

# National Cancer Institute

at the National Institutes of Health

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NATIONAL CANCER INSTITUTE  
**FactSheet**

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## 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.”)

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<sup>1</sup> and toremifene (Fareston®)<sup>2</sup>, bind to the ER and prevent estrogen binding. Another drug, fulvestrant (Faslodex®)<sup>3</sup>, 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®)<sup>4</sup>, exemestane (Aromasin®)<sup>5</sup>, and letrozole (Femara®)<sup>6</sup>.

#### 5. What are some other targeted therapies?

Targeted cancer therapies have been developed that interfere with a variety of other cellular processes. FDA-approved targeted therapies are listed below:

- Some targeted therapies block specific enzymes and growth factor receptors involved in cancer cell proliferation. These drugs are also called signal transduction inhibitors.
  - Imatinib mesylate (Gleevec®)<sup>7</sup> is approved 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®)<sup>8</sup> is approved to treat some patients with CML or acute lymphoblastic leukemia. The drug is a small-molecule inhibitor of several tyrosine kinase enzymes.
  - Nilotinib (Tasigna®)<sup>9</sup> is approved to treat some patients with CML. The drug is another small-molecule tyrosine kinase inhibitor.
  - Trastuzumab (Herceptin®)<sup>10</sup> is approved 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®)<sup>11</sup> is approved 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®)<sup>12</sup> is approved 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 \(Tarceva®\)](#)<sup>13</sup> is approved 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 \(Erbitux®\)](#)<sup>14</sup> is a monoclonal antibody that is approved 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 \(Vectibix®\)](#)<sup>15</sup> is approved to treat some patients with metastatic colon cancer. This monoclonal antibody attaches to EGFR and prevents it from sending growth signals.
  - [Temozolomide \(Temodar®\)](#)<sup>16</sup> is approved 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 \(Afinitor®\)](#)<sup>17</sup> is approved 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 \(Zactima™\)](#)<sup>18</sup> is approved 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 \(Zelboraf™\)](#)<sup>19</sup> is approved 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 \(Xalkori®\)](#)<sup>20</sup> is approved 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.
    - [Vorinostat \(Zolinza®\)](#)<sup>21</sup> is approved 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 \(Istodax®\)](#)<sup>22</sup> is approved 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 \(Targretin®\)](#)<sup>23</sup> is approved 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 \(Panretin®\)](#)<sup>24</sup> is approved 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 \(Vesanoid®\)](#)<sup>25</sup> is approved 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 induce cancer cells to undergo apoptosis (cell death).
    - [Bortezomib \(Velcade®\)](#)<sup>26</sup> is approved to treat some patients with [multiple myeloma](#). The drug is also approved 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 \(Folotyn®\)](#)<sup>27</sup> is approved 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.
  - [Bevacizumab \(Avastin®\)](#) <sup>28</sup> is a monoclonal antibody that is approved for the treatment of [glioblastoma](#). The therapy is also approved 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 \(Nexavar®\)](#) <sup>29</sup> is a small-molecule inhibitor of tyrosine kinases that is approved 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 \(Sutent®\)](#) <sup>30</sup> is another small-molecule tyrosine kinase inhibitor that is approved 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 \(Votrient®\)](#) <sup>31</sup> is approved for the treatment of patients with advanced renal cell carcinoma. Pazopanib is a small-molecule inhibitor of several tyrosine kinases, including VEGF receptors, c-kit, and [platelet-derived growth factor](#) receptor.
- Some targeted therapies act by helping the immune system to destroy cancer cells.
  - [Rituximab \(Rituxan®\)](#) <sup>32</sup> is a monoclonal antibody that is approved 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 \(Campath®\)](#) <sup>33</sup> is approved 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 \(Arzerra®\)](#) <sup>34</sup> is approved 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 \(Yervoy™\)](#) <sup>35</sup> is approved 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.
  - [Tositumomab and 131I-tositumomab \(Bexxar®\)](#) <sup>36</sup> is approved 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 \(Zevalin®\)](#) <sup>37</sup> is approved 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 \(Ontak®\)](#) <sup>38</sup> is approved 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 \(Adcetris™\)](#) <sup>39</sup> is approved 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](#)<sup>40</sup> includes information about monoclonal antibodies and cancer vaccines.
- [Cancer Vaccines](#)<sup>41</sup> contains information on vaccines intended to treat cancer, as well as those intended to prevent it.
- [Gene Therapy for Cancer](#)<sup>42</sup> discusses research with genetic material in developing cancer therapies, including risks, benefits, and ethical issues.

#### 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, drug names are links to search results for trials in [NCI's clinical trials database](#)<sup>43</sup>. For information about how to search the database, see "[Help Using the NCI Clinical Trials Search Form](#)<sup>44</sup>." 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 \(Campath®\)](#)<sup>45</sup>  
[Alitretinoin \(Panretin®\)](#)<sup>46</sup>  
[Anastrozole \(Arimidex®\)](#)<sup>47</sup>  
[Bevacizumab \(Avastin®\)](#)<sup>48</sup>  
[Bexarotene \(Targretin®\)](#)<sup>49</sup>  
[Bortezomib \(Velcade®\)](#)<sup>50</sup>  
[Brentuximab vedotin \(Adcetris™\)](#)<sup>51</sup>  
[Cetuximab \(Erbix®\)](#)<sup>52</sup>  
[Crizotinib \(Xalkori®\)](#)<sup>53</sup>  
[Dasatinib \(Sprycel®\)](#)<sup>54</sup>  
[Denileukin diftitox \(Ontak®\)](#)<sup>55</sup>  
[Erlotinib hydrochloride \(Tarceva®\)](#)<sup>56</sup>  
[Everolimus \(Afinitor®\)](#)<sup>57</sup>  
[Exemestane \(Aromasin®\)](#)<sup>58</sup>  
[Fulvestrant \(Faslodex®\)](#)<sup>59</sup>  
[Gefitinib \(Iressa®\)](#)<sup>60</sup>  
[Ibritumomab tiuxetan \(Zevalin®\)](#)<sup>61</sup>  
[Imatinib mesylate \(Gleevec®\)](#)<sup>62</sup>  
[Ipilimumab \(Yervoy™\)](#)<sup>63</sup>  
[Lapatinib ditosylate \(Tykerb®\)](#)<sup>64</sup>  
[Letrozole \(Femara®\)](#)<sup>65</sup>  
[Nilotinib \(Tasigna®\)](#)<sup>66</sup>  
[Ofatumumab \(Arzerra®\)](#)<sup>67</sup>  
[Panitumumab \(Vectibix®\)](#)<sup>68</sup>  
[Pazopanib hydrochloride \(Votrient®\)](#)<sup>69</sup>  
[Pralatrexate \(Foloty®\)](#)<sup>70</sup>  
[Rituximab \(Rituxan®\)](#)<sup>71</sup>  
[Romidepsin \(Istodax®\)](#)<sup>72</sup>  
[Sorafenib tosylate \(Nexavar®\)](#)<sup>73</sup>  
[Sunitinib malate \(Sutent®\)](#)<sup>74</sup>  
[Tamoxifen](#)<sup>75</sup>  
[Temsilimus \(Torise®\)](#)<sup>76</sup>  
[Toremifene \(Fareston®\)](#)<sup>77</sup>  
[Tositumomab and <sup>131</sup>I-tositumomab \(Bexxar®\)](#)<sup>78</sup>  
[Trastuzumab \(Herceptin®\)](#)<sup>79</sup>  
[Tretinoin \(Vesanoid®\)](#)<sup>80</sup>  
[Vandetanib \(Zactima™\)](#)<sup>81</sup>

[Vemurafenib \(Zelboraf™\)](#) <sup>82</sup>

[Vorinostat \(Zolinza®\)](#) <sup>83</sup>

#### 8. What are some resources for more information?

NCI's [Molecular Targets Laboratory](#) <sup>84</sup> (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.

