**Targeted Anticancer Therapy as a New Strategy of Treatment. Current and Future Scenary**

**Oliva B\*, Gómez NA and Fernández JR**

Pharmaceutical Department, Laboratory of Tumor Biology, Center for Genetic Engineering and Biotechnology (CIGB), P.O. Box 6162, Habana 10600, Cuba

**\*Corresponding author**: Brizaida Oliva Arguelles, Pharmaceutical Department, Laboratory of Tumor Biology, Center for Genetic Engineering and Biotechnology, Cubanacan, P.O. Box 6162, Habana CP 10600, Cuba. E-mail: [brizaida.oliva@cigb.edu.cu](mailto:brizaida.oliva@cigb.edu.cu), [brizaida.oliva@gmail.com](mailto:brizaida.oliva@gmail.com)

**Abstract:** Cancer is a disease with high incidence. Other therapies as surgery and radiotherapy is also used in the treatment of this disease. However, the effect adverse and the metastasis limited the use of these therapies. Target anticancer Targeted cancer treatment is an attractive approach where drugs or other substances which targets specific molecules to block the growth and spread of cancer cells. Identification of targets is essential for a successful development of molecular targeted therapies in cancer. This review summarizes current knowledge on the molecules target and the up to date of drugs in clinic assays as Targeted Anticancer Therapies.

**Keywords: Cancer; therapeutics; drugs; oncogene addiction; pharmacology; immunotherapy; small inhibitor**

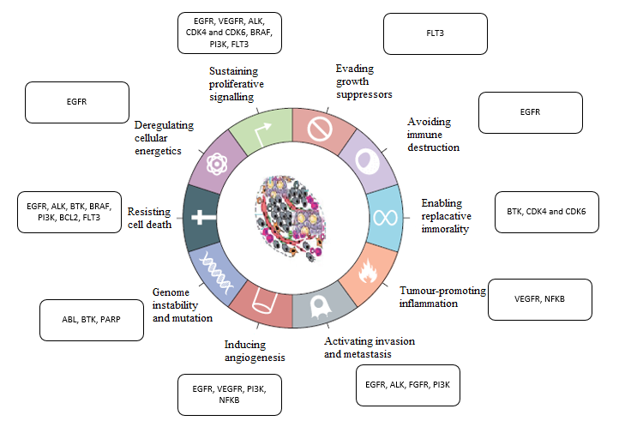
**Abbreviations:** AKT, ribosomal protein S6 kinase beta-1; 4EBP1, eukaryotic translation initiation factor binding protein 1; HER2, human epidermal growth factor receptor 2; DLT, dose limiting toxicity; PFS, progression-free survival; HIF, hypoxia-induced factor; NF-ΚB, nuclear transcription factor kappa B; CAFs, Cancer-associated fibroblasts; Bcl-2, B-cell lynphoma 2; Mcl-1 Myeloid, cell leukemia 1; Bcl-xL, B-cell lymphoma XL; Bak Bcl-2, homologous antagonist/killer; lncRNAs, Long non-coding RNA; miRNAs, Micro RNA; ADCC, Antibody-Dependent Cellular Cytotoxicity; ADCP, Antibody-Dependent Cellular Phagocytosis; PARP, Poly-(ADP-ribose) polymerase; DNA, Deoxyribonucleic acid; BRCA, Breast cancer; ATP, Adenosine 5’-triphosphate; ROS, Reactive oxygen species; MTH1, MutT-type nudix hydrolase 1; NUDT1, Nudix hydrolase 1; TAMs, tumour-associated; MDSC, myeloid-derived suppressor cells; STAT1, Signal Transducer and Activator of Transcription 1; STAT6, Signal Transducer and Activator of Transcription 6

**Cancer Disease and Treatment**

Cancer is currently one of the main causes of death worldwide and it is estimated that the number of deaths will reach 13.1 million in 2030. The incidence and mortality provided of website GLOBOCAN estimates 2.3 million new cases (11.7% of total case) of breast cancer, lung (11.4%), colorectal (10.0 %), prostate (7.3%), and stomach (5.6%) cancers. Therapeutic strategies are determined by early diagnosis, which guarantees surgery as the best therapeutic option, as well as the application of chemotherapy and/or radiotherapy regimens in more advanced stages of the disease. Despite the existence of multiple therapeutic modalities for the treatment of this disease, they have only resulted in discreet increases in survival. On the other hand, the toxicity events associated with the use of conventional chemotherapy regimens deteriorate the quality of life of the patient, constituting a limitation for its use, in addition to the development of resistance, mutagenicity and teratogenicity [1].

**Target Anticancer Therapy as a new alternative to treatment of cancer**

New findings in the study of cancer biology and the discovery of new genes or proteins related to cancer cell survival have allowed the identification of targets for the development of new drugs in cancer therapy. These target molecules are involved in important signaling pathways for the cancer cell: apoptosis, tumor growth, angiogenesis, (receptors, growth factors, kinase cascades). The objective of this new therapy is to affect specific targets that affect excessive cell growth of cancer and prevent the formation of metastases [2]. In addition, the main objective of these drugs is to reduce unwanted effects in non-tumor tissues and improve the patient's quality of life. Figure 1 shows the cancer hallmark-related proteins or genes that are targets of drugs that are from preclinical studies, clinical studies, or that are approved for cancer therapy [3, 4,5].



