# PRECISION ONCOLOGY: MYTH OR REALITY?

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Cancer incidence rates are growing at an alarming pace pressing for the development of innovative personalized approaches to treating this disease. The absence of clinical symptoms in the early stages delays the onset of adequate treatment. Traditional therapies are not always as effective as they should be and do not guarantee long-lasting relapse-free survival. Metastatic cancers pose a particular challenge to healthcare professionals. This review touches upon the immunologic mechanisms underlying the development of malignancies, talks about conventional and innovative therapeutic modalities, such as targeted, gene or specific immunotherapies, and analyzes the literature on the use of different approaches that form a basis for precision oncology.

**Keywords:** cancer, nonspecific immunotherapy, cytokine therapy, targeted therapy, monoclonal antibodies, immune checkpoints, cancer vaccines, gene therapy, nanotechnologies, precision medicine

**Author contribution:** Slavyanskaya TA conceived and planned this review, collected, analyzed and interpreted literature data, reviewed the manuscript, provided images, and wrote conclusions. Salnikova SV collected and analyzed literature data and prepared the draft of the manuscript.

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# ПРЕЦИЗИОННАЯ МЕДИЦИНА В ОНКОЛОГИИ: МИФ ИЛИ РЕАЛЬНОСТЬ?

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Бурный рост числа онкологических заболеваний во всем мире диктует необходимость разработки новых, инновационных и персонализированных подходов к их лечению. Отсутствие клинических проявлений на ранних стадиях болезни не позволяет своевременно назначить адекватную терапию. Традиционные методы лечения, не всегда обладающие удовлетворительной эффективностью, не предотвращают рецидивирование, не обеспечивают достаточную ремиссию и продолжительность жизни больного. Значительные трудности представляет собой лечение инвазивного, метастатического рака. В статье представлен краткий обзор иммунологических механизмов развития злокачественных новообразований, современных традиционных и инновационных методов лечения рака, а также анализ литературных данных по использованию методов таргетной, генной терапии, специфической иммунотерапии и других подходов, лежащих в основе прецизионной медицины в онкологии.

**Ключевые слова:** рак, неспецифическая иммунотерапия, цитокинотерапия, таргетная терапия, моноклональные антитела, иммунные чек-поинты, противоопухолевые вакцины, генная терапия, нанотехнологии, прецизионная медицина

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Fighting cancer is still a top priority for global healthcare. The overall success achieved in treating a wide range of diseases [1–3], including malignancies [4–10], over the past few decades is indisputable. Advances in molecular biology, genetics and immunology have shed light on the immunogenetic and immunobiological features of tumors and expanded our knowledge of the protective role of the innate and adaptive immunity against cancer. There is convincing evidence that the efficacy of immunotherapy depends on the immunologic components of a tumor. Research into the mechanisms underlying cancer development and the processes unfolding in the tumor microenvironment [11] has paved the way to new strategies and integral approaches to treating malignancies [12–14]. The discovery of new therapeutic targets and the development of innovative methods for personalized therapy can improve treatment outcomes in patients with cancer [4, 5, 15, 16].

## The role of the innate and adaptive immunities in anticancer defense

Rapid proliferation of cancer cells is caused, in the first place, by a breach in the immune defense (the cancer-immunity cycle) that allows cancer cells to evade the immune system. Three phases of immunoediting, a model of cancer development, include elimination, equilibrium and escape that either control or promote tumor growth. In the elimination phase, the initiated T-cell response is guided against malignant cells. During the equilibrium phase, limited immune control allows cancer cells to be in a state of dormancy and mutate. The inhibitory attacks of T cells drive the escape phase characterized by both local tumor growth and the spread of metastases [17–19].

### *Innate immunity*

Malignant cells are eliminated by natural killers (NK), natural killer T cells (NKT), gamma-delta T cells (γδ-T), macrophages, and granulocytes.

NK play the key role in non-specific elimination of tumor cells. Their functions are regulated by cytokines (IL2, IL15), co-stimulatory molecules (CD40, CD70, CD80, CD86, ICOS) and killer activation receptors (NKp30, NKp44, NKp46, NKp80) that, apart from producing IFNγ and perforins, mediate the effector function of NK and inhibitory receptors (KIR, CD94) [18, 19].

NKT cells constitute a subset of lymphocytes expressing both NK markers and T-cell differentiation antigens. The effector function of NKT relies on the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL12 [20]. NKT are crucial regulators of immune response that confer protection against tumor nascence, growth and metastasis.

γδ-T cells localized in the epithelium of the skin, gastrointestinal tract and urogenital system are a bridge between the innate and adaptive immunities. They can act as antigen-presenting cells (APC) [18].

