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Molecular targets for metastasis-directed therapy in malignant tumors

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ABSTRACT

Over the past two decades, targeted therapy has actively developed and, demonstrating impressive clinical results, has gained an increasingly important role in the treatment of cancer. This was facilitated to a large extent by an in-depth understanding of the mechanisms of cancer development, and mainly, the discovery of molecular targets. Despite the fact that targeted therapy can radically change the results of treatment and the prognosis of the disease course in some cancer cases, its effectiveness is sometimes replaced by drug resistance, in others.

The authors of the lecture analyzed and systematized therapeutic approaches to addressing a number of important molecular targets that are key for implementing a specific stage in human tumor pathogenesis. These include maintaining chronic proliferative signaling, promoting evasion of cell growth suppressors, inducing angiogenesis, forming immune surveillance, and activating invasion and metastasis. The lecture presented targeted therapy drugs used in the Russian Federation, including antibody-based drugs and small molecule tyrosine kinase inhibitors. It also analyzed mechanisms of molecular interaction between these drugs and their targets, as well as possible factors for developing resistance and ways to overcome these resistance mechanisms.

Keywords: EGFR, HER2, VEGF, BCR-ABL1, CDK4/6, CTLA-4, PD-1, c-Met

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Молекулярные мишени таргетной терапии злокачественных новообразований

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РЕЗЮМЕ

В течение последних двух десятилетий таргетная терапия активно развивается и, демонстрируя впечатляющие клинические результаты, завоевывает все большую роль в терапии онкологических заболеваний. В значительной мере этому способствовало углубленное понимание механизмов развития рака и главным образом открытие молекулярных мишеней. Однако таргетная терапия способна радикально изменять результаты лечения и прогнозы течения заболевания в одних онкологических контекстах, в других же эффективность сменяется лекарственной устойчивостью.

В лекции проанализированы и систематизированы терапевтические подходы нацеливания на ряд важнейших молекулярных мишеней, которые являются ключевыми для осуществления конкретного этапа в многостадийном процессе патогенеза опухолей человека: поддерживающих хроническую пролиферативную передачу сигналов, способствующих уклонению от супрессоров клеточного роста, обеспечивающих индукцию ангиогенеза, формирующих иммунный надзор и активирующих инвазию и метастазирование. Представлены применяемые в России таргетные терапевтические препараты на основе антител и низкомолекулярные ингибиторы тирозинкиназ, проанализированы механизмы молекулярного взаимодействия препаратов и мишеней, а также возможные факторы развития резистентности и способы преодоления резистентных механизмов.

Ключевые слова: EGFR, HER2, VEGF, BCR-ABL1, CDK4/6, CTLA-4, PD-1, c-Met

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INTRODUCTION

Targeted therapy is a novel and most promising method for drug treatment of malignant tumors. Over the past two decades, in-depth investigation of cancer development mechanisms, including the discovery of molecular targets, has contributed to the impetuous development of targeted medicine. As per the hypothesis proposed by Hanahan and Weinberg, the primary hallmarks of cancer include maintenance of proliferative signaling, evasion of cell growth suppressors, induction of angiogenesis, evasion of immune surveillance, activation of invasion and metastasis, and resistance to cell death. Tumor cell genome mutation is defined as a fundamental feature that initiates malignant transformation [1, 2].

Currently, oncologists have a wide range of targeted therapeutic agents in their arsenal. These drugs are directed at molecular targets that are key to a definite stage in human tumor pathogenesis. Generally, targeted therapy is based on the use of low-molecular-weight tyrosine kinase inhibitors (ending in the suffix -ib) (Table 1) and monoclonal antibodies (ending in the suffix -mab) (Table 2). Tumor targets can represent receptor tyrosine kinases and their ligands (Figure).

Receptor tyrosine kinases (RTKs) are transmembrane proteins consisting of three parts, namely an extracellular domain that functions as a receptor for site-specific binding to ligands, a transmembrane domain, and a catalytic intracellular tyrosine kinase domain. The tyrosine kinase domain provides phosphorylation of substrates (transferring the phosphate residue of adenosine triphosphate (ATP) to the tyrosine residue of specific cellular target proteins for serine or threonine kinases). Ligand binding to the tyrosine kinase receptor leads to constitutive

activation of downstream signaling pathways. Therefore, tyrosine kinase receptors transmit signals from extracellular ligands to downstream signaling effectors, involving mainly serine / threonine kinases or other important proteins, such as RAS (retrovirus-associated DNA sequences).

