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ОБЗОРЫ

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Original drugs approved by the Food and Drug Administration (Center for Drug Evaluation and Research) in 2024

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The U.S. Food and Drug Administration (FDA), in particular the Center for Drug Evaluation and Research (CDER), plays a key role in ensuring the safety, efficacy, and innovation of medicines entering the U.S. market, and then the world. The annual review of new medicines approved by the FDA is an important tool for analyzing current trends in pharmacology and medicine, reflecting progress in the treatment of complex diseases, including cancers, orphan diseases, and infections. The review is compiled to familiarize medical specialists and pharmacologists with current trends in the registration of original medicines and in the therapy of malignant neoplasms, orphan diseases.

The aim. To summarize and systematize data on the newest medicines that entered the market in 2024, as well as to analyze the mechanisms of their action. The article aims to inform medical specialists and pharmacologists about current trends in the development and registration of innovative medicines in 2024.

Materials and methods. The presented data are taken from open sources and supplemented with the results of individual studies on new mechanisms and approaches in therapy. The main list of new drugs and introductory information about them are taken from the FDA report "Novel Drug Approvals for 2024". Data on medicine prescriptions, as well as information on the mechanism of action, are taken from published summary of product characteristics (SmPC) published on this resource, as well as from the Drugs.com website. To describe previously registered medicines for which a new indication is presented, Drugs.com reports were also used. Structural formulas of drugs are taken from the PubChem resource. In case of the absence of structural formula, data from their SmPC or third-party resources, such as Drugbank, were used. The search for literature data on fundamental studies relating to the mechanisms of action of the presented medicines was carried out in the PubMed, ResearchGate, Google Scholar and elibrary.ru databases.

Results. A statistical analysis of registrations, the dynamics of changes in the shares of various types of medicines and basic data on new original drugs registered by CDER are presented. In 2024, the FDA registered 50 original medicines, among which 48% contain a "first-in-class" molecule as an active substance. Small molecules include active substances — 60%, and biopharmaceuticals — 34% (the remaining 6% are imaging agents). At the same time, monoclonal antibodies (mAb) of antitumor and anti-inflammatory action occupy a larger share among biopharmaceuticals.

Conclusion. The large proportion of biopharmaceuticals among those newly registered in 2024 emphasizes the dynamic development of the pharmaceutical industry and its focus on personalized medicine and biotechnology. Therapy based on mAbs interacting with receptors, as well as immunotherapy based on newly discovered mechanisms of antitumor immunity, occupies a separate part in the structure of registered original medicines. The search for new rational combinations of

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antibiotics remains relevant. Most of the original drug market is still made up of small molecules, among which there are medicines — ligands of new targets and oligonucleotide sequences.

Keywords: FDA; original drugs; immunotherapy; small molecules; biopharmaceuticals; medicines for orphan diseases treatment

Abbreviations: BCG — Bacillus Calmette-Guerin; MIC — minimum inhibitory concentration; NSCLC — non-small cell lung cancer; SmPC — summary of product characteristics; PTH — parathyroid hormone; UDCA — ursodeoxycholic acid; cAMP — cyclic adenosine monophosphate; cGMP — cyclic guanosine monophosphate; ADCC — antibody-dependent cell-mediated cytotoxicity; ALK — anaplastic lymphoma kinase; CD — cluster of differentiation; CDER — Center for Drug Evaluation and Research; CFTR — cystic fibrosis transmembrane regulator; CLDN18.2 — claudin 18.2; CRF — corticotropin-releasing factor; CXCR4 — chemokine receptor that regulates cell migration in the immune system; EGF — epidermal growth factor; EGFR — epidermal growth factor receptor; ESBL — extended-spectrum beta-lactamase; Fc-fragment — crystallizing fragment of immunoglobulin; FcR — receptor for the Fc-fragment; FDA — US Food and Drug Administration; HER — human epidermal growth factor receptor; HR — hormone receptor; IFN — interferon; Ig — immunoglobulin; mAb — monoclonal antibody; MRSA — methicillin-resistant *Staphylococcus aureus*; MSSA — methicillin-sensitive *Staphylococcus aureus*; NK — natural killer; NPC — mutation causing Niemann-Pick disease type C; OAT3— organic anion transporter 3; PBP — penicillin-binding protein; PD — programmed cell death receptor, or death receptors; PD-L — programmed cell death receptor ligand; PH — hypoxia-inducible prolyl hydroxylase; PPAR — peroxisome proliferator-activated receptors; SDF-1α/CXCL12 — stromal cell factor 1α / ligand 12 to chemokine CXC; TFPI — tissue factor pathway inhibitor; TGF — transforming growth factor; TLR — Toll-like receptor; TNF — tumor necrosis factor; VEGF — vascular endothelial growth factor; VEGFR — vascular endothelial growth factor receptor.

Оригинальные лекарственные препараты, одобренные Food and Drug Administration (Center for Drug Evaluation and Research) в 2024 году

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Управление по санитарному надзору за качеством пищевых продуктов и медикаментов США (U.S. Food and Drug Administration, FDA), в частности Центр по оценке и изучению лекарственных препаратов (Center for Drug Evaluation and Research, CDER), играет ключевую роль в обеспечении безопасности, эффективности и инновационности лекарственных препаратов (ЛП), поступающих на рынок США, а затем и всего мира. Ежегодный обзор новых ЛП, одобренных FDA, представляет собой важный инструмент для анализа современных тенденций в фармакологии и медицине, отражая прогресс в лечении сложных заболеваний, включая онкологические патологии, орфанные болезни и инфекционные процессы. Обзор составлен с целью ознакомления медицинских специалистов и фармакологов с современными тенденциями в регистрации оригинальных ЛП и в терапии злокачественных образований, орфанных болезней.

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Цель. Обобщение и систематизация данных о новейших ЛП, вышедших на рынок в 2024 году, а также анализ механизмов их действия. Статья направлена на информирование медицинских специалистов и фармакологов в части современных тенденций в разработке и регистрации инновационных ЛП в 2024 году.

Материалы и методы. Представленные данные взяты из открытых источников и дополнены результатами отдельных исследований, посвящённых изучению новых механизмов и подходов в терапии. Основной список новых ЛП и вводная информация о них взяты из отчета FDA «Novel Drug Approvals for 2024». Данные по назначениям ЛП, а также информация о механизме действия, взяты из опубликованных общих характеристик лекарственных препаратов (ОХЛП), опубликованных на этом ресурсе, а также с сайта Drugs.com. Для описания ранее зарегистрированных лекарственных препаратов, для которых представлено новое назначение, также использованы отчеты Drugs.com. Структурные формулы ЛП взяты с ресурса PubChem. В случае отсутствия структурной формулы на этом ресурсе использовали данные их ОХЛП, либо сторонние ресурсы, например Drugbank. Поиск литературных данных о фундаментальных исследованиях, касающихся механизмов действия представленных ЛП осуществляли в базах данных PubMed, ResearchGate, Google Академия и elibrary.ru.

Результаты. Приведён статистический анализ регистраций, динамика изменения долей различных видов ЛП и основные данные о новых оригинальных ЛП, зарегистрированных CDER. За 2024 год в FDA было зарегистрировано 50 оригинальных ЛП, среди которых 48% ЛП в качестве активного вещества содержат «первую в классе» молекулу. К малым молекулам относятся активные субстанции — 60% ЛП, а к биопрепаратам — 34% (оставшиеся 6% — визуализирующие агенты). При этом среди биопрепаратов бóльшую долю занимают моноклональные антитела (mAb) противоопухолевого и противовоспалительного действия.

Заключение. Большая доля биопрепаратов среди вновь зарегистрированных ЛП в 2024 году подчёркивает динамичное развитие фармацевтической отрасли и ее ориентацию на персонализированную медицину и биотехнологии. Терапия, основанная на mAb, взаимодействующих с рецепторами, а также иммунотерапия, основанная на новых открытых механизмах противоопухолевого иммунитета, занимает отдельную часть в структуре зарегистрированных оригинальных ЛП. Остаётся актуальным поиск новых рациональных комбинаций антибиотиков. Большую часть рынка оригинальных ЛП все еще составляют малые молекулы, среди которых появляются ЛП — лиганды новых мишеней и олигонуклеотидные последовательности.

Ключевые слова: FDA; оригинальные препараты; иммунотерапия; малые молекулы; биопрепараты; препараты для лечения орфанных болезней

Список сокращений: БЦЖ — бацилла Кальметта-Герена; МПК — минимальная подавляющая концентрация; НМРЛ — немелкоклеточный рак легкого; ОХЛП — общая характеристика лекарственного препарата; ПТГ — паратиреоидный гормон; УДХК — урсодезоксихолевая кислота; цАМФ — циклический аденозинмонофосфат; цГМФ — циклический гуанозинмонофосфат; ADCC — антиген-зависимая клеточная цитотоксичность; ALK — киназа анапластической лимфомы; CD — кластер дифференцировки; CDER — Центр по оценке и изучению лекарственных препаратов; CFTR — трансмембранный регулятор муковисцидоза; CLDN18.2 — клаудин 18.2; CRF — кортикотропин-релизинг фактор; CXCR4 — хемокиновый рецептор, который регулирует миграцию клеток в иммунной системе; EGF — эпидермальный фактор роста; EGFR — рецептор эпидермального фактора роста; ESBL — бета-лактамаза расширенного спектра; Fc-фрагмент — кристаллизующийся фрагмент иммуноглобулина; FcR — рецептор к Fc-фрагменту; FDA — Управление по санитарному надзору за качеством пищевых продуктов и медикаментов США; HER — рецептор эпидермального фактора роста человека; HR — рецептор гормона; IFN — интерферон; Ig — иммуноглобулин; mAb — моноклональное антитело; MRSA — устойчивые к метициллину *Staphylococcus aureus*; MSSA — чувствительные к метициллину *Staphylococcus aureus*; NK — натуральный киллер; NPC — мутация, вызывающая болезнь Ниманна-Пика типа С; OAT3— переносчик органических анионов 3; PBP — пенициллинсвязывающий белок; PD — рецептор запрограммированной клеточной гибели, или рецепторы смерти; PD-L — лиганд рецептора запрограммированной клеточной гибели; PH — индуцируемая гипоксией пропилгидроксилаза; PPAR — рецепторы, активируемые пролифераторами пероксисом; SDF-1α/CXCL12 — стромальный клеточный фактор 1α / лиганд 12 к химокину CXC; TFPI — ингибитор пути тканевого фактора; TGF — трансформирующий фактор роста; TLR — Toll-подобный рецептор; TNF — фактор некроза опухоли; VEGF — фактор роста эндотелия сосудов; VEGFR —рецептор фактора роста эндотелия сосудов.

INTRODUCTION

Increasing life expectancy, improving its quality, and preserving and restoring health are priority areas for medical and social services, with a multidisciplinary approach appearing to be the only possible one to solving these problems [1]. Pharmacotherapy is the main element of human health management, and life expectancy and its quality directly depend on the availability of innovative medicines [2]. Modern pharmacy is one of the most science, technology-, and resource-intensive industries and occupies a leading position in attracting investment [3, 4]. The global pharmaceutical market is constantly undergoing processes, tending to help the largest companies dominate through the creation of advantages, including the development and implementation of various kinds of innovations[1]. Medicines can traditionally be divided into several types — original (innovative), a new dosage form or delivery system of a previously known drugs, combined, reproduced, or those registered for new indications. It is important to take into account the existence of non-equivalent exchange in resources and their unequal

[1] STATISTA. Global pharmaceutical industry - statistics & facts. Available from: https://www.statista.com/topics/1764/global-pharmaceutical-industry/

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availability (financial, labor, technological, logistical, and many others, the use of which is necessary throughout the life cycle of a medicine from idea to post-marketing monitoring). The creation of an original medicine is traditionally considered an extremely science-intensive, lengthy, and risky process, while the development of a generic or medicine in a new dosage form requires a developed technological infrastructure and an effectively built marketing component [5]. However, though the development of developing biosimilar medicines is similar to the process of creating a generic, specialists have to re-develop the original product[2], using reverse engineering methods. Registration of a drug for new indications requires reliable evidence of efficacy and safety, which is impossible without a perfectly built system for organizing and conducting clinical trials (CTs): the development of reproduced drugs will be unprofitable if there is no developed marketing system for implementation and promotion[3, 4]. The above facts reflect the increasing (as science, technology, and competition develop) complexity and dynamism of the processes taking place in the field of drug development and research, while integration into the global market multiplies the requirements for applicants[5].

The success of domestic pharmaceutical companies in 2024 indicates abilities and impressive results in the development of both original and reproduced medicines. Thus, the company JSC "R-Pharm" (Russia) registered a drug with the trade name Artserix® (INN: goflicept) for the treatment of such an orphan disease as idiopathic recurrent pericarditis (indications for use may be expanded during clinical trials) and a drug with the trade name Viltepso® (INN: viltolarsen) for the treatment of Duchenne muscular dystrophy with a confirmed mutation in the dystrophin protein gene, amenable to exon 53 skipping. Also, the company JSC "R-Pharm" received the right to conduct clinical trials of generics of anticancer drugs with the trade name Zenlistik® (INN: abemaciclib) and Lynparza® (INN: olaparib), and a drug for the treatment of hepatitis C — Maviret® (glecaprevir+pibrentasvir); biosimilar of the drug Keytruda® with the trade name Arfleida® (INN: pembrolizumab).

The company JSC "Generium" registered a drug with the trade name Lantesens® (nusinersen, analogue of Spinraza®) for the treatment of spinal muscular atrophy. The company PJSC "Promomed" registered an drug with the trade name Velgia® (INN: semaglutide; also received permission to conduct phase I CTs of a generic drug with INN tirzepatide from Eli Lilly), LLC "Geropharm" — Semavik® (in 2024 they also registered RinGluzin® [INN: insulin glulisine] and the company received the right to conduct CT of its own long-acting insulin — GP40201), and the company LLC "PSK Pharma" — Insudaiv® (also registered "Tedizolid PSK®" in 2024 [INN: tedizolid]), which are generics of the original Ozempic® (Novo Nordisk). The company LLC "Petrovax Pharm" registered a medicine with the trade name Areima® (INN: camrelizumab) — an anticancer drug used in the treatment of esophageal and nasopharyngeal cancer. The company "Biocad" was granted permission to conduct phase III CT of the first Russian gene therapy drug in the form of a solution for infusions for the treatment of hemophilia type B.

In the field of academic science and development, several important facts can be noted. For example, the St. Petersburg State Chemical Pharmaceutical University attracts investors to conduct Phase II clinical trials of three of its own drugs developed on the basis of the synthesis of original molecules. The National Medical Research Center for Hematology received permission from the Ministry of Health of the Russian Federation to conduct Phase I–II CTs of the first Russian cell gene therapy (CAR-T) drug, which received the trade name Utzhefra® (INN: hemagenlecleucel). The Siberian State Medical University announced the completion of Phase I of CTs of two original drugs (a cholesterol-lowering agent and an antitumor agent), as well as the early stage of development of an innovative medicine that increases bone tissue regeneration (potentially in demand in dentistry and cosmetology). Three Russian institutions announced the development of vaccines against HIV infection.

In 2024, the U.S. Food and Drug Administration (FDA) confirmed the registration of 50 medicines that are classified as "original" (Table 1).

THE AIM. To systematize and analyze current trends in the development of new medicines registered with the FDA in 2024, with a focus on innovative mechanisms of action and their application in oncology, treatment of rare (orphan) diseases, and infections. This review aims to inform medical professionals and pharmacologists about current trends in the development and registration of innovative medicines in 2024.

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Table 1 – Medicines registered with the U.S. Food and Drug Administration in 2024

Registration date	Trade name	Manufacturer	INN	Pharmaceutical form	Class	Indication
Dec 20	Alhemo	Novo Nordisk Inc.	Concizumab-mtci	Solution for subcutaneous administration	Monoclonal antibody	Reducing the frequency of bleeding episodes in adults and children over 12 years of age with hemophilia A and hemophilia B
Dec 20	Alyftrek	Vertex Pharmaceuticals Incorporated	Vanzacaftor+tezacaftor +deutivacaftor	Tablets for oral administration	Regulatory protein ligand	Cystic fibrosis
Dec 19	Tryngolza	Ionis Pharmaceuticals, Inc.	Olezarsen	Solution for subcutaneous administration	Oligonucleotide	Familial chylomicronemia
Dec 18	Ensacove	Xcovery Holdings, Inc	Ensartinib	Capsules for oral administration	Kinase inhibitor	NSCLC
Dec 13.	Crenessity	Neurocrine Biosciences, Inc.	Crinecerfont	Capsules for oral administration or solution for oral administration	Selective CRH 1 antagonist	An adjunct to glucocorticoid replacement therapy for the control of androgens in adults and children aged 4 years and older with classic congenital adrenal hyperplasia
Dec 13	Unloxcyt	Checkpoint Therapeutics, Inc.	Cosibelimab-ipdl	Solution for intravenous administration	Antibody	Metastatic or locally advanced cutaneous squamous cell carcinoma when radiotherapy or surgery is not possible
Dec 04	Bizengri	Merus N.V	Zenocutuzumab-zbco	Solution for intravenous administration	Bispecific antibody to HER2 and HER3	NSCLC
Nov 27	Iomervu	BIPSO GmbH	Iomeprol	Solution for intra-arterial or intravenous administration	Radiographic contrast	Visualization during intra-arterial and intravenous procedures
Nov 22	Rapiblyk	AOP Orphan Pharmaceuticals GmbH	Landiolol	Solution for intravenous administration	Beta-blocker	Short-term reduction of ventricular rate in adult patients with supraventricular tachycardia, including atrial fibrillation or flutter
Nov 22	Attruby	BridgeBio Pharma, Inc.	Acoramidis	Tablets for oral administration	Transthyretin quaternary structure stabilizer	Transthyretin amyloid cardiomyopathy
Nov 20	Ziihera	Jazz Pharmaceuticals Ireland Limited	Zanidatamab-hrii	Solution for intravenous administration	HER2 antibody	Previously treated, unresectable or metastatic bile duct cancer positive for HER2 mutation (IHC 3+)