**Figure 1 Molecular targets related with hallmarks of cancer**

**Inflamatory Scenary**

There is a strong relationship between inflammation and cancer. The tumor microenvironment is an important component in the cancer niche and contributes to the activation of genes related to angiogenesis, cell crime, modulation of genes that are linked to cancer progression, and cell growth. During an inflammatory process, the cells of the immune system predominate and are the main component in the tumor. The tumor-associated macrophage has been the major component of the leukocyte infiltrate. These cells secrete pro-inflammatory cytokines that stimulate other cells of the immune system and strengthen the inflammatory microenvironment [6]. Interferon, Tumor Necrosis Factor, IL6 and IL17 are some of the cytokines that also cause the activation of transcription factors with NFkB, STAT1, STAT6 that regulate genes involved in apoptosis, metastasis, cell proliferation. On the other hand, as an art of the inflammatory microenvironment, cancer stem cells are an essential component in the tumor, since they are capable of maintaining the growth and differentiation properties of the cells. Therefore, its presence in the tumor is related to tumorigenesis, metastasis and tumor progression. The most abundant lymphoid cells in the tumor are TAM and MDSC, whose presence in the tumor favors tumor immunosuppression and strengthens the cancer stem cell phenotype. All these factors of the tumor environment are targets for cancer therapies. These strategies could eliminate the functions of the TAMs, reactivate the antitumor functions of the macrophage (ADCC, ADCP, and M1 like phenotypes) and the elimination of cancer stem cells [8], a new quote from the photo there is a strong relationship between inflammation and cancer. The tumor microenvironment is an important component in the cancer niche and contributes to the activation of genes related to angiogenesis, cell crime, modulation of genes that are linked to cancer progression, and cell growth. During an inflammatory process, immune cells predominate and are the main component in the tumor. The tumor-associated macrophage has been the major component of the leukocyte infiltrate. These cells secrete proinflammatory cytokines that stimulate other cells of the immune system and strengthen the inflammatory microenvironment [6]. Interferon, Tumor Necrosis Factor, IL6 and IL17 are some of the cytokines that also cause the activation of transcription factors with NFkB, STAT1, STAT6 that regulate genes involved in apoptosis, metastasis, cell proliferation. On the other hand, as an art of the inflammatory microenvironment, cancer stem cells are an essential component in the tumor, since they are capable of maintaining the growth and differentiation properties of the cells. Therefore, its presence in the tumor is related to tumorigenesis, metastasis and tumor progression. The most abundant lymphoid cells in the tumor are TAM and MDSC, whose presence in the tumor favors tumor immunosuppression and strengthens the cancer stem cell phenotype. all these factors of the tumor environment are targets for cancer therapies. These strategies could eliminate the functions of the TAMs, reactivate the antitumor functions of the macrophage (ADCC, ADCP, and M1 like phenotypes) and the elimination of cancer stem cells [8], new photo quote

**Cancer-associated fibroblasts**

The tumor microenvironment is made up of cells of the immune system (macrophages, lymphocytes), tumor cells, stromal cells (endothelial cells, stromal fibroblasts) and non-cellular components such as hyaluronan, fibronectin, laminin, among others. These components stimulate cancer cell diversity, increase drug resistance, progression and metastasis. Cancer-associated fibroblasts (CAFs) play a very important role in the interaction of cancer cells with the microenvironment, since it favors the reduction of apoptosis, increases the proliferation, migration and survival of the cancer cell. Therefore, CAFs is an atractive target to anticancer therapies [9].

**Apoptosis and Metabolic Stress**

Mitochondrial apoptosis is a cascade of signals whose end is the death of the cell. Therefore, it is a highly regulated cascade to maintain the homeostasis of the organism. A number of proteins positively and negatively regulate this pathway (pro-apoptotic and antiapoptotic proteins). Cancer cells escape cell apoptosis through low expression of pro-apoptotic proteins or overexpression of anti-apoptotic proteins or transcription factors that favor the activation of genes that keep this pathway inhibited. The Bcl2 protein is the most frequently overexpressed protein in tumors, being highly important in leukemia due to its function in leukogenesis. On the other hand, Mcl-1 is overexpressed in acute myeloid leukemia and its function is very important for the development and maintenance of B and T lymphocytes, it is also of great importance in the survival of leukemia cells, being very important in AML. Therefore, both Bcl2 and Mcl-1 are attractive targets for cancer therapy in AML. Due to its role in tumors, the expression of these proteins exists in several drugs in preclinical studies [11]

On the other hand, the fatty acid synthesis, glutamine metabolism and aerobic glycolysis are other pathways that are failing in cancer cells to increase energy consumption. These aspects of metabolism favor cell growth, survival and exacerbated growth [12, 13,14]. Various mechanisms of the normal cell, the cancer cell regulates, such as glucose transporters, increases glycolysis, lipid metabolism among other pathways to provide NADPH and other molecules that participate in aerobic glycolysis. In addition, a hypoxic niche originates in the tumor, in which glucose transporters and the enzymes that participate in glycolysis are exacerbated. All these irregularities in glucose metabolism allow the cancer cell to evade apoptosis, favor metastasis and resistance to therapies. For this reason, the glycolysis pathway and the factors that favor this pathway are targets for the development of drugs against cancer [15, 16, 17,18] .