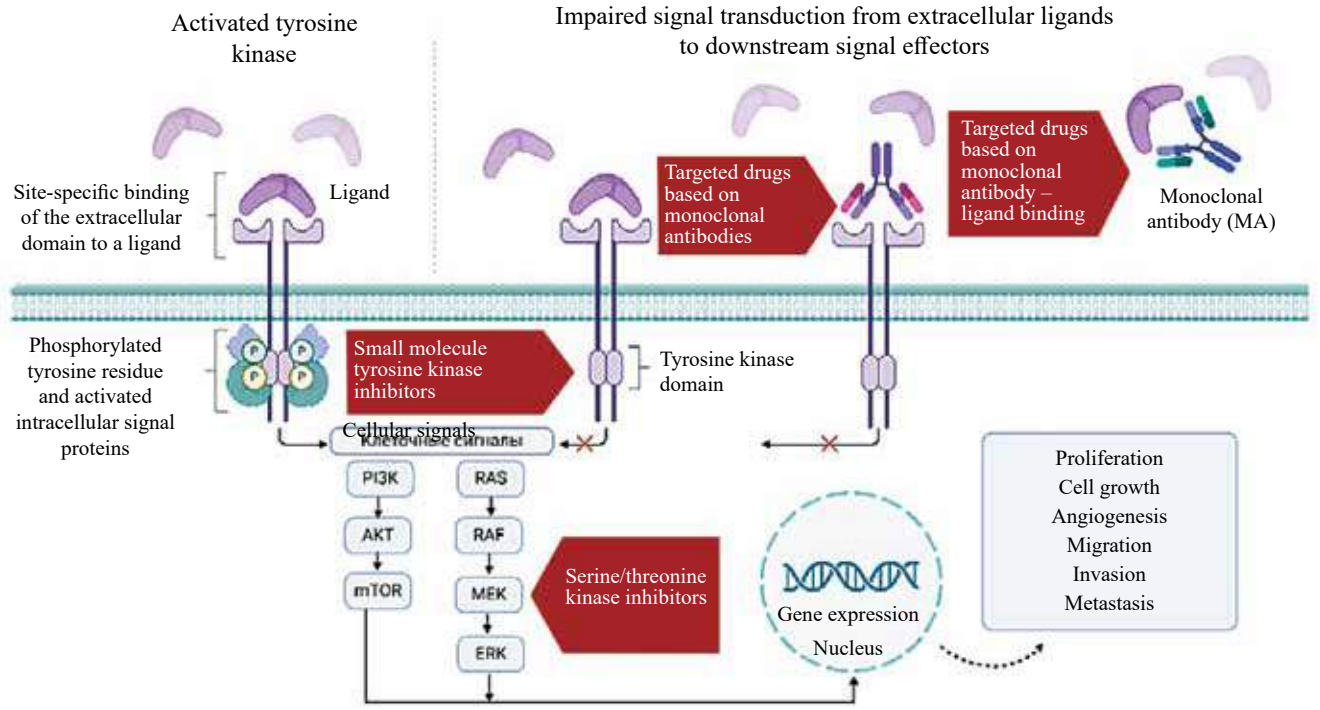

Figure. Methods of targeted therapy

Many kinases, being regulators of normal cellular processes in a healthy organism, such as angiogenesis, proliferation, differentiation, survival, and migration, are also crucial for cancer formation and progression. As a result of an oncogenic mutation or translocation, target kinase proteins can be overexpressed, intercept downstream signaling pathways, be resistant to regulatory mechanisms, and perform functions that promote tumor formation and growth. Both well-established in clinical practice and novel targeted drugs are directed at targets that are critical to the pathogenesis of tumor development.

Tyrosine kinase inhibitors (TKIs) can function by competing for ATP in the ATP binding pocket of the kinase in an active (TKI type I) or inactive conformation (TKI type II); perform interactions beyond the ATP binding site, causing allosteric inhibition of kinase activity (TKI type III); form an irreversible covalent bond with the active center of the kinase, most often by reacting with a nucleophilic cysteine residue (TKI type IV, irreversible inhibition) [3, 4]. TKIs have a cytostatic effect, leading to inhibition of tumor growth.

Monoclonal antibodies bind to the extracellular domain of the target receptor and act through a variety of mechanisms, including antibody-dependent cellular cytotoxicity, internalization followed by degradation, or inhibition of receptor dimerization [5, 6]. Monoclonal antibodies are divided into chimeric (-ximab), humanized (-zumab) or fully human (-umab). Monoclonal antibody-based drugs are used separately or in conjugation with a cytotoxic agent (trastuzumab emtansine, trastuzumab deruxtecan, brentuximab vedotin, enfortumab vedotin).

The aim of this lecture was both to analyze therapeutic approaches to directing a few important molecular targets of malignant neoplasms and to consider the problem of resistance to targeted drugs and strategies to overcome these resistance mechanisms. The material of the lecture would be of interest to researchers and specialists in the field of targeted therapy and oncology.

TARGETING CELL STRUCTURES THAT SUSTAIN CHRONIC PROLIFERATIVE SIGNALING

Normal cells require mitogenic growth signals mediated by transmembrane receptors to transfer from a quiescent state to a phase of active proliferation. On the contrary, tumor cells are capable of autonomously maintaining chronic proliferation. Sustained proliferation is carried out by increasing the amount of growth factor ligands, increasing the expression of receptor proteins on the surface of tumor cells, stabilization of the receptor in the dimeric state, and activation in the absence of ligand.

Epidermal growth factor (EGF) and its receptors with tyrosine kinase activity, members of the ErbB family: EGFR (HER1, ErbB-1), HER2/c-neu (ErbB-2), and Her 3 (ErbB-3), are common and well understood growth factors. ErbB family receptors ensure proliferation, survival, and differentiation of normal cells, while they are overexpressed in a variety of malignancies. Thus, EGFR (HER1) overexpression is found in non-small cell lung cancer, disseminated prostate cancer, head and neck cancer, glioma and glioblastoma, and also in colorectal and pancreatic cancers. HER2/c-neu overexpression is most commonly found in breast cancer (15–20% of cases) and less frequently in ovarian, gastric, prostate, and pancreatic neoplasms. The relevance of HER3 overexpression in malignant tumors is not as high as that of HER1 and HER2. This phenomenon can be observed in breast, ovarian, gastric, and prostate cancers [7].

