric cancer[36, 37]. The EMA approved it in the same indication and it was designated as orphan drug[38].

2.3 HIF-2α inhibitor

Hypoxia-induced factors (HIFs) are transcription factors that regulate the expression of genes and play a role in the adaptation of cells to the hypoxic environment. There are 2 subunits, α and β, of which β is expressed constitutively, while α is regulated by several factors, including oxygen level. For example, in normoxia, prolyl hydroxylase (PHD) hydroxylates HIF-α, then von Hippel-Lindeau (VHL) protein ubiquitinates it, leading to its degradation. When α is active, coactivators and the β subunit bind to it, and the expression of HIF-regulated genes is initiated. The HIF-1 subtype plays an important role in acute hypoxia, while HIF-2 accumulates more slowly, and has more significance in chronic hypoxia[39].

Belzutifan is a first-in-class small molecule HIF-2α inhibitor. It binds to HIF-2α and prevents its interaction with HIF-1β, thus blocking the transcription of HIF-regulated genes. Belzutifan was approved by the FDA in 2021 for the treatment of VHL disease-associated tumors: renal cell carcinoma (RCC), central nervous system hemangioblastomas, and pancreatic neuroendocrine tumors[40]. Besides this, the EMA also approved it for the treatment of advanced clear cell renal cell carcinoma (when the disease has worsened after 2 or more prior treatments, including a checkpoint inhibitor and at least 2 types of VEGF-targeting medicines)[41].

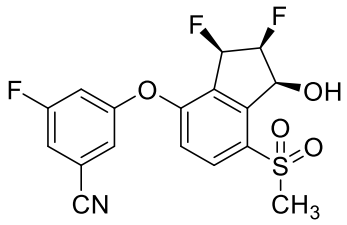


***Figure 7**.:* The structure of belzutifan

3. Discussion

The first discovered anticancer medicines were cytotoxic agents with little selectivity towards the tumor cells. Since then, cancer chemotherapy has undergone great progression, developing modern, more specific drugs, which target tumor-specific or overexpressed molecules rather than showing general cytotoxicity. Newly approved antineoplastic medicines typically belong to this group. The family of kinase inhibitors and monoclonal antibodies are still under intensive development. Besides the well-known drug classes, it is important to develop drugs with new mechanisms of action that allow the treatment of previously untreatable diseases. The first HIF-2α inhibitor

was approved as the first medicine for the treatment of von Hippel-Lindeau disease, which may pave the way for the development of new types of anticancer medicines in the future.

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