

Targeted Cancer Therapies

Key Points

- Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression.
- Because scientists call these specific molecules “molecular targets,” therapies that interfere with them are sometimes called “molecularly targeted drugs,” “molecularly targeted therapies,” or other similar names.
- Targeted cancer therapies that have been approved for use in specific cancers include drugs that interfere with cell growth signaling or tumor blood vessel development, promote the specific death of cancer cells, stimulate the immune system to destroy specific cancer cells, and deliver toxic drugs to cancer cells.

1. What are targeted cancer therapies?

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. Because scientists often call these molecules “molecular targets,” targeted cancer therapies are sometimes called “molecularly targeted drugs,” “molecularly targeted therapies,” or other similar names. By focusing on molecular and cellular changes that are specific to cancer, targeted cancer therapies may be more effective than other types of treatment, including chemotherapy and radiotherapy, and less harmful to normal cells.

Many targeted cancer therapies have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of specific types of cancer (see details in Questions 4 and 5). Others are being studied in clinical trials (research studies with people), and many more are in preclinical testing (research studies with animals).

Targeted cancer therapies are being studied for use alone, in combination with other targeted therapies, and in combination with other cancer treatments, such as chemotherapy.

2. How do targeted cancer therapies work?

Targeted cancer therapies interfere with cancer cell division (proliferation) and spread in different ways. Many of these therapies focus on proteins that are involved in cell signaling pathways, which form a complex communication system that governs basic cellular functions and activities, such as cell division, cell movement, cell responses to specific external stimuli, and even cell death. By blocking signals that tell cancer cells to grow and divide uncontrollably, targeted cancer therapies can help stop cancer progression and may induce cancer cell death through a process known as apoptosis. Other targeted therapies can cause cancer cell death directly, by specifically inducing apoptosis, or indirectly, by stimulating the immune system to recognize and destroy cancer cells and/or by delivering toxic substances directly to the cancer cells.

The development of targeted therapies, therefore, requires the identification of good targets—that is, targets that are known to play a key role in cancer cell growth and survival. (It is for this reason that targeted therapies are often referred to as the product of “rational drug design.”)



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For example, most cases of chronic myeloid leukemia (CML) are caused by the formation of a gene called *BCR-ABL*. This gene is formed when pieces of chromosome 9 and chromosome 22 break off and trade places. One of the changed chromosomes resulting from this switch contains part of the *ABL* gene from chromosome 9 fused to part of the *BCR* gene from chromosome 22. The protein normally produced by the *ABL* gene (Abl) is a signaling molecule that plays an important role in controlling cell proliferation and usually must interact with other signaling molecules to be active. However, Abl signaling is always active in the protein (Bcr-Abl) produced by the *BCR-ABL* fusion gene. This activity promotes the continuous proliferation of CML cells. Therefore, Bcr-Abl represents a good molecule to target.

3. How are targeted therapies developed?

Once a target has been identified, a therapy must be developed. Most targeted therapies are either small-molecule drugs or monoclonal antibodies. Small-molecule drugs are typically able to diffuse into cells and can act on targets that are found inside the cell. Most monoclonal antibodies cannot penetrate the cell's plasma membrane and are directed against targets that are outside cells or on the cell surface.

Candidates for small-molecule drugs are usually identified in studies known as drug screens—laboratory tests that look at the effects of thousands of test compounds on a specific target, such as Bcr-Abl. The best candidates are then chemically modified to produce numerous closely related versions, and these are tested to identify the most effective and specific drugs.

Monoclonal antibodies, by contrast, are prepared first by immunizing animals (typically mice) with purified target molecules. The immunized animals will make many different types of antibodies against the target. Next, spleen cells, each of which makes only one type of antibody, are collected from the immunized animals and fused with myeloma cells. Cloning of these fused cells generates cultures of cells that produce large amounts of a single type of antibody, known as a monoclonal antibody. These antibodies are then tested to find the ones that react best with the target.

Before they can be used in humans, monoclonal antibodies are “humanized” by replacing as much of the animal portion of the antibody as possible with human portions. This is done through genetic engineering. Humanizing is necessary to prevent the human immune system from recognizing the monoclonal antibody as “foreign” and destroying it before it has a chance to interact with and inactivate its target molecule.