Studying the crystal structure revealed that the extracellular domain of ErbB family receptors consists of four subdomains, of which domains I and III are involved in ligand binding, and domains II and IV are involved in intramolecular interactions and provide autoinhibition. EGF receptors usually are in an inactive monomeric state as a compact "bound" conformation determined by intramolecular binding between domains II and IV. These receptors are activated upon binding to a ligand and subsequent dimerization. To accomplish this process, domains I and III form a ligand-binding pocket and expose subdomain II, allowing for dimerization between identical receptors (homodimerization) or with other family members (heterodimerization). However, unlike other family members, HER2 exists in a stable open conformation that enables dimerization without ligand binding.

For many tyrosine kinase receptors, the transition to an active kinase conformation is provided by autophosphorylation of the activation loop in the kinase domain. Nevertheless, for ErbB receptors, the transition to an active conformation is mediated by the formation of a kinase domain dimer, in which one kinase allosterically activates the other. Next, kinase domains catalyze the phosphorylation of tyrosine residues (outside the kinase domain in the C-terminus), creating binding sites for proteins or enzymes involved in downstream signal transduction. The interaction of EGF receptors with extracellular ligand triggers a cascade of biochemical reactions through the RAS-RAF-MAPK, PI3k/AKT, and phosphoinositide-specific phospholipase C (PLCγ) signaling pathways [7, 8].

Currently, there are three generations of EGFR/HER1-directed TKIs approved for the treatment of non-small cell lung cancer (NSCLC). The use of first-generation reversible ATP-conjugating TKIs (gefitinib, erlotinib, icotinib) and second-generation TKIs (afatinib and dacotinib) with irreversible inhibition has significantly improved the efficacy of the therapy compared to classical chemotherapy. At the same time, despite a favorable initial response to therapy, in the majority of patients, tumor progression slows down after 9–14 weeks. Tumor progression is caused by the development of resistance, which in about half of the cases is due to the second-site T790M mutation in exon 20 [1].

The irreversible third-generation TKI, *osimertinib*, covalently binds to cysteine at the ATP interaction site of the EGFR intracellular domain, increasing the efficacy of therapy against the T790M mutation by nearly 200 times and has demonstrated potential efficacy in the treatment of brain metastases. Another advantage of this drug is significant reduction of cutaneous and gastrointestinal toxicity compared to wild-type TKIs. The development of resistance caused by a point mutation of cysteine at position 797 (C797X), which is the binding site for osimertinib, remains an urgent and unresolved problem. In addition, mutations of other amino acid residues of EGFR, EGFR amplification, and EGFR-independent resistance, in particular activation of bypass signaling pathways for signal transduction, may be observed during treatment.

EGFR/HER1-directed antibodies approved for treatment in the Russian Federation include cetuximab (chimeric IgG1 monoclonal antibody) and panitumumab (recombinant human IgG2 monoclonal

antibody). As a result of binding to EGFR, the antibodies prevent intracellular ligand-mediated tyrosine kinase phosphorylation, leading to inhibition of downstream signaling pathways, including RAS-RAF-MAPK and PI3K-Akt/mTOR pathways. Drugs in this group are used for the therapy of metastatic colorectal cancer (panitumumab) and head and neck cancer (cetuximab).

Lapatinib is a dual tyrosine kinase inhibitor that blocks the activity of the HER1 and HER2 tyrosine kinases by interacting with the ATP-binding site of the intracellular receptor domain. Lapatinib is approved for the therapy of HER2-positive breast cancer (BC).

HER2-directed antibodies approved for BC therapy include trastuzumab and pertuzumab. Trastuzumab, as a HER2-directed humanized IgG1monoclonal antibody, binds to subdomain IV, suppresses the intracellular PI3K and MAPK signaling pathways, and activates the immune response. Pertuzumab is a monoclonal antibody that, by binding to subdomain II of HER2, inhibits the dimerization of HER2 with other receptors of EGFR, HER3, and HER4. Clinical studies have indicated that trastuzumab in combination with pertuzumab provides a more effective blockade of the HER signaling pathway.

A new class of targeted therapy in cancer treatment, monoclonal antibody-drug conjugates, have proven to be highly effective with acceptable systemic toxicity. Such conjugates consist of three main parts, namely a monoclonal antibody, a chemical linker, and a cytotoxic agent. Highly active tubulin inhibitors (auristatin analogs and maitansin analogs); DNA damaging compounds (duocarmazine, calicheamicins, and pyrrolobenzodiazepines), RNA polymerase II inhibitors (amanitin), and topoisomerase I inhibitors (deruxtecan, govitecan) are used as cytotoxic compounds [9, 10]. In addition to effects mediated by cytotoxic agents, monoclonal antibodies may exhibit intrinsic antitumor activity, such as blocking target antigens and triggering antibody-dependent immune responses [11].