NCI's [Chemical Biology Consortium](#) <sup>85</sup> (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.

#### Related Resources

- [Angiogenesis Inhibitors](#) <sup>86</sup>
- [Cancer Clinical Trials](#) <sup>87</sup>
- [Targeted Therapies Tutorials](#) <sup>88</sup>
- [What You Need To Know About™ Cancer](#) <sup>89</sup>

## Glossary Terms

### acetylation (a-SEH-tih-LAY-shun)

A chemical reaction in which a small molecule called an acetyl group is added to other molecules. Acetylation of proteins may affect how they act in the body.

### acute lymphoblastic leukemia (uh-KYOOT LIM-foh-BLAS-tik loo-KEE-mee-uh)

An aggressive (fast-growing) type of leukemia (blood cancer) in which too many lymphoblasts (immature white blood cells) are found in the blood and bone marrow. Also called acute lymphocytic leukemia and ALL.

### acute promyelocytic leukemia (uh-KYOOT proh-MY-eh-loh-SIH-tik loo-KEE-mee-uh)

An aggressive (fast-growing) type of acute myeloid leukemia in which there are too many immature blood-forming cells in the blood and bone marrow. It is usually marked by an exchange of parts of chromosomes 15 and 17. Also called APL and promyelocytic leukemia.

### adenocarcinoma (A-den-oh-KAR-sih-NOH-muh)

Cancer that begins in cells that line certain internal organs and that have gland-like (secretory) properties.

### AIDS

A disease caused by the human immunodeficiency virus (HIV). People with AIDS are at an increased risk for developing certain cancers and for infections that usually occur only in individuals with a weak immune system. Also called acquired immunodeficiency syndrome.

### angiogenesis (AN-jee-oh-JEH-neh-sis)

Blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. This is caused by the release of chemicals by the tumor.

### antifolate (AN-tee-FOH-layt)

A substance that blocks the activity of folic acid. Antifolates are used to treat cancer. Also called folate antagonist.

### antigen (AN-tih-jen)

Any substance that causes the body to make a specific immune response.

### apoptosis (A-pop-TOH-sis)

A type of cell death in which a series of molecular steps in a cell leads to its death. This is the body's normal way of getting rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells. Also called programmed cell death.

### aromatase inhibitor (uh-ROH-muh-tays in-HIH-bih-ter)

A drug that prevents the formation of estradiol, a female hormone, by interfering with an aromatase enzyme. Aromatase inhibitors are used as a type of hormone therapy for postmenopausal women who have hormone-dependent breast cancer.

**B cell** (... sel)

A type of immune cell that makes proteins called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B cell is a type of white blood cell. Also called B lymphocyte.

**BCR-ABL fusion gene** (... FYOO-zhun jeen)

A gene formed when pieces of chromosomes 9 and 22 break off and trade places. The ABL gene from chromosome 9 joins to the BCR gene on chromosome 22, to form the BCR-ABL fusion gene. The changed chromosome 22 with the fusion gene on it is called the Philadelphia chromosome. The BCR-ABL fusion gene is found in most patients with chronic myelogenous leukemia (CML), and in some patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML).

**blood vessel** (blud VEH-sel)

A tube through which the blood circulates in the body. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins.

**breast cancer** (brest KAN-ser)

Cancer that forms in tissues of the breast, usually the ducts (tubes that carry milk to the nipple) and lobules (glands that make milk). It occurs in both men and women, although male breast cancer is rare.

**cancer** (KAN-ser)

A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinoma is a cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Central nervous system cancers are cancers that begin in the tissues of the brain and spinal cord. Also called malignancy.

**cell cycle** (sel SY-kul)

The process a cell goes through each time it divides. The cell cycle consists of a series of steps during which the chromosomes and other cell material double to make two copies. The cell then divides into two daughter cells, each receiving one copy of the doubled material. The cell cycle is complete when each daughter cell is surrounded by its own outer membrane. Also called mitotic cycle.

**cell differentiation** (sel DIH-feh-REN-shee-AY-shun)

The process during which young, immature (unspecialized) cells take on individual characteristics and reach their mature (specialized) form and function.

**cell proliferation** (sel proh-LIH-feh-RAY-shun)

An increase in the number of cells as a result of cell growth and cell division.

**chemotherapy** (KEE-moh-THAYR-uh-pee)

Treatment with drugs that kill cancer cells.

**chromosome** (KROH-muh-some)

Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes.

**chronic lymphocytic leukemia** (KRAH-nik LIM-foh-SIH-tik loo-KEE-mee-uh)

An indolent (slow-growing) cancer in which too many immature lymphocytes (white blood cells) are found mostly in the blood and bone marrow. Sometimes, in later stages of the disease, cancer cells are found in the lymph nodes and the disease is called small lymphocytic lymphoma. Also called CLL.

**chronic myeloid leukemia** (KRAH-nik MY-eh-loyd loo-KEE-mee-uh)

A slowly progressing disease in which too many white blood cells (not lymphocytes) are made in the bone marrow. Also called chronic granulocytic leukemia, chronic myelogenous leukemia, and CML.

**clinical trial** (KLIH-nih-kul TRY-ul)

A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.

**colorectal cancer** (KOH-loh-REK-tul KAN-ser)

Cancer that develops in the colon (the longest part of the large intestine) and/or the rectum (the last several inches of the large intestine before the anus).

**cutaneous** (kyoo-TAY-nee-us)

Having to do with the skin.

**cutaneous T-cell lymphoma** (kyoo-TAY-nee-us ... lim-FOH-muh)

Any of a group of T-cell non-Hodgkin lymphomas that begins in the skin as an itchy, red rash that can thicken or form a tumor. The most common types are mycosis fungoides and Sézary syndrome.

**cytotoxic** (SY-toh-TOK-sik)

Cell-killing.

**cytotoxic T lymphocyte** (SY-toh-TOK-sik ... LIM-foh-site)

A type of immune cell that can kill certain cells, including foreign cells, cancer cells, and cells infected with a virus. Cytotoxic T lymphocytes can be separated from other blood cells, grown in the laboratory, and then given to a patient to kill cancer cells. A cytotoxic T lymphocyte is a type of white blood cell and a type of lymphocyte. Also called cytotoxic T cell and killer T cell.