**BRCA–PARP**

Healthy cells in the human body managed to cope with genomic mutations through different mechanisms of repairing damage or variations in the DNA molecule. These mechanisms are non-homologous end joining (NHEJ), homologous recombination (HR), and base excision repair. Cells became more dependent on some of these pathways for their survival once one of them loses its activity. Under this principle, specific therapies have been developed that take into account synthetic lethality in two DNA repair pathways. This treatment is currently being considered in BRCA-deficient breast and ovarian cancer. Treatment consists of the administration of inhibitors of the enzyme (poly ADP ribose polymerase) that cancel the NHEJ pathway. Therefore, tumor cells with DNA damage will resort to alternative repair mechanisms, in this case BRCA1 or BRCA2. By not finding these genes available in these types of cancer, an accumulation of unrepaired DNA will occur and this will ultimately lead to specific cell death in these tumors [19].

**Oxidative stress**

Oxidative stress is a predominant feature in cancer cells and not so in normal cells [20]. The main cause of this stress may be due to oncogenic signaling, which leads to a greater generation of reactive oxygen species (ROS) [21, 22]. DNA mutations that cause genomic instability are part of the damage caused by ROS to cell biomolecules [23]. Previous studies have shown the important role that the removal of oxidized nucleotides from available free nucleotides plays in the survival of tumor cells. The NVDT1 gene participates in reducing the damage to free nucleotides caused by oxidative stress. It was shown that the activity of this gene is essential for the survival of these cells with abnormal growth. This fact was verified with gene inhibitors, which caused the selective death of cancer cells. An alternative for cancer therapy is the induction of high levels of ROS from the inhibition of antioxidant proteins. This treatment model has obtained positive results in the preclinical setting where agents such as piperlongumine, dichloroacetate and beta-phenylethyl isothiocyanate have shown potent antitumor effects. These studies show that a good strategy to fight cancer may be the imbalance in the levels of oxidative stress [24, 25].

**Target Anticancer Agents**

Several types of cancer affect the world population. For the treatment of this disease, a group of drugs for the treatment with targeted activity has been developed and is being investigated. These are defined and grouped as monoclonal antibodies, small molecules, and gene therapy [26]. The promotion of cell death, the interruption of the cell division process, and the inhibition of signals that participate in the growth and development of cancer cells are some of the events that are part of the mechanism of action of these drugs with antitumor activity [1].

**Immunotherapeutic drugs**

An alternative of great value in targeted molecular therapy against cancer are monoclonal antibodies. These perform their function through direct and indirect mechanisms. The direct mechanism is due to the effect of cell death by the binding of monoclonal antibodies conjugated to a drug with antitumor activity to biological structures such as cell receptors and membrane-bound proteins in the tumor microenvironment [27]. On the other hand, the indirect mechanism is based on the effector activity of specific cells for this purpose such as NK killer cells and the Complement System, as well as through the phagocytosis process, after a group of cellular signals given by the interaction of cell-specific antigens with monoclonal antibodies [28]. Several monoclonal antibodies have been registered and approved for the treatment of cancer and others are still in clinical studies (Table 1).

**Table 1 List of monoclonal antibodies that act on critical cancer targets**

|  |  |  |  |
| --- | --- | --- | --- |
| Monoclonal  Antobody | Targets | Cancer types | References |
| Brentuximab vedotin | CD30 | Hodgkin’s lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL) | [29] |
| Adotrastuzumab  emtansine | HER2+ | HER2-positive metastatic breast cancer (MBC) | [30] |
| Y-Ibritumomab  tiuxetan | CD20 | non-Hodgkin’s lymphoma (NHL) | [31,29] |
| Bevacizumab | VEGF | Metastatic colorectal cancer (mCRC), nonsquamous, nonsmall  cell lung cancer (NSCLC) glioblastoma, and metastatic renal cell carcinoma. | [32] |
| Alemtuzumab | CD52 | Chronic lymphocytic leukemia (CLL) | [33] |
| Ofatumumab | CD20 | Chronic lymphocytic  leukemia (CLL) | [34] |
| Nivolumab | PD-L1 | NSCLC, RCC, hepatocellular carcinoma (HCC) | [35] |
| Gemtuzumab  ozogamicin | CD33 | Acute myeloid leukemia | [36] |

\*CD, cluster of differentiation; HER2, human epidermal growth factor receptor 2; PD-L1, Programmed death-ligand

Trastuzumab mertansine (T-DM1) is an antibody-drug conjugate consisting of trastuzumab bound to the cytotoxic agent mertansine (DM1). This drug works by interrupting the cellular development of cancer cells by interacting with HER2, a human epidermal growth factor, then mertansine is internalized inside the cells and induces their death by binding to tubulin and inhibiting the assembly of structural microtubules. Clinical studies have demonstrated the effectiveness of this therapeutic agent in comparison with combination therapies of other drugs such as lapatinib and capecitabine; where T-DM1 has an improvement of 5.8 months in patient survival. For treatment with T-DM1, those treated must have previously received therapy for the disease [37].