4. What was the first target for targeted cancer therapy?

The first molecular target for targeted cancer therapy was the cellular receptor for the female sex hormone estrogen, which many breast cancers require for growth. When estrogen binds to the estrogen receptor (ER) inside cells, the resulting hormone-receptor complex activates the expression of specific genes, including genes involved in cell growth and proliferation. Research has shown that interfering with estrogen's ability to stimulate the growth of breast cancer cells that have these receptors (ER-positive breast cancer cells) is an effective treatment approach.

Several drugs that interfere with estrogen binding to the ER have been approved by the FDA for the treatment of ER-positive breast cancer. Drugs called selective estrogen receptor modulators (SERMs), including [tamoxifen](#) and [toremifene \(Fareston®\)](#), bind to the ER and prevent estrogen binding. Another drug, [fulvestrant \(Faslodex®\)](#), binds to the ER and promotes its destruction, thereby reducing ER levels inside cells.

Aromatase inhibitors (AIs) are another class of targeted drugs that interfere with estrogen's ability to promote the growth of ER-positive breast cancers. The enzyme aromatase is necessary to produce estrogen in the body. Blocking the activity of aromatase lowers estrogen levels and inhibits the growth of cancers that need estrogen to grow. AIs are used mostly in women who have reached menopause because the ovaries of premenopausal women can produce enough aromatase to override the inhibition. Three AIs have been approved by the FDA for the treatment of ER-positive breast cancer: [Anastrozole \(Arimidex®\)](#), [exemestane \(Aromasin®\)](#), and [letrozole \(Femara®\)](#).

5. What are some other targeted therapies?

Targeted cancer therapies have been developed that interfere with a variety of other cellular processes. For example, some targeted therapies block specific enzymes and growth factor receptors involved in cancer cell proliferation. These drugs, which are also called signal transduction inhibitors, are listed below.

- [Imatinib mesylate \(Gleevec®\)](#) is approved by the FDA to treat gastrointestinal stromal tumor (a rare cancer of the gastrointestinal tract), certain kinds of leukemia, dermatofibrosarcoma protuberans, myelodysplastic/myeloproliferative disorders, and systemic mastocytosis. The drug targets several members of a class of proteins called tyrosine kinase enzymes that participate in signal transduction. These enzymes are overactive in some cancers, leading to uncontrolled growth. It is a small-molecule drug, which means that it can pass through cell membranes and reach targets inside the cell.
- [Dasatinib \(Sprycel®\)](#) is approved by the FDA to treat some patients with CML or acute lymphoblastic leukemia. The drug is a small-molecule inhibitor of several tyrosine kinase enzymes.
- [Nilotinib \(Tasigna®\)](#) is approved by the FDA to treat some patients with CML. The drug is another small-molecule tyrosine kinase inhibitor.
- [Trastuzumab \(Herceptin®\)](#) is approved by the FDA for the treatment of certain types of breast cancer as well as some types of gastric or gastroesophageal junction adenocarcinoma. The therapy is a monoclonal antibody that binds to the human epidermal growth factor receptor 2 (HER-2). HER-2, a receptor with tyrosine kinase activity, is expressed at high levels in some breast cancers and also some other types of cancer. The mechanism by which trastuzumab acts is not completely understood, but one likely possibility is that by binding to HER-2 on the surface of tumor cells that express high levels of HER-2, it prevents HER-2 from sending growth-promoting signals. Trastuzumab may have other effects as well, such as inducing the immune system to attack cells that express high levels of HER-2.
- [Lapatinib \(Tykerb®\)](#) is approved by the FDA for the treatment of certain types of advanced or metastatic breast cancer. This small-molecule drug inhibits several tyrosine kinases, including the tyrosine kinase activity of HER-2. Lapatinib treatment prevents HER-2 signals from activating cell growth.
- [Gefitinib \(Iressa®\)](#) is approved by the FDA to treat patients with advanced non-small cell lung cancer. This small-molecule drug is restricted to use in patients who, in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitinib treatment. Gefitinib inhibits the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), which is overproduced by many types of cancer cells.
- [Erlotinib \(Tarceva®\)](#) is approved by the FDA to treat metastatic non-small cell lung cancer and pancreatic cancer that cannot be removed by surgery or has metastasized. This small-molecule drug inhibits the tyrosine kinase activity of EGFR.
- [Cetuximab \(Erbix®\)](#) is a monoclonal antibody that is approved by the FDA for treating some patients with squamous cell carcinoma of the head and neck or colorectal cancer. The therapy binds to the external portion of EGFR, thereby preventing the receptor from being activated by growth signals, which may inhibit signal transduction and lead to antiproliferative effects.
- [Panitumumab \(Vectibix®\)](#) is approved by the FDA to treat some patients with metastatic colon cancer. This monoclonal antibody attaches to EGFR and prevents it from sending growth signals.
- [Temsirolimus \(Torisel®\)](#) is approved by the FDA to treat patients with advanced renal cell carcinoma. This small-molecule drug is a specific inhibitor of a serine/threonine kinase called mTOR that is activated in tumor cells and stimulates their growth and proliferation.
- [Everolimus \(Afinitor®\)](#) is approved by the FDA to treat patients with advanced kidney cancer whose disease has progressed after treatment with other therapies, patients with subependymal giant cell astrocytoma who also have tuberous sclerosis and are unable to have surgery, or patients with pancreatic neuroendocrine tumors that cannot be removed by surgery, are locally advanced, or have metastasized. This small-molecule drug binds to a protein called immunophilin FK binding protein-12, forming a complex that in turn binds to and inhibits the mTOR kinase.