**dermatofibrosarcoma protuberans** (DER-muh-toh-FY-broh-sar-KOH-muh proh-TOO-beh-ranz)

A type of tumor that begins as a hard nodule and grows slowly. These tumors are usually found in the dermis (the inner layer of the two main layers of tissue that make up the skin) of the limbs or trunk of the body. They can grow into surrounding tissue but do not spread to other parts of the body. These tumors are related to giant cell fibroblastomas.

**DNA**

The molecules inside cells that carry genetic information and pass it from one generation to the next. Also called deoxyribonucleic acid.

**drug** (drug)

Any substance, other than food, that is used to prevent, diagnose, treat or relieve symptoms of a disease or abnormal condition. Also refers to a substance that alters mood or body function, or that can be habit-forming or addictive, especially a narcotic.

**endothelial cell** (EN-doh-THÉE-lee-ul sel)

The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart.

**enzyme** (EN-zime)

A protein that speeds up chemical reactions in the body.

**epidermal growth factor receptor** (eh-pih-DER-mul grothe FAK-ter reh-SEP-ter)

The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called EGFR, ErbB1, and HER1.

**estrogen** (ES-truh-jin)

A type of hormone made by the body that helps develop and maintain female sex characteristics and the growth of long bones. Estrogens can also be made in the laboratory. They may be used as a type of birth control and to treat symptoms of menopause, menstrual disorders, osteoporosis, and other conditions.

**estrogen receptor** (ES-truh-jin reh-SEP-ter)

A protein found inside the cells of the female reproductive tissue, some other types of tissue, and some cancer cells. The hormone estrogen will bind to the receptors inside the cells and may cause the cells to grow. Also called ER.

**fludarabine** (floo-DAR-uh-been)

The active ingredient in a drug used to treat B-cell chronic lymphocytic leukemia (CLL) that has not responded to treatment with other anticancer drugs or that has gotten worse. Fludarabine blocks cells



from making DNA and may kill cancer cells. It is a type of purine antagonist and a type of ribonucleotide reductase inhibitor.

**gastric** (GAS-trik)

Having to do with the stomach.

**gastroesophageal junction** (GAS-troh-ee-SAH-fuh-JEE-ul JUNK-shun)

The place where the esophagus is connected to the stomach.

**gastrointestinal stromal tumor** (GAS-troh-in-TES-tih-nul STROH-mul TOO-mer)

A type of tumor that usually begins in cells in the wall of the gastrointestinal tract. It can be benign or malignant. Also called GIST.

**gastrointestinal tract** (GAS-troh-in-TES-tih-nul trakt)

The stomach and intestines. The gastrointestinal tract is part of the digestive system, which also includes the salivary glands, mouth, esophagus, liver, pancreas, gallbladder, and rectum.

**gene** (jeen)

The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

**gene therapy** (jeen THAYR-uh-pee)

A type of experimental treatment in which foreign genetic material (DNA or RNA) is inserted into a person's cells to prevent or fight disease. Gene therapy is being studied in the treatment of certain types of cancer.

**genetic** (jeh-NEH-tik)

Inherited; having to do with information that is passed from parents to offspring through genes in sperm and egg cells.

**genomics** (jeh-NOH-mix)

The study of the complete genetic material, including genes and their functions, of an organism.

**glioblastoma** (GLEE-oh-blas-TOH-muh)

A fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord and has cells that look very different from normal cells. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord. Also called GBM, glioblastoma multiforme, and grade IV astrocytoma.

**hepatocellular carcinoma** (heh-PA-toh-SEL-yoo-ler KAR-sih-NOH-muh)

A type of adenocarcinoma and the most common type of liver tumor.

**histone deacetylase** (HIS-tone dee-uh-SEH-tih-lays)

An enzyme that removes a small molecule called an acetyl group from histones (proteins found in chromosomes). This changes the way the histones bind to DNA and may affect its activity. Histone deacetylase inhibitors are being studied in the treatment of cancer. Also called HDAC.

**hormone** (HOR-mone)

One of many chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be made in the laboratory.

**human epidermal growth factor receptor 2** (HYOO-mun eh-pih-DER-mul grothe FAK-ter reh-SEP-ter ...)

A protein involved in normal cell growth. It is found on some types of cancer cells, including breast and ovarian. Cancer cells removed from the body may be tested for the presence of human epidermal growth factor receptor 2 to help decide the best type of treatment. Human epidermal growth factor receptor 2 is a type of receptor tyrosine kinase. Also called c-erbB-2, HER2/neu, and human EGF receptor 2.

**immune response** (ih-MYOON reh-SPONTS)

The activity of the immune system against foreign substances (antigens).

**immune system** (ih-MYOON SIS-tem)

The complex group of organs and cells that defends the body against infections and other diseases.

**interleukin-2** (in-ter-LOO-kin...)

One of a group of related proteins made by leukocytes (white blood cells) and other cells in the body. Interleukin-2 is made by a type of T lymphocyte. It increases the growth and activity of other T lymphocytes and B lymphocytes, and affects the development of the immune system. Aldesleukin (interleukin-2 made in the laboratory) is being used as a biological response modifier to boost the immune system in cancer therapy. Interleukin-2 is a type of cytokine. Also called IL-2.

**iodine** (I-oh-dine)

An element that is necessary for the body to make thyroid hormone. It is found in shellfish and iodized salt.

**Kaposi sarcoma** (kuh-POH-zee sar-KOH-muh)

A type of cancer characterized by the abnormal growth of blood vessels that develop into skin lesions or occur internally.

**kidney cancer** (KID-nee KAN-ser)

Cancer that forms in tissues of the kidneys. Kidney cancer includes renal cell carcinoma (cancer that forms in the lining of very small tubes in the kidney that filter the blood and remove waste products) and renal pelvis carcinoma (cancer that forms in the center of the kidney where urine collects). It also includes Wilms tumor, which is a type of kidney cancer that usually develops in children under the age of 5.

**kinase** (KY-nays)

A type of enzyme that causes other molecules in the cell to become active. Some kinases work by adding chemicals called phosphates to other molecules, such as sugars or proteins. Kinases are a part of many cell processes. Some cancer treatments target certain kinases that are linked to cancer.

**laboratory test** (LA-bruh-tor-ee...)

A medical procedure that involves testing a sample of blood, urine, or other substance from the body. Tests can help determine a diagnosis, plan treatment, check to see if treatment is working, or monitor the disease over time.

**leukemia** (loo-KEE-mee-uh)

Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of blood cells to be produced and enter the bloodstream.

**mantle cell lymphoma** (MAN-tul sel lim-FOH-muh)

An aggressive (fast-growing) type of B-cell non-Hodgkin lymphoma that usually occurs in middle-aged or older adults. It is marked by small- to medium-size cancer cells that may be in the lymph nodes, spleen, bone marrow, blood, and gastrointestinal system.

**medullary thyroid cancer** (MED-yoo-LAYR-ee THY-royd KAN-ser)

Cancer that develops in C cells of the thyroid. The C cells make a hormone (calcitonin) that helps maintain a healthy level of calcium in the blood.

**melanoma** (MEH-luh-NOH-muh)

A form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines.