It is impossible to estimate the contribution of granulocytes and macrophages in the early stages of carcinogenesis. In the advanced stages, macrophages promote tumor growth [18].

*Adaptive immunity*

Antigen presentation by APC is essential for activating the adaptive immunity. In most cases antigen presentation is done by dendritic cells (DC); however, endothelial cells, B lymphocytes and even cancer cells can also act as APC [19]. Apart from that, DC are involved in inducing and maintaining self-tolerance.

In healthy individuals, an adequate immune response is initiated by signal exchange between DC and T helper cells (Th) that can come into direct contact with each other or "communicate" at a distance. Their direct interaction is facilitated by a group of molecules on a T-cell membrane. Specifically, a number of consecutive interactions occur between CD2, MHC class II complexed to an antigen, CD40, ICAM I, CD 80/86, and CD 83 on the surface of APC and the following receptors on the Th surface: CD58, TCR, CD154, CD11a/CD18, CD28, and CD152.

The signal is transmitted into the cell by a group of second messengers, the most well studied being inositol trisphosphate, calmodulin and a group of kinases associated with T-cell receptors. The result of their direct and indirect interaction is the activation of Th1 and Th2 and, respectively, cellular and humoral immunity.

In terms of anticancer defense, the cell-mediated immune response is more important than the humoral immune component. T cells express a variety of receptors known for the ability to stimulate or inhibit the activation of their secretors (Fig. 1). The effect of T-cell activation is determined by how much those receptors are involved. Research into co-inhibitory T-cell receptors, as well as into monoclonal antibodies (mAb) that block inhibitory molecules on the surface of immunocompetent and tumor cells, seeks to improve the efficacy of the antitumor immune response.

A few *in vivo* studies have demonstrated that antibody-dependent cellular cytotoxicity also contributes to the elimination of cancer cells. In advanced stages of cancer, the humoral immunity prevents malignant cells from being killed [18, 19].

A tumor, especially a nascent one, does not produce antigens that would distinguish it from healthy tissue and is not recognized by the body as "foreign".

During the equilibrium phase, tumor cells that survived previous attacks continue to mutate and proliferate, and angiogenesis is activated. DC and macrophages emerge in the tumor microenvironment. A tumor clone is formed from the mutated cancer cells. In this phase, the immune system behaves like it did in the surveillance phase, but oncogenic processes prevail over protective immunological reactions, and the tumor gradually grows in size.

The escape phase is characterized by a shift towards immune suppression regulated by cytokines, an imbalance in the number of effector and suppressor immunocompetent cells, defective antigen recognition and presentation, and impaired signal transduction into the cell [19].

Cytokines are regulatory peptides secreted by the body. Transforming growth factor beta (TGF-$\beta_{1-3}$) is a regulatory peptide that participates in a variety of biological processes, including carcinogenesis, wound healing, and maintenance of immunological homeostasis. TGF-$\beta_s$ exerts its biological functions via types I and II serine/threonine receptors (TGF-βRI, TGF-βRП). This cytokine promotes immunological tolerance by sending signals to $CD4^+$- and $CD8^+$-lymphocytes and NK cells. TGF-β guides the differentiation of $CD4^+$ cells into regulatory subpopulations ($CD4^+CD25^+$ T-regulatory cells or natural Tregs), inhibits the expression of perforins, granzyme B and FAS-ligand in $CD8^+$-lymphocytes, suppresses the IL12-induced production of IFN-r by NK [20–22].

Interleukin IL10 exerts its functions via IL10R1 and IL10R2 receptors localized on the surface of DC and Th cells. It inhibits the production of IL12 and co-stimulatory molecules, downregulates the expression of MHC class II antigens on DC, disrupting their maturation, and blocks cytokine secretion by $CD4^+$-cells [19]. The IL23 heterodimer consists of two subunits, one of which (p40) is identical to that of IL12. Both IL23 and IL12 are secreted by innate immunity cells but regulate the functions of adaptive immunity components. IL12 promotes T-cell maturation and triggers the production of IL6, IL15, IL18, TNFβ, and GM-CSF, while IL23 promotes the differentiation of immature cells into Th17 and stimulates the secretion of IL17, IL17F, IL6, and TNFα. Some studies have demonstrated that IL23 stimulates angiogenesis by upregulating the expression of matrix metalloproteinase 9 (MMP9) [18, 19, 22].

Vascular endothelial growth factor (VEGF) is a major proangiogenic factor produced by both tumors and immune competent cells. So far, 7 VEGF isoforms are known of which VEGF-α has the most significance for angiogenesis and immunomodulation. VEGF inhibits DC maturation and promotes the secretion of immature myeloid cells (iMC) that, in turn, suppress T-cell activity [19].