- [Vandetanib \(Zactima™\)](#) is approved by the FDA to treat patients with metastatic medullary thyroid cancer who are ineligible for surgery. This small-molecule drug binds to and blocks the growth-promoting activity of several tyrosine kinase enzymes, including EGFR, several receptors for vascular endothelial growth factor receptor (VEGF), and RET.
- [Vemurafenib \(Zelboraf™\)](#) is approved by the FDA to treat certain patients with inoperable or metastatic melanoma. This small-molecule drug blocks the activity of a permanently activated mutant form of the serine/threonine kinase BRAF (known as BRAF V600E).
- [Crizotinib \(Xalkori®\)](#) is approved by the FDA to treat certain patients with locally advanced or metastatic non-small cell lung cancer. This small-molecule drug inhibits the tyrosine kinase activity of a fusion protein called EML4-ALK, resulting in decreased tumor cell growth, migration, and invasiveness.

Other targeted therapies modify the function of proteins that regulate gene expression and other cellular functions. Examples of these drugs are listed below.

- [Vorinostat \(Zolinza®\)](#) is approved by the FDA for the treatment of cutaneous T-cell lymphoma (CTCL) that has persisted, progressed, or recurred during or after treatment with other medicines. This small-molecule drug inhibits the activity of a group of enzymes called histone deacetylases (HDACs), which remove small chemical groups called acetyl groups from many different proteins, including proteins that regulate gene expression. By altering the acetylation of these proteins, HDAC inhibitors can induce tumor cell differentiation, cell cycle arrest, and apoptosis.
- [Romidepsin \(Istodax®\)](#) is approved by the FDA for the treatment of CTCL in patients who have received at least one prior systemic therapy. This small-molecule drug inhibits members of one class of HDACs and induces tumor cell apoptosis.
- [Bexarotene \(Targretin®\)](#) is approved by the FDA for the treatment of some patients with CTCL. This drug belongs to a class of compounds called retinoids, which are chemically related to vitamin A. Bexarotene binds selectively to, and thereby activates, retinoid X receptors. Once activated, these nuclear proteins act in concert with retinoic acid receptors to regulate the expression of genes that control cell growth, differentiation, survival, and death.
- [Alitretinoin \(Panretin®\)](#) is approved by the FDA for the treatment of cutaneous lesions in patients with AIDS-related Kaposi sarcoma. This retinoid binds to both retinoic acid receptors and retinoid X receptors.
- [Tretinoin \(Vesanoid®\)](#) is approved by the FDA for the induction of remission in certain patients with acute promyelocytic leukemia. This retinoid binds to and thereby activates retinoic acid receptors.