Cetuximab is a monoclonal antibody against cancer that works by blocking the epidermal growth factor receptor (EGFR), thereby interrupting cell signaling that induces its proliferation and slows down tumor growth. It is indicated as therapy for head and neck squamous cell carcinoma (SCC) in conjunction with radiation therapy; Metastatic head and neck SCC plus 5-fluorouracil. EGFR mutations and overexpression are common in patients with colorectal cancer (CRC). This monoclonal antibody in clinical studies showed a significant antitumor effect in people with CRC as single therapy with an objective response rate of 10.8%, a progression-free survival of 1.5 months, and an overall survival of 6.9 months. While treatment together with irinotecan resulted in a 22.9% response rate, 4.6 months of stability until disease progression, and 8.6 months of overall survival [38]. In other clinical studies for patients with CRC, cetuximab was applied as a combination treatment with FOLFIRI; the latter is a chemotherapy that includes folinic acid, fluorouracil and irinotecan. These trials performed better in terms of disease progression than FOLFIRI as single therapy [39].

Panitumumab is a humanized IgG 2 type monoclonal antibody. It works by binding to EGFR and blocking its activity during cell growth. Its mechanism of action is therefore similar to that of cetiximab. This medicine is indicated in the CCR as main therapy together with FOLFOX; the latter is the combination of the drugs folinic acid, fluorouracil, and oxaliplatin. In addition, it is used as a treatment in pancreatic cancer as second-line therapy and in gastric cancer as palliative therapy [40].

**Small molecule drugs**

Small molecules are defined as relatively low molecular weight compounds (<900 daltons) that can penetrate cells to target specific proteins within cells [41]. Many known small molecule inhibitors focus on inactivating kinases and disrupting signaling pathways that are dysregulated during carcinogenesis. In addition, small molecules can be used to target proteasomes, cyclin-dependent kinases (CDKs), and inhibitors of poly ADP-ribose polymerase (PARP) to activate the cell cycle checkpoint, trigger apoptosis, and coordinate cell production. DNA repair [42] (Table 2).

**Table 2 List of FDA approved drugs used in the clinic**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| Drugs | Targets | Cancer types | References |
| Gefitinib | EGFR | Non-small cell lung cancer (NSCLC) | [4]3 |
| Lapatinib | EGFR/ERBB2 | EGFR/ERBB2 ERBB2-positive breast cancer | [43] |
| Sorafenib | VEGFR kinase, RAF, PDGFR | Renal cancer, Hepatocellular carcinoma | [43,44] |
| Crizotinib | ALK kinase | NSCLC | [45] |
| Sunitinib | VEGF, PDGFR, SCF | Gastrointestinal stromal tumour (GIST)  Advanced renal cell carcinoma (RCC)  Advanced pancreatic neuroendocrine tumours  (pNET) | [46] |
| Pazopanib | VEGFR, PDGFR, FGFR,  SCF, Itk, Lck | Advanced soft tissue sarcoma (STT),  Advanced renal cell carcinoma (RCC) | [26] |
| Imatinib | PDGFR, ABL kinase | Chronic mylogenous leukemia, Gastrointestinal stromal tumours | [47] |
| Acalabrutinib  Ibrutinib | BTK inhibitor | Mantle cell lymphoma  Chronic lymphocytic leukemia (CLL) | [48] |
| Carfilzomib  Bortezomib  Ixazomib | Proteasome | Multiple Myeloma | [49] |
| Ribociclib  Palbociclib | CDK4, CDK6 | Metastatic breast cancer | [50,51] |
| Rucaparib | PARP | BRCA-positive ovarian cancer | [52] |
| Olaparib | PARP | gBRCA-mutated advanced ovarian cancer | [53] |
| Niraparib | PARP | Epithelial ovarian, fallopian tube, or primary peritoneal cancer | [54] |
| Alectinib  Brigatinib | ALK | Non-small-lung cell carcinoma | [55,56] |
| Encorafenib | BRAF | Melanoma | [57] |
| Alpelisib | PI3K | Breast cancer | [58] |
| Duvelisib  Idelalisib | PI3K | Chronic lymphocytic leukemia and small lymphocytic lymphoma, follicular lymphoma | [59,60] |
| Venetoclax | BCL2 | Chronic myeloid leukaemia, acute myeloid leukaemia | [61] |
| Afatinib | EGFR | Non-small-lung cell carcinoma | [62] |
| Erlotinib | EGFR | Non-small-lung cell carcinoma, pancreatic cancer | [63] |
| Midostaurin | FLT3 | Acute myeloid leukaemia | [64] |
| Talazoparib | PARP1 and PARP2 | Breast cancer | [65] |
| Cabozantinib | VEGFR | Medullary thyroid, hepatocellular carcinoma, and renal cell cancer | [66] |
| CIGB552 peptide | NFKB | Advanced solid tumors | [67] |
| BEZ235 | PI3K | Melanoma, breast, and colorectal cancer and  sarcoma | [68] |

\*EGFR, epidermal growth factor receptor; ERBB, VEGFR, endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptors; SCF, stem-cell factor receptor; ALK, anaplastic lymphoma kinase; FGFR, Fibroblast growth factor receptors; Itk, Interleukin-2 receptor-inducible T-cell kinase; Lck, Leukocyte-specific protein tyrosine kinase; BTK, Bruton's tyrosine kinase; BRCA, breast cancer gene; CDK, Cyclin-dependent kinases; PARP, Poly (ADP-ribose) polymerase; BRAF, gene that codes for the receptor for Epidermal Growth Factor; PI3K, phosphoinositol 3-kinase; FLT3, tyrosine kinase factor 3 gene; BCL2, B-cell lymphoma 2