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Registration date	Trade name	Manufacturer	INN	Pharmaceutical form	Class	Indication
Nov 15	Revuforj	Syndax Pharmaceuticals	Revumenib	Tablets for oral administration	Menin inhibitor	Relapsed or refractory acute leukemia with lysine methyltransferase 2A (KMT2A) gene translocation in children from 1 year and adults
Oct 25	Orlynvah	Iterum Therapeutics U.S. Limited	Sulopenem etzadroxil and probenecid	Tablets for oral administration	Carbapenem + inhibitor of transport through renal tubules	Urinary tract infections caused by *Escherichia coli, Klebsiella pneumoniae* or *Proteus mirabilis*
Oct 18	Vyloy	Astellas Pharma US, Inc.	Zolbetuximab-clzb	Solution for intravenous administration	Antibody against claudin 18.2	Combined with fluoropyrimidine or platinum-based therapy for patients with locally advanced unresectable or metastatic HER2-negative CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma
Oct 11	Hympavzi	Pfizer Inc. (Pfizer Labs)	Marstacimab-hncq	Solution for subcutaneous administration	Antagonist of the tissue factor pathway inhibitor	Reduction in the frequency of bleeding episodes in adults and children over 12 years of age with hemophilia A and hemophilia B
Oct 10	Itovebi	Genentech USA, Inc.	Inavolisib	Tablets for oral administration	Kinase inhibitor	Locally advanced or metastatic breast cancer, provided it is endocrine-resistant, has a PIK3CA mutation, HR-positive, HER2-negative after relapse, during or after completion of adjuvant endocrine therapy
Sep 27	Flycardo	GE Healthcare Inc.	Flurpiridaz	Solution for intravenous administration	Radiopharmaceutical for positron emission tomography	Myocardial perfusion imaging with positron emission tomography
Sep 26	Cobenfy	Bristol-Myers Squibb Company	Xanomeline and trospium chloride	Capsules for oral administration	Muscarinic receptor agonist + antagonist	Schizophrenia in adults
Sep 24	Aqneursa	IntraBio Inc.	Levacetylleucine	Suspension for oral administration	Amino acid derivation	Niemann-Pick disease type C in children with body weight >15 kg and in adults
Sep 20	Miplyffa	Zevra Therapeutics, Inc.	Arimoclomol	Capsules for oral administration	Drug for the treatment of ALS with an unknown mechanism of action	Niemann-Pick disease type C in children over 2 years of age and in adults
Sep 13	Ebglyss	Eli Lilly and Company	Lebrikizumab-lbkz	Solution for subcutaneous administration	Interleukin 13 antagonist	Moderate to severe atopic dermatitis in children over 12 years of age and adults, with a body weight of at least 40 kg, with ineffectiveness or contraindications to the use of topical drugss
Aug 19	Lazcluze	Janssen Biotech, Inc	Lazertinib	Tablets for oral administration	Kinase inhibitor	NSCLC with exon 19 deletion or L858R substitution in exon 21 of the *EGFR* gene in combination with amivantamab

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Registration date	Trade name	Manufacturer	INN	Pharmaceutical form	Class	Indication
Aug 14	Niktimvo	Incyte Corporation	Axatilimab-csfr	Solution for intravenous administration	CSF-1 receptor blocking antibody	Chronic graft-versus-host disease
Aug 14	Livdelzi	Gilead Sciences, Inc.	Seladelpar	Capsules for oral administration	Peroxisome proliferator-activated receptor delta agonist	Primary biliary cholangitis in combination with UDCA in adults with inadequate response to UDCA monotherapy
Aug 12	Nemluvio	Galderma Laboratories	Nemolizumab-ilto	Solution for subcutaneous injection	Interleukin 31 receptor antagonist	Nodular prurigo
Aug 09	Yorvipath	Ascendis Pharma Bone Diseases A/S	Palopegteriparatide	Solution for subcutaneous injection	Parathyroid hormone analog	Adult hypoparathyroidism
Aug 06	Voranigo	Servier Pharmaceuticals LLC	Vorasidenib	Tablets for oral administration	Isocitrate dehydrogenase 1 and 2 inhibitor	Grade 2 astrocytoma or oligodendroglioma (diffuse forms) in adults and children over 12 years of age
Jul 25	Leqselvi	Halo Pharmaceutical Inc.	Deuruxolitinib	Tablets for oral administration	Janus kinase inhibitor	Severe alopecia areata
Jul 02	Kisunla	Eli Lilly and Company	Donanemab-azbt	Solution for intravenous administration	Monoclonal antibody to beta-amyloid	Alzheimer's disease
Jun 26	Ohtuvayre	Verona Pharma, Inc.	Ensifentrine	Inhalation suspension	Phosphodiesterase 3 and 4 inhibitor	Chronic obstructive pulmonary disease
Jun 20	Piasky	Genentech, Inc.	Crovalimab-akkz	Solution for intravenous or subcutaneous administration	Complement component C5 inhibitor	Complement-dependent intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria
Jun 18	Sofdra	Botanix SB Inc.	Sofpironium	Topical gel	Anticholinergic	Primary axillary hyperhidrosis in adults and children 9 years of age and older
Jun 10	Iqirvo	Ipsen Biopharmaceuticals, Inc.	Elafibranor	Tablets for oral administration	Peroxisome proliferator-activated receptor agonist	Primary biliary cholangitis in combination with UDCA in adults with inadequate response to UDCA monotherapy

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Registration date	Trade name	Manufacturer	INN	Pharmaceutical form	Class	Indication
Jun 06	Rytelo	Geron Corporation	Imetelstat	Solution for intravenous administration	Telomerase oligonucleotide inhibitor	Low- and intermediate-risk myelodysplastic syndromes in adult patients with anemia requiring transfusions of 4 or more units of red blood cell mass within 8 weeks in case of ineffectiveness or impossibility of using erythropoiesis-stimulating agents
May 16	Imdelltra	Amgen Inc.	Tarlatamab-dlle	Solution for intravenous administration	Bispecific delta-like ligand 3 (DLL3) targeting CD3-cell engager	Advanced small cell lung cancer at the time of progression or after platinum-based therapy in adults
Apr 26	Xolremdi	X4 Pharmaceuticals, Inc.	Mavorixafor	Capsules for oral administration	CXC-chemokine receptor 4 antagonist	Increase in the number of mature neutrophils and lymphocytes in the peripheral blood in adults and children over 12 years of age with WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis)
Apr 23	Ojemda	Day One Biopharmaceuticals, Inc.	Tovorafenib	Oral solution	Kinase inhibitor	Relapsed or refractory pediatric low-grade glioma in children 6 months and older
Apr 22	Anktiva	Altor BioScience, LLC	Nogapendekin alfa inbakicept-pmln	Solution for intravesical administration	IL-15 agonist	Treatment of BCG-unresponsive non-muscle invasive bladder cancer with carcinoma *in situ* with or without papillary tumors in adults in combination with BCG vaccine
Apr 17	Lumisight	Lumicell, Inc.	Pegulicianine	Solution for intravenous administration	Dye	Detection of cancerous tissue in the resection cavity after removal of the primary tumor during lumpectomy in adult patients with breast cancer
Apr 03	Zevtera	Basilea Pharmaceutica International Ltd	Ceftobiprole medocaril sodium	Solution for intravenous administration	Cephalosporin	*Staphylococcus aureus* bacteremia, including right-sided infective endocarditis in adults; acute bacterial skin and skin structure infections in adults; community-acquired pneumonia in adults and children 3 months and older.
March 29	Voydeya	Alexion Pharmaceuticals, Inc.	Danicopan	Tablets for oral administration	Complement factor D inhibitor	Add-on therapy to ravulizumab or eculizumab for extravascular hemolysis in adults with paroxysmal nocturnal hemoglobinuria.
March 27	Vafseo	Akebia Therapeutics, Inc.	Vadadustat	Tablets for oral administration	Hypoxia-inducible factor prolyl hydroxylase inhibitor	Anemia due to chronic kidney disease in adults who have been on dialysis for at least 3 months

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Registration date	Trade name	Manufacturer	INN	Pharmaceutical form	Class	Indication
March 26	Winrevair	Merck Sharp & Dohme LLC	Sotatercept-csrk	Solution for subcutaneous injection	Activin signaling inhibitor	Pulmonary arterial hypertension
March 21	Duvyzat	ITF Therapeutics, LLC	Givinostat	Oral suspension	Histone deacetylase inhibitor	Duchenne muscular dystrophy in children aged 6 years and older
March 19	Tryvio	Idorsia Pharmaceuticals US Inc	Aprocitentan	Tablets for oral administration	Endothelin receptor antagonist	Arterial hypertension in combination with other blood pressure-lowering drugs in adults when adequate blood pressure control cannot be achieved
March 14	Rezdiffra	UPM Pharmaceuticals	Resmetirom	Tablets for oral administration	Thyroid hormone β agonist	Treatment (in conjunction with diet and exercise) of non-alcoholic steatohepatitis without cirrhosis with moderate to advanced fibrosis
March 13	Tevimbra	BeiGene USA, Inc.	Tislelizumab-jsgr	Solution for intravenous administration	Antibody to programmed cell deathprotein	Unresectable or metastatic squamous cell carcinoma of the esophagus in adults after chemotherapy that did not contain PD-1 inhibitors or PD-L1 inhibitors
Feb 29	Letybo	Hugel, Inc.	Letibotulinumtoxin A-wlbg	Solution for intramuscular injection	*Botulinum* toxin	Temporary improvement in the appearance of moderate to severe glabellar (between the eyebrows, on the forehead and above the nose) wrinkles
Feb 22	Exblifep	Allecra Therapeutics SAS, 68300 Saint Louis, France	Cefepime and enmetazobactam	Solution for intravenous administration	Cephalosporin and beta-lactamase inhibitor	Complicated urinary tract infections
Jan 05	Zelsuvmi	EPIH SPV, LLC	Berdazimer	Topical gel	NO-releasing agent	*Molluscum contagiosum*

Note: HER — human epidermal growth factor receptor; PD — programmed death protein 1; HR — hormone receptor; IL — interleukin; INN — international nonproprietary name; NSCLC — non-small cell lung cancer; CSF-1 — colony-stimulating factor 1.

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MATERIALS AND METHODS

The review describes drugs approved for use by the FDA. Data on the indications and mechanisms of action of drugs were taken from the Summary of Product Characteristics (SmPC) published by the FDA (https://www.fda.gov/) and supplemented with descriptions from the Drugs.com website. Structural formulas of drugs were taken from the PubChem resource. In cases where PubChem did not contain the required formula, the molecular structure was taken from the Drugs.com website or from the instructions for medical use of the medicine with this active substance. The ChemDraw program was used to unify the appearance of the formulas.

To update the literature data, a search for publications on preclinical and clinical studies of the medicine or its active substance, as well as publications on fundamental research, was carried out in the validated bibliographic database of the US National Library of Medicine (NLM) PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), on the ResearchGate (https://www.researchgate.net/) and Google Scholar (https://scholar.google.ru/) websites, as well as in Russian scientific online libraries (http://elibrary.ru and http://cyberleninka.ru/). Search queries included combinations of keywords in combination with pharmacological properties (for example, "arimoclomol in Niemann-Pick disease", etc.). Articles with a publication date no later than 2015 were used. For describing studies of fundamental mechanisms, no restrictions were placed on the publication date.

The review also presents data from the reports of the Center for Drug Evaluation and Research (CDER) "Advancing Health Through Innovation"[6, 7, 8, 9] for the periods from 2021 to 2024.

RESULTS

The dynamics of CDER FDA registration are presented in Figure 1. The ratio of the number of medicines depending on their class is presented in Table 2. Figure 2 reflects the change in the proportion of drugs belonging to different segments and registration strategies.

[6] CDER. Advancing Health Through Innovation: New Drug Therapy Approvals 2021. Available from: https://www.fda.gov/media/155227/download?attachment

[7] CDER. Advancing Health Through Innovation: New Drug Therapy Approvals 2022. Available from: https://www.fda.gov/media/164429/download?attachment

[8] CDER. Advancing Health Through Innovation: New Drug Therapy Approvals 2023. Available from: https://www.fda.gov/media/175253/download?attachment

[9] CDER. Advancing Health Through Innovation: New Drug Therapy Approvals 2024. Available from: https://www.fda.gov/media/184967/download?attachment

Table 2 – Distribution of drugs approved by the FDA in 2024 by groups depending on the nature and mechanism of action

Segment	Group	Subgroup	Quantity, *n*	Share of all registered, %	
Small molecules	Receptor ligands		9	18%	60%
	Ligands	Kinase inhibitors	5	10%	
		Non-enzyme ligands	5	10%	
		Other enzyme inhibitors	7	14%	
	Antibiotics		4	8%	
Biologics	Peptides, proteins and oligonucleotides		5	10%	34%
	mAb	Antitumor	6	12%	
		Anti-inflammatory	3	6%	
		Other	3	6%	
Imaging agents			3	6%	6%

Note: mAb — monoclonal antibody.

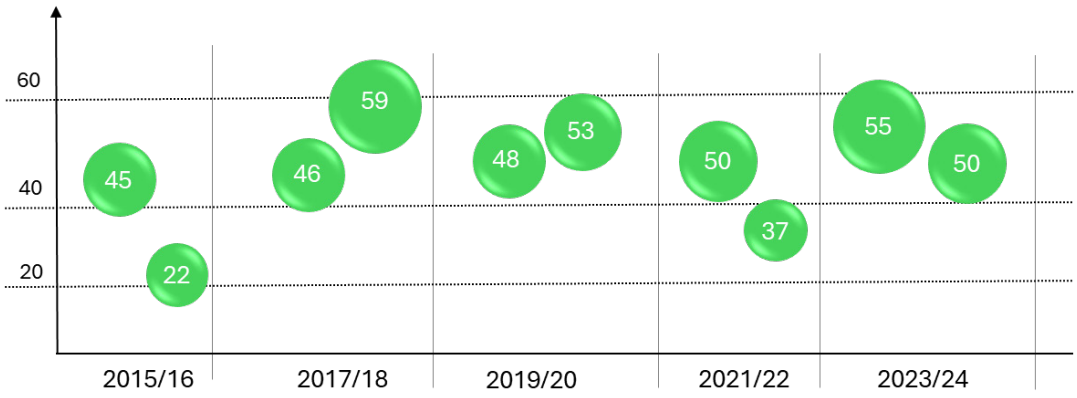

Figure 1 – Number of medicines registered with the CDER from 2015 to 2024
Note: the X-axis represents years, the Y-axis represents the number of registered medicines.

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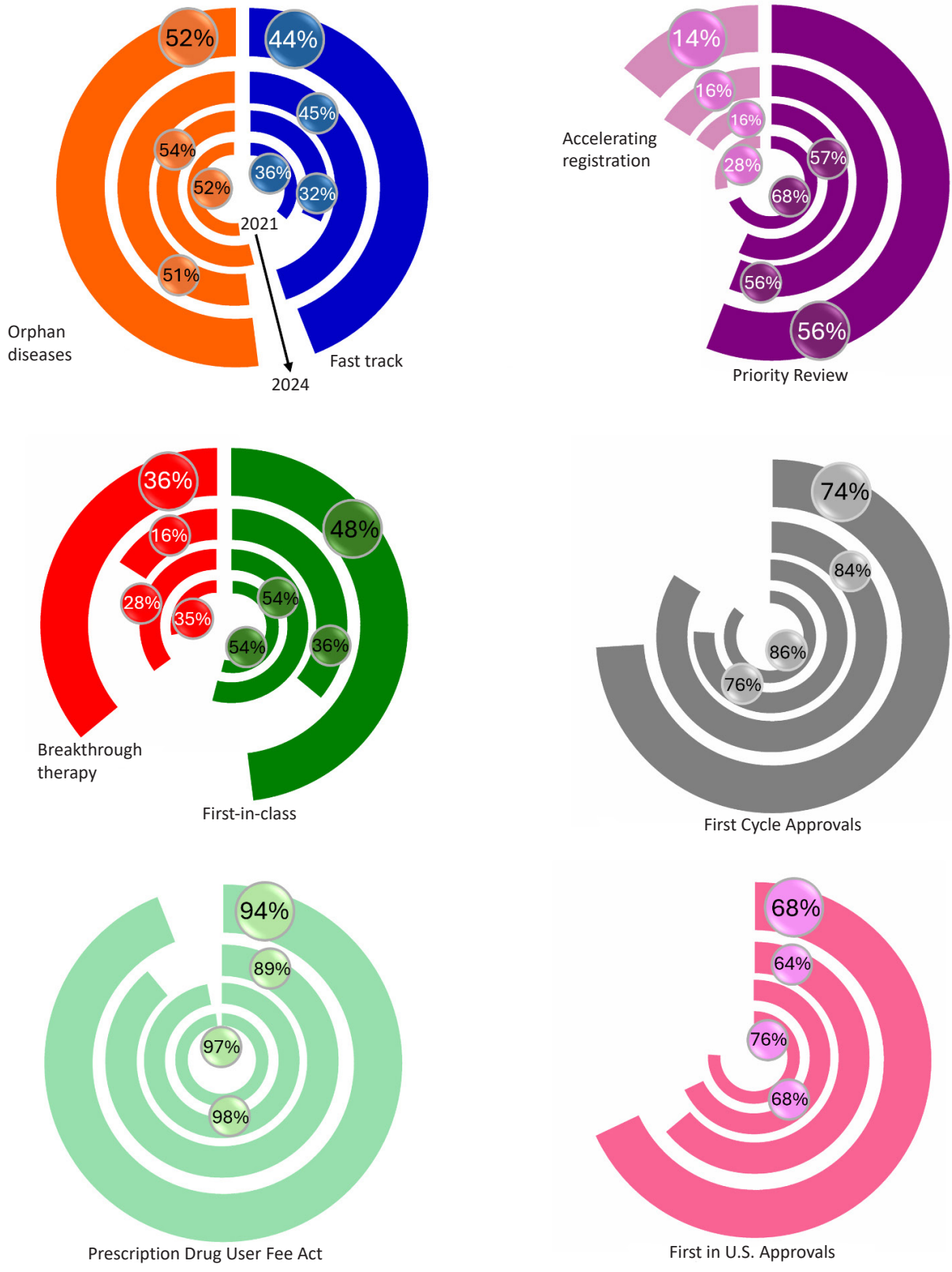

Figure 2 – Shares of original medicines from 2021 to 2024 by market segment
Note: data are presented as the proportion of drugs in the specified segment from the total number of drugs registered for the specified year.

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The descriptions and structural formulas of the original medicines registered in 2024 are presented below.

Small Molecules

Receptor Ligands

Crinecerfont

Crinecerfont (CRENESSITY™, capsules for oral administration or solution for oral administration) is a selective corticotropin-releasing hormone (CRH) receptor type 1 antagonist used as an adjunct to glucocorticoid replacement therapy to control androgens in adults and children aged 4 years and older with classic congenital adrenal hyperplasia. Crinecerfont (Fig. 3A) blocks the binding of CRH to the CRH type 1 receptor, but not to the type 2 receptor, which leads to suppression of adrenocorticotropic hormone secretion from the pituitary gland, resulting in a decrease in adrenal androgen production[10, 11].

Landiolol

Landiolol (RAPIBLYK, solution for intravenous administration) is a selective β1-adrenergic receptor antagonist used for short-term reduction of ventricular rate in adult patients with supraventricular tachycardia, including atrial fibrillation or flutter. Landiolol (Fig. 3B) suppresses the positive chronotropic effects of catecholamines (adrenaline and noradrenaline) on the heart. Landiolol does not exhibit membrane-stabilizing activity or intrinsic sympathomimetic activity at the recommended dosage *in vitro*[12, 13].