Some targeted therapies, such as those listed below, induce cancer cells to undergo apoptosis (cell death).

- [Bortezomib \(Velcade®\)](#) is approved by the FDA to treat some patients with multiple myeloma. The drug is also approved by the FDA for the treatment of some patients with mantle cell lymphoma. Bortezomib causes cancer cells to die by interfering with the action of a large cellular structure called the proteasome, which degrades proteins. Proteasomes control the degradation of many proteins that regulate cell proliferation. By blocking this process, bortezomib causes cancer cells to die. Normal cells are affected too, but to a lesser extent.
- [Pralatrexate \(Folotyn®\)](#) is approved by the FDA for the treatment of some patients with peripheral T-cell lymphoma. Pralatrexate is an antifolate, which is a type of molecule that interferes with DNA synthesis. Other antifolates, such as methotrexate, are not considered targeted therapies because they interfere with DNA synthesis in all dividing cells. However, pralatrexate appears to selectively accumulate in cells that express RFC-1, a protein that may be overexpressed by some cancer cells.

Other targeted therapies block the growth of blood vessels to tumors (angiogenesis). To grow beyond a certain size, tumors must obtain a blood supply to get the oxygen and nutrients needed for continued growth. Treatments that interfere with angiogenesis may block tumor growth. Examples of these drugs are listed below.

- [Bevacizumab \(Avastin®\)](#) is a monoclonal antibody that is approved by the FDA for the treatment of glioblastoma. The therapy is also approved by the FDA for some patients with non-small cell lung cancer, metastatic colorectal cancer, and metastatic kidney cancer. Bevacizumab binds to VEGF and prevents it from interacting with receptors on endothelial cells, blocking a step that is necessary for the initiation of new blood vessel growth.
- [Sorafenib \(Nexavar®\)](#) is a small-molecule inhibitor of tyrosine kinases that is approved by the FDA for the treatment of advanced renal cell carcinoma and some cases of hepatocellular carcinoma. One of the kinases that sorafenib inhibits is involved in the signaling pathway that is initiated when VEGF binds to its receptors. As a result, new blood vessel development is halted. Sorafenib also blocks an enzyme that is involved in cell growth and division.
- [Sunitinib \(Sutent®\)](#) is another small-molecule tyrosine kinase inhibitor that is approved by the FDA for the treatment of patients with metastatic renal cell carcinoma, gastrointestinal stromal tumor that is not responding to imatinib, or pancreatic neuroendocrine tumors that cannot be removed by surgery, are locally advanced, or have metastasized. Sunitinib blocks kinases involved in VEGF signaling, thereby inhibiting angiogenesis and cell proliferation.
- [Pazopanib \(Votrient®\)](#) is approved by the FDA for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma. Pazopanib is a small-molecule inhibitor of several tyrosine kinases, including VEGF receptors, c-kit, and platelet-derived growth factor receptor.

Some targeted therapies, such as those listed below, act by helping the immune system to destroy cancer cells.

- [Rituximab \(Rituxan®\)](#) is a monoclonal antibody that is approved by the FDA to treat certain types of B-cell non-Hodgkin lymphoma and, when combined with other drugs, to treat chronic lymphocytic leukemia (CLL). The therapy recognizes a molecule called CD20 that is found on B cells. When rituximab binds to these cells, it triggers an immune response that results in their destruction. Rituximab may also induce apoptosis.
- [Alemtuzumab \(Campath®\)](#) is approved by the FDA to treat patients with B-cell CLL. The therapy is a monoclonal antibody directed against CD52, a protein found on the surface of normal and malignant B and T cells and many other cells of the immune system. Binding of alemtuzumab to CD52 triggers an immune response that destroys the cells.
- [Ofatumumab \(Arzerra®\)](#) is approved by the FDA for the treatment of some patients with CLL that does not respond to treatment with fludarabine and alemtuzumab. This monoclonal antibody is directed against the B-cell CD20 cell surface antigen.
- [Ipilimumab \(Yervoy™\)](#) is approved by the FDA to treat patients with unresectable or metastatic melanoma. This monoclonal antibody is directed against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), which is expressed on the surface of activated T cells as part of a “checkpoint” to prevent a runaway immune response. By inhibiting CTLA-4, ipilimumab stimulates the immune system to attack melanoma cells.