The tumor microenvironment is the main battlefield in the fight between the immune system and a tumor. In the escape phase, the proportion of immature DC and Tregs in the general cell population increases. Mature DC express on their surface CD40, CD80, CD83, and CD86 and secrete high levels of IL12. VEGF, IL6, TGF-β, IL10, COX-2, PGE2, and gangliosides found in the tumor microenvironment prevent DC from differentiating and maturing, rendering impossible an adequate immune response [19].

Regulatory T cells are components of the adaptive immunity. They are derived from immature T cells and suppress the effective immune response by regulating the functions of effector cells. At present, 3 Treg types are distinguished: $CD4^+CD25^+Foxp3^+$, Treg1 and Treg2 cells (formerly known as Th3); both Treg1 and Treg2 cells are induced Tregs. Besides them, there are suppressors with a $CD8^+$ phenotype but their function is still poorly understood. The major role in immune suppression in cancer patients is played by $CD4^+CD25^+$ Tregs originating in the bone marrow. Their concentrations are highly elevated in patients with breast, colorectal, lung, or pancreatic cancers. These cells arise from the same precursors as Th cells in the presence of the increased concentrations of TGF-β, IL10 and VEGF. The mechanism underlying the suppressor effect of $CD4^+CD25^+$ Tregs is associated with the secretion of suppressor cytokines (TGF-β, IL10), competition for ligands (IL2), induction of DC tolerance, and in some cases their direct lysis [23].

Molecular abnormalities in DC and lymphocytes are another important characteristic of the escape phase. Specifically, this phase is characterized by the loss of expression of MHC class I and II molecules, CD80, CD86, and CD154 on the surface of tumor cells, as well as low expression of Th TCR ξ-chain [23].

Not only the functional activity of lymphocytes is disrupted in cancer development; the expression of integrins on the surface of tumor cells and their composition also change. This can reduce the strength of cell-cell contacts and promote neoangiogenesis. The abnormal expression of selectins (CD44, ELAM-1) on the surface of cancer cells correlates with poor clinical outcome.

Gangliosides significantly contribute to the suppression of lymphocyte response in the tumor microenvironment. Among them are GD1a, GD2, GD3, GM1, and GM2 expressed on the surface of cancer cells and then shed into the extracellular matrix. They are capable of suppressing the function of tumor-infiltrating lymphocytes (TILs) by interfering with signal transduction. The impaired effector function of lymphocytes is reflected in the reduced expression of granzyme B and kinases complexed with TCR-p59fyn and ZAP-70.

A declining proliferative index, the reduced expression of α- and β-subunits of the IL2 receptor, and the low phosphorylation degree of the protein encoded by *Rb* all signal compromised immunity. Such changes typically affect peripheral lymphocytes and tumor-infiltrating cells but their severity varies. The expression levels of IL2 receptor, TCR ξ-chain, CD54, and some other molecules amount to about 80% for peripheral lymphocytes (relative to the norm observed in healthy individuals) and 30% for tumor-infiltrating lymphocytes [23]. The changes listed above are typical for patients with local or disseminated cancers.

Summing up, the immune system has a pivotal role in fighting malignancies. In patients with cancer, immunodepression is multifactorial; the situation is often exacerbated by the ability of a tumor clone to resist the attacks of effector cells. At the same time, the understanding of key mechanisms underlying tumor growth and its escape from immune surveillance has become a springboard for specific immunotherapy that forms a basis for precision oncology.

## Innovative methods of treating malignancies

The idea of using nonspecific immunotherapy (NSIT) in patients with cancer is not new. The BCG vaccine alone or in combination with IL or anti-IL monoclonal antibodies (mAb against IL) has been long used to prevent recurrences in patients with urothelial cancer (UC) [6, 24]. It has been established that a combination of BCG-based NSIT and some *toll-like receptors* (TLR2, TLR4, TLR9, TRAIL) reduces the relapse rate. TLR7 and TLR9 agonists have also shown promise in a series of clinical trials [25].

At present, increasing attention is being paid to *adaptive immunotherapy*, a method based on inoculating the patient with his/her own immune cells activated in vitro [6].

*Targeted therapy with mAb* has become a real breakthrough in the management of cancer. mAb bind to the growth factors and receptors that are abundantly expressed by many human cancers and, therefore, can be regarded as a potential therapeutic target [26]. Researchers are currently studying the antitumor effect of therapeutic agents involved in angiogenesis, including VEGF, EGFR (epidermal growth factor receptor) and some others [27].