Aprocitentan

Aprocitentan (TRYVIO™, tablets for oral administration) is an endothelin receptor antagonist used to treat arterial hypertension in combination with other medicines that lower blood pressure in adults when adequate blood pressure control cannot be achieved. Aprocitentan (Fig. 4A) binds to endothelin 1 receptors A and B and prevents the development of the latter's pathogenetics: endothelial dysfunction, hypertrophy and vascular remodeling, as well as sympathetic activation of aldosterone synthesis[14, 15].

Sofpironium

Sofpironium (SOFDRA™, gel for topical use) is an anticholinergic medicine intended for the treatment of primary axillary hyperhidrosis in adults and children over 9 years of age. It is a competitive inhibitor of acetylcholine receptors located in some peripheral tissues (including axillary sweat glands). Sofpironium (Fig. 4B) has an indirect effect on excessive sweating, preventing the activation of acetylcholine receptors[16, 17].

Seladelpar

Seladelpar (LIVDELZI®, capsules for oral administration) is an agonist of the peroxisome proliferator-activated receptor delta (PPAR) δ, intended for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with insufficient efficacy of UDCA as monotherapy. The mechanism by which seladelpar (Fig. 5A) exerts its therapeutic effect in patients with primary biliary cholangitis has not been well studied. The therapeutic effect includes inhibition of bile acid synthesis through activation of PPARδ, which is a nuclear receptor expressed in most cells, including hepatocytes. Seladelpar activates PPARδ, which leads to a decrease in bile acid synthesis activity by suppressing cytochrome P450 (CYP) 7A1 via a fibroblast growth factor 21 (FGF21)-dependent mechanism. CYP7A1 is a key enzyme in the synthesis of bile acids from cholesterol. The indication for the use of seladelpar was established based on its ability to reduce alkaline phosphatase activity. The effect on survival or prevention of liver function decompensation has not been proven[18, 19].

[10] Drugs. com. Crenessity. Available from: https://www.drugs.com/crenessity.html
[11] CRENESSITY. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218808s000,218820s000lbl.pdf
[12] Drugs. com. Rapiblyk. Available from: https://www.drugs.com/rapiblyk.html
[13] RAPIBLYK. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217202s000lbl.pdf
[14] Drugs. com. Tryvio. Available from: https://www.drugs.com/tryvio.html
[15] TRYVIO. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217686s000lbl.pdf
[16] Drugs. com. Sofdra. Available from: https://www.drugs.com/sofdra.html
[17] SOFDRA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217347s000lbl.pdf
[18] Drugs. com. Livdelzi. Available from: https://www.drugs.com/livdelzi.html
[19] LIVDELZI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217899s000lbl.pdf

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Elafibranor

Elafibranor (IQIRVO®, oral tablets) is a PPAR agonist indicated for the treatment of primary biliary cholangitis in combination with UDCA in adults with inadequate response to UDCA as monotherapy. In vitro, elafibranor (Fig. 5B) has affinity for PPARα, PPARγ, and PPARδ. However, the mechanism of this drug in patients with primary biliary cholangitis has not been established. It is assumed that the therapeutic effect is mediated by inhibition of bile acid synthesis, which, in turn, is regulated by PPARα and PPARδ[20, 21].

Xanomeline+trospium chloride

Xanomeline and trospium chloride (COBENFY™, oral capsules) is a combination of a muscarinic receptor agonist and antagonist with antipsychotic activity, indicated for the treatment of schizophrenia in adults. The exact mechanism of action of the combination is unknown. Xanomeline (Fig. 6A) binds to muscarinic receptors. The Ki of xanomeline for binding to the M1 receptor is 10 nmol/L, for binding to M2 — 12 nmol/L, to M3 — 17 nmol/L, to M4 — 7 nmol/L, and for binding to M5 — 22 nmol/L. Thus, xanomeline has the most pronounced agonistic effect on the M1 and M4 receptors. Trospium chloride (Fig. 6B) is a muscarinic receptor antagonist that acts primarily in the tissues of the peripheral nervous system. The combination of these compounds is the first antipsychotic medicine whose action is based on interaction with cholinergic receptors, rather than with dopamine receptors, which was the basis of the action of medicines that have long served as the standard of treatment[22, 23].

Mavorixafor

Mavorixafor (XOLREMDI™, oral capsules) is an antagonist of receptor 4 to CXC-chemokine, used in adults and children over 12 years of age with WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis) to increase the number of mature neutrophils and lymphocytes in peripheral blood. Mavorixafor (Fig. 7A) is a *CXCR4* antagonist that prevents the binding of the stromal cell factor 1α ligand (stromal-derived factor-1α [SDF-1α]/CXC Chemokine Ligand 12 [CXCL12] SDF-1/CXCL12). This ligand modulates the transport of lymphocytes from the bone marrow to the blood and back. Functional mutations in the *CXCR4* gene, which are found in patients with WHIM syndrome, lead to increased sensitivity to *CXCL12* and retention of leukocytes in the bone marrow. Mavorixafor inhibits the interaction of *CXCL12* with *CXCR4*, both with the mutant form and with the wild-type form. The use of mavorixafor leads to the mobilization of neutrophils and lymphocytes from the bone marrow into the peripheral blood[24, 25].

Resmetirom

Resmetirom (REZDIFFRA, oral tablets) is a thyroid hormone receptor beta (THR-β) agonist indicated in combination with diet and exercise for the treatment of non-alcoholic steatohepatitis without cirrhosis with moderate to severe fibrosis (Stage F2–F3). The use of resmetirom in patients with decompensated cirrhosis is contraindicated. Resmetirom (Fig. 7B) is a partial THR-β agonist, causing an effect that is 83.8% of that developing in response to triiodothyronine exposed to THR-β. Since THR-β is the main form of the thyroid hormone receptor in the liver, the main effect of the medicine is to reduce the concentration of triglycerides in the liver[26, 27].

Berdazimer

Berdazimer (ZELSUVMI™, topical gel) is a nitric oxide (NO) releasing agent used to treat molluscum contagiosum. Its action is associated with the release of NO, which is believed to help fight the virus, although the exact mechanism is not fully understood. Berdazimer is a polymer formed from sodium 1-hydroxy-3-methyl-3-(3-(trimethoxysilyl)propyl)-1-triazene-2-oxide and tetraethyl silicate. The structural formula is shown in Figure 8[28, 29].

[20] Drugs. com. Iqirvo. Available from: https://www.drugs.com/iqirvo.html
[21] IQIRVO. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218860s000lbl.pdf
[22] Drugs. com. Cobenfy. Available from: https://www.drugs.com/cobenfy.html
[23] COBENFY. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216158s000lbl.pdf
[24] Drugs.com. Xolremdi. Available from: https://www.drugs.com/xolremdi.html
[25] XOLREMDI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218709s000lbl.pdf
[26] Drugs.com. Rezdiffra. Available from: https://www.drugs.com/rezdiffra.html
[27] REZDIFFRA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217785s000lbl.pdf
[28] Drugs.com. Zelsuvmi. Available from: https://www.drugs.com/zelsuvmi.html
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Ligands of enzymes and other proteins

Kinase inhibitors

Ensartinib

Ensartinib (ENSACOVE™, oral capsules) is an anaplastic lymphoma kinase (ALK) inhibitor that also suppresses the activity of other kinases, including MET and ROS1. Ensartinib (Fig. 9A) is indicated for adult patients with locally advanced or metastatic ALK-positive NSCLC who have not previously received ALK inhibitors. In vitro, ensartinib inhibited ALK phosphorylation, leading to blockade of downstream signaling pathways, thereby preventing proliferation in cells containing ALK fusion proteins and its mutated forms. In vivo, ensartinib had an antitumor effect in an NSCLC xenograft (ALK fusion) in mice[30, 31].

Inavolisib

Inavolisib (ITOVEBI, oral tablets) is a phosphatidylinositol 3-kinase (PI3K) inhibitor, predominantly active against PI3Kα. Inavolisib (Fig. 9B) is used to treat locally advanced or metastatic breast cancer, provided that it is endocrine-resistant, has a PIK3CA mutation, is HR-positive, HER2-negative after recurrence, during or after completion of adjuvant endocrine therapy[32, 33].

In vitro, the medicine induces degradation of the p110α subunit, mutated PI3K, inhibits phosphorylation and the protein kinase B (AKT) cascade, leading to a decrease in cell proliferation and apoptosis of breast cancer cells with the *PIK3CA* mutation. In vivo, inavolisib inhibits the growth of breast cancer xenografts in mice. The combination of inavolisib with palbociclib and fulvestrant inhibits tumor growth more significantly than each of the drugs separately.

Lazertinib

Lazertinib (LAZCLUZE™, oral tablets) is an epidermal growth factor receptor (EGFR) kinase inhibitor intended for the treatment of NSCLC. The medicine (Fig. 9B) suppresses EGFR activity at lower concentrations than when exposed to the wild-type receptor. In NSCLC cells and in mouse xenografts of these cells with exon 19 deletion or L858R substitution in exon 21, lazertinib has antitumor activity. In similar models, lazertinib enhances the antitumor effect of amivantamab[34, 35].

Tovorafenib

Tovorafenib (OJEMDA, oral solution) is a kinase inhibitor (rapidly accelerated fibrosarcoma RAF) type II kinases, B form of RAF kinase (BRAF) V600E mutation, wild-type BRAF, and wild-type CRAF. This medicine is used to treat relapsed or refractory pediatric low-grade glioma in children older than 6 months. Tovorafenib (Fig. 11A) had antitumor activity in animals with a tumor xenograft carrying mutations provoking fibrosarcoma with BRAF mutations[36, 37].

Deucravacitinib

Deucravacitinib (LEQSELVI™, oral tablets) is a Janus kinase (JAK) inhibitor intended for the treatment of adults with severe alopecia areata. JAK regulates the signaling pathways of a number of cytokines and growth factors that play an important role in hematopoiesis and immunity. JAK signaling involves the activation of signal transducers and activators of transcription to cytokine receptors, which leads to modulation of the expression of certain genes. In vitro, deucravacitinib (Fig. 10A) inhibited JAK1 and JAK2 more significantly than JAK3. The relationship between JAK inhibition and the therapeutic activity of deucravacitinib has not been fully studied[38, 39].

Other enzyme inhibitors

Vorasidenib

Vorasidenib (VORANIGO®, oral tablets) is an isocitrate dehydrogenase (IDH) 1 and IDH2 inhibitor intended for the treatment of grade 2 astrocytoma or oligodendroglioma (diffuse forms) in adults and children 12 years and older. Voracidenib in medicinal forms is used as a co-crystal of hemihydrate and hemicitric acid (Fig. 11B). *In vitro*, voracidenib suppresses the activity of wild-type and mutant variants of IDH1,

[30] Drugs.com. Ensacove. Available from: https://www.drugs.com/ensacove.html
[31] ENSACOVE. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218171s000lbl.pdf
[32] Drugs.com. Itovebi. Available from: https://www.drugs.com/itovebi.html
[33] ITOVEBI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219249s001lbl.pdf
[34] Drugs.com. Lazcluze. Available from: https://www.drugs.com/lazcluze.html
[35] LAZCLUZE. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219008s000lbl.pdf
[36] Drugs.com. Ojemda. Available from: https://www.drugs.com/ojemda.html
[37] OJEMDA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218033s000lbl.pdf
[38] Drugs.com. Leqselvi. Available from: https://www.drugs.com/leqselvi.html
[39] LEQSELVI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217900Orig1s000correctedlbl.pdf

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including forms with R132H substitution. In animal models using tumors expressing mutant IDH1 and IDH2, administration of vorasidenib reduced the production of 2-hydroxyglutarate and partially normalized impaired cell differentiation[40, 41].

Ensifentrine

Ensifentrine (OHTUVAYRE, inhalation suspension) is a phosphodiesterase (PDE) 3 and 4 inhibitor used to treat chronic obstructive pulmonary disease. PDE3 predominantly hydrolyzes cAMP and has the ability to hydrolyze cGMP, while PDE4 hydrolyzes only cGMP. Ensifentrine (Fig. 10B) inhibits the activity of PDE3 and PDE4, which leads to the accumulation of intracellular cAMP and cGMP and, as a result, to the suppression of intracellular signal transduction[42, 43].

Imetelstat

Imetelstat (RYTELO, solution for intravenous administration) is an oligonucleotide telomerase inhibitor intended for the treatment of myelodysplastic syndromes with low and intermediate risk in adult patients with anemia requiring transfusions of 4 or more units of red blood cell mass within 8 weeks with ineffectiveness or impossibility of using erythropoiesis-stimulating agents. Imetelstat (Fig. 12) inhibits human telomerase by binding to the template region of its RNA component, which leads to suppression of the activity of this enzyme and prevention of telomere elongation. Increased activity and expression of RNA reverse transcriptase of telomerase was found in myelodysplastic syndromes, in cancer stem and progenitor cells. According to the results of preclinical studies, imetelstat reduced telomere length, suppressed the proliferation of malignant stem and progenitor cells, and induced apoptosis[44, 45].

Givinostat

Givinostat (DUVYZAT, suspension for oral administration; Fig. 13) is a histone deacetylase inhibitor used to treat Duchenne muscular dystrophy in children aged 6 years and older. The mechanism of alleviation is unknown. In a study involving children who were given the drug for 18 months, it was noted that the increase in the fraction of fat in the lateral broad muscle of the thigh was 7.48 *vs* 10.89% (in the group of patients using placebo)[46, 47].

Vadadustat

Vadadustat (VAFSEO®, tablets for oral administration) is an inhibitor of hypoxia-inducible prolyl hydroxylase (HIF-prolyl-4-hydroxylases, PH) intended for the treatment of anemia caused by chronic kidney disease in adults who have been on dialysis for at least 3 months. Vadadustat (Fig. 14A) is a reversible inhibitor of PH1, PH2 and PH3. Due to this activity, the use of vadadustat leads to stabilization and accumulation of transcription factors 1α and 2α induced by hypoxia, as well as an increase in the production of erythropoietin[48, 49].

Danicopan

Danicopan (VOYDEYA™, tablets for oral administration) is an inhibitor of factor D of the complement system, intended for additional therapy to ravulizumab or eculizumab for extravascular hemolysis in adults with paroxysmal nocturnal hemoglobinuria[50, 51].

In paroxysmal nocturnal hemoglobinuria, intravascular hemolysis occurs with the participation of a membrane-attacking complex, and the development of extravascular hemolysis is enhanced by opsonization with the participation of complement system fragment C3. Danicopan prevents the development of extravascular hemolysis, while ravulizumab or eculizumab prevents intravascular hemolysis.

Danicopan (Fig. 14B), reversibly binding to factor D (adipsin, C3 proactivator convertase) of the complement system, inhibits the alternative pathway of its activation. The effect of danicopan on factor D

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[41] VORANIGO. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218784s000lbl.pdf
[42] Drugs.com. Ohtuvayre. Available from: https://www.drugs.com/ohtuvayre.html
[43] OHTUVAYRE. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217389s000lbl.pdf
[44] Drugs.com. Rytelo. Available from: https://www.drugs.com/rytelo.html
[45] RYTELO. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217779s000lbl.pdf
[46] Drugs.com. Duvyzat. Available from: https://www.drugs.com/duvyzat.html
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[48] Drugs.com. Vafseo. Available from: https://www.drugs.com/vafseo.html
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[50] Voydeya. Available from: https://www.drugs.com/voydeya.html
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prevents the cleavage of factor B into Ba and Bb, which are necessary for the formation of C3 component convertase and activation of subsequent effectors of the complement system, including C3 opsonization.

Non-enzyme ligands

Vanzacaftor+tezacaftor+deutivacaftor

Vanzacaftor, tezacaftor and deutivacaftor (ALYFTREK, tablets for oral administration) is a combination of cystic fibrosis transmembrane regulator (*CFTR*) ligands intended for the treatment of cystic fibrosis in patients aged 6 years and older with at least one F508del mutation or another mutation in the *CFTR* gene. The structural formulas of the components included in the drug product are shown in Figure 15. Vanzacaftor and tezacaftor bind to different regions of *CFTR* and additively contribute to the processing and expression of mutant forms of *CFTR* on the cell surface. Deutivacaftor increases the probability of opening the *CFTR* channel on the cell surface. Together, these 3 molecules enhance *CFTR* activity, which leads to increased chloride transport across the cell membrane and alleviation of cystic fibrosis[52, 53].

Revumenib

Revumenib (REVUFORJ, tablets for oral administration) is a menin inhibitor used to treat relapsed or refractory acute leukemia with translocation of the lysine methyltransferase 2A (histone-lysine N-methyltransferase 2A, *KMT2A*) gene in children from 1 year and adults. Revumenib (Fig. 16G) blocks the interaction of *KMT2A* and the *KMT2A*-menin hybrid protein. Binding of the *KMT2A*-menin hybrid protein is involved in the mechanism of reorganization of acute leukemia under the control of *KMT2A*, which occurs after activation of leukemogenic transcription. In preclinical studies, suppression of the interaction of menin and *KMT2A* in cells expressing *KMT2A* hybrid proteins with revumenib led to a change in the transcription of a number of genes, including differentiation markers. Revumenib had an antiproliferative and antitumor effect *in vitro* and *in vivo* against cells containing *KMT2A* hybrid proteins[54, 55].

Acoramidis

Acoramidis (ATTRUBY™, tablets for oral administration) is a transthyretin stabilizer used to treat transthyretin amyloid cardiomyopathy (cardiomyopathy of transthyretin-mediated amyloidosis ATTR-CM), with wild-type or variant form of the transthyretin gene in adults to reduce mortality and hospitalizations due to cardiovascular disorders. Acoramidis (Fig. 16A) is a selective transthyretin stabilizer. By binding to transthyretin at the thyroxine binding site, acoramidis slows down the dissociation of the transthyretin tetramer, which is the limiting stage of amyloidogenesis[56, 57].

Drugs for the treatment of Niemann-Pick disease type C

Levacetylleucine

Levacetylleucine (AQNEURSA™, suspension for oral administration) is a leucine derivative used to treat Niemann-Pick disease type C (NPC1 or NPC2 mutation, cell membrane proteins) in children with a body weight >15 kg and in adults. The mechanism of action of levacetylleucine (Fig. 16B) is unknown[58, 59].

Arimoclomol

Arimoclomol (MIPLYFFA, capsules for oral administration) is an experimental compound used to treat Niemann-Pick disease type C (NPC1 or NPC2 mutation, cell membrane proteins) in adults and children over 2 years of age. The mechanism of action of arimoclomol (Fig. 16C) is unknown[60, 61].