Another class of targeted therapies includes monoclonal antibodies that deliver toxic molecules to cancer cells specifically. Examples of these therapies are listed below.

- [Tositumomab and 131I-tositumomab \(Bexxar®\)](#) is approved by the FDA to treat certain types of B-cell non-Hodgkin lymphoma. The therapy is a mixture of monoclonal antibodies that recognize the CD20 molecule. Some of the antibodies in the mixture are linked to a radioactive substance called iodine-131. The 131I-tositumomab component delivers radioactive energy to CD20-expressing B cells specifically, reducing collateral damage to normal cells. In addition, the binding of tositumomab to the CD20-expressing B cells triggers the immune system to destroy these cells.

- [Ibritumomab tiuxetan \(Zevalin®\)](#) is approved by the FDA to treat some patients with B-cell non-Hodgkin lymphoma. The therapy is a monoclonal antibody directed against CD20 that is linked to a molecule that can bind radioisotopes such as indium-111 or yttrium-90. The radiolabeled forms of Zevalin deliver a high dose of radioactivity to cells that express CD20.
- [Denileukin diftitox \(Ontak®\)](#) is approved by the FDA for the treatment of some patients with CTCL. Denileukin diftitox consists of interleukin-2 (IL-2) protein sequences fused to diphtheria toxin. The drug binds to cell surface IL-2 receptors, which are found on certain immune cells and some cancer cells, directing the cytotoxic action of the diphtheria toxin to these cells.
- [Brentuximab vedotin \(Adcetris™\)](#) is approved by the FDA for the treatment of systemic anaplastic large cell lymphoma and Hodgkin lymphoma that has not responded to prior chemotherapy or autologous stem cell transplantation. This agent consists of a monoclonal antibody directed against a molecule called CD30, which is found on some lymphoma cells, linked to a drug called monomethyl auristatin E (MMAE). The antibody part of the agent binds to and is internalized by CD30-expressing tumor cells. Once inside the cell, the MMAE is released, where it induces cell cycle arrest and apoptosis.

Cancer vaccines and gene therapy are often considered to be targeted therapies because they interfere with the growth of specific cancer cells. Information about these treatments can be found in the following NCI fact sheets, which are available online or by calling NCI's Cancer Information Service at 1-800-4-CANCER:

- *Biological Therapies for Cancer* includes information about monoclonal antibodies and cancer vaccines. This fact sheet is available at <http://www.cancer.gov/cancertopics/factsheet/Therapy/biological>.
- *Cancer Vaccines* contains information on vaccines intended to treat cancer, as well as those intended to prevent it. This fact sheet is at <http://www.cancer.gov/cancertopics/factsheet/Therapy/cancer-vaccines>.
- *Gene Therapy for Cancer* discusses research with genetic material in developing cancer therapies, including risks, benefits, and ethical issues. This fact sheet can be found at <http://www.cancer.gov/cancertopics/factsheet/Therapy/gene>.

6. What impact will targeted therapies have on cancer treatment?

Targeted cancer therapies give doctors a better way to tailor cancer treatment, especially when a target is present in some but not all tumors of a particular type, as is the case for HER-2. Eventually, treatments may be individualized based on the unique set of molecular targets produced by the patient's tumor. Targeted cancer therapies also hold the promise of being more selective for cancer cells than normal cells, thus harming fewer normal cells, reducing side effects, and improving quality of life.

Nevertheless, targeted therapies have some limitations. Chief among these is the potential for cells to develop resistance to them. In some patients who have developed resistance to imatinib, for example, a mutation in the BCR-ABL gene has arisen that changes the shape of the protein so that it no longer binds this drug as well. In most cases, another targeted therapy that could overcome this resistance is not available. It is for this reason that targeted therapies may work best in combination, either with other targeted therapies or with more traditional therapies.