One of the critical pathways in cancer is the phosphatidylinositol 3-kinase (PI3K) signaling pathway that has an impact on survival, growth, metabolism, motility, and cancer progression [69]. The PI3K family catalyzes the phosphorylation of phosphatidylinositols at its third position and is organized into class I, class II, and class III. Only class IA signaling changes are involved in human cancers [70]. Dactolisib, also known as BEZ235, is a drug with an antitumor effect that acts as a specific inhibitor of PI3K and TORC1/2. This intervenes in the G1 phase of the cell cycle, affecting consequently the processes of cell proliferation; furthermore, it inhibits the activity of AKT, S6K and 4EBP1. Dactolisib is indicated to combat breast and colorectal cancer. This therapeutic agent has been evaluated in phase I and II clinical trials with patients presenting with advanced cancer. Therapy in the dactolisib trials was combined with other drugs such as trastuzumab and paclitaxel [71]. Specifically, in a phase IB study in 15 patients with breast cancer, dactolisib was administered in combination with trastuzumab, the results were a tolerable treatment for the patients, and 40% of them managed to maintain the disease stable [68].

One of the most attractive biological targets for the development of new antitumor agents is the epidermal growth factor receptor. The epidermal growth factor binds to its receptor, favoring the formation of dimers and cell signals through the enzyme tyrosine kinase. This mechanism involves important events such as cell survival and proliferation, and metastasis development of cancer cells [72]. Afatinib is an oral drug that is a specific EGFR inhibitor. This drug has been evaluated in conjunction with pemetrexed in people with lung adenocarcinoma in phase III clinical trials. In relation to the results in comparison with standard chemotherapy, a greater progression-free survival was evidenced in treatment with afatinib. Another drug that acts on this pathway is lapatinib, indicated for breast cancer with an overexpression of HER2, a growth receptor. This treatment is applied together with capecitabine. Cetuximab, panitumumab, and erlotinib are other drugs with antitumor activity that target EGFR as their biological target [73].

Anaplastic lymphoma kinase is a protein involved in cell cycle control. It originates from the anaplastic lymphoma kinase (ALK) gene. This gene presents modifications in some cancers such as non-small cell lung cancer. Several drugs have been developed that inhibit ALK. Crizotinib is one of them and as the main treatment during therapy, it presented less toxicity and higher progression-free survival compared to chemotherapy. Ceritinib is another ALK inhibitor that has shown greater antitumor effect in clinical trials than crizotinib. This type of treatment is proposed to patients after they have been previously treated with crizotinib. In phase I clinical studies, the objective response rate was 58% and progression-free survival of 7 months. Ongoing studies are comparing ceritinib treatment with chemotherapy in people with non-small cell lung cancer. Others are investigating ceritinib as a single therapy in bile duct and thyroid cancer. Another ALK inhibitor is alictinib, a second-generation drug that has been evaluated in phase I/II clinical trials in treatment-naïve patients with non-small cell lung cancer; the results of these studies were encouraging with a response rate of 93.5% [74].

In the relentless search for an effective therapy against cancer, antitumor peptides have become attractive agents due to their high specificity, small molecular weight, and low tissue toxicity relative to traditional therapies. CIGB552 is a second-generation synthetic peptide with antitumor activity that arose from structural modifications to the L-2 peptide. The latter owes its origin to changes made with the aim of obtaining greater anticancer activity in the primary structure of the CIGB550 peptide designed from the 31-52 sequence of a protein from the limulus polyfermous horseshoe crab. The anticancer peptide CIGB-552 interacts with the intracellular protein COMMD1 and increases its protein levels in tumor cells. Upregulation of the COMMD1 protein supports the ubiquitination and degradation of NF-κB, a transcription factor that stimulates the expression of oncogenes, angiogenesis, and cell proliferation proteins [75]. COMMD1 also regulates HIF-1, which has a key role in cell survival in areas of hypoxia, a common feature of tumors [76]. In preclinical studies of this drug, it’s in vitro cytotoxicity has been demonstrated in several cell lines of colon cancer and lung cancer [77,78]. In vivo antitumor activity was also demonstrated in a mouse model inducing solid tumors of carcinoma of murine colon CT-26 and HT-29 originating in the human colon [79], and in dog solid tumor models with evidence of regression in tumor size [80]. CIGB552 is already in the stage of clinical studies, a phase I clinical trial was carried out where safety, pharmacokinetic profile, evaluation of CD4+ and CD8+ lymphocytes and preliminary activity in patients with advanced tumors were evaluated. Stable disease was observed in a significant number of patients, including two metastatic soft sarcomas. CIGB-552 at a dose of 4.7 mg was defined to be well tolerated with no significant adverse effects and appeared to provide some clinical benefit [67]. Studies of the antiproliferative activity of the peptide and in combination with other traditional chemotherapeutic drugs in lung cancer cells were also carried out. CIGB552 and cisplatin were evaluated as pretreatment and concomitantly at different concentrations. These assays were performed in the NCI-H460, A549 cell line and in mouse models of lung cancer. The results showed an effective antitumor response with the drug combination, without adverse effects and signs of deterioration.

Target-directed therapy is emerging as an alternative for cancer treatment. Researchers and clinicians must work together for the development of novel, tumor-selective and effective drugs. Combination therapy It has become the most effective modality for the treatment of cancer. Targeted drugs and standard therapy allow increasing the effectiveness of the treatments and increasing the survival of the patients. In addition, this form of treatment decreases the adverse effects and the effect on normal cell.