A clinical study was conducted involving 50 patients aged 2 to 18 years suffering from Niemann-Pick disease type C. Participants took arimoclomol at a dose of 16, 31 or 62 mg orally in capsules 3 times a day, or placebo. The primary endpoint was the change in the score on the five-structure scale of Niemann-Pick disease type C (Niemann-Pick Disease Type C Clinical Severity Scale, NPCCSS) from the start of the study to 12 months. As a result, it was found that arimoclomol

[52] Drugs.com. Alyftrek. Available from: https://www.drugs.com/alyftrek.html
[53] ALYFTREK. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218730s000lbl.pdf
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[55] REVUFORJ https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218944s000lbl.pdf
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[57] ATTRUBY. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216540s000lbl.pdf
[58] Drugs.com. Aqneursa. Available from: https://www.drugs.com/aqneursa.html
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[60] Drugs.com. Miplyffa. Available from: https://www.drugs.com/miplyffa.html
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significantly slowed the progression of the disease. The average decrease in progression in patients taking arimoclomol was 0.76 versus 2.15 in patients taking placebo. The difference in progression (estimated through statistical analysis) was approximately 1.40, which is significant and indicates a decrease in the rate of the disease. Side effects occurred in 88% of treated patients, but there were fewer serious complications — 14.7 *vs* 31.3% in patients taking placebo [6].

Antibiotics

Ceftobiprole medocaril sodium

Ceftobiprole medocaril sodium (ZEVTERA, solution for intravenous administration) is a cephalosporin used to treat:

- *Staphylococcus aureus* bacteremia, including right-sided infectious endocarditis in adults;
- Acute bacterial infections of the skin and skin structures in adults;
- Community-acquired pneumonia in adults and children over 3 months[62, 63].

The antibacterial activity of ceftobiprole (Fig. 17) is mediated by the suppression of bacterial wall synthesis. In vitro, ceftobiprole was active against both gram-positive and gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA)[64].

Bactericidal activity is justified by the binding of the drug to penicillin binding protein (PBP) and inhibition of their transpeptidase activity, which is necessary for the synthesis of the peptidoglycan layer of the bacterial cell wall. Ceftobiprole has a high affinity for PBP 1–4 *Staphylococcus aureus*, including penicillin-resistant *Streptococcus pneumoniae*.

Ceftobiprole is not active against bacteria producing ESBL, TEM, SHV or CTX-M families, as well as against serine carbapenemases, metallo-β-lactamases of classes B and C (AmpC). No cross-resistance of ceftobiprole and antibiotics of other classes has been identified. Resistance may be present in strains resistant to cephalosporins.

Cefepime+enmetazobactam

Cefepime and enmetazobactam (EXBLIFEP®, solution for intravenous administration) is a combination of a cephalosporin and a β-lactamase inhibitor used to treat complicated urinary tract infections. Cefepime (Fig. 18A), which is part of the drug product, belongs to β-lactam antibiotics of the cephalosporin group IV generation. The chemical structure includes β-lactam and iminotetrahydrothiazine rings, as well as an N-methylpyrrolidine side chain, which improves penetration through bacterial walls and binding to PBP. Enmetazobactam (Fig. 18B) is a β-lactamase inhibitor that protects cefepime from cleavage by some serine β-lactamases, such as ESBL[65, 66].

The spectrum of antibacterial activity of the medicine EXBLIFEP® is presented in Table 3. Mechanisms of resistance include: modification of PBP, increased production of β-lactamases resistant to enmetazobactam, increased production of efflux pumps, as well as mutations of the membrane porin.

Table 3 – Spectrum of antibacterial activity of the combination of cefepime and enmetazobactam[67]

Clinically proven effectiveness	
Gram-negative bacteria	*Escherichia coli*
	Klebsiella pneumoniae
	Pseudomonas aeruginosa
	Proteus mirabilis
	Enterobacter cloacae
Efficacy confirmed *in vitro*, but there is no data on clinical significance	
Gram-negative bacteria	*Citrobacter freundii*
	Klebsiella aerogenes
	Klebsiella oxytoca
	Providencia stuartii
	Providencia rettgeri
	Serratia marcescens

Sulopenem etzadroxil+probenecid

Sulopenem etzadroxil and probenecid (ORLYNVAH™, tablets for oral administration) is a combined medicine of a tubular transport inhibitor and an antibiotic recommended for the treatment of urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae* or *Proteus mirabilis*. Probenecid (Fig. 19A) reduces the clearance of sulopenem (Fig. 19B) by suppressing its excretion through OAT3, which leads

[62] Drugs.com. Zevtera. Available from: https://www.drugs.com/zevtera.html
[63] ZEVTERA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218275s000lbl.pdf
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[65] Drugs.com. Exblifep. Available from: https://www.drugs.com/exblifep.html
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[67] Ibid.

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to an increase in the concentration of the antibiotic in the blood plasma[68, 69, 70].

For sulopenem, as for other β-lactam antibiotics, a correlation has been proven between the duration of the drug in plasma, at a concentration above MIC, and antimicrobial activity, which justifies the combination with a renal excretion inhibitor.

Sulopenem etzadroxil is a prodrug. Sulopenem *in vitro* is active against gram-positive and gram-negative aerobes and anaerobes. The antimicrobial activity of sulopenem is mediated by its ability to suppress cell wall synthesis, as well as by the binding of the drug product to PBP. The binding affinity of sulopenem to PBP in *Escherichia coli* is in the following order: PBP2 >PBP1A >PBP1B >PBP4 >PBP3 >PBP5/6.

Factors of bacterial resistance to sulopenem may be extended-spectrum β-lactamases (ESBL), including carbapenemases. Changes in PBP, an increase in the number of efflux pumps and a decrease in the number of porins on the outer membrane also affect. Sulopenem is active against *Enterobacterales* expressing some ESBL, for example, AmpC, CTX-M, TEM, SHV. Lines resistant to sulopenem were selected *in vitro* with a frequency of 1×10^{-8}.

Biologics

Peptides, proteins and oligonucleotides

Olezarsen

Olezarsen (TRYNGOLZA, solution for subcutaneous injection) is an antisense oligonucleotide directed against the apolipoprotein C-III (APOC-III) gene and indicated as an adjunct to diet to reduce triglyceride concentrations in adults with familial chylomicronemia syndrome. Olezarsen (Fig. 20) is an ASO-GalNAc3 conjugate that binds to apolipoprotein C-III mRNA, which leads to its degradation and a decrease in APOC-III concentration in blood serum. A decrease in APOC-III concentration leads to an increase in the clearance of triglycerides and very low density lipoproteins[71, 72].

Nogapendekin alfa inbakicept-pmln

Nogapendekin alfa inbakicept-pmln (ANKTIVA®, solution for intravesical administration) is an IL-15 receptor agonist used in combination with Bacillus Calmette-Guerin (BCG) vaccine for the treatment of BCG-unresponsive invasive bladder cancer with carcinoma in situ in adults with or without papillomas. IL-15 transmits signals through a heterotrimeric receptor consisting of γ-chain, β-chain and IL-15-specific α-subunit. On the surface of CD4+ and CD8+ T-cells, as well as on the surface of natural killers (NK), IL-15 interaction is carried out through the combined IL-2/IL-15 receptor. Binding of nogapendekin alfa inbakicept-pmln to this receptor leads to proliferation and activation of NK cells, CD8+-cells and memory cells, without activating the proliferation of regulatory T-cells. In vivo, intravesical administration of the drug product alone or in combination with BCG led to the development of an antitumor effect in a rat bladder cancer model induced by a carcinogen[73, 74].

Palopegteriparatide

Palopegteriparatide (YORVIPATH®, solution for subcutaneous injection) is a structural analogue of parathyroid hormone (amino acid sequence from 1 to 34, PTH[1-34]) intended for the treatment of hypoparathyroidism in adults. The structure of palopegteriparatide is shown in Figure 21. Under physiological conditions, palopegteriparatide releases PTH(1-34) with the achievement of prolonged systemic exposure. Endogenous PTH regulates extracellular calcium homeostasis in blood serum and reduces the concentration of phosphate in it. These effects of PTH are mediated by interaction with bone tissue and mobilization of calcium and phosphate in it, as well as stimulation of renal reabsorption of calcium and excretion of phosphates. Like endogenous PTH, PTH(1-34) released from palopegteriparatide has a parathyroid effect through the parathyroid hormone receptor 1, expressed on the surface of osteoblasts, osteocytes, renal tubule cells and in some other tissues[75, 76].

[68] Drugs.com. Orlynvah. Available from: https://www.drugs.com/orlynvah.html
[69] Drugs.com. Sulopenem etzadroxil and probenecid (Monograph). Available from: https://www.drugs.com/monograph/sulopenem-etzadroxil-and-probenecid.html
[70] ORLYNVAH. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213972s000lbl.pdf
[71] Drugs.com. Tryngolza. Available from: https://www.drugs.com/tryngolza.html
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[73] Drugs.com. Anktiva. Available from: https://www.drugs.com/anktiva.html
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[75] Drugs.com. Yorvipath. Available from: https://www.drugs.com/yorvipath.html
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Sotatercept-csrk

Sotatercept-csrk (WINREVAIR™, solution for subcutaneous injection) is an activin signaling inhibitor used to treat pulmonary arterial hypertension. Chemically, sotatercept is a homodimeric recombinant hybrid protein consisting of the extracellular domain of the human activin receptor type IIA (ActRIIA) and the Fc domain of human immunoglobulin (Ig) G1 associated with it. It binds to activin A and other ligands of the TGF-β superfamily. As a result of this interaction, sotatercept normalizes the balance of proproliferative and antiproliferative signaling pathways that modulate angiogenesis. In studies using rats with experimental pulmonary arterial hypertension, it was noted that an analogue of sotatercept reduced inflammation and suppressed the proliferation of endothelial and smooth muscle cells in case of vascularization disorders. This effect led to the cessation of right ventricular remodeling and improved hemodynamics[77, 78].

Letibotulinumtoxin A-wlbg

Letibotulinumtoxin A-wlbg (LETYBO, solution for intramuscular injection) is a modified botulinum toxin, an inhibitor of acetylcholine release and a blocker of neuromuscular transmission, intended for temporary improvement of the appearance of glabellar (between the eyebrows, on the forehead and above the nose) wrinkles of moderate to severe severity. Letibotulinumtoxin A-wlbg, when administered intramuscularly, penetrates into the nerve ending, cleaves the SNAP25 protein, which is necessary for the release of acetylcholine into the synaptic cleft, which leads to a dose-dependent decrease in muscle function. Restoration of muscle function occurs gradually due to the degradation of the neurotoxin and the formation of axonal processes. Reinnervation of muscles occurs, which leads to a slow elimination of the pharmacological effects of letibotulinumtoxin A-wlbg[79, 80].

Monoclonal antibodies of antitumor action

Most registered mAb medicines are prescribed for the treatment of malignant neoplasms.

Cosibelimab-ipdl

Cosibelimab-ipdl (UNLOXCYT, solution for intravenous administration) is an antibody blocking the programmed death receptor-1 (PD-1) ligand, intended for the treatment of adult patients with metastatic or locally advanced squamous cell skin cancer who cannot undergo radiation therapy or surgical treatment.

The PD-1 ligand is expressed on tumor and immune cells infiltrating the tumor. This suppresses antitumor signals in the tumor microenvironment. Binding of the ligand to PD-1 and B7.1 on the surface of T-cells and antigen-presenting cells suppresses cytostatic activity, proliferation and cytokine production by T-lymphocytes. Cosibelimab binds to the PD-1 ligand and, thus, blocks the interaction between it and PD-1 and B7.1. This effect weakens the inhibitory effect of the PD-1 ligand on the antitumor response. Cosibelimab causes ADCC *in vitro*[81, 82].

Zenocutuzumab-zbco

Zenocutuzumab-zbco (BIZENGRI®, solution for intravenous administration) is a bispecific antibody to HER2, HER3, intended for the treatment of:

- adults with advanced unresectable or metastatic NSCLC, carriers of the neuregulin 1 (*NRG1*) gene fusion, provided the disease progresses during or after systemic therapy;
- adults with advanced, unresectable or metastatic pancreatic adenocarcinoma containing the NRG1 gene fusion, provided the disease progresses during or after systemic therapy.

Zenocutuzumab-zbco binds to the extracellular domains of HER2 and HER3 expressed on the surface of cells, including tumor cells, suppressing HER2:HER3 dimerization and preventing *NRG1* binding to HER3. This leads to a decrease in proliferation and signal transduction involving the PI3K-AKT-mammalian target of rapamycin (mTOR). In addition, zenocutuzumab-zbco induces ADCC. In studies on mouse models, zenocutuzumab-zbco showed antitumor activity in *NRG1* fusions in lung and pancreatic cancer[83, 84].

[77] Drugs.com. Winrevair. Available from: https://www.drugs.com/winrevair.html
[78] WINREVAIR. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761363s000lbl.pdf
[79] Drugs.com. LETYBO. Available from: https://www.drugs.com/letybo.html
[80] LETYBO. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761225s000lbl.pdf
[81] Drugs.com. Unloxcyt. Available from: https://www.drugs.com/unloxcyt.html
[82] UNLOXCYT. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761297s000lbl.pdf
[83] Drugs.com. Bizengri. Available from: https://www.drugs.com/bizengri.html
[84] BIZENGRI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761352s001lbl.pdf

Zanidatamab-hrii

Zanidatamab-hrii (ZIIHERA®, solution for intravenous administration) is a bispecific antibody directed to HER2, used to treat adult patients with previously treated, unresectable or metastatic bile duct tumor positive for HER2 mutation (IHC 3+). The antibody binds to two extracellular regions of HER2, which leads to internalization (immersion of the receptor inside the cell) and a decrease in HER2 on the surface of tumor cells. Zanidatamab-hrii activates complement-mediated cytotoxicity, antibody-dependent cytotoxicity and antibody-dependent cellular phagocytosis. All these mechanisms led to the suppression of tumor growth and cell death *in vitro* and *in vivo*[85, 86].

Zolbetuximab-clzb

Zolbetuximab-clzb (VYLOY®, solution for intravenous administration) is a chimeric (human/mouse) antibody that, in combination with claudin 18.2 (CLDN18.2), causes antigen- and complement-dependent cytolysis of cells expressing CLDN18.2. Zolbetuximab-clzb enhances the antitumor activity of chemotherapeutic agents in a mouse tumor model expressing CLDN18.2. The "exposure-response" relationship, in relation to the efficacy and safety of the recommended doses of zolbetuximab-clzb in patients with locally advanced unresectable or metastatic HER2-negative CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma, has not been fully studied[87, 88].

Tislelizumab-jsgr

Tislelizumab-jsgr (TEVIMBRA™, solution for intravenous administration) is an antibody that blocks PD-1, used to treat unresectable or metastatic squamous cell carcinoma of the esophagus in adults after chemotherapy that did not contain PD-1 inhibitors or PD-1 ligand inhibitors. Binding of *PD-1* located on the surface of T-cells to PD-L1 and PD-L2 ligands leads to a decrease in T-cell proliferation and cytokine production. Upregulation of PD-L-dependent signaling pathways occurs in some tumors, which leads to suppression of immune surveillance of T-cells over these tumors. Tislelizumab-jsgr, binding to *PD-1*, blocks its interaction with PD-L1 and PD-L2, which allows the development of an antitumor immune response. In in vivo experiments using transgenic mice carrying the human PD-1 gene with tumor xenografts, tislelizumab suppressed tumor growth[89, 90].

Crovalimab-akkz

Crovalimab-akkz (PIASKY, solution for intravenous or subcutaneous administration) is an antibody with high affinity for the C5 component of the complement. Crovalimab inhibits the breakdown of C5 into C5a and C5b, preventing the formation of a membrane-attacking complex. Thus, crovalimab suppresses complement-dependent intravascular hemolysis in patients with nocturnal paroxysmal hemoglobinuria[91, 92].

Tarlatamab-dlle

Tarlatamab-dlle (IMDELLTRA™, solution for intravenous administration) is a bispecific delta-like ligand 3 (DLL3) directed to capture CD3-cells. It is intended for the treatment of advanced small cell lung cancer at the time of progression or after therapy with platinum medicines in adults. Tarlatamab-dlle causes T-cell activation, release of pro-inflammatory cytokines and lysis of cells expressing DLL3. The medicine showed antitumor activity in a mouse model of small cell lung cancer[93, 94].

mAb of anti-inflammatory action

Lebrikizumab-lbkz

Lebrikizumab-lbkz (EBGLYSS, solution for subcutaneous injection) is a mAb (IgG4) that blocks IL-13, used to treat moderate to severe atopic dermatitis in children over 12 years of age and adults, with a body weight of at least 40 kg, with ineffectiveness or contraindications to the use of topical drugs. The medicine can be used in combination with topical corticosteroids. Lebrikizumab, binding to IL-13, allows it to bind to the α1 receptor to IL-13, while suppressing

[85] Drugs.com. Ziihera. Available from: https://www.drugs.com/ziihera.html
[86] ZIIHERA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761416s000lbl.pdf
[87] Drugs.com. Vyloy. Available from: https://www.drugs.com/vyloy.html
[88] VYLOY. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761365s000lbl.pdf
[89] Drugs.com. Tevimbra. Available from: https://www.drugs.com/tevimbra.html
[90] TEVIMBRA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761232Orig1s000lbl.pdf
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[92] PIASKY. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761388s000lbl.pdf
[93] Drugs.com. Imdelltra. Available from: https://www.drugs.com/imdelltra.html
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the signal transduction pathway through the receptor complex e IL-4Rα/IL-13Rα1. IL-13 is a cytokine involved in the development of type II inflammation, plays an important role in the pathogenesis of atopic dermatitis. By interfering with the work of IL-13, the medicine suppresses the release of pro-inflammatory cytokines, chemokines and IgE[95, 96].

Axatilimab-csfr

Axatilimab-csfr (NIKTIMVO™, solution for intravenous administration) is a mAb that blocks the receptor to colony-stimulating factor 1 (CSF-1R), used to treat chronic graft-versus-host disease. Blocking CSF-1R reduces the concentration of circulating pro-inflammatory and profibrotic monocytes and monocyte-derived macrophages. This effect leads to a decrease in the number of non-classical monocytes (cluster of differentiation [cluster of differentiation, CD] 14+, CD16+), which suppresses the activity of pathogenic macrophages in tissues[97, 98].

Nemolizumab-ilto

Nemolizumab-ilto (NEMLUVIO®, solution for subcutaneous injection) is a humanized mAb (IgG2) that selectively binds to the IL-31 receptor, intended for the treatment of nodular prurigo. IL-31 is involved in the pathogenesis of prurigo — inflammation, epithelial deregulation and fibrosis. Nemolizumab-ilto inhibits IL-31-mediated reactions, including the release of cytokines and chemokines[99, 100.]

Others

Marstacimab-hncq

Marstacimab-hncq (HYMPAVZI, solution for subcutaneous injection) is a human IgG1 mAb to the Kunitz 2 domain of tissue factor pathway inhibitor (TFPI). TFPI is an anticoagulant — the main inhibitor of coagulation activation via the extrinsic pathway. It binds to the active site of factor X_a (Stuart-Prower) using the Kunitz domain. Inhibition of TFPI with marstacimab enhances coagulation, therefore it is used to reduce the frequency of bleeding episodes in adults and children over 12 years of age with hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency)[101, 102].