*Angiogenesis inhibitors* are also in the focus of scientific research. However, little is known about their effect on a tumor's blood vessels. Studies of VEGF inhibitors (AG013736 and VEGF-Trap) have shown that these molecules halt angiogenesis or cause the existing tumor vessels to regress. They induce early and persistent changes in endothelial cells, pericytes and the vascular basement membrane in RIP-Tag2 transgenic mice with spontaneous pancreatic islet cancer and in mice with subcutaneously transplanted Lewis lung

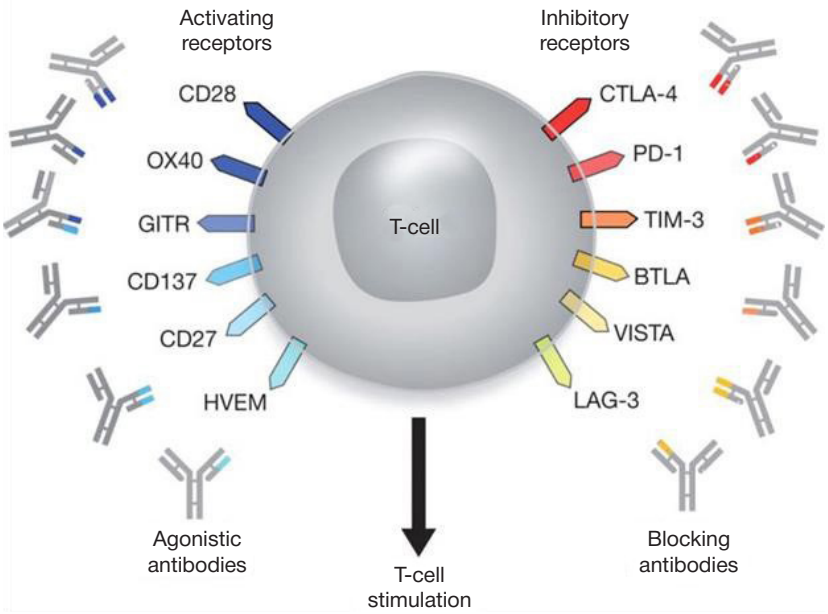


**Fig. 1.** T-cell activating and inhibitory receptors [21]. T cells express a variety of receptors known for the ability to stimulate or inhibit the activation of their secretors. The effect of T-cell activation is determined by how much those receptors are involved. *Inhibitory receptors*: CTLA-4 — cytotoxic T-lymphocyte antigen 4, a negative regulator of T-cell activation; PD-1 — programmed cell death 1 receptor. PD-1 plays an important role in the negative regulation of the immune system by preventing the activation of T cells, increasing self-tolerance and reducing autoimmunity; TIM — T-cell immunoglobulin mucin protein BTLA or B- and T-lymphocyte attenuator — an antigen that attenuates B- and T-cell functions; it participates in the regulation of T cells in the immune response. It is encoded by the BTLA gene. BTLA is expressed following T-cell activation and stays on the surface of Th1, but not Th2 cells. VISTA — V-domain Ig suppressor of T-cell activation; LAG-3 (CD223) — lymphocyte-activation gene. *Activating receptors*: CD28 — a co-stimulatory receptor; OX40 — a co-stimulatory receptor; GITR — a glucocorticoid-induced TNF receptor; CD137 — a co-stimulatory receptor; CD27 — a co-stimulatory receptor; HVEM — a membrane protein from a superfamily of tumor necrosis factor receptors 14 (TNFRSF14) and a herpes virus entry mediator

carcinomas. For example, an over 70% decline in vascular density was observed following treatment with angiogenesis inhibitors; the remaining endothelial cells acquired a normal phenotype and expressed less EGFT [27].

*Integrins* facilitate contacts between cells and the extracellular matrix, control cell proliferation, survival, migration, and adhesion [28]. The role of integrins in immune surveillance in general and their expression levels in particular are being studied extensively. At present, several integrin-targeting mAb are undergoing clinical trials, including etaracizumab and cilengitide [29, 30]. Although etaracizumab (a mAb that recognizes integrin αvβ3) demonstrated its efficacy against a range of tumors in phase I clinical trials, the results were not confirmed during phase II [29]. By contrast, the efficacy of cilengitide (a mAb that recognizes integrins αvβ3 and αvβ5) against glioblastomas and its good tolerance were confirmed in phase I and II clinical trials; in 69% of cases, 6-month relapse-free survival was observed [31].

Other molecules may also have a potential to become therapeutic targets, especially those participating in transmitting signals that suppress immune response in the tumor environment. Many leukocytes express an *integrin-associated protein* CD47 (membrane receptor protein) on their surface. It is capable of binding to beta-3-integrin, thrombospondin-1, signal-regulatory alpha protein (SIRP-α) and other signal proteins involved in the regulation of T-cell activation, cell migration, phagocytosis, and other activities of the immune system. CD47 is expressed by tumors and cancer stem cells, allowing the latter to survive and therefore leading to late relapses. A combination of CD47 and mAb has proved to be effective against acute lymphocytic leukemia, acute myeloid leukemia, and leiomyosarcoma in mouse models. At present, a phase I clinical trial is ongoing aimed at studying CD47 inhibition in patients with UC and acute myeloid leukemia [32].