Consequently, for patients whose disease progresses after therapy with a combination of trastuzumab and pertuzumab, trastuzumab emtansine is the standard second-line treatment. Trastuzumab emtansine (T-DM1) consists of an IgG1 monoclonal antibody against HER2 фтв trastuzumab conjugated via a non-degradable thioester linker to the cytotoxic agent DM1, an inhibitor of microtubule tubulin polymerization.

Trastuzumab deruxtecan (T-DXd*)* is a new HER2-directed antibody conjugate with a drug and consists of humanized IgG1monoclonal antibody, with the same amino acid sequence as in trastuzumab, conjugated to the cytotoxic agent deruxtecan. Deruxtecan bound to the antibody via a maleimide tetrapeptide linker cleaved by cathepsins inhibits DNA topoisomerase I. The increased activity of cathepsins in malignant cells and in the tumor microenvironment allows for targeted release of a cytotoxic drug [12]. Thus, after binding to HER2 on tumor cells, T-DXd undergoes internalization and intracellular cleavage of the linker by lysosomal enzymes; and upon release, the cytotoxic agent DXd penetrates into the nucleus and causes DNA damage and apoptotic cell death.

Despite impressive advances in antibody – drug conjugate therapy, limitations of its use include congenital and acquired resistance and toxicity of the drugs. In particular, trastuzumab deruxtecan more often causes myelosuppression and interstitial lung disease, in particular pneumonia, compared to trastuzumab emtansine. At the same time, trastuzumab emtansine is characterized by a higher risk of hepatotoxicity, cardiotoxicity, and thrombocytopenia compared to trastuzumab deruxtecan [13].

Another target that enables for intense and unregulated cell growth is the chimeric protein BCR-ABL1. BCR-ABL1 promotes malignant degeneration and enhanced proliferation of hematopoietic cells in the bone marrow with their subsequent entry into the blood. An abnormal Philadelphia chromosome (Ph) carrying the BCR-ABL1 oncogene forms in a blood stem cell as a result of reciprocal translocation. In this process, a part of chromosome 9 containing the ABL gene translocates to chromosome 22 and joins the BCR gene. The BCR-ABL1 oncogene encodes the chimeric BCR-ABL1 protein in isoforms that vary in size depending on the specific breakpoint in the BCR gene, less often – on variations in the ABL1 breakpoint.

The three most common BCR-ABL1 isoforms are identified by protein molecular weight as p210 (e13a2 or e14a2, 210 kDa), p190 (e1a2, 190 kDa), and p230 (e19a2, 230 kDa) [14]. Expressed in approximately 95% of patients, p210 is a characteristic feature of chronic myeloid leukemia (CML) [15, 16]. Between 20 and 30% of patients with acute lymphoblastic leukemia (ALL) are also BCR-ABL1 positive (Ph+ ALL). These patients tend to have a worse prognosis compared to BCR-ABL negative patients. More than two thirds of patients with Ph-positive ALL express a

shorter p190 isoform, while only a third express p210 [17, 18]. The fused protein BCR-ABL1 increases the activity of ABL kinase, leading to the formation of a GRB2/GAB2/SOS complex and subsequent activation of the PI3K/AKT, MAPK, and JAK/STAT signaling pathways [19]. Reduced demand in growth and apoptotic factors and improved viability and proliferation are observed in hematopoietic cells transformed with the BCR-ABL1 gene [20, 21].

Therapies targeting mutant BCR-ABL1 include TKIs, which function by competing for ATP at the ABL kinase ATP-binding site, which leads to inhibition of tyrosine phosphorylation of proteins involved in signal transduction. Therapy with imatinib, the first-generation TKI, has improved patient outcomes by demonstrating long-term cytogenetic remission. However, some patients did not respond to imatinib, while others experienced disease progression after treatment failure was identified. The main cause of resistance to imatinib is point mutations in the BCR-ABL kinase domain, which are found in ≥ 50% of patients. Mutations in the kinase domain can interfere with the binding of imatinib, which leads to drug resistance [22, 23].

Most of these imatinib-resistant BCR-ABL mutations are inhibited by dasatinib, nilotinib, and bosutinib (second-generation TKIs), with the exception of T315I. The following mutations are relevant for the selection of second-generation TKIs: V229L (nilotinib therapy is preferred), F317L/V/I/C, T315A (bosutinib or nilotinib therapy), Y153H and E255K/V, F259V/C (bosutinib or dasatinib therapy) [24]. The T315I mutation, which replaces the amino acid threonine (Thr315) with isoleucine (Ile315) at position 315 in the kinase domain of ABL1, is the most resistant to drug inhibition. This is due to several factors, including loss of hydrogen bonding between the T315 side chain at the drug – target binding site, changes in the topology of the ATP binding pocket, and an increase in its own kinase activity [22, 23, 25, 26]. For these reasons, the T315I variant of the mutant kinase is difficult to inhibit with ATP mimetics.

Asciminib and ponatinib, the third generation of TKIs (imatinib- and dasatinib-resistant), have been developed to overcome the T315I mutation. These drugs are indicated for patients with chronic myeloid leukemia or Ph+ acute myeloid leukemia who are resistant and / or intolerant to imatinib, dasatinib or nilotinib, or who have the T315I mutation. Unlike second-generation TKIs, ponatinib does not form hydrogen bonds with the T315 side chain in the ABL kinase domain (ABL-1). Instead, asciminib has a different binding site and is the first STAMP (specifically targeting the ABL myristoyl pocket) inhibitor to suppress BCR-ABL1 kinase activity by interacting with the myristoyl pocket [24, 26].