**References**

Xing Ke, Lisong Shen, Molecular targeted therapy of cancer: The progress and future prospect, Frontiers in Laboratory Medicine, Volume 1, Issue 2,2017, Pages 69-75

H.-C. Wu, D.-K. Chang, C.-T. Huang, Targeted therapy for cancer, J. Cancer Mol.2 (2006) 57–66

T.M. Allen, Ligand-targeted therapeutics in anticancer therapy, Nat. Rev. 1807Cancer 2 (2002) 750–763

F. Danhier, O. Feron, V. Préat, to exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drugdelivery, J. Control. Release 148 (2010) 135–146

Pérez-Herrero E, Fernández-Medarde A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. Eur J Pharm Biopharm. 2015 Jun; 93:52-79. doi: 10.1016/j.ejpb.2015.03.018. Epub 2015 Mar 23. PMID: 25813885

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144:646–74; Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008; 454:436–44

Coussens LM, Zitvogel L, Palucka AK. Neutralizing tumor-promoting chronic inflammation: a magic bullet Science. 2013; 339:286–91

Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017 Jul;14(7):399-416

Wu F, Yang J, Liu J, Wang Y, Mu J, Zeng Q, Deng S, Zhou H. Signaling pathways in cancer-associated fibroblasts and targeted therapy for cancer. Signal Transduct Target Ther. 2021 Jun 10;6(1):218. doi: 10.1038/s41392-021-00641-0. PMID: 34108441; PMCID: PMC8190181

Bochtler T, Fröhling S, Krämer A. Role of chromosomal aberrations in clonal diversity and progression of acute myeloid leukemia. Leukemia. 2015; 29:1243–1252. doi: 10.1038/leu.2015.32

Carter JL, Hege K, Yang J, Kalpage HA, Su Y, Edwards H, Hüttemann M, Taub JW, Ge Y. Targeting multiple signaling pathways: the new approach to acute myeloid leukemia therapy. Signal Transduct Target Ther. 2020 Dec 18;5(1):288. doi: 10.1038/s41392-020-00361

Gale RE, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood. 2008; 111:2776–2784. doi: 10.1182/blood-2007-08-109090

Othus M, et al. Declining rates of treatment-related mortality in patients with newly diagnosed AML given ‘intense’ induction regimens: a report from SWOG and MD Anderson. Leukemia. 2014; 28:289–292. doi: 10.1038/leu.2013.176

Zeidan AM, et al. Patterns of care and clinical outcomes with cytarabine-anthracycline induction chemotherapy for AML patients in the United States. Blood Adv. 2020; 4:1615–1623. doi: 10.1182/bloodadvances.2020001728

Bloomfield CD, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. Cancer Res. 1998; 58:4173–4179; Koreth J, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. 2009; 301:2349–2361. doi: 10.1001/jama.2009.813

Koreth J, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. 2009; 301:2349–2361. doi: 10.1001/jama.2009.813

Juliusson G, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood. 2009; 113:4179–4187. doi: 10.1182/blood-2008-07-172007

Dombret H, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood. 2015; 126:291–299. doi: 10.1182/blood-2015-01-621664

Nagel R, Semenova EA, Berns A. Drugging the addict: non-oncogene addiction as a target for cancer therapy. EMBO Rep. 2016 Nov;17(11):1516-1531. doi: 10.15252/embr.201643030. Epub 2016 Oct 4. PMID: 27702988; PMCID: PMC5090709

Tong L, Chuang CC, Wu S, Zuo L (2015) Reactive oxygen species in redox cancer therapy. Cancer Lett 367

Lee AC, Fenster BE, Ito H, Takeda K, Bae NS, Hirai T, Yu ZX, Ferrans VJ, Howard BH, Finkel T (1999) Ras proteins induce senescence by altering the intracellular levels of reactive oxygen species. J Biol Chem 274: 7936 – 7940

Vafa O, Wade M, Kern S, Beeche M, Pandita TK, Hampton GM, Wahl GM (2002) c-Myc can induce DNA damage, increase reactive oxygen species, and mitigate p53 function: a mechanism for oncogene-induced genetic instability. Mol Cell 9: 1031 – 1044

Luo M, He H, Kelley MR, Georgiadis MM (2010) Redox regulation of DNA repair: implications for human health and cancer therapeutic development. Antioxid Redox Signal 12: 1247 – 1269

Trachootham D, Zhou Y, Zhang H, Demizu Y, Chen Z, Pelicano H, ChiaoPJ, Achanta G, Arlinghaus RB, Liu J et al (2006) Selective killing of oncogenically transformed cells through a ROS-mediated mechanism by b- phenylethyl isothiocyanate. Cancer Cell 10: 241 – 252

Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thomp-son R, Lee CT, Lopaschuk GD, Puttagunta L, Bonnet S et al (2007)

National Cancer Institute, 2013. Biological Therapies for Cancer. [WWW Document]. URLhttps://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet

van de Donk, N.W.C.J., Moreau, P., Plesner, T., Palumbo, A., Gay, F., Laubach, J.P., Malavasi, F., Avet- Loiseau, H., Mateos, M.-V., Sonneveld, P., 2015. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma. Blood blood-2015-10-646810