Concizumab-mtci

Concizumab-mtci (ALHEMO®, solution for subcutaneous injection) is a mAb-antagonist of TFPI, used for common prophylaxis and reduction of the frequency of bleeding episodes in adults and children over 12 years of age with hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency)[103, 104].

Donanemab-azbt

Donanemab-azbt (KISUNLA, solution for intravenous administration) is a humanized IgG1 mAb directed to aggregated forms of insoluble N-terminally truncated pyroglutamate beta-amyloid, intended for the treatment of Alzheimer's disease. The accumulation of amyloid plaques in the brain is a key pathophysiological mechanism in the development of Alzheimer's disease. Donanemab reduces the number of beta-amyloid plaques in the brain[105, 106].

Imaging agents

Iomeprol

Iomeprol (IOMERVUTM, solution for intra-arterial or intravenous administration) is a radiographic iodinated contrast agent used during intra-arterial procedures:

- Cerebral arteriography, including intra-arterial digital subtraction angiography (IA-DSA), in adults and children
- Visceral and peripheral arteriography and aortography, including IA-DSA, in adults and children;
- Coronary arteriography and cardiac ventriculography in adults;
- Radiographic assessment of heart chambers

[95] Drugs.com. Ebglyss. Available from: https://www.drugs.com/ebglyss.html
[96] EBGLYSS. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761306Orig1s000correctedlbl.pdf
[97] Drugs.com. Niktimvo. Available from: https://www.drugs.com/niktimvo.html
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[99] Drugs.com. Nemluvio. Available from: https://www.drugs.com/nemluvio.html
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[101] Drugs.com. Hympavzi. Available from: https://www.drugs.com/hympavzi.html
[102] HYMPAVZI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761369s000lbl.pdf
[103] Drugs.com. Alhemo. Available from: https://www.drugs.com/alhemo.html
[104] ALHEMO. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761315s000lbl.pdf
[105] Drugs.com. Kisunla. Available from: https://www.drugs.com/kisunla.html
[106] KISUNLA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761248s000lbl.pdf

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and adjacent arteries in pediatric patients;
During intravenous procedures:

- CT of the head and body in adults and children;
- CT angiography of intracranial, visceral arteries and arteries of the lower extremities in adults and children;
- CT angiography of coronary vessels in adults and children;
- CT urography in adults and children.

The mechanism of action of iomeprol (Fig. 22A) is based on its ability to penetrate into the tissue of blood vessels and other structures of the body and slow down X-ray photons. Iodinated contrast agents (CA) diffuse from blood vessels into the extravascular space. In the brain with an intact BBB, CA does not diffuse into the extravascular space, and contrast enhancement is usually associated with the presence of CA in the vascular space. In patients with BBB damage, CA accumulates in the extravascular space in the area of the disorder[107, 108].

Flurpiridaz

Flurpiridaz F18 (FLYRCADO™, solution for intravenous administration) is a radiopharmaceutical indicated for myocardial perfusion imaging with positron emission tomography. It is used at rest or during pharmacological/physical stress on the heart in adult patients with coronary artery disease to assess the severity of ischemia and myocardial infarction. Flurpiridaz F18 (Fig. 22B) is a structural analogue of pyridabene — an inhibitor of mitochondrial complex 1. Flurpiridaz F18 is excreted from the myocardium in proportion to the blood flow rate in it and binds to active mitochondria. Thus, the detectable radioactivity in the viable myocardium is higher than in the ischemic tissue[109, 110].

Pegulicianine

Pegulicianine (LUMISIGHT™, solution for intravenous administration) is an imaging agent used in adult patients with breast cancer during lumpectomy as an auxiliary agent for detecting cancerous tissue in the resection cavity after removal of the primary tumor. Pegulicianine (Fig. 23) is a prodrug that does not have optical activity. When the peptide bond in the pegulicianine molecule is cleaved under the action of cathepsins and matrix metalloproteinases, “fragment 2” and “fragment 3”, which are fluorescent metabolites, are formed as a result of enzymatic cleavage. “Fragment 1” is a fluorescence quencher, its cleavage leads to the activation of molecules. Since the amount of cathepsins and metalloproteinases in tumor cells and cells adjacent to tumor cells is significantly greater than in healthy cells, this medicine visualizes areas of tissue affected by tumor growth. The absorption peak of fluorescent fragments of the pegulicianine molecule is 650 nm, and the emission peak is 675 nm[111, 112].

DISCUSSION

The main mechanisms of immunotherapy relevant to newly registered biologics

Tumor microenvironment and immune checkpoints

The tumor microenvironment (TME) is a complex and dynamic environment in which tumor cells develop. It consists of various cellular and molecular components that interact with each other and with tumor cells, forming a unique ecosystem that promotes cancer progression [7, 8].

The TME of the tumor consists of cancer cells, stromal cells (fibroblasts and others), as well as immune cells — predominantly macrophages and T-lymphocytes. The extracellular environment of the TME contains signaling ligands that bind to receptors located on the surface of tumor cells, antigen-presenting cells and immune cells. The interaction between immune cells and the tumor plays a key role in determining the dynamics of the pathological process [9–11].

Immune checkpoints are inhibitory receptors and signaling pathways that are involved in the regulation of the immune response. They play a key role in maintaining autotolerance and preventing an excessive immune response that can lead to damage to the body’s own tissues. Immunotherapy of cancers is aimed, among other things, at the interaction of the drug product with targets that are part of the system of immune checkpoints [12, 13].

[107] PubChem. Iomeprol. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/3731
[108] IOMERVU. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216017s000,216017s000lbl.pdf
[109] Drugs.com. Flyrcado. Available from: https://www.drugs.com/pro/flyrcado.html
[110] FLYRCADO. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215168s000lbl.pdf
[111] Drugs.com. Lumisight. Available from: https://www.drugs.com/pro/lumisight.html
[112] LUMISIGHT. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/214511s000lbl.pdf

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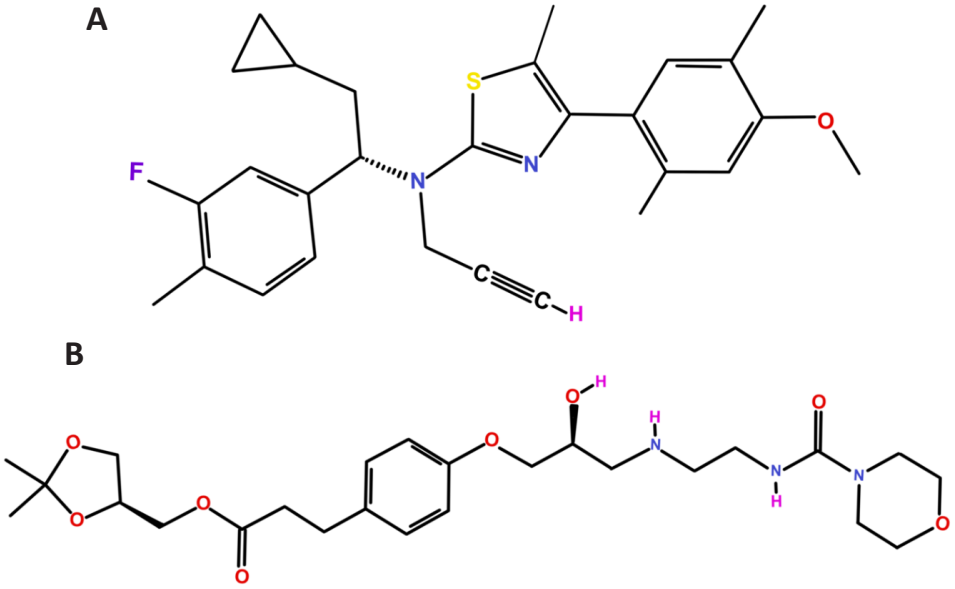

Figure 3 – Structures of crinecerfont (A) and landiolol (B)

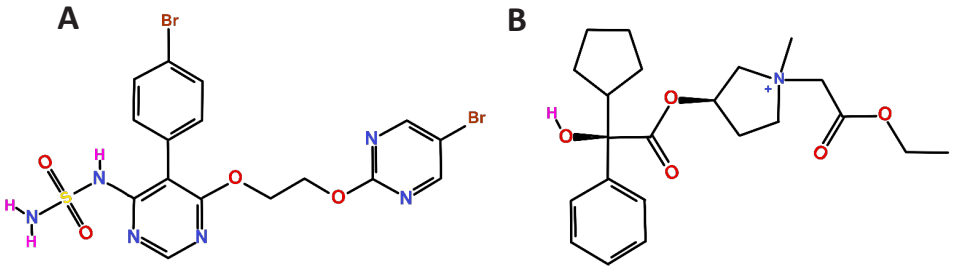

Figure 4 – Structures of aprocitentan (A) and sofpironium (B)

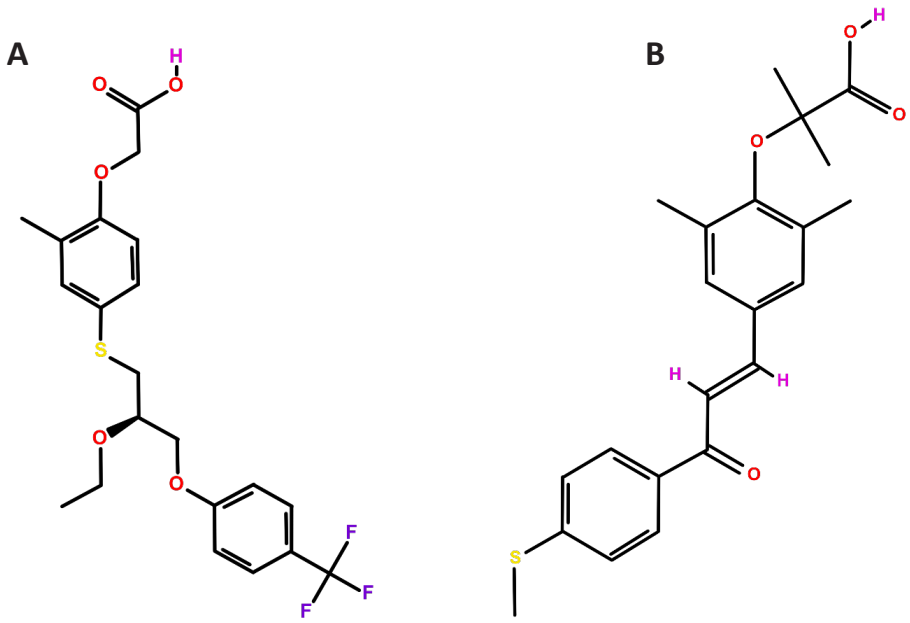

Figure 5 – Structures of seladelpar (A) and elafibranor (B)

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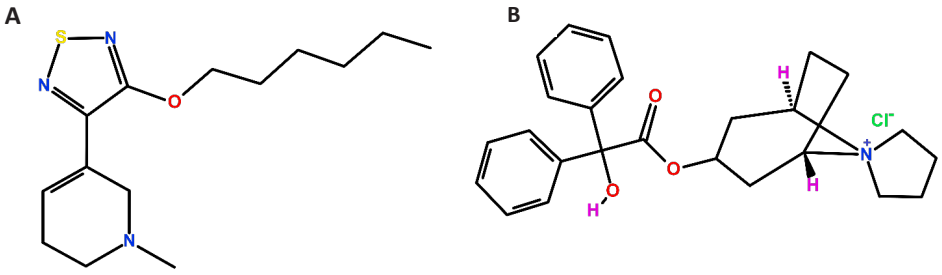

Figure 6 – Structures of xanomeline (A) and trospium chloride (B)

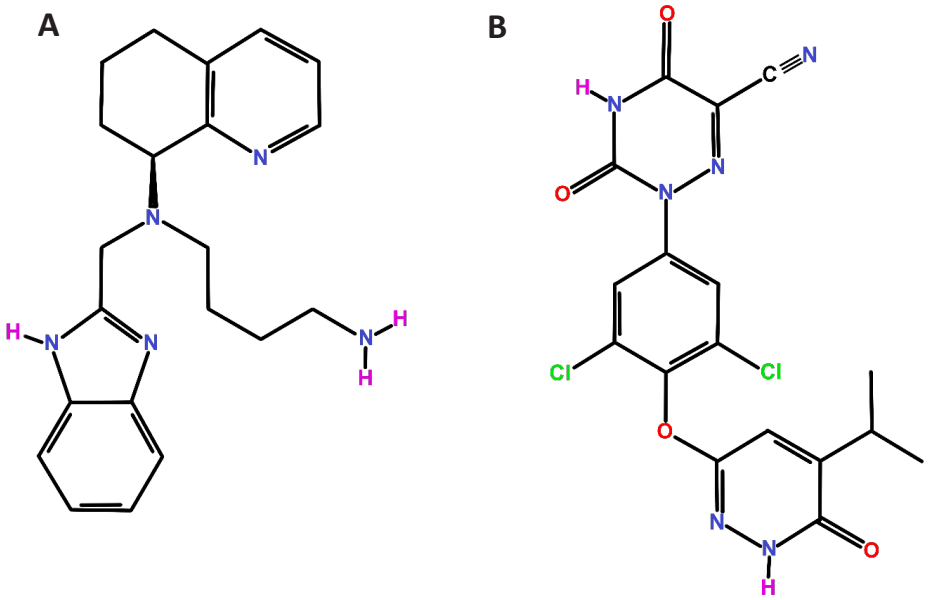

Figure 7 –Structures of mavorixafor (A) and resmetirom (B)

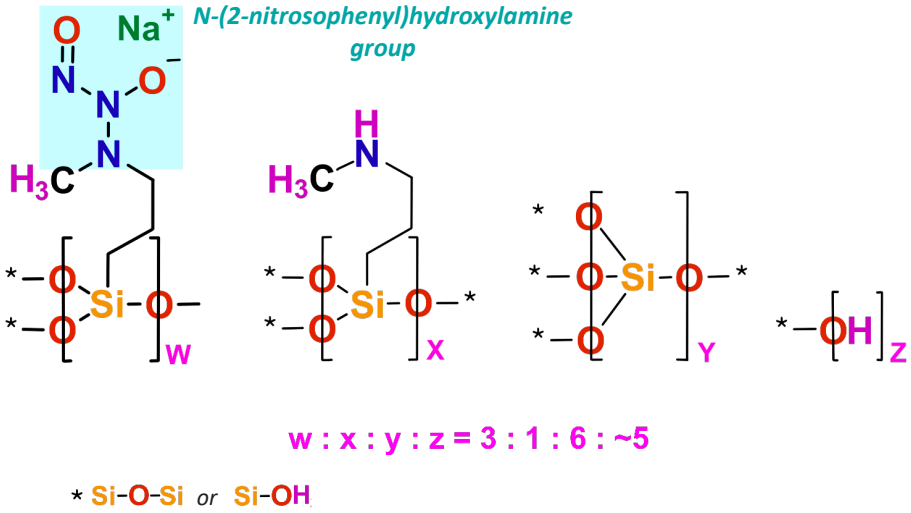

Figure 8 – Structural formula of berdazimer

Note: * is a common oxygen atom that binds structural components of the molecule through polyxyloxane fragments Si-O-Si or Si-OH.

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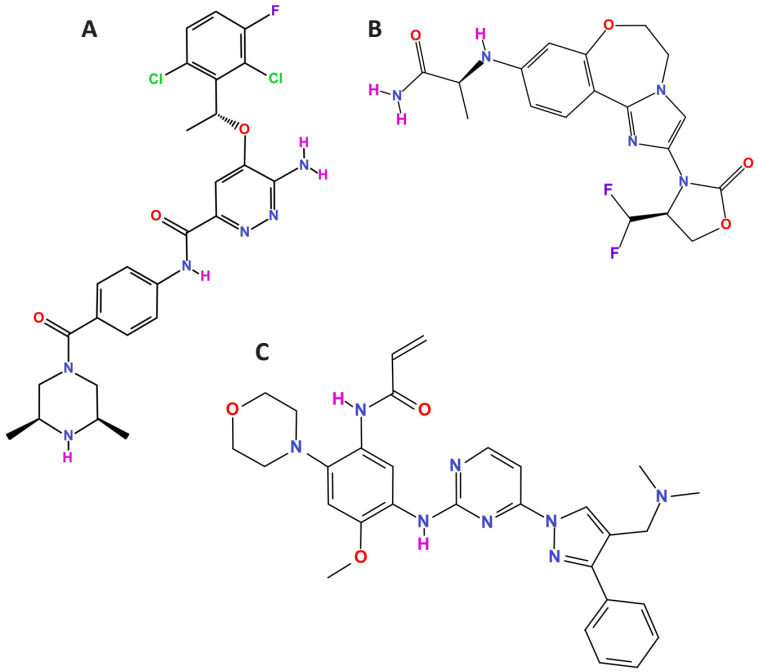

Figure 9 – Structures of ensartinib (A), inavolisib (B) and lazertinib (C)

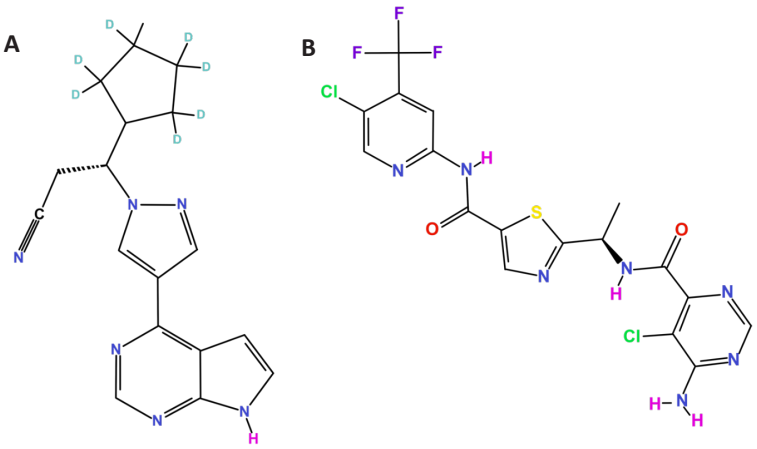

Figure 10 –Structures of deucravacitinib (A) and ensifentrine (B)