AIMING AT THE TARGETS THAT PROMOTE EVASION OF CELL GROWTH SUPPRESSORS

Besides maintaining stable signals of proliferative activity, tumor cells must evade mechanisms that inhibit proliferation. The action of cyclin-dependent protein kinases (CDKs), activated by their interaction with D-type cyclins, controls the transition from one phase of the cell cycle to another. For example, the transition from G1 to S phase of the cell cycle occurs when CDK4 and CDK6 bind to cyclin D1, leading to the phosphorylation of retinoblastoma-associated protein 1 (Rb1). When CDK4 and CDK6 are inhibited, Rb1 is dephosphorylated, and the progression of the cell cycle is inhibited [27].

In about 75% of cases of disseminated breast cancer, the tumors are HER2-negative but have high levels of estrogen and / or progesterone receptors. HER2-targeted therapy is not indicated for such patients. Patients with hormone-sensitive tumors often have overexpression of cyclin D1, which plays a key role in cell cycle regulation. The efficacy of cyclin-dependent inhibitors, such as abemaciclib, palbociclib, and ribociclib, depends on sustained activation of the cyclin D1-CDK4/6 complex. These inhibitors block Rb phosphorylation and arrest the cell cycle from G1 to S phase, leading to apoptosis of tumor cells [28].

AIMING AT THE TARGETS INDUCING ANGIOGENESIS

The progressive growth of the tumor and the development of metastases are accompanied by a continuous increase in the number of new blood vessels [29], which is triggered by the angiogenic switch. This process involves a shift in the balance of pro- and anti-angiogenic factors toward activators, leading to an increase in tissue vascularization [30]. Hypoxia as a result of rapid tumor growth is the main driver for the production of angiogenic inducers. It is interesting to note that the activation of angiogenesis has been observed in the early stages of carcinogenesis, preceding the appearance of solid tumors, suggesting that its induction is a discrete process in carcinogenesis [29].

Vascular endothelial growth factor (VEGF) is a strong pro-angiogenic factor. Signaling proteins, such

as VEGF, as well as basic fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF), bind to cell surface receptors on vascular endothelial cells and regulate the angiogenic switch [31, 32].

Multi-targeted inhibitors represent TKI therapy, which aims at promoting angiogenesis in the tumor microenvironment. The drugs specified below have been approved for the treatment of thyroid carcinoma. Vandetanib is a TKI targeting angiogenic VEGFR-2, EGFR, and RET tyrosine kinases involved in tumor growth, progression, and angiogenesis. Lenvatinib is a multikinase inhibitor of VEGF1-3 and FGF1-4 receptors. Regorafenib, a diphenylurea multikinase inhibitor targeting angiogenic (VEGFR1-3, TIAM), stromal (PDGFRβ, FGFR), and oncogenic (KIT, RET and RAF) tyrosine kinase receptors, has also been approved for the treatment of metastatic colorectal cancer. Axitinib, a TKI with an affinity for angiogenic VEGF receptors (1, 2 and 3), PDGFR and c-KIT, is approved for the treatment of renal cell carcinoma. Sunitinib is a multikinase inhibitor approved for the treatment of gastrointestinal stromal tumors, renal cell carcinoma, and neuroendocrine tumors of the pancreas with activity against more than 80 kinases, including platelet growth factor receptors (PDGFRa and PDGRFß), vascular endothelial growth factor (VEGRF1, VEGRF2 and VEGRF3), KIT, FLT, CSF-IR, and RET. Sorafenib is another TKI approved for the treatment of hepatocellular carcinoma, renal cell carcinoma, and thyroid cancer. Bevacizumab and ramucirumab are IgG1 monoclonal antibodies that selectively bind to VEGF, inhibit its biological activity, and are approved for the treatment of tumors of various localizations.

TARGETING IMMUNE CHECKPOINTS

Normally, cells with oncogenic potential, due to genetic and epigenetic changes, are recognized as foreign by immune cells and destroyed by NK cells, dendritic cells, and T lymphocytes. However, cancer cells can effectively evade immune surveillance by reducing surface human leukocyte antigen (HLA) expression, tumor-associated antigens on their surface, or directly blocking T lymphocyte activation through clonal deletion or anergy.

Immune checkpoints are receptors and their ligands that regulate the immune response. Immune checkpoints that suppress T lymphocyte activation pathways include cytotoxic T lymphocyte-associated glycoprotein 4 (CTLA-4), programmed cell death receptor 1 (PD-1), and its ligands (PD-L1 and PD-L2). CTLA-4, in particular, is thought to regulate T lymphocyte proliferation during the early stages of an immune response, primarily in the lymph nodes. On the other hand, PD-1 suppresses T cell activity during later stages of immune response development, primarily in peripheral tissues [33]. Monoclonal antibodies targeting these molecules are used in therapy to inhibit immune checkpoints. Blockade of these receptors or ligands can prevent acquired peripheral tolerance to tumor antigens and restore an effective anti-tumor immune response.