*Tumor necrosis factor receptors* (TNF-R), such as glucocorticoid-induced TNF-R (GITR, CD357), CD27, OX40 (CD134) and 4-1BB (CD137), are a family of proteins responsible for transducing additional co-stimulatory signals required to activate T lymphocytes that participate in eliminating cancer cells. In order to use this important signaling cascade, agonistic mAb and specific ligand complexes were developed capable of interacting with TNF-R and initiating further reactions [33]. Varlilumab, a human IgG1 agonistic mAb targeting CD27 (aCD27), has already successfully completed a phase I clinical trial. Experimental studies in mice have shown that its combination with antiPD-1 leads to 100% elimination of tumor cells due to the ability of aCD27 to stimulate cytotoxic T lymphocytes. The response to varlilumab was stronger than to a combination therapy with aPD-1/aCTLA-4 [33].

*The colony stimulating factor 1 receptor* (CSF1R) is a cell surface receptor expressed by macrophages and monocytes. CSF1R signaling activates macrophages (M) and promotes their transformation into phenotype M2 (M2 macrophages participate in type 2 T-helper-mediated immune reactions and stimulate cell proliferation and angiogenesis). CSF1R blockade or depletion of cells expressing CSF1R facilitate macrophage differentiation into type M1; M1 macrophages stimulate the production of proinflammatory cytokines and cytotoxic molecules and are also involved in type 1 T-helper immune reactions. The efficacy of CSF1R inhibition has been demonstrated in the experiments conducted in animals [34]. Currently, a combination of a CSF1R inhibitor Plexxikon (PLX3397) and pembrolizumab is undergoing phase I and II clinical trials in patients with progressing malignancies. A few companies have synthesized mAb targeting CSF1R (FPA008, Five Prime Therapeutics; Emactuzumab, Hoffmann-La Roche).

Successful immunotherapy is impossible without understanding the processes occurring in the tumor microenvironment. The scope of tumor infiltration by T cells is a crucial factor, which can be estimated by studying macrophages, vascular endothelial cells, fibroblasts, and immunosuppressive metabolites, such as kynurenine, in the tumor microenvironment [7].

Tregs are potent *immunosuppressors* present in the tumor microenvironment. Experimental attempts were made to inhibit

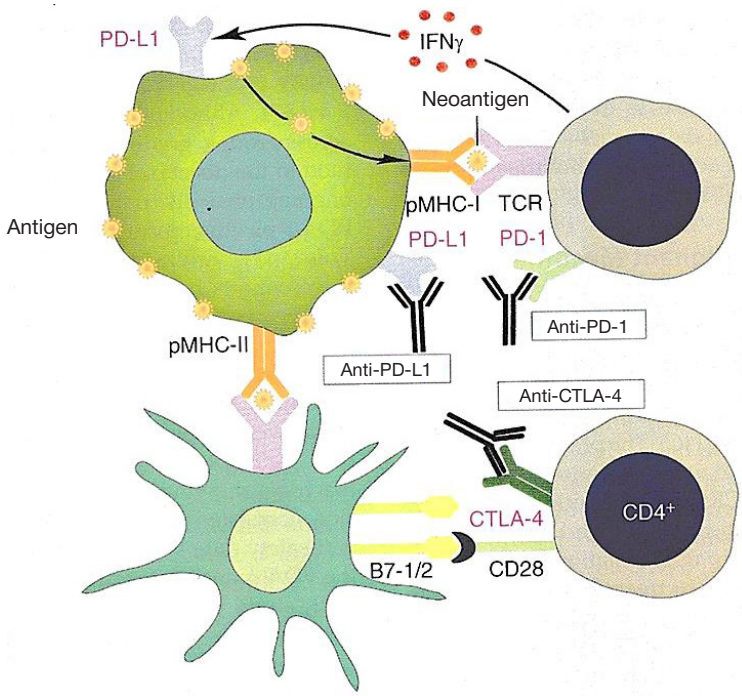


**Fig. 2.** The mechanism of neoantigen recognition and immune checkpoint blockade [42]. Anti-PD-1, anti-PDL-1 and anti-CTLA-4-antibodies block signaling pathways, facilitating neoantigen recognition and T cell activation. CD4+ — T cells expressing cluster of differentiation antigen 4 (CD4); recognizes MHC class II antigens; CD28 — T cells expressing cluster of differentiation antigen 28; CTLA-4 — antigen 4 associated with cytotoxic T lymphocytes; IFN — interferon; PD-L1 — programmed death-ligand 1; PD-1 — programmed cell death 1 receptor; pMHC — peptide-major histocompatibility complex receptor complementary to TCR; TCR — a T-cell receptor