**menopause** (MEH-nuh-pawz)

The time of life when a woman's ovaries stop producing hormones and menstrual periods stop. Natural menopause usually occurs around age 50. A woman is said to be in menopause when she hasn't had a period for 12 months in a row. Symptoms of menopause include hot flashes, mood swings, night sweats, vaginal dryness, trouble concentrating, and infertility.

**metastatic** (meh-tuh-STA-tik)

Having to do with metastasis, which is the spread of cancer from the primary site (place where it started) to other places in the body.

**molecule** (MAH-leh-kyool)

The smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules are made up of one or more atoms. If they contain more than one atom, the atoms can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms.

**monoclonal antibody** (MAH-noh-KLOH-nul AN-tee-BAH-dee)

A type of protein made in the laboratory that can bind to substances in the body, including tumor cells. There are many kinds of monoclonal antibodies. Each monoclonal antibody is made to find one substance. Monoclonal antibodies are being used to treat some types of cancer and are being studied in the treatment of other types. They can be used alone or to carry drugs, toxins, or radioactive materials directly to a tumor.

**mTOR**

A protein that helps control several cell functions, including cell division and survival, and binds to rapamycin and other drugs. mTOR may be more active in some types of cancer cells than it is in normal cells. Blocking mTOR may cause the cancer cells to die. It is a type of serine/threonine protein kinase. Also called mammalian target of rapamycin.

**multiple myeloma** (MUL-tih-pul MY-eh-LOH-muh)

A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

**mutation** (myoo-TAY-shun)

Any change in the DNA of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

**myelodysplasia** (MY-eh-loh-dis-PLAY-zhuh)

Abnormal bone marrow cells that may lead to myelogenous leukemia.

**myeloma** (MY-eh-LOH-muh)

Cancer that arises in plasma cells, a type of white blood cell.

**myeloproliferative disorder** (MY-eh-loh-proh-LIH-feh-ruh-tiv dis-OR-der)

A group of slow growing blood cancers, including chronic myelogenous leukemia, in which large numbers of abnormal red blood cells, white blood cells, or platelets grow and spread in the bone marrow and the peripheral blood.

**neuroendocrine tumor** (NOOR-oh-EN-doh-krin TOO-mer)

A tumor that forms from cells that release hormones in response to a signal from the nervous system. Some examples of neuroendocrine tumors are carcinoid tumors, islet cell tumors, medullary thyroid carcinomas, pheochromocytomas, and neuroendocrine carcinomas of the skin (Merkel cell cancer). These tumors may secrete higher-than-normal amounts of hormones, which can cause many different symptoms.

**non-Hodgkin lymphoma** (non-HOJ-kin lim-FOH-muh)

Any of a large group of cancers of lymphocytes (white blood cells). Non-Hodgkin lymphomas can occur at any age and are often marked by lymph nodes that are larger than normal, fever, and weight loss. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing) and indolent (slow-growing) types, and they can be formed from either B-cells or T-cells. B-cell non-Hodgkin lymphomas include Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma. T-cell non-Hodgkin lymphomas include mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma. Lymphomas that occur after bone marrow or stem cell transplantation are usually B-cell non-Hodgkin lymphomas. Prognosis and treatment depend on the stage and type of disease. Also called NHL.

**non-small cell lung cancer** (... sel lung KAN-ser)

A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Non-small cell lung cancer is the most common kind of lung cancer.

**nutrient** (NOO-tree-ent)

A chemical compound (such as protein, fat, carbohydrate, vitamin, or mineral) contained in foods. These compounds are used by the body to function and grow.

**ovary** (OH-vuh-ree)

One of a pair of female reproductive glands in which the ova, or eggs, are formed. The ovaries are located in the pelvis, one on each side of the uterus.

**oxygen** (OK-sih-jen)

A colorless, odorless gas. It is needed for animal and plant life. Oxygen that is breathed in enters the blood from the lungs and travels to the tissues.

**pancreatic** (PAN-kree-A-tik)

Having to do with the pancreas.

**pancreatic cancer** (PAN-kree-A-tik KAN-ser)

A disease in which malignant (cancer) cells are found in the tissues of the pancreas. Also called exocrine cancer.

**peripheral T-cell lymphoma** (peh-RIH-feh-rul ... lim-FOH-muh)

One of a group of aggressive (fast-growing) non-Hodgkin lymphomas that begins in mature T lymphocytes (T cells that have matured in the thymus gland and goes to other lymphatic sites in the body, including lymph nodes, bone marrow, and spleen.) Also called mature T-cell lymphoma.

**plasma membrane** (PLAZ-muh MEM-brayn)

The outer membrane of a cell.

**platelet-derived growth factor** (PLAYT-let-deh-RIVED grothe FAK-ter)

A family of molecules released from platelets (tiny pieces of cells that are found in the blood and that help the blood clot). Forms of platelet-derived growth factor help to heal wounds and to repair damage to blood vessel walls. They also help blood vessels grow. Also called PDGF.

**premenopausal** (pree-MEH-nuh-PAW-zul)

Having to do with the time before menopause. Menopause ("change of life") is the time of life when a woman's menstrual periods stop permanently.

**protein** (PROH-teen)

A molecule made up of amino acids that are needed for the body to function properly. Proteins are the basis of body structures such as skin and hair and of substances such as enzymes, cytokines, and antibodies.

**proteomics** (proh-tee-OH-mix)

The study of the structure and function of proteins, including the way they work and interact with each other inside cells.

**quality of life** (KWAH-lih-tee ... life)

The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out various activities.

**radioactive** (RAY-dee-oh-AK-tiv)

Giving off radiation.

**radioisotope** (RAY-dee-oh-I-suh-tope)

An unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. Radioisotopes may occur in nature or be made in a laboratory. In medicine, they are used in imaging tests and in treatment. Also called radionuclide.

**radiolabeled** (RAY-dee-oh-LAY-buld)

Any compound that has been joined with a radioactive substance.

**radiotherapy** (RAY-dee-oh-THAYR-uh-pee)

The use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

**receptor** (reh-SEP-ter)

A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell.

**recur** (ree-KER)

To come back or to return.

**remission** (reh-MIH-shun)

A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

**renal cell carcinoma** (REE-nul sel KAR-sih-NOH-muh)

The most common type of kidney cancer. It begins in the lining of the renal tubules in the kidney. The renal tubules filter the blood and produce urine. Also called hypernephroma, renal cell adenocarcinoma, and renal cell cancer.

**retinoic acid** (REH-tih-NOH-ik A-sid)

A nutrient that the body needs in small amounts to function and stay healthy. Retinoic acid is made in the body from vitamin A and helps cells to grow and develop, especially in the embryo. A form of retinoic acid made in the laboratory is put on the skin to treat conditions such as acne and is taken by mouth to treat acute promyelocytic leukemia (a fast-growing cancer in which there are too many immature blood-forming cells in the blood and bone marrow). Retinoic acid is being studied in the prevention and treatment of other types of cancer. Also called all-trans retinoic acid, ATRA, tretinoin, and vitamin A acid.

**retinoid** (REH-tih-noyd)

Vitamin A or a vitamin A-like compound.

**SERM**

A drug that acts like estrogen on some tissues but blocks the effect of estrogen on other tissues. Tamoxifen and raloxifene are SERMs. Also called selective estrogen receptor modulator.