To date, there are two main types of immune checkpoint antibodies, namely mAbs targeting CTLA-4 and mAbs targeting PD-1 and / or its ligand PD-L1. The first approved drug for the treatment of unresectable or metastatic melanoma is ipilimumab, which targets CTLA-4. Pembrolizumab and nivolumab, which target PD-1, have also been approved to treat patients with advanced melanoma. These drugs have since been approved to treat tumors in other sites, including non-small cell lung cancer, renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck, and Hodgkin's lymphoma [34].

It should be noted that most patients do not respond to monotherapy with drugs of this class, and cases of primary and acquired resistance to treatment are not uncommon, leading to loss of immunity and tumor progression. Double blockade of immune checkpoints through the combined use of CTLA-4 and PD-1 inhibitors is a more effective therapeutic strategy and shows a synergistic anti-tumor effect. Anti-CTLA-4 and anti-PD-1 agents enhance the anti–cancer immune response through different but complementary mechanisms as they act at different times and in different sites throughout the evolution of T cells. One well-known combination is the use of ipilimumab and nivolumab.

AIMING AT THE TARGETS ACTIVATING INVASION AND METASTASIS

The spread of tumor cells from a primary lesion to other organs and tissues is a major cause of cancer-related mortality. According to the metastatic cascade theory, this process involves successive stages, which can be divided into the stages described below. The first stage is physical dissemination of tumor cells away from the original site, which involves transformation of the tumor cells and their invasion deep into the adjacent tissues. This includes intravasation, migration of cells into lymphatic and vascular capillaries, and extravasation to sites of release. The next stage is

colonization and growth of new tumors, leading to the development of microscopic metastases with the potential for progression to larger tumors.

Epithelial – mesenchymal transition (EMT) is the process by which epithelial cells undergo morphological and functional transformation and acquire mesenchymal properties, including increased invasiveness, mobility, and migration. Inducers of EMT include transforming growth factor beta (TGFβ), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), insulin-like growth factors (IGFs), etc.

The hepatocyte growth factor receptor (c-Met) is involved in the initiation and development of various types of cancer in humans, and it mediates the proliferation, migration, and invasion of tumor cells. The interaction of c-Met with its ligand, HGF, activates downstream PI3K/Akt and Ras/MAPK signaling pathways. This triggers cytoskeletal restructuring and various cellular reactions, such as cell migration, mitogenesis, morphogenesis, proliferation, invasion, and angiogenesis.

Small-molecule C-Met inhibitors can be divided into selective and multikinase ones. Capmatinib is a selective ATP-competitive TKI that targets C-Met, including the mutant variant produced by skipping exon 14 (METex14 mutation). Skipping exon 14 results in a truncated C-Met receptor lacking the regulatory domain, which reduces its negative regulation and consequently reduces the possibility of degradation of the C-Met protein, leading to its stable activation and oncogenesis [35]. Multikinase TKIs, specifically those with C-Met inhibition, include crizotinib (targeting ALK, ROS1, C-Met, and RON), which is used to treat patients with ALK+ or ROS1+ NSCLC, and cabozantinib (targeting MET, VEGF, GAS6 (AXL), RET, ROS1, TYRO3, MER, KIT, TRKB, FLT3, and TIE-2) to treat RCC. Amplification of the MET gene has been associated with acquired resistance to therapy with EGFR family agents. MET activation has also been shown to increase VEGF-A expression, which is a promoter of angiogenesis and endothelial cell growth.

Monoclonal antibody therapy is divided into antibodies against c-Met (such as onartuzumab and emibetuzumab) and antibodies against HGF (such as ficlatuzumab and rilotumumab), which are FDA-approved but have not yet been approved in Russia [36].

Table 1

Tyrosine kinase inhibitors registered in the Russian Federation, classified according to the target

Mechanism of action	Target (kinases)	Name of drug	Indications
Inhibition of overexpressed or mutant protein (angiogenesis)	VFGFR1, VFGFR2, VFGFR3	Axitinib (Axitinib, Inlita®)	Renal cell carcinoma
	VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3 (FLT4), FGFR1, FGFR2, FGFR3, FGFR4, PDGFRa, and tyrosine kinase receptors KIT and RET	Lenvatinib (Lenvatinib, Lenvima®)	Thyroid cancer
	VFGFR1, VFGFR2, VFGFR3, PDGFR α and β, FGFR1, FGFR2, FGFR3	Nintedanib (Vargatef®)	Non-small cell lung cancer
	TIE, KIT, RET, RAF-1, BRAF, BRAFv600E, PDGFR, FGFR, CSF1R	Regorafenib (Stivarga®)	Colorectal cancer, gastrointestinal stromal tumors
	Multikinase (>80 kinases), including: PDGFRα, PDGRFß, VEGRF1, VEGRF2 and VEGRF3, KIT, FLT, CSF-IR, RET.	Sunitinib (Flutrixan, Sunitinib, Sunitinib-Amedart, Sunitinib-Himrar, Valeotinib, Sutent®, Sunitinib-Promomed)	Gastrointestinal stromal tumors, renal cell carcinoma, neuroendocrine tumors of the pancreas
Inhibition of overexpressed or mutant protein (angiogenesis, proliferation)	VEGF, EGFR/HER1	Vandetanib (Caprelsa)	Thyroid cancer
Inhibition of overexpressed or mutant protein (proliferation)	EGFR/HER1, HER2, HER3, and HER4	Afatinib (Giotrif®, Gefitinib-Promomed)	Non-small cell lung cancer with EGFR mutations
	EGFR/HER1, HER2, HER3, and HER4	Gefitinib (Gefitinib, Valkyra®, Gefitinib-Tl, Getinex®, Geftessa, Langerra)	Non-small cell lung cancer with EGFR mutations
	EGFR/HER1, HER2, and HER4	Dacomitinib (Visimpro®)	Non-small cell lung cancer with EGFR mutations