Tregs by mAb and DC-based vaccines [7]. Tregs accumulate in the blood, ascitic fluid, metastases, and primary tumors. Clinical studies of daclizumab, sorafenib, sunitinib, and imatinib demonstrate that these mAb reduce Treg levels in patients with cancer, correlating with survival rates [7, 8]. A few research teams investigated the inhibitory effect of Tregs in combination with infiltrating myeloid-derived suppressor cells (MDSC) on the immune response to cancer progression in patients with renal cell carcinoma and soft tissue sarcoma [8]. In a preclinical study, MDSC exhibited sensitivity to a TRAIL-receptor 2 (TRAIL-R2) agonist. A phase I clinical trial has shown that TRAIL-R2 (DS-8273a) effectively lowers MDSC levels in 50% of patients with advanced UC, melanoma or hepatocellular carcinoma, but does not affect neutrophils, monocytes and other lymphoid and myeloid populations. A drop in MDSC negatively correlates with relapse-free survival [7, 8].

Low peripheral blood Tregs and a shift in the immune balance towards an effective immune response can be achieved by administering tyrosine kinase inhibitors (sorafenib). In a clinical study, neoadjuvant therapy with sorafenib caused a significant drop in the proportion of tumor-infiltrating Tregs in comparison with patients who did not receive the drug: 17.3% vs 28.1% on average ($p$ = 0.046) [35]. The activity of Tregs in patients with renal cancer, leukemias, and gastrointestinal stromal tumors can be downregulated by daclizumab, sorafenib, sunitinib, and imatinib [36, 37].

Studies of the tumor microenvironment have stressed the role of intercellular adhesion molecules. Poor intercellular adhesion is typical for the majority of epithelial cancers. The key component of intercellular adhesion in epithelial tissue is *E-cadherin*. The loss of its expression is observed in almost 85% of lobular breast carcinomas; besides, its expression is extremely suppressed in esophageal, gastric and hepatocellular carcinomas [38]. Slowly growing and benign tumors preserve normal levels of E-cadherin expression. The suppression or the total loss of E-cadherin correlates with tumor invasiveness, metastatic spread and poor clinical outcome [39].

The discovery of regulatory molecules responsible for preventing the hyperactivation of T lymphocytes and their programmed death has paved the way to an innovative method of targeted immunotherapy called *immune checkpoint blockade* (ICPB). It has already received approval as a standard therapy for many types of cancer. There have been experiments with neoadjuvant and adjuvant ICPB regimens. Tumors with identical histological characteristics demonstrated suppressed the immune system in a variety of different ways. They modulated PD-1 expression or had different levels of infiltrating lymphocytes in their microenvironment [40, 41]. ICPB is used to block a tumor's systems of control and restore the anticancer immune response (Fig. 2). Among immune checkpoint blockers are anti-CTLA-4 (ipilimumab), anti-PD-1 (pembrolizumab and nivolumab) [43] and anti-PD-L1 (avelumab, atezolizumab). All of them have been proved to be highly effective against a number of malignancies, including advanced UC. The success of PD-1 and PD-L1 inhibitors reminds us of the versatility of immunotherapy as a cancer-treating modality. These drugs have become a standard therapeutic option for a few types of malignant tumors.

A combination of standard chemotherapy (CT) and ipilimumab stimulates the activity of $CD4^+$-and $CD8^+$-T-cells, as well as the production of proinflammatory cytokines (IL2, IL12) and GM-CSF [44]. However, since ipilimumab is very toxic, its use in patients with UC is limited. Pembrolizumab has been approved for first- and second-line treatment of metastatic UC, whereas nivolumab is recommended as a second-line therapy after platinum-based CT regimens have been exhausted [9].

Clinical trials show that PD-1 and CTLA-4 pathways have an irregular role in inhibiting the immune response to cancer growth [10, 45]. A combination of nivolumab and ipilimumab has proved to be more effective in patients with metastatic melanoma than monotherapy. In 2016, a combination therapy with these two drugs was approved for inoperable or metastatic melanoma [43]. Durvalumab and avelumab (antiPD-L1 inhibitors) have also been approved for clinical use [46].

Immunotherapy of malignancies with *4-1BB agonists* renders possible *in vivo* tumor elimination [33]. At present, two agonistic mAb against human 4-1BB (a4-1BB) are undergoing clinical trials (urelumab, IgG4 mAb, and utomilumab, IgG2 mAb) [33, 47]. To guide the immune response against tumor cells, a drug (PRS-343) has been developed consisting of agonistic mAb against 4-1BB and mAb against HER2 (trastuzumab) [33].