**side effect** (side eh-FEKT)

A problem that occurs when treatment affects healthy tissues or organs. Some common side effects of cancer treatment are fatigue, pain, nausea, vomiting, decreased blood cell counts, hair loss, and mouth sores.

**signal transduction** (SIG-nul tranz-DUK-shun)

The process by which a cell responds to substances in its environment. The binding of a substance to a molecule on the surface of a cell causes signals to be passed from one molecule to another inside the cell. These signals can affect many functions of the cell, including cell division and cell death. Cells that have permanent changes in signal transduction molecules may develop into cancer.

**signaling pathway** (SIG-nuh-ling ...)

Describes a group of molecules in a cell that work together to control one or more cell functions, such as cell division or cell death. After the first molecule in a pathway receives a signal, it activates another molecule. This process is repeated until the last molecule is activated and the cell function involved is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. This may help block cancer cell growth and kill cancer cells.

**spleen** (spleen)

An organ that is part of the lymphatic system. The spleen makes lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach.

**squamous cell carcinoma of the head and neck** (SKWAY-mus sel KAR-sih-NOH-muh ...)

Cancer of the head and neck that begins in squamous cells (thin, flat cells that form the surface of the skin, eyes, various internal organs, and the lining of hollow organs and ducts of some glands). Squamous cell carcinoma of the head and neck includes cancers of the nasal cavity, sinuses, lips, mouth, salivary glands, throat, and larynx (voice box). Most head and neck cancers are squamous cell carcinomas.

**subependymal giant cell astrocytoma** (SUB-eh-PEN-dih-mul JY-unt sel AS-troh-sy-TOH-muh)

A benign (not cancer), slow-growing tumor that usually forms in the walls of fluid-filled spaces in the brain. The tumors are made up of large, star-shaped cells called astrocytes. Subependymal giant cell astrocytomas are common in patients with tuberous sclerosis (an inherited disorder in which benign tumors form in the brain and other parts of the body). Also called SEGA.

**systemic mastocytosis** (sis-TEH-mik MAS-toh-sy-TOH-sis)

A rare disease in which too many mast cells (a type of immune system cell) are found in the skin, bones, joints, lymph nodes, liver, spleen, and gastrointestinal tract. Mast cells give off chemicals such as histamine that can cause flushing (a hot, red face), itching, abdominal cramps, muscle pain, nausea, vomiting, diarrhea, low blood pressure, and shock.

**systemic therapy** (sis-TEH-mik THAYR-uh-pee)

Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body.

**T cell** (... sel)

A type of immune cell that can attack foreign cells, cancer cells, and cells infected with a virus. T cells can also help control immune responses. A T cell is a type of white blood cell. Also called T lymphocyte and thymocyte.

**targeted therapy** (TAR-geh-ted THAYR-uh-pee)

A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatments.

**therapy** (THAYR-uh-pee)

Treatment.

**tuberous sclerosis** (TOO-ber-us skleh-ROH-sis)

A genetic disorder in which benign (not cancer) tumors form in the kidneys, brain, eyes, heart, lungs, and skin. This disease can cause seizures, mental disabilities, and different types of skin lesions.

**tumor** (TOO-mer)

An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer), or malignant (cancer). Also called neoplasm.

**tyrosine kinase inhibitor** (TY-ruh-seen KY-nays in-HIH-bih-ter)

A drug that interferes with cell communication and growth and may prevent tumor growth. Some tyrosine kinase inhibitors are used to treat cancer.

**unresectable** (UN-ree-SEK-tuh-bul)

Unable to be removed with surgery.

**vaccine** (vak-SEEN)

A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.

**vascular endothelial growth factor** (VAS-kyoo-ler EN-doh-THÉE-lee-ul grothe FAK-ter)

A substance made by cells that stimulates new blood vessel formation. Also called VEGF.

**vitamin A** (VY-tuh-min ...)

A nutrient that the body needs in small amounts to function and stay healthy. Vitamin A helps in vision, bone growth, reproduction, growth of epithelium (cells that line the internal and external surfaces of the body), and fighting infections. It is fat-soluble (can dissolve in fats and oils). Vitamin A is found in liver, egg yolks, and whole milk dairy products from animals and in fish oils. It can also be made in the body from a substance found in some fruits and vegetables, such as cantaloupes, carrots, spinach, and sweet potatoes. Vitamin A is being studied in the prevention and treatment of some types of cancer. Also called retinol.

**yttrium** (IH-tree-um)

A metal of the rare earth group of elements. A radioactive form of yttrium may be attached to a monoclonal antibody or other molecule that can locate and bind to cancer cells and be used to diagnose or treat some types of cancer.

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- <sup>3</sup> <http://www.cancer.gov/cancertopics/druginfo/fulvestrant>
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- **Multi-Targeted Therapy Is Extending Non-Chemotherapy Options for MBC**

(<http://her2support.org/vbulletin/showthread.php?t=48604>)

Hopeful

01-31-2011 03:02 PM

### Multi-Targeted Therapy Is Extending Non-Chemotherapy Options for MBC

Dr. Cliff Hudis: Multi-Targeted Therapy Is Extending Non-Chemotherapy Options in Advanced Breast Cancer

2011 Jan 4, Interview by L Scott Zoeller

Dr. Clifford A. Hudis is Chief, Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer, New York, NY.

OncologySTAT: In your view, which development in advanced breast cancer research that occurred in 2010 could have the most impact on oncology?

Dr. Hudis: I think that the big advances in breast cancer research are in targeted therapy, primarily those drugs that are targeting HER2, but also including, obviously, the Poly (ADP-ribose) polymerase (PARP) inhibitors and, potentially, others. This is a somewhat global answer to the question; however, the point I want to make, which is echoed not just in breast cancer but throughout solid tumor oncology, is that it is increasingly clear that many subtypes of individual malignancies are driven by either oncogenes or other narrowly activated targets. These, in turn, can be inhibited in order to treat these malignancies.

The global theme is continued expansion, if not an explosion, in the availability of viable targets for treatment development. This has, I think, the greatest potential impact on all of oncology, not just breast cancer. However, it carries with it a very obvious cost, which is we are going away from, as we have predicted for years we would, the notion of one disease universally consistent across patients.

It is becoming very clear that even people who have similar, if not identical, conventionally defined histologic types of cancer may indeed have molecular biology that is different. This is going to be a huge issue because the rarity of important targets across populations will make drug development increasingly challenging.

OncologySTAT: What specific changes in oncology have you observed or do you foresee as a result of this development?

Dr. Hudis: It is becoming increasingly clear that at least some patients with advanced breast cancer for some period of time may be able to obtain treatment that does not involve conventional cytotoxic chemotherapy. This is an advance in that it represents, at a minimum, a likely quality-of-life improvement, if not an effectiveness improvement, as well.

OncologySTAT: Could you put this development into historical perspective for the practicing oncologist?