Table 1 (continued)

Mechanism of action	Target (kinases)	Name of drug	Indications
Inhibition of overexpressed or mutant protein (proliferation)	EGFR/HER1, HER2	Lapatinib (Brestocer, Lapatinib-Promomed, Lapatinib-Himrar, Tyverb®)	HER2+ breast cancer
	EGFR/HER1	Osimertinib (Osimertinib, Retezmo™)	Non-small cell lung cancer with EGFR mutations (deletions in exon 19 or L858R substitutions in exon 21, with the T790M mutation)
	EGFR/HER1	Erlotinib (Erlotinib, Erlater, Erlotinib-Tl)	Non-small cell lung cancer
Inhibition of overexpressed or mutant protein (evasion of cell growth suppressors)	CDK4/6	Abemaciclib (Zenlistik)	HR+ and HER2- breast cancer
	CDK4/6	Palbociclib (Itulsi)	HR+ and HER2- breast cancer
	CDK4/6	Ribociclib (Risarg)	HR+ and HER2- breast cancer
Inhibition of intracellular kinases (downstream signaling pathways)	MEK	Binimetinib (Mektovi)	Melanoma
	MEK1/2	Cobimetinib (Cotellic®)	Melanoma with BRAF V600 mutations
	MEK1/2	Selumetinib (Coselugo)	Plexiform neurofibroma
Inhibition of intracellular kinases (downstream signaling pathways)	BRAF	Vemurafenib (Zelboraf®)	Melanoma with the BRAF V600 mutation
	BRAF	Encorafenib (Braftovi)	Melanoma with BRAF mutations, colon cancer with BRAF mutations
Inhibition of overexpressed or mutant protein and intracellular kinases	c-CRAF, BRAF, mutant BRAF, KIT, FLT-3, RET, RET/PTC, VEGFR1, VEGFR2, VEGFR3, and PDGFRß	Sorafenib (Sorafenib, Sorafenib-Amedart, Effaronix®, Nexavar®, Sorafenib-Promomed)	Hepatocellular carcinoma, renal cell carcinoma, and thyroid cancer
Inhibition of overexpressed or mutant protein	Bruton's tyrosine kinase (BTK)	Zanubrutinib (Brukinza®)	Mantle cell lymphoma
	Bruton's tyrosine kinase (BTK)	Ibrutinib (Ibrutinib-Nativ)	Mantle cell lymphoma
	Bruton's tyrosine kinase (BTK)	Acalabrutinib (Calquence®)	Chronic lymphocytic leukemia / small cell lymphocytic lymphoma, mantle cell lymphoma
Inhibition of overexpressed or mutant protein	BCR-ABL1, c-KIT	Imatinib (Imatinib, Neopax®, Imatinib-Teva, Imatinib Grindex)	Ph+ chronic myeloid leukemia, Ph+ acute lymphoblastic leukemia
	BCR-ABL1, BCR-ABL1 mutant forms except for T315I mutation, c-KIT, Eph, PDGFß	Nilotinib (Nilotinib, Nilotinib-Promomed)	Ph+ chronic myeloid leukemia
	BCR-ABL1, BCR-ABL1 mutant forms except for 315I mutation, Src family (including Src, Lyn and Hck), c-KIT, Eph, PDGFß	Dasatinib (Dasatinib, Mirsonib, Dasatinib-nativ, Dasatinib-Himrar)	Ph+ chronic myeloid leukemia, Ph+ acute lymphoblastic leukemia
	BCR-ABL1, BCR-ABL1 mutant forms except for T315I mutation, Src family (including Src, Lyn, and Hck)	Bozutinib (Bozutinib, Bozulif)	Ph+ chronic myeloid leukemia
	BCR-ABL1, BCR-ABL1 mutant forms (including T315I mutation)	Asciminib (Scemblix)	Ph+ chronic myeloid leukemia, chronic myeloid leukemia with T315I mutation
	BCR-ABL1, BCR-ABL1 mutant forms (including T315I mutation)	Ponatinib (Iclusig®)	Ph+ chronic myeloid leukemia, Ph+ chronic myeloid leukemia with T315I mutation, Ph+ acute lymphoblastic leukemia
Inhibition of overexpressed or mutant protein	ALK	Alecetinib (Alecensa®)	ALK+ non-small cell lung cancer
	ALK	Ceritinib (Zykadia®)	ALK+ non-small cell lung cancer

Table 1 (continued)