7. Where can I find information about clinical trials of targeted therapies?

The list below provides links to active clinical trials of FDA-approved targeted therapies. Because trials begin and end regularly, it is possible that, at any given time, a particular drug will not have any trials available. If you are viewing this fact sheet online (<http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted>), the drug names are links to search results for trials in NCI's clinical trials database. This database can also be searched on NCI's website by visiting <http://www.cancer.gov/clinicaltrials/search>. For information about how to search the database, see "Help Using the NCI Clinical Trials Search Form" at <http://www.cancer.gov/clinicaltrials/search-form-help>. The database includes all NCI-funded clinical trials and many other studies conducted by investigators at hospitals and medical centers in the United States and other countries around the world.

Targeted Cancer Therapies Being Studied in Clinical Trials:

[Alemtuzumab \(Campath®\)](#)
[Alitretinoin \(Panretin®\)](#)
[Anastrozole \(Arimidex®\)](#)
[Bevacizumab \(Avastin®\)](#)
[Bexarotene \(Targretin®\)](#)
[Bortezomib \(Velcade®\)](#)
[Brentuximab vedotin \(Adcetris™\)](#)
[Cetuximab \(Erbix®\)](#)
[Crizotinib \(Xalkori®\)](#)
[Dasatinib \(Sprycel®\)](#)
[Denileukin diftitox \(Ontak®\)](#)
[Erlotinib hydrochloride \(Tarceva®\)](#)
[Everolimus \(Afinitor®\)](#)
[Exemestane \(Aromasin®\)](#)
[Fulvestrant \(Faslodex®\)](#)
[Gefitinib \(Iressa®\)](#)
[Ibritumomab tiuxetan \(Zevalin®\)](#)
[Imatinib mesylate \(Gleevec®\)](#)
[Ipilimumab \(Yervoy™\)](#)
[Lapatinib ditosylate \(Tykerb®\)](#)
[Letrozole \(Femara®\)](#)
[Nilotinib \(Tasigna®\)](#)
[Ofatumumab \(Arzerra®\)](#)
[Panitumumab \(Vectibix®\)](#)
[Pazopanib hydrochloride \(Votrient®\)](#)
[Pralatrexate \(Folotyn®\)](#)
[Rituximab \(Rituxan®\)](#)
[Romidepsin \(Istodax®\)](#)
[Sorafenib tosylate \(Nexavar®\)](#)
[Sunitinib malate \(Sutent®\)](#)
[Tamoxifen](#)
[Temsirolimus \(Torisel®\)](#)
[Toremifene \(Fareston®\)](#)
[Tositumomab and ¹³¹I-tositumomab \(Bexxar®\)](#)
[Trastuzumab \(Herceptin®\)](#)
[Tretinoin \(Vesanoid®\)](#)
[Vandetanib \(Zactima™\)](#)
[Vemurafenib \(Zelboraf™\)](#)
[Vorinostat \(Zolinza®\)](#)

8. What are some resources for more information?

NCI's Molecular Targets Laboratory (MTL), part of NCI's Center for Cancer Research (CCR), is working to identify and evaluate molecular targets that may be candidates for drug development. The initial goal of the MTL is to facilitate the discovery of compounds that may serve as bioprobes for functional genomics, proteomics, and molecular target validation research, as well as leads or candidates for drug development. The MTL's website is located at <https://ccrod.cancer.gov/confluence/display/CCRMTDPBeu/Introduction+to+MTL>.

NCI's Chemical Biology Consortium (CBC) facilitates the discovery and development of new agents to treat cancer. The CBC is part of the NCI Experimental Therapeutics Program, which is a collaborative effort of CCR and NCI's Division of Cancer Treatment and Diagnosis. More information about the CBC can be found at <http://next.cancer.gov/discoveryResources/cbc.htm>.

Related Resources

- *Angiogenesis Inhibitors*
(<http://www.cancer.gov/cancertopics/factsheet/Therapy/angiogenesis-inhibitors>)

- *Cancer Clinical Trials*
(<http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials>)
- *Understanding Cancer Series: Targeted Therapies Tutorial*
(<http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies>)
- *What You Need To Know About™ Cancer*
(<http://www.cancer.gov/cancertopics/wyntk/cancer>)

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