Dr. Hudis: In terms of breast cancer, we have had targeted therapy in the form of hormone treatment dating back more than a century, starting with ovarian ablation and suppression. We more recently have had a second viable target, of course—HER2, targeted by trastuzumab. This is revolutionary, although it might not at first seem like it. By targeting these pathways in multiple ways, or by targeting them with more effective drugs, we are essentially able to extend the non-chemotherapy option to patients with disease other than hormone receptor-positive breast cancer.

Now, it is conceivable that we could have several lines of therapy for patients with HER2-positive breast cancers that are chemotherapy sparing, if not chemotherapy avoiding. It is conceivable that we could have even non-chemotherapy-containing regimens for triple-negative breast cancer; albeit, not tomorrow.

OncologySTAT: Would you sum up in a single sentence why you chose this development as the top story of the past year?

Dr. Hudis: We are in the beginning or maybe even middle of a long-awaited transition with functional, practical, and

clinically relevant importance that is both redefining breast cancer and its treatment.

Hopeful

All times are GMT -7. The time now is 11:19 AM.

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Memorial Sloan-Kettering  
Cancer Center

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# Center News Magazine: Public CancerSmart Lecture Highlights the Science of Breast Cancer Treatment

Tuesday, June 1, 2010

More than 300 members of the public gathered in Memorial Sloan-Kettering's Rockefeller Research Laboratories Auditorium on March 18 to hear medical oncologist Clifford A. Hudis speak on “New Concepts, New Targets, New Directions, New Hope” in treating breast cancer. Dr. Hudis is Chief of the Breast Cancer Medicine Service in Memorial Hospital.

During the lecture, part of the Center's *CancerSmart* series, Dr. Hudis told attendees about the science of breast cancer. For example, he explained the meaning of relative risk and discussed some of the details about how breast cancer develops and how it metastasizes, or spreads, to other parts of the body. He also discussed some of the risk factors for breast cancer, including gender, age, diet, and the use of hormone replacement therapy.

Much of Dr. Hudis' talk focused on the genetic causes of breast cancer, and how those genetics are related to the development of targeted therapies. “What I'm sharing with you is a way in which our understanding of the science — specifically the genetics — can begin to inform our treatment of patients both at the global level and individually,” he said. He explained the science behind the development and use of several targeted therapies for breast cancer, including trastuzumab, tamoxifen, and aromatase inhibitors, which are currently part of standard treatment for many breast cancers, as well as PARP inhibitors, a new class of drug currently under investigation. Following his talk, he took questions from the audience on a range of topics related to breast cancer.

Memorial Sloan-Kettering has held free educational lectures on topics of interest to the public since 1995. Previous topics in the *CancerSmart* series have included end-of-life issues and the role of



## VIDEOS

[New Concepts, New Directions, New Hope in Breast Cancer](#)

## EDITORIALS



## Crizotinib — Latest Champion in the Cancer Wars?

Bengt Hallberg, Ph.D., and Ruth H. Palmer, Ph.D.

Three articles in this issue of the *Journal* report on the therapeutic potential of a new kid on the kinase inhibitor block: crizotinib, an ATP-competitive inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase.

Kwak et al.<sup>1</sup> summarize a study involving patients with non–small-cell lung cancer who were enrolled in a phase 1 trial, starting in 2008, hot on the heels of a study in which cell lines derived from non–small-cell lung tumors were shown to be sensitive to NVP-TAE684<sup>2</sup> and crizotinib (PF-02341066).<sup>3,4</sup> From a cohort of 1500 patients with non–small-cell lung cancer, 82 (5.5%) were found to carry an *ALK* rearrangement on fluorescence in situ hybridization (FISH). The authors note that not all of these genetic rearrangements were confirmed as *EML4-ALK*,<sup>5</sup> which suggests that other *ALK* fusions may be present, such as *TFG-ALK*<sup>6</sup> and *KIF5B-ALK*.<sup>7</sup> Although the best-studied *ALK* fusion is the nucleophosmin (NPM)-*ALK* protein found in lymphoma, it is reasonable to expect that a number of the signaling pathways activated by *NPM-ALK* will also be involved in transformation by variants such as *EML4-ALK* (Fig. 1).

Most of the patients with non–small-cell lung cancer who carried the *EML4-ALK* translocation were nonsmokers and had adenocarcinomas. Even though more than 90% of these patients had undergone at least one previous line of therapy, the investigators observed a 57% response rate to crizotinib, according to Response Evaluation Criteria in Solid Tumors (RECIST), with a rate of disease control of 87% at 8 weeks. Although a control group was lacking in this study, these results compare very favorably with the reported 10% response with second-line chemo-

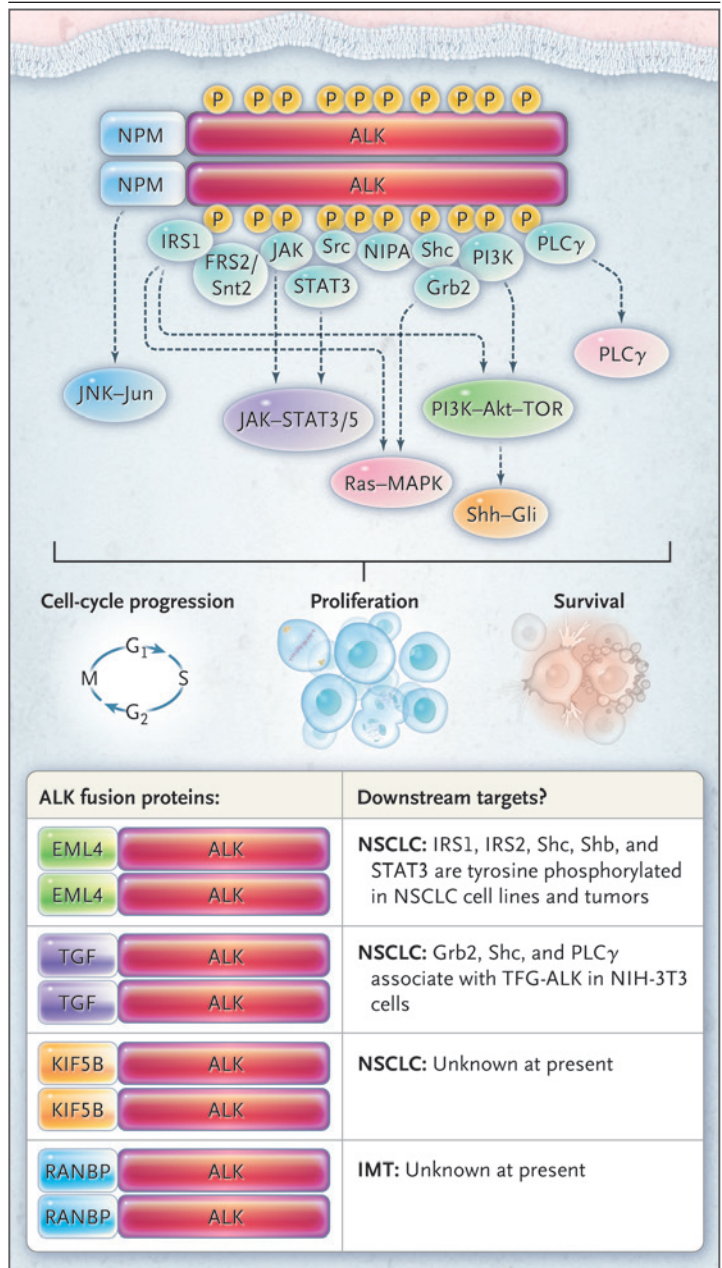
therapy. At a mean treatment duration of 6.4 months, 27 patients had stable disease, 46 had a partial response, and 1 had a complete response. All patients tested negative for amplification of *MET*, another target for crizotinib, which suggested that the therapeutic effect is through inhibition of *ALK*.