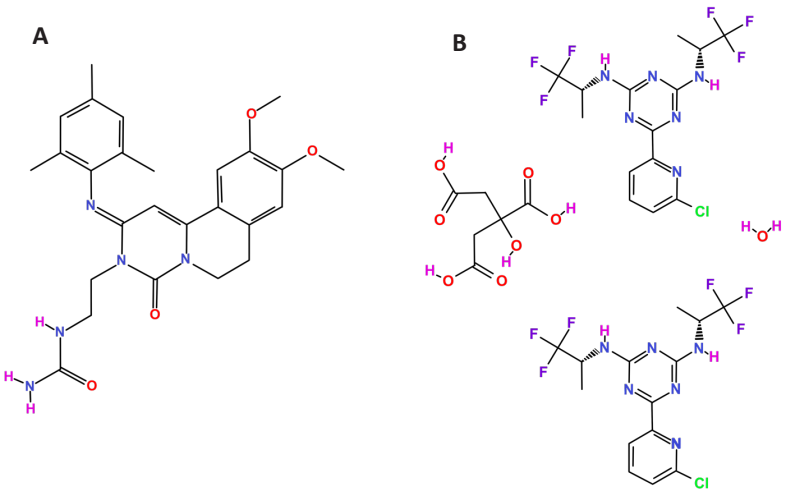

Figure 11 – Structures of tovorafenib (A) and vorasidenib cocrystal

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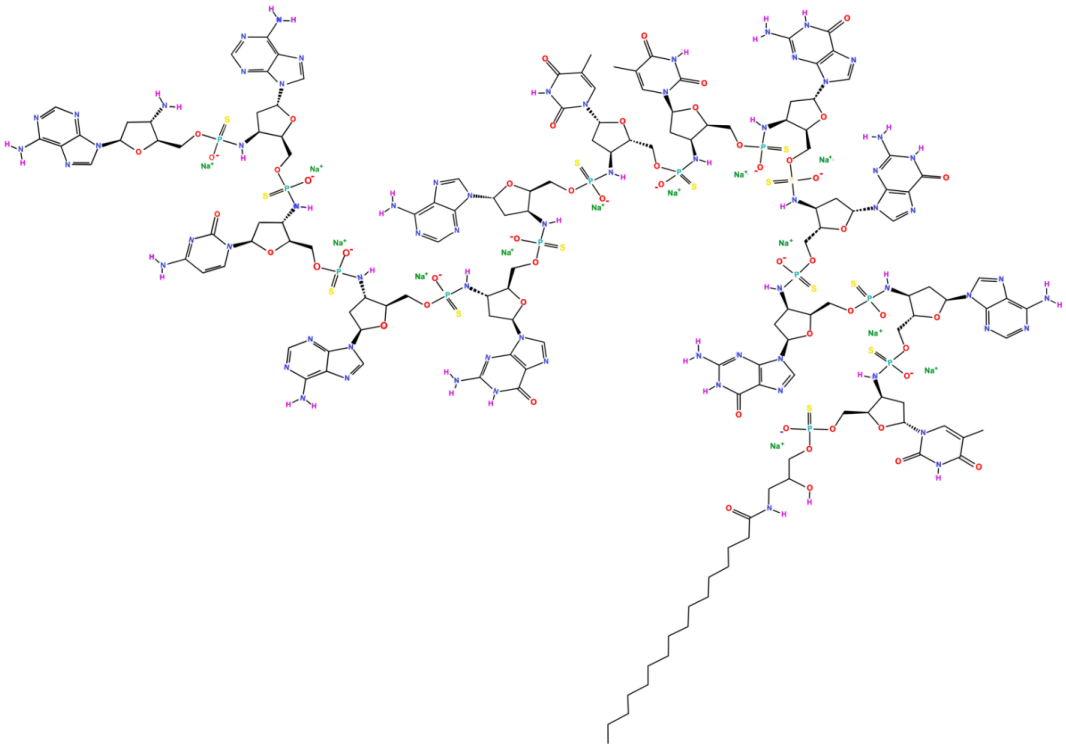

Figure 12 – Structures of imetelstat sodium

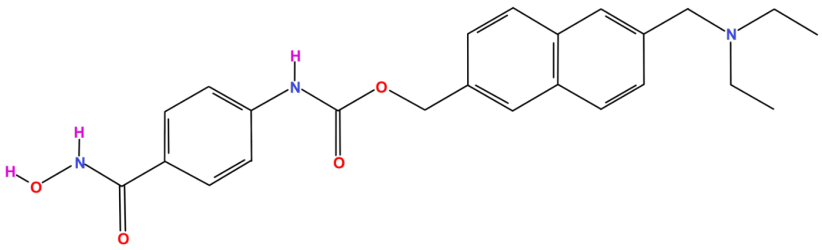

Figure 13 – Structures of givinostat

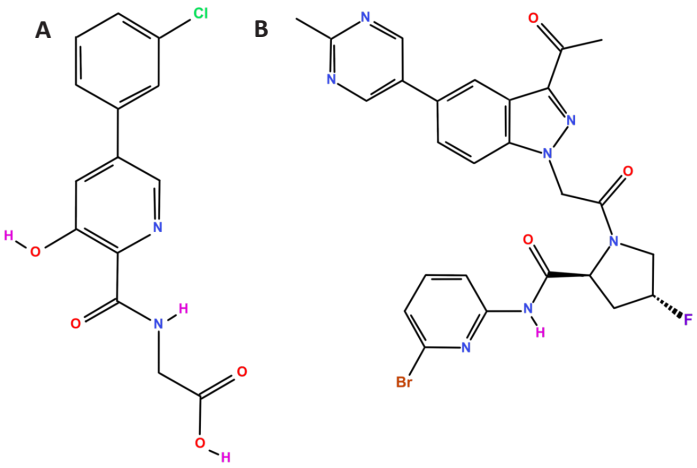

Figure 14 – Structures of vadadustat (A) and danicopan (B)

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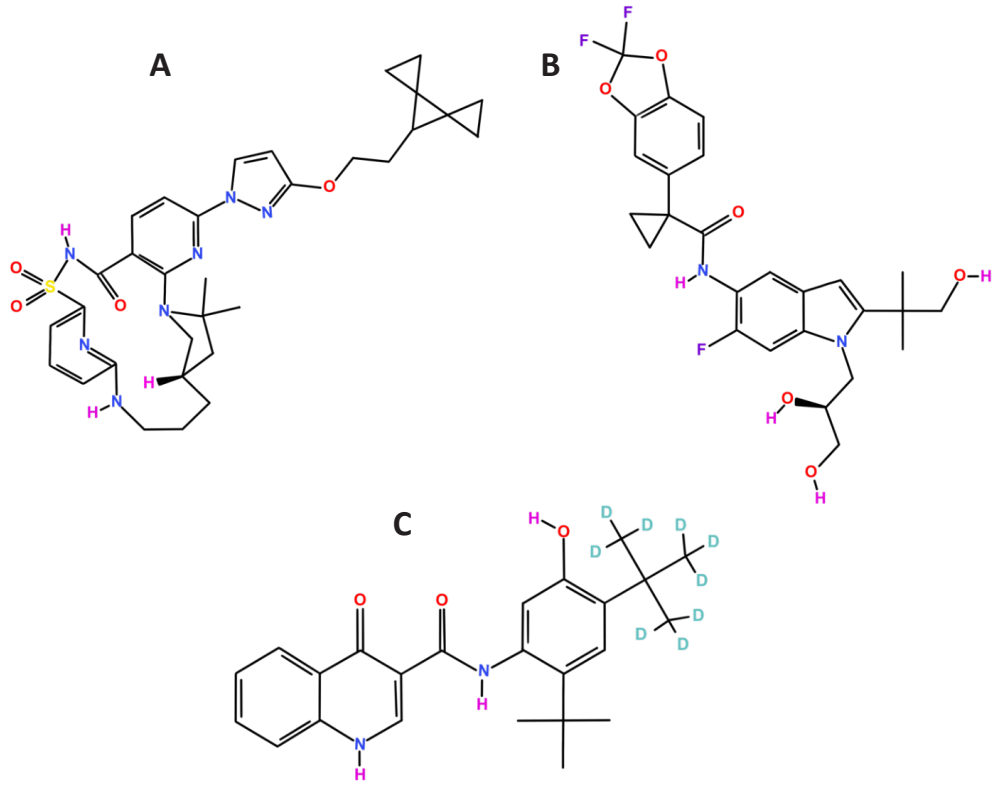

Figure 15 – Structures of vanzacaftor (A), tezacaftor (B) and deutivacaftor (V)

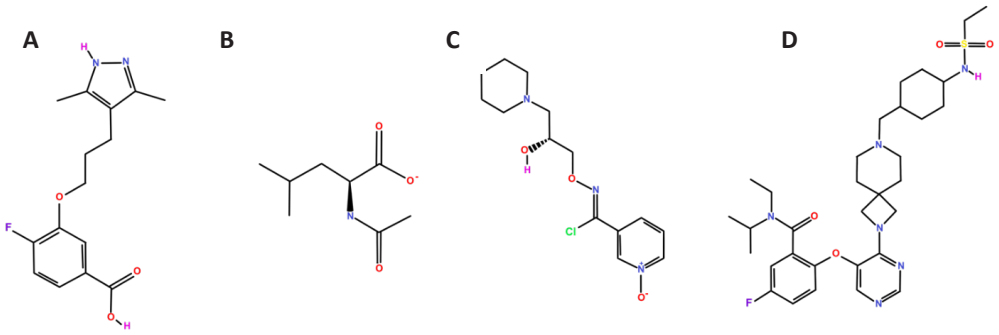

Figure 16 – Structures of acoramidis (A), levacetylleucine (B), arimoclomol (C) and revumenib (D)

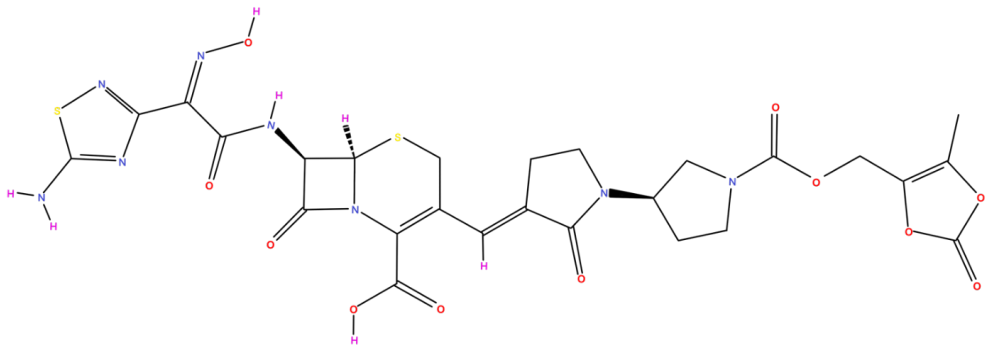

Figure 17 – Structures of ceftobiprole medocaril

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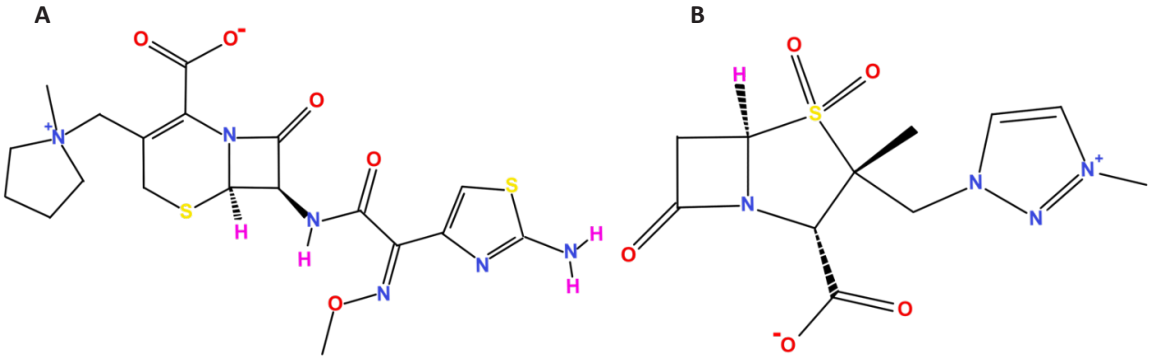

Figure 18 – Structures of cefepime (A) and enmetazobactam (B)

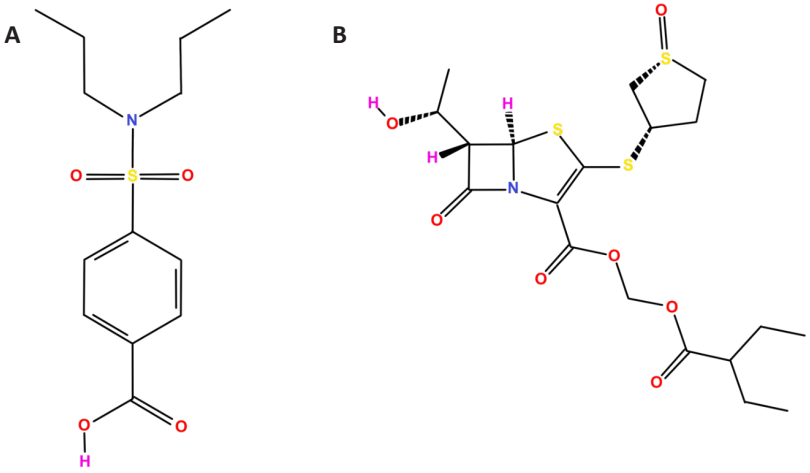

Figure 19 – Structures of probenecid (A) and sulopenem etzadroxil (B)

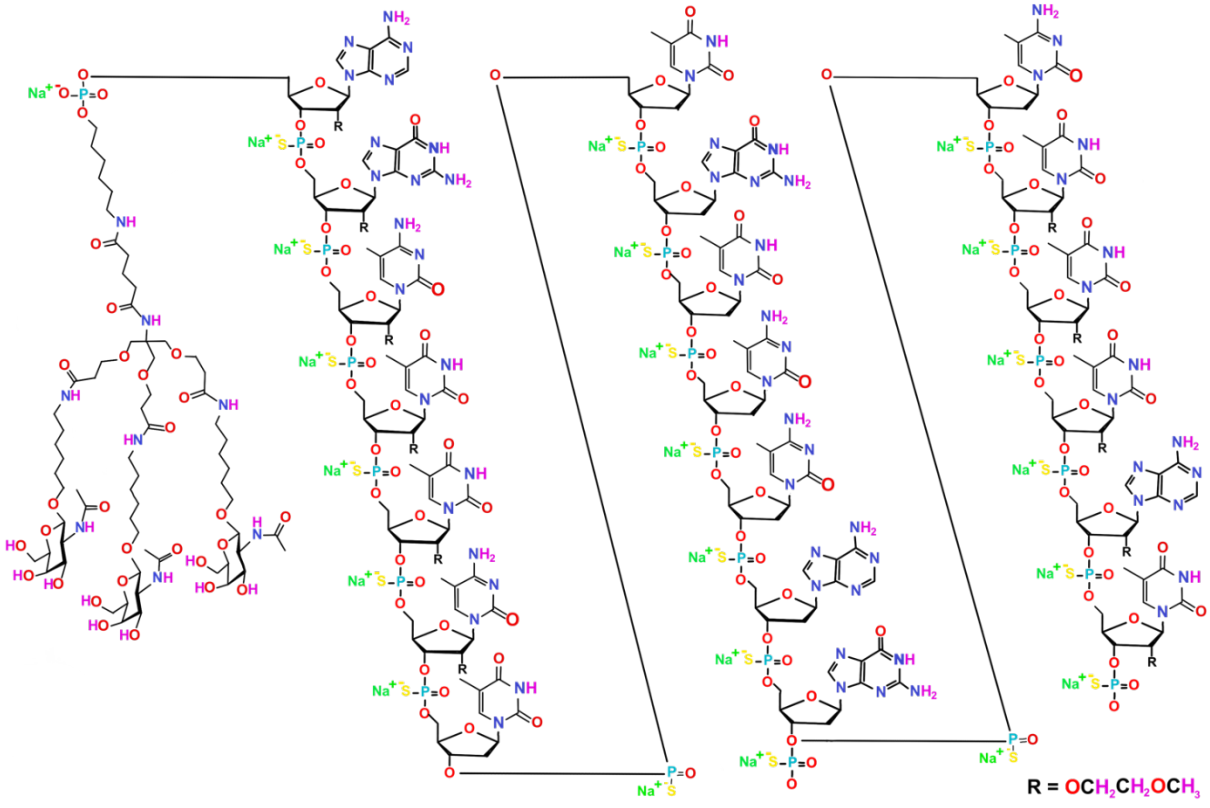

Figure 20 – Structures of olezarsen

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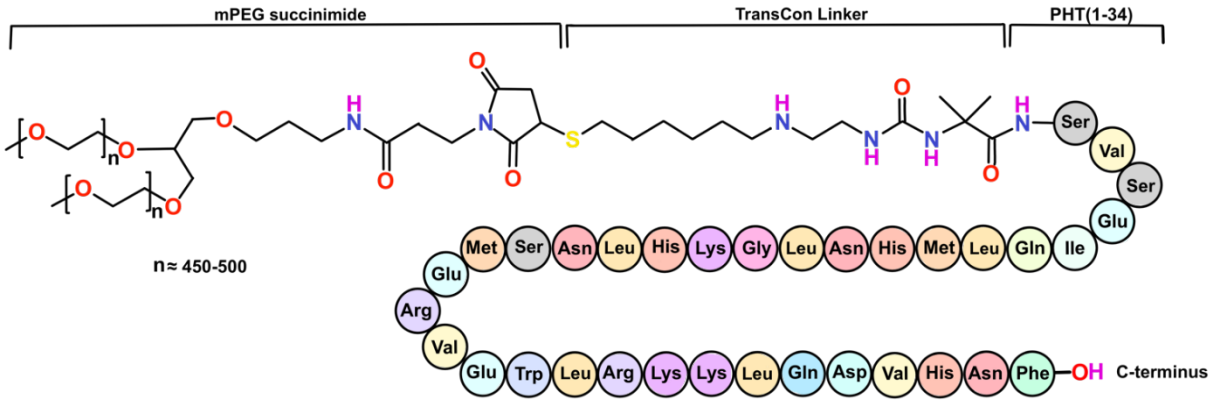

Figure 21 – Structure of palopegteriparatide

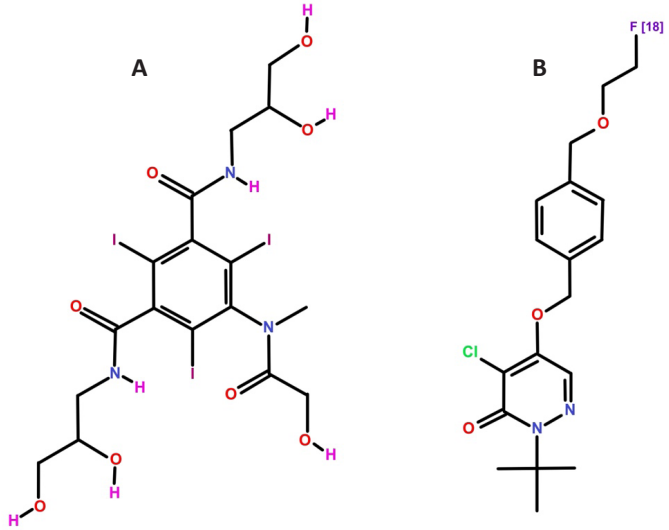

Figure 22 – Structuresla of iomeprol (A) and flurpiridaz F18 (B)