Foltz, I.N., Karow, M., Wasserman, S.M., 2013. Evolution and Emergence of Therapeutic Monoclonal Antibodies. Circulation 127, 2222–2230

van de Donk, N.W.C.J., Dhimolea, E., 2012. Brentuximab vedotin, in: MAbs. Taylor & Francis, pp. 458– 465

Barok, M., Joensuu, H., Isola, J., 2014. Trastuzumab emtansine: mechanisms of action and drug resistance. Breast cancer Res. 16, 209

Jacobs, S.A., 2007. 90Yttrium ibritumomab tiuxetan in the treatment of non-Hodgkin’s lymphoma: current status and future prospects. Biol. targets Ther. 1, 215

Glassman, P.M., Balthasar, J.P., 2014. Mechanistic considerations for the use of monoclonal antibodies for cancer therapy. Cancer Biol. Med. 11, 20

Gallo, P., Centonze, D., Marrosu, M.G., 2017. Alemtuzumab for multiple sclerosis: the new concept of immunomodulation. Mult. Scler. Demyelinating Disord. 2, 7

Zhang, J., Yang, P.L., Gray, N.S., 2009. Targeting cancer with small molecule kinase inhi bitors. Nat. Rev.Cancer 9, 28

Guo, L., Zhang, H., Chen, B., 2017. Nivolumab as programmed death-1 (PD-1) inhibitor for targeted immunotherapy in tumor. J. Cancer 8, 410

Rowe, J.M., Löwenberg, B., 2013. Gemtuzumab ozogamicin in acute myeloid leukemia: a remarkable saga about an active drug. Blood 121, 4838–4841

Mustacchi G, Biganzoli L, Pronzato P, Montemurro F, Dambrosio M, Minelli M, Molteni L, Scaltriti L (2015) HER2-positive metastatic breast cancer: a changing scenario. Crit Rev Oncol/ Hematol. doi: 10.1016/j.critrevonc.2015.02.002

Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351(4):337–345

Licitra L, Storkel S, Kerr KM, Van Cutsem E, Pirker R, Hirsch FR, Vermorken JB, von Heydebreck A, Esser R, Celik I, Ciardiello F (2013) Predictive value of epidermal growth factor receptor expression for first-line chemotherapy plus cetuximab in patients with head and neck and colorectal cancer: analysis of data from the EXTREME and CRYSTAL studies. Eur J Cancer 49(6):1161–1168

Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocakova I, Ruff P, Blasinska-Morawiec M, Smakal M, Canon JL, Rother M, Oliner KS, Tian Y, Xu F, Sidhu R (2014) Final results from PRIME: randomized phase III study of Panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 25(7):1346–1355

Joo, W.D., Visintin, I., Mor, G., 2013. Targeted cancer therapy–Are the days of systemic chemotherapy numbered? Maturitas 76, 308–314

Lheureux, S., Denoyelle, C., Ohashi, P.S., De Bono, J.S., Mottaghy, F.M., 2017. Molecularly targeted therapies in cancer: a guide for the nuclear medicine physician. Eur. J. Nucl. Med. Mol. Imaging 44, 23 41–54

Hoelder, S., Clarke, P.A., Workman, P., 2012. Discovery of small molecule cancer drugs: successes, challenges and opportunities. Mol. Oncol. 6, 155–176

Llovet, J.M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J.-F., de Oliveira, A.C., Santoro, A., Raoul, J.-L., Forner, A., 2008. Sorafenib in advanced hepatocellular carcinoma. N. Engl. J. Med. 359, 378–390

Kwak, E.L., Bang, Y.-J., Camidge, D.R., Shaw, A.T., Solomon, B., Maki, R.G., Ou, S.-H.I., Dezube, B.J., Jänne, P.A., Costa, D.B., 2010. Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer. N. Engl. J. Med. 363, 1693–1703

Lahner, H., Rinke, A., Unger, N., Poeppel, T.D., Kühl, H., Lehmann, N., Führer, D., 2016. Sunitinib efficacy in patients with advanced pNET in clinical practice. Horm. Metab. Res. 48, 575–580

DrugBank, 2017. Imatinib. [WWW Document]. URL <https://www.drugbank.ca/drugs/DB00619>

Mullard A. BTK inhibitors get a boost. Nat Rev Drug Discov. 2017 Nov 28; 16 (12):818

Hideshima T, Qi J, Paranal RM, Tang W, et al. Discovery of selective small-molecule HDAC6 inhibitor for overcoming proteasome inhibitor resistance in multiple myeloma. Proc Natl Acad Sci U S A. 2016 Nov 15;113(46):13162-13167

Beaver, J.A., Amiri-Kordestani, L., Charlab, R., Chen, W., Palmby, T., Tilley, A., Zirkelbach, J.F., Yu, J., Liu, Q., Zhao, L., 2015. FDA Approval: Palbociclib for the Treatment of Postmenopausal Patients with Estrogen Receptor–Positive, HER2-Negative Metastatic Breast Cancer. Clin. Cancer Res. 21, 4760–4766

Tripathy, D., Bardia, A., Sellers, W.R., 2017. Ribociclib (LEE011): mechanism of action and clinical impact of this selective cyclin-dependent kinase 4/6 inhibitor in various solid tumors. Clin. Cancer Res. clincanres. 3157.2016