Another area of research looks at the possibility of inducing an antitumor immune response by *activating the genes involved in innate immunity signaling via STING* (a transmembrane protein 173 that contributes to immune response modulation by stimulating production of type I interferon, IFN-I) and TLR. In a preclinical trial, TLR boosted the secretion of cytokines inducing the immune response mediated by Langerhans cells, macrophages and lymphocytes, and stimulated proliferation of T cells via a protein kinase pathway. At the same time, TLR agonists inhibit tumor growth, averting the suppression of the anticancer immune response in the tumor microenvironment [48]. For example, Imiquimod (a TLR agonist) is reported to be effective against glioma, melanoma and breast cancer in 72% of patients [49]. In addition, some authors suggest that TLR agonists can be used as adjuvants for cancer vaccines [18, 49–51].

*The T-cell chimeric antigen receptor* (CAR) has recently been in the focus of scientific research. It is a membrane receptor capable of binding to a specific cancer antigen and containing an intracellular domain that activates a T cell in the presence of this antigen [52]. CAR-T cells can initiate co-stimulatory signaling (for CD28 or CD137) that activates T cells and entails a sustained immune response [53].

Another strategy is a *combination immunotherapy* involving the use of *oncolytic viruses*, such CD40L- or 4-1BBL-expressing adenoviruses. This type of treatment is intended to stimulate immunity against cancer by delivering specific agents into the tumor microenvironment that are capable of triggering T-cell reactions, alone or in combination with other immunologic drugs [54]. However, design of such combinations targeting the cells of a particular tumor poses a certain challenge.

A number of therapeutic combinations are being tested at the moment in prostate cancer and sarcoma models, including an agonistic mAb against OX40 with atezolizumab (aPD-L1); an agonistic mAb against OX40 with bevacizumab (the latter is a recombinant humanized anti-VEGF mAb); and an agonistic mAb against (PF-04518600) with an agonistic mAb against a4-1BB (NCT02315066) [55]. Avelumab (mAb against aPD-L1) can be used in a range of combinations, including avelumab + 4-1BB agonist (PF-05082566); avelumab + an agonistic mAb against OX40 (PF-04518600); avelumab + mAb against colony stimulating factor 1 (PD 0360324); Avelumab + mAb against 4-1BB and mAb against OX40 (NCT02554812). The combination therapy with mAb against OX40/CTLA-4 has been shown to improve survival and promote tumor regression [56, 57].

At the moment, there are ongoing phase I clinical trials of the following combination of drugs in patients with stage III/IV melanoma: humanized IgG1 mAb that do not contain aglycosyl (an agonist of the glucocorticoid-induced tumor necrosis factor receptor, GITR) + nivolumab or ipilimumab or both drugs [58].

GR-MD-02 is a constituent of another interesting therapeutic combination. It is a drug that specifically inhibits *Galectin-3*. Galectin-3 is a marker of tumor transformation that participates in the regulation of all processes involved in tumor progression. It is active in many different cancers, and its expression levels correlate with a tumor's metastatic potential and poor clinical prognosis. Besides, Galectin-3 can have a role in immune suppression. Preclinical trials have shown that GR-MD-02 combined with against OX40 or inhibiting checkpoints improves survival and causes tumor regression, as compared to the regimens based solely on immunotherapy [56]. These findings inspired a phase I clinical trial in patients with advanced cancer in which a combination of a GR-MD-02 inhibitor and ipilimumab or pembrolizumab was tested (NCT02117362, NCT02575404) [33].

*Indoleamine 2,3-dioxigenase 1* (IDO1) is a promising therapeutic target. It causes T-cell proliferation to decline and promotes neovascularization, disrupting interferon gamma effects [59]. Currently, IDO1 inhibitors are being tested in combination with other immunomodulating agents; for example, a phase III trial of a PD-1 inhibitor (pembrolizumab) is being carried out in patients with melanoma [60].

Advanced cancer is normally associated with EGFR hyperexpression by cancer cells. The efficacy of cetuximab (C225) has been tested in phase II and III clinical trials. Cetuximab is a recombinant chimeric mAb exhibiting high specificity to an extracellular EGFR domain and capable of competing with natural ligands (EGF, TGF-a) for binding to the receptor. The drug was synthesized from a mouse mAb (M225) attached to a fragment of human IgG1 to reduce immunogenicity. This drug used alone or in combination with cisplatin was then tested for efficacy. Two of 52 patients with progressing head and neck tumors achieved partial remissions [61].