Mechanism of action	Target (kinases)	Name of drug	Indications
Inhibition of overexpressed or mutant protein	ALK, ROS1 TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK.	Lorlatinib (Lorviqua®)	Thyroid carcinoma, ALK+ non-small cell lung cancer
Inhibition of overexpressed or mutant protein (proliferation, invasion-metastasis, etc.)	ALK, ROS1, c-Met, RON	Crizotinib (Xalkori®)	ALK+ or ROS1+ non-small cell lung cancer
Inhibition of overexpressed or mutant protein (invasion-metastasis)	MET	Capmatinib (Tabrecta)	Non-small cell lung cancer with the METex14 mutation.
Inhibition of overexpressed or mutant protein (invasion-metastasis, angiogenesis, etc.)	METH, VEGF, GAS6 (AXL), RET, ROS1, TYRO3, MER, KIT, TRKB, FLT3, and TIE-2.	Cabozantinib (Cabometyx®)	Renal cell carcinoma
Inhibition of overexpressed or mutant protein (genome mutation)	PARP1, PARP2, and PARP3	Olaparib (Lynparza®)	Ovarian, fallopian tube, or peritoneal cancer with mutation of the BRCA gene
Inhibition of overexpressed or mutant protein	TRKA, TRKB and TRKC encoded by the NTRK1, NTRK2, and NTRK3 genes	Larotrectinib (Vitrakvi®)	Solid tumors expressing the NTRK fusion gene
	TRKA, TRKB, and TRKC encoded by the genes NTRK1, NTRK2 and NTRK3, ROS1	Entrectinib (Roslitrek®)	Solid tumors expressing the NTRK fusion gene ROS1- positive non-small cell lung cancer

Table 2

Classification of targeted drugs based on monoclonal antibodies (including conjugates of monoclonal antibodies with cytotoxic agents) registered in the Russian Federation

Mechanism of carcinogenesis	Target	Name of drug	Indications
Proliferative signal transduction	EGFR	Cetuximab (Erbitux®)	Metastatic colorectal cancer, head and neck cancer
		Panitumumumab (Vectibix)	Metastatic colorectal cancer with wild-type RAS genes in the tumor
	HER2	Pertuzumab (Perjeta®)	Breast cancer
		Trastuzumab (Herceptin®, Herticad®, Trasimera®)	Breast cancer
		Trastuzumab Deruxtecan (Enchertu)	Breast cancer
		Trastuzumab Emtansine (Cadsila®)	Breast cancer
Angiogenesis	VEGF	Bevacizumab (Avastin®, Avegra® Biocad, Versavo®, Stibevara®)	Metastatic colorectal cancer
		Ramucirumab (Ciramza®)	Gastric cancer, gastroesophageal junction adenocarcinoma, non-small cell lung cancer, metastatic colorectal cancer, hepatocellular carcinoma
Immunotherapy: immune checkpoints	CTLA- 4	Ipilimumab (Yervoy®)	Melanoma
		Tremelimumab (Imjudo)	Non-small cell lung cancer, bladder cancer, head and neck cancer, liver cancer and hemoblastosis
	PD-L1	Avelumab (Bavencio®)	Merkel cell carcinoma
		Atezolizumab (Tecentriq®)	Locally advanced or metastatic urothelial cancer
		Durvalumab (Imfinzi®)	Non-small cell lung cancer

Table 1 (continued)

Mechanism of carcinogenesis	Target	Name of drug	Indications
Immunotherapy: immune checkpoints	PD-1	Nivolumab (Opdivo®)	Melanoma, non-small cell lung cancer, advanced renal cell carcinoma
		Pembrolizumab (Kitruda®, Pembroria)	Melanoma
		Prolgolimumab (Forteca®)	Melanoma
Immunotherapy	CD19, CD3	Blinatumomab (Blincyto®)	Acute lymphoblastic leukemia
	CD20	Obinutuzumab (Gazyva®)	Chronic lymphocytic leukemia
		Ofatumumumab (Bonspree®)	Chronic lymphocytic leukemia
		Rituximab (Redditux®, Rituxara®, Acellbia®, Mabthera®)	B-cell non-Hodgkin's lymphomas
	CD20, CD3	Mosunetuzumab (Lansumio®)	Follicular lymphoma
	CD22	Inotuzumab Ozogamicin (Bisponsa)	CD22-positive B-cell acute lymphoblastic leukemia
	CD30	Brentuximab Vedotin (Adcetris®)	CD30-positive Hodgkin's lymphoma
	CD33	Gemtuzumab Ozogamicin (Mylotarg®)	CD33-positive acute myeloid leukemia
	CD38	Daratumumumab (Darzalex)	Multiple myeloma
		Isatuximab (Sarcliza®)	Multiple myeloma
	CD79b	Polatuzumab Vedotin (Polayvi®)	Diffuse B-large cell lymphoma
	GD2	Dinutuximab Beta (Carziba)	Neuroblastoma
	SLAMF7	Elotuzumab (Emplicity®)	Multiple myeloma
Proliferation, migration, and adhesion	Nectin-4	Enfortumumab Vedotin (Padtsev Onco)	Non-muscle invasive bladder cancer

CONCLUSION

The development of novel targeted drugs with low toxicity and the ability to bypass resistance mechanisms is a major challenge for medicine in the XXI century. In this regard, it is essential to understand the mechanisms of malignancy and identify the key targets in the development of a particular tumor.

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