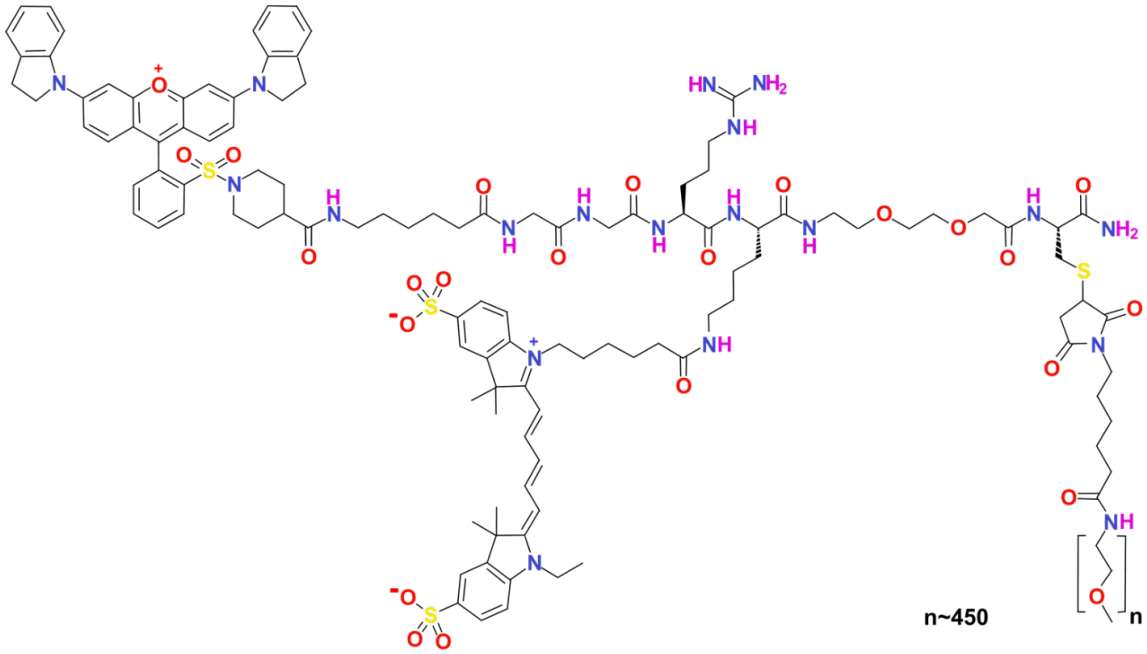

Figure 23 – Structures of pegulicianine acetate

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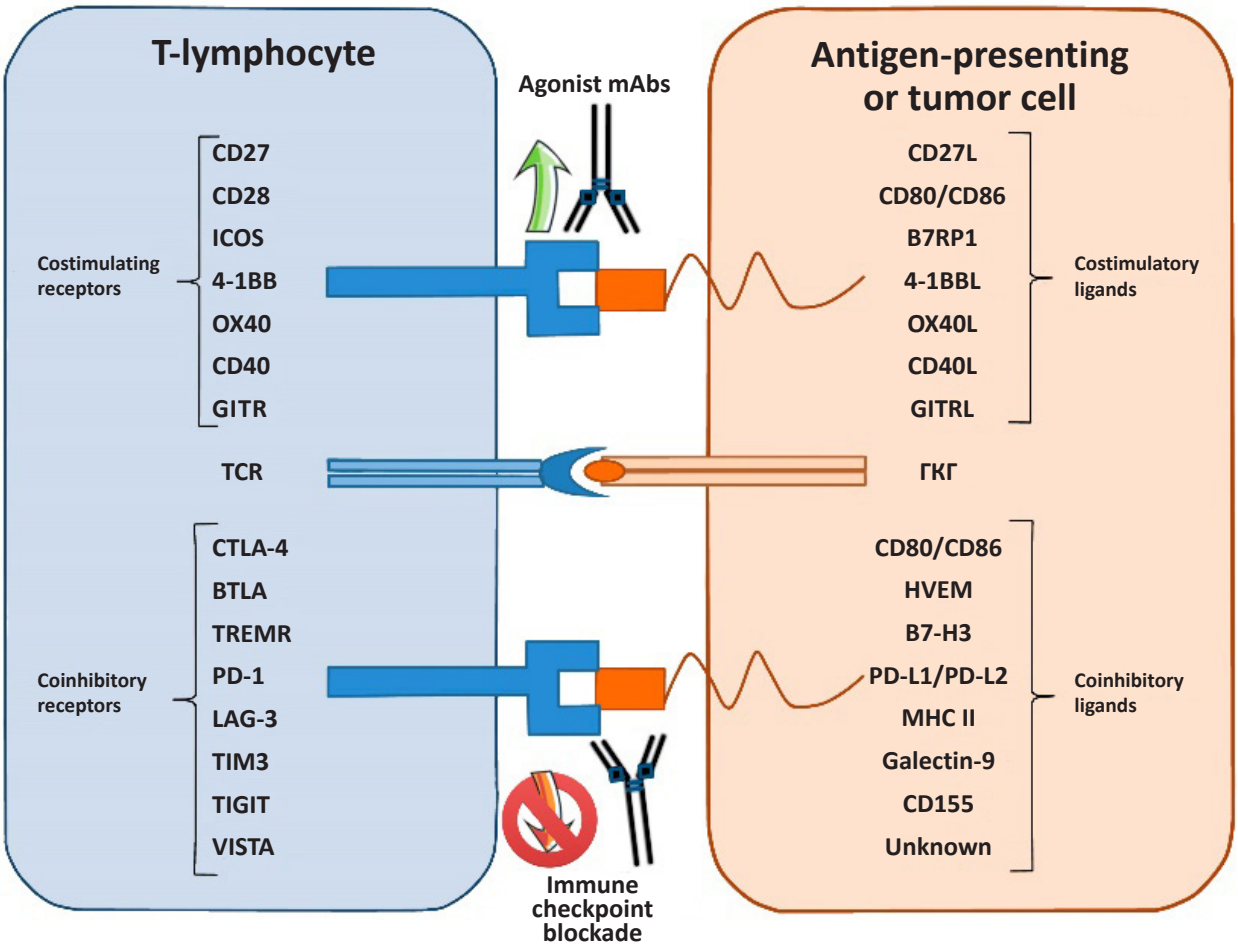

Figure 24 – Mechanisms and factors involved in the regulation of Immune checkpoint

Note: mAbs — monoclonal antibodies; CD — cluster of differentiation; ICOS — inducible costimulator; 4-1BB — receptor from the superfamily of tumor necrosis factor receptors, cluster of differentiation 137 (tumor necrosis factor ligand superfamily, member 9); 4-1BBL — 4-1BB ligand; OX40 — receptor from the superfamily of tumor necrosis factor receptors, cluster of differentiation 134 (tumor necrosis factor receptor superfamily, member 4); OX40L — OX40 ligand; GITR — glucocorticoid-induced TNFR-related protein; GITRL — GITR ligand; TCR — T-cell receptor; CTLA-4 — cytotoxic T-lymphocyte-associated protein 4; BTLA — B- and T-lymphocyte attenuator; TREMR — triggering receptor expressed on myeloid cells, cluster of differentiation 354; PD-1 — programmed cell death receptor 1; PD-L1/PD-L2 — ligands 1 and 2 of the programmed cell death receptor; LAG-3 — membrane immunoglobulin, gene product 3 activated by lymphocytes, cluster of differentiation 223 (lymphocyte-activation gene 3); TIM3 — T-cell immunoglobulin and mucin-domain containing-3; TIGIT — T-cell immunoreceptor with Ig and ITIM domains; VISTA — V-domain Ig suppressor of T cell activation; B7RP1 — RP1 protein of the B7 family; HVEM — Herpesvirus entry mediator, TNFRSF14; B7-H3 — H3 protein of the B7 family (cluster of differentiation 276); MHC — major histocompatibility complex.

Immune checkpoint play a key role in the activation of T-cells and determine the effects that occur when various ligands act on the T-cell receptor (TCR). Blocking the immune checkpoints CTLA-4 and PD-1 has already become one of the most successful methods of cancer immunotherapy. Promising applied points are proteins of the B7 family [14] — B7-H3 [15, 16], B7S1 [17, 18] and VISTA [19, 20].

B7-H3 can have both an inhibitory and an activating effect on T-cells. Studies show that its expression can contribute to tumor regression and increase the immunogenicity of tumors, contributing to the development of specific CD8+ cytotoxic T-cells. In people with B7-H3 deficiency, an increase in tumor size was noted [21, 22]. The role of B7-H3 is controversial, since in some cases it can act as an inhibitor of the T-cell response, depending on the expression of isoforms and the fucosylation pattern of the molecule on cells. B7-H3 also affects the migration and inhibition of cellular invasion of tumor cells, which is supposedly one of the mechanisms of its action in pancreatic cancer cells and other types of cancer. Thus, B7-H3 can act as an activator for some immunobiological cascades, and as an inhibitor for others. This protein is promising for studying its ligands for immunotherapy [14].

B7S1 is recognized as a negative regulator of T-cell responses, since its binding to receptors on T-cells leads to suppression of their proliferation, cytokine secretion and the development of effector functions.

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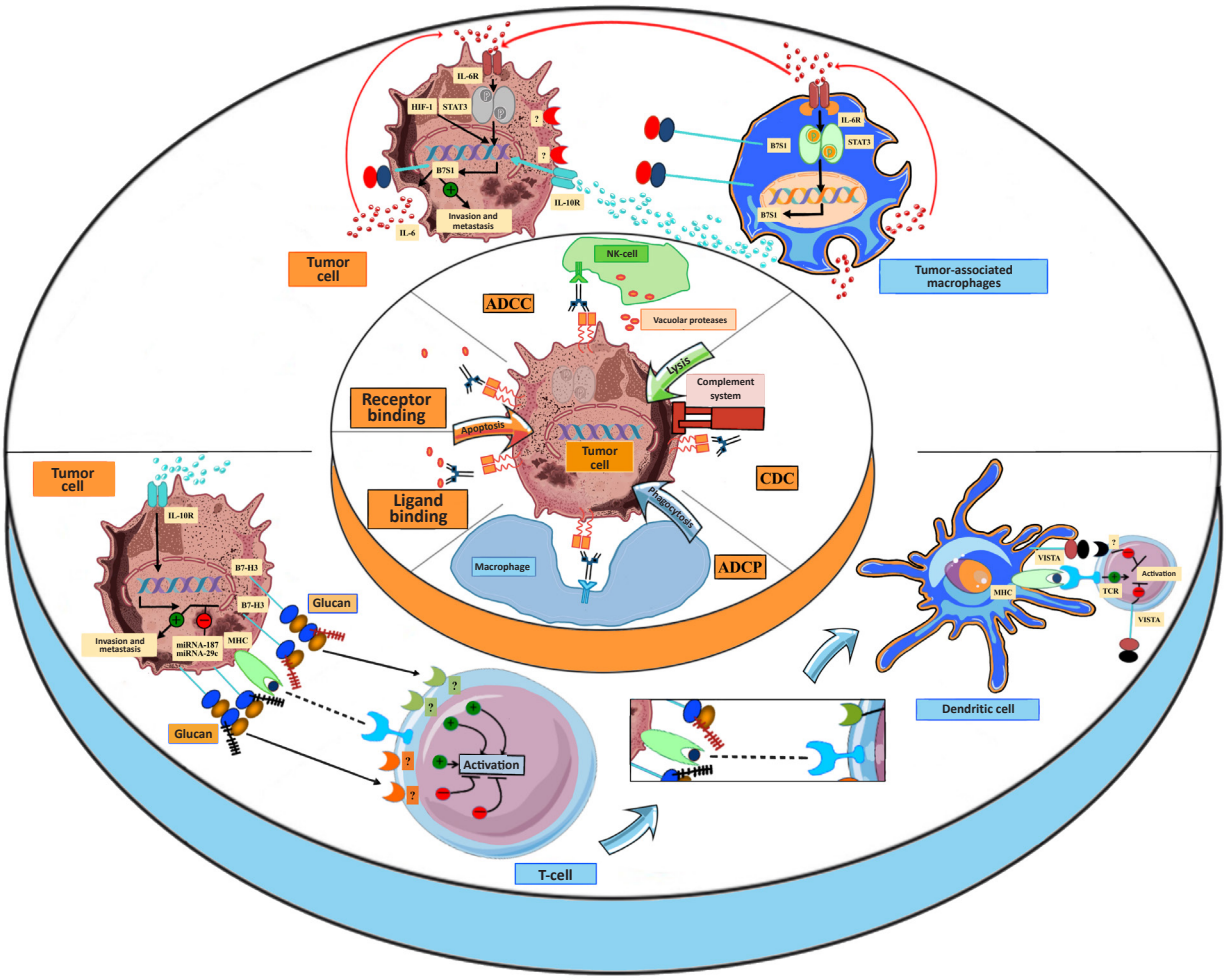

Figure 25 – Some mechanisms involved in the antitumor action of mAbs

Note: the symbol "?" indicates unidentified factors of the process; IL-6 – interleukin 6; IL-6R – interleukin 6 receptor; IL-10R – interleukin 10 receptor; HIF-1 – Hypoxia-inducible factor 1; STAT3 – signal transducer and activator of transcription 3; B7S1 – protein S1 of the B7 family (integral protein of antigen-presenting cells, transmitting a co-stimulatory signal to T-cells); ADCC – antibody-dependent cellular cytotoxicity; Natural Killer Cell – NK-cell (natural killer); CDC – complement-dependent cytotoxicity; ADCP – antibody-dependent cellular phagocytosis; B7-H3 – protein H3 of the B7 family (cluster of differentiation 276); MHC – major histocompatibility complex; miRNA-187 – microRNA 187 product; miRNA-29c – microRNA 29c product; TCR – T-cell receptor; VISTA – V-domain Ig suppressor of T cell activation.

"B7S1 contributes to protecting tumor cells from the anti-tumor immune response. Transformation of T cells under the influence of B7S1 led to their arrest in the cell cycle and an increase in apoptosis levels. B7S1 may support tumor growth by promoting immunosuppression in the tumor microenvironment. Binding of B7S1 to receptors disrupts the phosphorylation of key kinases such as ERK and AKT, which in turn reduces T- cell proliferation and IL-2 secretion. B7S1 may facilitate the metastasis of cancer cells by enabling them to evade the immune response [14]."

VISTA functions as a negative regulator of T-cell activation. It suppresses early T-cell activation, preventing their proliferation and secretion of cytokines such as interferon (IFN) γ and TNF-α. Thus, B7S1 and VISTA are co-inhibitors that suppress T-cell activation at different stages of this process. VISTA has an established role in maintaining T-cells in a state of tolerance through mechanisms aimed at weakening T-cell activity when interacting with APCs [14].

The main receptor of T-lymphocytes is the CD28 molecule, which is present on all naive T-leukocytes. Ligands for CD28 on the surface of antigen-presenting cells (APCs) are B7.1 (CD80) and B7.2 (CD86) molecules. The interaction of CD28 with these ligands leads to the activation of phospholipase C, Akt, and Vav

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enzymes, which enhances most of the effects caused by TCR stimulation. These processes are only possible with the simultaneous arrival of two signals. Receptors of the TNF family (OX40, 4-1BB, CD30, and CD27) are the main co-stimulatory receptors of B-lymphocytes and activate Akt and NFκB. In addition, stimulation can occur through direct interaction of the pathogen with pattern recognition receptors, such as Toll-like receptors (TLRs). Currently, the concept of co-stimulation is being revised and expanded due to the discovery of new co-stimulatory receptors that implement their functions through various mechanisms. It has been demonstrated that co-stimulation, for example, through the GITR receptor, not only enhances TCR signaling but also participates in determining the direction of T-cell differentiation [23]. Inhibitors of co-stimulatory receptors may become the basis for the development of new safe and effective treatments for graft-versus-host disease [24].

Hybrid proteins

Hybrid proteins (fusion proteins) are molecules that are formed as a result of the combination of two or more genes that are initially located in different regions of the genome [25]. This fusion leads to the formation of a new protein that may have unique properties different from the original proteins. Hybrid proteins are involved in a number of biological processes, such as the translation of genetic information and cell signaling pathways [26].

The merging process can occur through various mechanisms, including errors in DNA replication, gene recombination, or chromosomal translocations [27]. Often, such changes may be associated with the development of diseases, including cancer.

Hybrid proteins are considered an important marker of malignancy, as they arise from genetic changes that can cause uncontrolled cell growth. Examples include the transformation of cells into cancerous ones through the activation of oncogenes, such as BCR-ABL1, which is a hybrid protein typical for chronic myelogenous leukemia [28].

Gene fusion can lead to the expression of proteins with increased enzymatic activity or proteins that regulate key cellular processes, such as the cell cycle, apoptosis, or signaling pathways, leading to uncontrolled cell division and tumor development [29].

Currently, it is known if hybrid proteins can be the result of random mutations. The detection of hybrid proteins in tumor cells is rarely used as a marker for monitoring the course of the disease and personalizing treatment. Hybrid proteins can be targets for targeted therapy, such as tyrosine kinase inhibitors, for the treatment of chronic myelogenous leukemia [30, 31].

Monoclonal antibodies and their mechanisms of action

Among the 16 registered biologics, 12 are immunotherapeutic. Thus, among the medicines registered with the FDA in 2024, 24% are mAbs. In 2023, 12 antibodies and 1 antibody-protein conjugate medicine were registered.

The most commonly used group in mAb therapy is IgG, since this class of antibodies interacts with the type of FcR, FcγR, associated with them, found on NK, as well as neutrophils, monocytes, dendritic cells, and eosinophils to participate in the performance of specialized functions, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). The IgG class can be divided into groups depending on the ability of the Fc region to perform these functions. IgG1 and IgG3 are capable of causing ADCC and CDC, while IgG2 and IgG4, on the contrary, cannot [32]. IgG1 is the most relevant subclass of monoclonal antibodies used in cancer immunotherapy [33].

Previously, the mechanism of action of mAbs with antitumor effects was justified by the action on a receptor or other molecule expressed on the surface of a tumor cell. Over the past few years, it has been found that the action of mAbs is multifactorial — a large role is now assigned to their regulatory properties. Recently, the most successful mAb-based strategies have moved away from targeting tumor antigens and focused on interacting with immune cells to enhance their antitumor potential. One of the first approaches to stimulating antitumor immunity with mAbs was the development of bispecific T-cell engagers (BiTEs), which simultaneously target a tumor antigen, such as CD19, and the activating receptor CD3 on T-cells. BiTEs combine direct effects on tumor cells with the recruitment of cytotoxic T-cells into the TME of the tumor and lead to tumor regression even when administered at doses three orders of magnitude lower than the parent mAb alone. One of the first approaches to stimulating antitumor immunity with mAbs was the development of bispecific antibodies BiTEs, which simultaneously target a tumor antigen, such as CD19, and the activating receptor CD3 on T-cells. BiTEs combine direct effects on tumor cells with the recruitment of cytotoxic T-cells into the TME of the tumor and lead to tumor regression even when administered at doses significantly lower than the parent mAbs alone [34].