These results raise the question of whether crizotinib will yield equally strong responses as the first therapeutic intervention or whether a combined approach will be more beneficial. At a rate of approximately 5% positivity for the *ALK* rearrangement, the number of potential patients for crizotinib therapy is substantial, approaching 10,000 annually in the United States alone. Clearly, with mutant epidermal growth factor receptor (EGFR), *K-RAS*, and *ALK* as important clinical determinants in this type of lung cancer, the use of genotyping as standard practice must be considered as a move toward personalized therapy.

As with the kinase inhibitors already in use, such as imatinib and EGFR inhibitors, kinase inhibition frequently leads to the appearance of drug-resistance mutations within the target kinase itself. Although Kwak et al. do not address this issue, it is possible that in a number of *ALK*-positive patients who had a limited response in this study, such mutations may have developed either before or during treatment with crizotinib. This factor is clearly illustrated in a study by Choi et al.,<sup>10</sup> who describe mutations in *EML4-ALK* that confer resistance to crizotinib. Their data support the independent appearance of mutations leading to C1156Y and L1196M coding changes in a patient with non–small-cell lung cancer who had an initial strong clinical response to

**Figure 1. Signaling Pathways Activated by ALK Fusion Proteins.**

In oncogenic fusion genes consisting of anaplastic lymphoma kinase (ALK) and *NPM*, *EML4*, *TFG*, *KIF3B*, and *RANBP*, the various fusion partners act by conferring dimerization and constitutive kinase activity. *NPM*-ALK in the context of anaplastic large-cell lymphoma is the most studied variant and activates numerous signaling pathways to promote tumorigenesis. These signaling pathways include those involving Ras and mitogen-activated protein kinase (MAPK); phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), and target of rapamycin (TOR); sonic hedgehog (Shh); phospholipase C $\gamma$  (PLC $\gamma$ ); JUN kinase (JNK); and Janus kinase (JAK) and signal transducer and activator of transcription (STAT).<sup>8</sup> With the use of proteomics to conduct a large-scale survey of tyrosine kinase activity in cell lines derived from non-small-cell lung cancers (NSCLCs), a large number of putative tyrosine substrates were identified for *EML4*-ALK and *TGF*-ALK fusion proteins.<sup>6</sup> *TFG*-ALK has also been shown to interact with growth factor receptor-bound protein 2 (Grb2), Shc, and PLC $\gamma$  when expressed in NIH-3T3 cells.<sup>9</sup> Although many of the described interacting proteins will probably be conserved among the various ALK fusion proteins, there is variation not only in the fusion partner but also in the cell types in which they are expressed. This variation may lead to differences in substrate molecular and signaling pathways that are activated. Careful analysis will be required to untangle the relevant differences in signaling among the numerous ALK fusion proteins to identify future points of additional therapeutic intervention. *FRS2* denotes fibroblast growth factor receptor substrate 2, *Gli* GLI family zinc finger 1, *IMT* inflammatory myofibroblastic tumor, *IRS1/2* insulin receptor substrate 1/2, and *NIPA* nuclear interaction partner of ALK.



crizotinib. On the basis of structural considerations of the crystal structure of the ALK kinase domain,<sup>11,12</sup> L1196M represents a mutation of the gatekeeper residue, similar to the T790M gefitinib-resistance mutations observed in EGFR and T315I mutations in ABL, and it would be predicted to prevent crizotinib binding to ALK. The effect of the C1156Y mutation is unclear, since it appears unlikely to have a direct effect on crizotinib binding. Further studies will be required to establish the mechanism of action behind C1156Y resistance. Choi et al. found that these *EML4*-ALK mutants are less sensitive to crizotinib than is wild-type *EML4*-ALK when expressed in Ba/F3 cells, in agreement with the loss of clinical response in this patient. The resistance of the C1156Y variant to crizotinib was not as great in vitro as in vivo, suggesting that

this mutation may require interaction with additional factors in the cell to have strong drug sensitivity.

The appearance of crizotinib-resistance mutations in this patient indicates that additional ALK inhibitors will be required to target *EML4*-ALK mutants that are insensitive to crizotinib in a clinical setting. This brings clinical reality to the predictions from a recent prospective mutagenesis study on *NPM*-ALK in which strong resis-

tance to ALK inhibitors in mouse tumor models was observed with the NPM-ALK mutant L256M, which is in the same residue as L1196M of EML4-ALK.<sup>13</sup> Thus, a familiar story line emerges, highlighting the need for basic scientists and clinicians to work together to plan a step ahead of the evolving tumor. It is encouraging that some progress in this area has already been made, and a number of such drugs are in the pipeline, including a new ALK inhibitor.<sup>14</sup>

Although patients with ALK-positive non-small-cell lung cancers make up the largest group of patients who may benefit from crizotinib, other patients with rarer diseases, such as those with ALK-positive non-Hodgkin's lymphoma or inflammatory myofibroblastic tumor (IMT), also stand to benefit. This is illustrated in a study by Butrynski et al.,<sup>15</sup> in which the authors describe two patients with IMT, one of whom carried the RANBP2-ALK fusion protein. Both patients were treated with crizotinib, with the ALK-positive patient having a strong response for several months. However, there was subsequent identification of growth in three lesions, which were resected before resumption of crizotinib postoperatively. A complete radiographic remission was reported in June 2010. It will be interesting to understand more about the nature of the masses that were surgically removed, since it is possible they carried crizotinib-insensitive RANBP2-ALK variants. Therefore, ALK-positive IMT, like non-small-cell lung cancer, appears to have an Achilles' heel when it comes to inhibition of ALK signaling.

One major problem for cancer drugs, including kinase inhibitors, is toxic effects. Both Kwak et al. and Butrynski et al. report that crizotinib produced only grade 2 side effects in patients when used at the therapeutic dose of 250 mg twice daily. This is good news for patients facing the prospect of long-term cancer therapy.

Together, these three studies provide an optimistic view of the successful treatment of ALK-positive cancers. One positive offshoot is the potential use of crizotinib in treating neuroblastoma, a devastating childhood cancer, in which ALK gain-of-function mutations have been reported in approximately 10% of patients.<sup>16</sup> Clearly, in groups of patients with cancers in which ALK is implicated, a standard genotyping approach will be important for a more personalized ther-

apeutic protocol. Future clinical studies of crizotinib and other ALK inhibitors will tell us whether they will be the latest champions in the cancer wars.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Department of Molecular Biology, Umeå University, Umeå, Sweden.

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## The 39th David A. Karnofsky Lecture: Bench-to-Bedside Translation of Targeted Therapies in Multiple Myeloma

Kenneth C. Anderson

From the Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.