Although most patients benefit from targeted therapy, some of them fail to achieve a full therapeutic response. This dictates the need for developing other, more effective treatment modalities. The use of *cancer vaccines and oncolytic viruses* that boost antitumor immune response by facilitating the presentation of antigens to T cells is an innovative approach that can improve the efficacy of cancer treatment [33, 54].

In animal models, *whole-cell vaccines*, which are essentially cancer cells deprived of the ability to divide, induced a strong anticancer immune response, but their clinical trials were not successful [13, 62, 63].

*Peptide vaccines* based on the synthetic Survivin peptide (a complex of specific tumor-associated peptides and NY-ESO-1 + GM-CSF with a BCG-NSIT adjuvant) may also hold some promise. A few studies have shown that a personalized peptide vaccine (PPV) consisting of a combination of 4 peptides improves survival rates twofold [54, 63].

Attempts are being made to combine *DC vaccines with co-stimulatory agonists of anti OX40 or with mAb against anti 4-1BB*. The preliminary results of the studies conducted in mice demonstrate that combination vaccines ensure a better immune response in comparison with DC -based vaccines in transgenic Her-2/neu animals, leading to the complete elimination of the tumor [33, 64–67].

A phase II clinical trial of a DC-based Lapuleucel-T vaccine is ongoing. It is seeking to assess survival, safety and immune reactions in patients at a high risk for relapse (hypersecretion of HER-2 + bladder antigen UBC, NCT01353222) [68].

*Autologous DC vaccines* can initiate and enhance antigen-specific tumor reactions by activating both Th and cytotoxic T cells [67]. This approach is being actively studied in Russia in patients with advanced cancer who have no other therapeutic options left [4, 5, 69]. Autologous DC vaccines have already completed or are now undergoing phase II trials.

Because malignancies are sensitive to immunotherapy, *cancer vaccines* are seen as a promising therapeutic option [70]. Some of them are based on a *cancer-testis antigen* (NY-ESO-1), the *synthetic Survivin peptide* or its combination with IFN-α, and DC with supplemented blockade of the co-stimulatory B7-H1(PD-L1) molecule [71]. However, all those studies are few or still in the planning stage or have no clinical application yet.

*Nanomedicine* offers unique approaches to treating cancer with novel chemotherapy and immunotherapy drugs. Nanoparticles (NP) have been proposed to increase the therapeutic efficacy and mitigate the adverse effects of CT by directing chemotherapy agents towards cancer tissue and improving their bioavailability [72, 73].

*Immunoswitch* is a new technology, in which mAb and agonistic mAb bind to nanoparticles [73]. Immunoswitch NP are coated with two different antibodies capable of blocking the signal that inhibits the PD-L1 immune checkpoint and stimulating T cells via 4-1BB costimulatory pathways. *In vivo* research studies have demonstrated a significant delay in tumor growth and improved survival following administration of immunoswitch NP in mouse melanoma and colon cancer models in comparison with treatment with soluble antibodies and NP complexed with antibody inhibitors or stimulators. Immunoswitch NP are reported to improve the density, specificity and function of tumor-infiltrating cytotoxic lymphocytes [73].

Functionalized with specific mAb, NP can be used as a platform for targeted drug delivery to tumor cells, improving therapeutic outcomes and minimizing the side effects of treatment [73–76].

Nevertheless, molecular and cellular mechanisms underlying immune tolerance to tumors remain understudied. Today, NK cells are new promising therapeutic candidates, although their use is now limited to cases of hematological cancer. An experiment conducted in transgenic mice has revealed that natural killers can bind to a platelet-derived growth factor DD (PDGF-DD) via a NKp44 receptor and subsequently halt tumor growth [77].

*Gene therapy*, including CRISPR-technologies for genome editing, is another new and vigorously developing approach to anticancer therapy.

## CONCLUSIONS

Precision (personalized) oncology is becoming a reality. Targeted therapy, nanotechnologies, immune checkpoint blockers, anticancer vaccines, molecular genetic research and the search for new promising targets and ways to overcome immunological tolerance will facilitate the diagnosis and treatment of cancer in its early stages, help oncologists to tailor a therapy to a specific patient and ultimately improve the patient's quality of life. Precision medicine based on a multidisciplinary approach to diagnosis, treatment and rehabilitation of cancer patients is gradually winning over conventional approaches. To benefit the patient, the advances of oncoimmunology should be used in combination with chemo- and immunotherapies. The most effective therapeutic options should be offered first, otherwise the patient will lose the chance to receive any treatment if all other therapies have been exhausted. Clinical efficacy (total survival rates, relapse-free survival and control of the disease), safety (toxicity control), efficiency, and the quality of life are essential components of successful therapy. Treatment strategies vary depending on cancer localization and its biological characteristics.

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