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Targeted mAbs, by binding to antigens unique to tumor cells or expressing antigens excessively, can cause tumor cell death through various mechanisms. The main direct mechanism causing tumor cell death is blocking the signal from growth factor receptors (Fig. 25). Signaling that promotes tumor growth and survival is disrupted when mAbs bind to target growth factor receptors and alter their activation state or block ligand binding. For example, EGFR expression is elevated in many cancers, and signaling through EGFR leads to proliferation, migration, and invasion of tumor cells. KG anti-EGFR mAbs cause apoptosis in tumor cells by blocking ligand binding and receptor dimerization [34, 36].

ADCC is an immune mechanism that increases the specificity of immunity against cancer and infected cells and the ability to destroy them. ADCC is an immune response mediated primarily by NK cells, which are a type of lymphocyte. ADCC plays a key role in cancer immunotherapy when using mAbs. ADCC develops with the participation of a large number of effectors, primarily with the participation of NK cells. However, the mechanism affects other cells of the myeloid series — monocytes, macrophages, neutrophils, eosinophils, and dendritic cells [37].

Antibodies act as bridges, linking antigens on the surface of tumor cells through their Fab portions and effector cells through Fc fragments. For ADCC to occur, effector cells must express Fc receptors (FcR) that bind to antibodies. The main class of FcR associated with ADCC is FcγR, which includes activating receptors such as FcγRI (CD64), FcγRIIA (CD32A), and FcγRIIIA (CD16A), as well as inhibitory FcγRIIB (CD32B). Effector cells cause the death of target cells through the release of cytotoxic granules, Fas signals, and the initiation of reactive oxygen species. The effectiveness of many targeted mAbs in clinical practice largely depends on ADCC. Some mechanisms of resistance to therapy may be associated with depletion of NK cells and their reduced cytotoxic activity [37].

Most targeted mAbs are capable of activating the complement system. For example, the effectiveness of rituximab in vivo partially depends on CDC. In a preclinical model, the antitumor effects of rituximab were investigated in animals with a knockout of the C1q complement cascade component gene. In such animals, a complete absence of the effectiveness of the studied medicine was revealed [38]. The importance of CDC in mAb therapy is further confirmed by the fact that genetic polymorphisms in the C1qA gene correlate with the clinical response to rituximab in patients with follicular lymphoma [39].

ADCP studies are very limited, but there is some evidence that ADCP plays an important role in the destruction of circulating tumor cells after mAb therapy [40].

Each class of antibodies has a corresponding class of FcR, for example, FcγR, which binds IgG, and FcαR, which binds IgA. FcγR is the most significant class for ADCC of tumor cells and includes both activating FcγRI (CD64), FcγRIIA (CD32A), FcγRIIIA (CD16A), and inhibitory FcγRIIB (CD32B) receptors [41]. In additional studies to elucidate the mechanism of action using similar mouse models, it was confirmed that the expression of FcγR by immune effector cells is necessary for tumors to respond to mAb therapy [42]. When the activating FcγR on the effector cell binds the Fc region of the antibody receptor, a signal is propagated downstream. NK cells are the main type of effector cells that mediate ADCC; however, other cells of the myeloid series, such as monocytes, macrophages, neutrophils, eosinophils, and dendritic cells, are also capable of this [43].

Although many mAbs are capable of exerting effects through several of the above mechanisms, there is debate if they are important in vivo. It is known that many of the first mAb medicines mediate ADCC of tumor cells in vitro, but the question of how important ADCC is for their therapeutic effectiveness was initially little studied. Using mouse models, R.A. Clynes et al. were the first to demonstrate that ADCC is a key mechanism of action mediating the activity of trastuzumab and rituximab in vivo [44]. ADCC is the main therapeutic mechanism of rituximab in non-Hodgkin's lymphoma and anti-CD38 antibodies in multiple myeloma [45, 46].

The functionality of antibodies with respect to ADCC can be increased by modifying the Fc portion of the mAb to increase their binding affinity to the activating FcγRIIIA through site-directed mutagenesis, changing the glycosylation of the Fc domain, and/or removing the fucosylation of the Fc domain [47–50].

Rituximab — the first antibody, the drug of which was approved for the treatment of cancer — is a mAb to CD20 [51]. CD20 is a membrane protein of B-lymphocytes, the increased expression of which is a characteristic phenomenon for B-cell lymphomas. Since the registration of rituximab, the development of antitumor mAbs directed against membrane proteins of immune cells, the increased expression of which is specific and depends on the type of cancer, has intensified. Today, mAbs directed against targets such as EGFR and HER2 are widely used in the clinic for the treatment of colorectal cancer and breast cancer, respectively [52, 53].

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The tumor microenvironment contains many factors that are known to suppress the antitumor immune response, promote the growth of tumor cells, and prevent tumor angiogenesis. Targeting these crucial pro-tumor processes in the TME of the tumor has proven its clinical effectiveness. Historically, the most relevant target was VEGF, which is abundantly present in the TME of many solid tumors and binds to its receptor VEGFR, located on the endothelium of blood vessels adjacent to the tumor, stimulating angiogenesis. The inhibitor of tumor-associated macrophages, bevacizumab, targets VEGF and blocks the binding of VEGF to the receptor, is approved for the treatment of many types of cancer [54].

Currently, there are many other ways to use mAbs in cancer therapy, including antibody-drug conjugates, targeted antitumor compounds in the microenvironment, BiTEs, and immunological checkpoint inhibitors. It is possible to combine antibodies with effectors, for example, cytotoxic substances or radiopharmaceuticals. Immune checkpoints are pathways and a network of their receptors that are responsible for the homeostasis of the immune system, autotolerance, and also modulate immune reactions to limit concomitant tissue damage [55]. Such representatives of the immunoglobulin superfamily as lymphocyte activation gene 3 (LAG3), T-cell immunoglobulin and mucin domain 3 (TIM3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), and V-domain Ig suppressor of T-cell activation (VISTA) are being studied as potential therapeutic targets of immunological checkpoints [14, 56].

Registration trends

In 2024, CDER registered 26 (52%) medicines for the treatment of orphan diseases (not all of these medicines contain an orphan disease as an indication). Among the diseases that are an indication for the use of registered medicines are: Niemann-Pick disease type C, Duchenne muscular dystrophy, primary biliary cholangitis, familial chylomicronemia, classical congenital adrenal hyperplasia. Drugs have also been registered for the treatment of rare types of cancer: previously treated, unresectable or metastatic bile duct tumor positive for HER2 mutation (IHC 3+); diffuse forms of grade 2 astrocytoma or oligodendroglioma; locally advanced unresectable or metastatic HER2-negative CLDN18.2-positive adenocarcinoma of the stomach or gastroesophageal junction.

Defining a medicine as a breakthrough therapy includes all the characteristics of the Fast Track program and involves methodological support from the FDA in the medicine development process. Among the 50 registered medicines, 24 (48%) are first-in-class, and 18 of the 50 new ones (36%) are designated as breakthrough therapy. The described data are presented in Table 4.

Drugs with new indications for use

The presented list of medicines is not included in the list of registered for the first time. Nevertheless, it should be noted that adding a new indication is an actual registration strategy.

Alectinib (Alecensa) in capsules was first approved in 2015 for the treatment of ALK-positive metastatic NSCLC in adults with progression after the use of crizotinib or with its intolerance. In 2024, Alecensa was approved as adjuvant therapy (auxiliary treatment after the main one) in adults after tumor resection in ALK-NSCLC. ALK-NSCLC is caused by a gene fusion (connection of two genes), which leads to the formation of an abnormal ALK protein that causes the growth and spread of cancer cells in the lungs[113].

Belimumab (Benlysta) for intravenous administration was originally approved in 2019 for the treatment of children aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus receiving standard therapy. In 2024, Benlysta was approved in the form of a syringe pen for subcutaneous administration to children from 5 years and older, which allows them to receive treatment at home[114].

Daratumumab+hyaluronidase-fihj (Darzalex Faspro) for subcutaneous administration was originally approved in 2020 for the treatment of multiple myeloma. In 2024, CDER approved Darzalex Faspro in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation therapy in patients with newly diagnosed multiple myeloma who are candidates for autologous stem cell transplantation[115].

Fam-trastuzumab deruxtecan-nxki (Enhertu) for intravenous administration was first approved in 2019 for the treatment of unresectable or metastatic HER2-positive breast cancer. In 2024, CDER approved Enhertu for the treatment of adults with unresectable or metastatic HER2-positive (IHC 3+) solid tumors. Treatment with Enhertu is aimed at patients who have received systemic treatment and do not have satisfactory alternative treatment options.

[113] Drugs.com. Alecensa. Available from: https://www.drugs.com/alecensa.html
[114] Drugs.com. Benlysta. Available from: https://www.drugs.com/benlysta.html
[115] Drugs.com. Darzalex Faspro. Available from: https://www.drugs.com/darzalex-faspro.html

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Table 4 – Trends in FDA drug registration

Drug	New registration	New indication	Drugs for the treatment of orphan diseases	First in class	Breakthrough
Alhemo	Yes	No	Yes	No	No
Alyftrek	Yes	No	Yes	No	No
Anktiva	Yes	No	No	Yes	Yes
Aqneursa	Yes	No	Yes	Yes	No
Attruby	Yes	No	Yes	No	No
Bizengri	Yes	No	Yes	Yes	Yes
Cobenfy	Yes	No	No	Yes	No
Crenessity	Yes	No	Yes	Yes	Yes
Duvyzat	Yes	No	Yes	Yes	No
Ebglyss	Yes	No	No	No	No
Ensacove	Yes	No	No	No	No
Exblifep	Yes	No	No	No	No
Flyrcado	Yes	No	No	No	No
Hympavzi	Yes	No	Yes	Yes	No
Imdelltra	Yes	No	Yes	Yes	Yes
Iomervu	Yes	No	No	No	No
Iqirvo	Yes	No	Yes	Yes	Yes
Itovebi	Yes	No	No	No	Yes
Kisunla	Yes	No	No	No	Yes
Lazcluze	Yes	No	No	No	No
Leqselvi	Yes	No	No	No	No
Letybo	Yes	No	No	No	No
Livdelzi	Yes	No	Yes	No	Yes
Lumisight	Yes	No	No	Yes	No
Miplyffa	Yes	No	Yes	Yes	Yes
Nemluvio	Yes	No	No	Yes	Yes
Niktimvo	Yes	No	Yes	Yes	No
Ohtuvayre	Yes	No	No	No	No
Ojemda	Yes	No	Yes	No	Yes
Orlynvah	Yes	No	No	No	No
Piasky	Yes	No	Yes	No	No
Rapiblyk	Yes	No	No	No	No
Revuforj	Yes	No	Yes	Yes	Yes
Rezdiffra	Yes	No	No	Yes	Yes
Rytelo	Yes	No	Yes	Yes	–
Sofdra	Yes	No	No	No	No
Tevimbra	Yes	No	Yes	No	No
Tryngolza	Yes	No	Yes	Yes	Yes
Tryvio	Yes	No	No	Yes	–
Unloxcyt	Yes	No	No	No	No
Vafseo	Yes	No	No	No	No
Voranigo	Yes	No	Yes	No	Yes
Voydeya	Yes	No	Yes	Yes	Yes
Vyloy	Yes	No	Yes	Yes	No
Winrevair	Yes	No	Yes	Yes	Yes
Xolremdi	Yes	No	Yes	Yes	No
Yorvipath	Yes	No	Yes	No	No
Zelsuvmi	Yes	No	No	Yes	No
Zevtera	Yes	No	No	No	No
Ziihera	Yes	No	Yes	Yes	Yes
Alecensa	No	Yes	Yes	No	No
Benlysta	No	Yes	No	Yes	No
Darzalex Faspro	No	Yes	Yes	Yes	Yes
Enhertu	No	Yes	Yes	Yes	Yes
Epkinly	No	Yes	No	No	No
Fabhalta	No	Yes	No	No	No
Imfinzi	No	Yes	No	No	No
Livmarli	No	Yes	No	No	No
Otezla	No	Yes	No	Yes	No
Rybrevant	No	Yes	Yes	Yes	Yes
Wegovy	No	Yes	No	No	No
Xolair	No	Yes	No	Yes	No
Zepbound	No	Yes	No	No	No

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HER2-positive solid tumors are characterized by a high level of HER2 protein[116].

Epcoritamab-bysp (Epkinly) for subcutaneous administration was originally approved in 2023 for the treatment of relapsed or refractory diffuse large B-cell lymphoma. In 2024, CDER approved Epkinly for the treatment of adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy[117].

Iptacopan (Fabhalta) in capsules was first approved in 2023 for the treatment of paroxysmal nocturnal hemoglobinuria. In 2024, CDER approved Fabhalta to reduce proteinuria (protein in the urine) in adults with primary immunoglobulin A (IgA) nephritis at risk of rapid disease progression[118].

Durvalumab (Imfinzi) for intravenous administration was originally approved in 2017 for the treatment of locally advanced or metastatic urothelial cancer. In 2024, CDER approved Imfinzi for the treatment of patients with resectable NSCLC without known mutations in the epidermal growth factor receptor or rearrangements of anaplastic lymphoma kinase (ALK)[119].

Maralixibat (Livmarli) in the form of an oral solution was first approved in 2021 for the treatment of cholestatic itching in patients with Alagille syndrome. In 2024, CDER approved Livmarli for the treatment of progressive familial intrahepatic cholestasis — a rare genetic disorder that prevents normal bile secretion by the liver, leading to liver disease and subsequently to liver failure[120].

Apremilast (Otezla) in tablets was originally approved in 2014 for the treatment of active psoriatic arthritis. In 2024, CDER approved Otezla for the treatment of moderate to severe plaque psoriasis in adults[121].

Amivantamab-vmjw (Rybrevant) solution for intravenous administration was first approved in 2021. In 2024, CDER approved Rybrevant as a first-line therapy for adults with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations identified by FDA-approved tests (Guardant360 CDx, Oncomine Dx Target Test). EGFR exon 20 insertion mutations can cause uncontrolled cell growth and are a biomarker for lung cancer[122].

Semaglutide (Wegovy) solution for subcutaneous administration was originally approved in 2021. In 2024, CDER approved Wegovy to reduce the risk of serious adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and obesity or overweight[123].

Omalizumab (Xolair) solution for subcutaneous administration was originally approved in 2003 for the treatment of adults and adolescents (12 years and older) with moderate to severe persistent asthma. In 2024, CDER approved Xolair for the treatment of IgE-mediated food allergy in adults and pediatric patients aged 1 year and older to reduce allergic reactions (type I), including anaphylaxis, that may occur with accidental exposure to one or more foods (used in combination with allergen avoidance)[124].

Tirzepatide (Zepbound) for subcutaneous administration was first approved in 2023 for the treatment of type 2 diabetes and weight loss. In 2024, CDER approved Zepbound for the treatment of obstructive sleep apnea[125].

CONCLUSION

In the presented work, we tried to characterize the latest achievements and trends that can be observed in the global pharmaceutical market. It is possible to identify general patterns, such as the continuing trend towards the development of ligands to receptors (most medicines belong to this group) and the desire to develop biologics, the group of which is becoming more and more large-scale and heterogeneous every year, as well as medicines for the treatment of rare diseases. This not only allows therapy for patients but also gives rapid development, gives impetus (financial, marketing, population, etc.) to the area of knowledge and technologies, resources previously unavailable or the significance considered worthy of attention. Medicines from the group of first-in-class or recognized as breakthrough technologies also demonstrate increasing human capabilities, and their presence feeds hope for a further increase in life expectancy and its quality.

According to the results of FDA approvals in 2024,

[116] Drugs.com. Enhertu. Available from: https://www.drugs.com/enhertu.html
[117] Drugs.com. Epkinly. Available from: https://www.drugs.com/epkinly.html
[118] Drugs.com. Fabhalta. Available from: https://www.drugs.com/fabhalta.html
[119] Drugs.com. Imfinzi. Available from: https://www.drugs.com/imfinzi.html
[120] Drugs.com. Livmarli. Available from: https://www.drugs.com/livmarli.html
[121] Drugs.com. Otezla. Available from: https://www.drugs.com/otezla.html
[122] Drugs.com. Rybrevant. Available from: https://www.drugs.com/rybrevant.html
[123] Drugs.com. Wegovy. Available from: https://www.drugs.com/wegovy.html
[124] Drugs.com. Xolair. Available from: https://www.drugs.com/xolair.html
[125] Drugs.com. Zepbound. – [Электронный ресурс]. – Режим доступа: https://www.drugs.com/zepbound.html

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the pharmaceutical industry shows progress in the development and registration of innovative medicines aimed to develop targeted and biological medicines. The dynamic development of the biologics industry and, in particular, mAbs aimed at immunotherapy of cancers, reflects the transition from chemotherapy to immunotherapy. At the same time, the use of mAbs is not limited to this applied point: mAbs can be used to treat hemophilia and Alzheimer's disease. The observed trend has important applied and fundamental significance. The applied significance lies in the need to develop technologies and train personnel to create medicines based on the interaction of exogenous (xenobiotic) and endogenous macromolecules — receptors, factors, enzymes, ion channels, and their ligands. The fundamental significance of the growth in the share of biologics among the first-in-class lies in the need for a comprehensive study of the pathological mechanisms of widespread and rare diseases, with an emphasis on the role of protein factors.

We also note the important role of repurposing registered medicines. Despite the fact that in most cases, additions of indications do not imply a fundamentally new use, the development of a new dosage form or the identification of effectiveness against a type of cancer previously not indicated may benefit practical healthcare. A change in the dosage form, expanding the age range of patients, and the inclusion of a new form of cancer in the indications contribute to an increase in the number of patients for whom a drug is available, the clinical development of which has been completed, and production has already been established. Moreover, in many cases, a medicine with a new indication turns out to be a breakthrough therapy, from which one should not underestimate the repurposing of known medicines as a developed tactic.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Denis V. Kurkin — idea and planning of the structure of the work, design of graphic material, editing and approval of the final version of the manuscript; Nazar A. Osadchenko Anastasia R. Makarova, Dmitry A. Bakulin, Olga V. Marincheva, Yuliya V. Gorbunova, Dina V. Yunina, Ksenia N. Koryanova, Valentina I. Zvereva — collection of material and writing draft of the manuscript; Marina A. Dzhavakhyan, Olga O. Shatalova, Evgeny I. Morkovin, Andrey V. Strygin, Yury A. Kolosov — editing of the final version of the manuscript; Andrey V. Zaborovskiy, Vladimir I. Petrov, Roman V. Drai, Daria A. Galkina, Igor E. Makarenko, Anna S. Shuvaeva — consultations on highly specialized issues, approval of the final version of the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept and preparation of the article, read and approved the final version before publication).

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