Balasubramaniam, S., Beaver, J.A., Horton, S, et al, 2017. FDA Approval Summary: Rucaparib for the Treatment of Patients with Deleterious &lt; em&gt; BRCA&lt;/em&gt; Mutation–Associated Advanced Ovarian Cancer. Clin. Cancer Res. 23, 7165

Kim, G., Ison, G., McKee, A.E., Zhang, H., Tang, S., Gwise, T., Sridhara, R., Lee, E., Tzou, A., Philip, R., 2015. FDA approval summary: olaparib monotherapy in patients with deleterious germline BRCAmutated advanced ovarian cancer treated with three or more lines of chemotherapy. Clin. Cancer Res. 21, 4257–4261

Kanjanapan, Y., Lheureux, S., Oza, A.M., 2017. Niraparib for the treatment of ovarian cancer. Expert Opin. Pharmacother. 18, 631–640

Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 2016; 17: 234–42

Kim D-W, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol 2017; 35: 2490–98

Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med 2019; 381: 1632–43

Baselga J, Curigliano G, Martín M, et al. A phase Ib study of alpelisib (BYL719) + everolimus±exemestane in patients with advanced solid tumors or HR+/HER2-breast cancer. American Association for Cancer Research 107th annual meeting; New Orleans, LA, USA; April 16–20, 2016 (abstr CT061)

Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood 2018; 132: 2446–55

Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. J Clin Oncol 2019; 37: 1391–402

Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med 2016; 374: 311–22

Bedard PL, Li S, Kari B, et al. NCI molecular analysis for therapy choice (NCI-MATCH EAY131) arm B: phase II study of afatinib in patients (pts) with HER2 (ERBB2) activating mutations. American Association for Cancer Research annual meeting; Atlanta, GA, USA; March 29–April 3, 2019 (abstr CT139)

Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353: 123–32

Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017; 377: 454–64

Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018; 379: 753–63

Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013; 31: 3639–46

Vallespi M, Mestre B, Marrero M, et al. A first-in-class, first-in-human, phase I trial of CIGB-552, a synthetic peptide targeting COMMD1 to inhibit the oncogenic activity of NF-κB in patients with advanced solid tumors. Int. J. Cancer 2021;1–9

Arkenau H-T, Jones SF, Kurkjian C, Infante JR, Pant S, Burris HA et al (2012). The PI3K/mTOR inhibitor BEZ235 given twice daily for the treatment of patients (pts) with advanced solid tumors. In: ASCO annual meeting proceedings, vol 30, abstr. 3097

Cantley LC (2002) The phosphoinositide 3-kinase pathway. Science 296(5573):1655–1657. doi:10.1126/science.296.5573.1655

Zhao L, Vogt PK (2008) Helical domain and kinase domain mutations in p110alpha of phosphatidylinositol 3-kinase induce gain of function by different mechanisms. Proc Natl Acad Sci USA 105(7):2652–2657. doi:10.1073/pnas.0712169105

Krop IE, Saura C, Ahnert JR, Becerra C, Britten CD, Isakoff SJ et al (2012) A phase I/IB dose-escalation study of BEZ235 in combination with trastuzumab in patients with PI3-kinase or PTEN altered HER2+ metastatic breast cancer. In: ASCO annual meeting proceedings, vol 30, abstr. 508. doi:10.1200/ JCO.2011.40.5902

Ciardiello F, Tortora G (2008) EGFR antagonists in cancer treatment. N Engl J Med 358(11):1160–1174. doi:10.1056/ NEJMra0707704

Sequist LV, Yang JC, Yamamoto N, et al, (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31(27):3327– 3334. doi:10.1200/JCO.2012.44.2806

Shaw AT, Mehra R, Kim D-W et al (2013) Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC. In: ASCO meeting abstracts, vol 31, p 8010

Fernandez Masso JR, Oliva Arguelles B, Tejeda Y, et al. The antitumor peptide CIGB-552 increases COMMD1 and inhibits growth of human lung cancer cells. J AminoAcids. 2013; 2013:251398

Muller PA, van de Sluis B, Groot AJ, et al. Nuclear-cytosolic transport of COMMD1 regulates NF-kappa B and HIF-1 activity. Traffic. 2009; 10:514-527

Fernández Massó, J.R.; Oliva Argüelles, B.; Tejeda, Y.; Astrada, S.; Garay, H.; Reyes, O.; Delgado-Roche, L.; Bollati-Fogolín, M.; Vallespí, M.G. The Antitumor Peptide CIGB-552 Increases COMMD1 and Inhibits Growth of Human Lung Cancer Cells. J. Amino Acids 2013, 2013, 251398

Astrada, S.; Fernández Massó, J.; Vallespí, M.G, et al. Cell penetrating capacity and internalization mechanisms used by the synthetic peptide CIGB-552 and its relationship with tumor cell line sensitivity. Molecules 2018, 23, 801

Vallespi MG, Pimentel G, Cabrales –Rico A, et al. Antitumor efficacy, pharmacokinetic and biodistribution studies of the anticancer peptide CIGB-552 in mouse models. J Pept Sci. 2014; 20:850-859

Vallespi MG, Rodriguez JC, Seoane LC, et al. The first report of cases of pet dogs with naturally occurring cancer treated with the anti- tumor peptide CIGB-552. Res Vet Sci. 2017; 114:502-510

**Conflict of interests**

The authors declare that they have no conflict of interest