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Corresponding author: Kenneth C. Anderson, MD, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02115-5450; e-mail: [kenneth\\_anderson@dfci.harvard.edu](mailto:kenneth_anderson@dfci.harvard.edu).

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### ABSTRACT

Multiple myeloma (MM) is a remarkable example of rapid bench-to-bedside translation in new drug development. The proteasome inhibitor bortezomib and immunomodulatory drug lenalidomide targeted MM cells in the bone marrow (BM) microenvironment to overcome conventional drug resistance in laboratory and animal models and were rapidly translated into clinical trials demonstrating their efficacy in patients with relapsed and then newly diagnosed MM, with a doubling of the median survival as a direct result. The future is even brighter. First, immune-based therapies are being developed (eg, elotuzumab monoclonal antibody [MoAb]; CD138DM immunotoxin; MM cell–dendritic cell vaccines; CD138, CS-1, and XBP-1 peptide vaccines; anti-17 MoAb; and other treatments to overcome causes of immune dysfunction). Second, promising next-generation agents target the MM cell in its microenvironment (eg, deubiquitinating enzyme inhibitors; chymotryptic [carfilzomib, Onyx 0912, MLN 9708] and broader [NPI-0052] proteasome inhibitors; immunoproteasome inhibitors; and pomalidomide). Moreover, agents targeting bone biology (eg, zoledronic acid, anti-DKK-1 MoAb, anti-B-cell activating factor MoAb and bortezomib, Btk inhibitor) show promise not only in preserving bone integrity but also against MM. Third, rationally based combination therapies, including bortezomib with Akt, mammalian target of rapamycin, or histone deacetylase inhibitors, are active even in bortezomib-refractory MM. Finally, genomics is currently being used in the definition of MM heterogeneity, new target discovery, and development of personalized therapy. Myeloma therefore represents a paradigm for targeting the tumor in its microenvironment, which has already markedly improved patient outcome in MM and has great potential in other hematologic malignancies and solid tumors as well.

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### INTRODUCTION

Multiple myeloma (MM) is characterized by excess monoclonal plasma cells in the bone marrow (BM), in most cases associated with monoclonal protein in blood and/or urine. With the use of combined melphalan and prednisone nearly 50 years ago, median patient survival of patients with MM was extended to 2 to 3 years. Originally pioneered by Tim McElwain in the 1970s, high-dose melphalan followed by BM transplantation in the 1980s and with peripheral blood stem-cell rescue in the 1990s further increased patient median survival to 3 to 4 years. Since 1998, MM has represented a new paradigm in drug development because of the remarkable therapeutic efficacy of targeting tumor cells in their microenvironments.<sup>1,2</sup> In particular, the observation that proteasome inhibitor bortezomib and immunomodulatory drugs (IMiDs) thalidomide and lenalidomide target the MM cell in the BM microenvironment has rapidly translated from bench to bedside and six new US Food and Drug

Administration–approved treatments in the past 7 years, with a doubling of patient survival from 3 to 4 to 7 to 8 years as a direct result.<sup>3</sup> Our contributions have been in the areas of identifying novel targets in the tumor and microenvironment, validating inhibitors directed at these targets, and conducting clinical trials leading to their approval. These collaborative efforts have included basic and clinical investigators, the pharmaceutical industry, the National Cancer Institute, US Food and Drug Administration regulators, and patient advocacy groups, with a common focus and inspired by the sole goal of improving MM treatments.<sup>4</sup> Indeed, the use of novel targeted inhibitors to treat relapsed refractory MM, relapsed MM, and newly diagnosed MM and most recently as consolidation and maintenance therapies has totally transformed MM therapy and patient outcome.

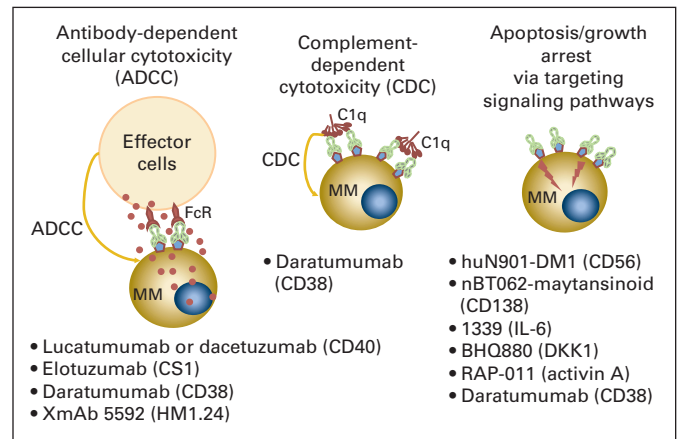
I have been carrying out bench-to-bedside research in MM for 38 years now, initially inspired by my mentor, Dr Richard L. Humphrey, who taught me the two most important lessons that have shaped my research and clinical practice. As a

medical student at Johns Hopkins, he instilled in me the opportunity in MM to “make science count for patients” by developing laboratory and animal models of disease and then rapidly translating promising leads from the bench to the bedside in clinical trials. Moreover, he imprinted in me the importance of treating patients as family. He has served as my inspiration and role model ever since.

## DEVELOPMENT OF IMMUNE-BASED THERAPIES

After an introduction to MM both in the laboratory and clinic at Johns Hopkins during my medical school and internal medicine training, I moved to the Dana-Farber Cancer Institute for training in medical oncology, hematology, and tumor immunology. There Drs George Canellos and Robert Mayer instilled in me the importance of clinical investigation. Under the tutelage of Drs Lee Nadler and Stuart Schlossman, I was part of a team that developed monoclonal antibodies (MoAbs) directed at B-cell malignancies, including MM.<sup>5,6</sup> It was an extraordinary time, because these MoAbs allowed for identification of the lineage and stage of differentiation of B-cell malignancies as well as comparison of the neoplastic B cell with its normal cellular counterpart. A panel of B-cell MoAbs was useful to complement histopathologic diagnosis and identify non-T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia and lymphomas, and MM as tumors corresponding to pre-B cells, isotype diversity B differentiative stages, and plasma cells, respectively.<sup>5</sup>

Right from the outset, these MoAbs were also used in innovative treatment strategies in MM, and our efforts to develop immune-based MoAb and immunotoxin therapies, tumor vaccines, and mechanisms to abrogate host immunosuppression continue to the present. Specifically, high-dose therapy and autologous BM transplantation achieved remarkable extent and frequency of response, and early on, we examined whether cocktails of MoAbs (eg, CD10, CD20, PCA-1) could purge MM cells from autografts *ex vivo* before autologous BM transplantation.<sup>7</sup> Although effective at purging two to three logs of MM cells, impact on overall outcome was unaffected, likely because of residual systemic tumor burden. T cell (CD6) –directed MoAb was used to purge T cells from allogeneic BM grafts to abrogate graft-versus-host disease.<sup>8</sup> However, the transplant-related mortality of allo-transplantation in MM remains unacceptably high to the present, and we continue to carry out studies to identify targets of allogeneic graft-versus-myeloma effect<sup>9</sup> and clinical protocols of nonmyeloablative allografting to exploit graft-versus-myeloma effect while avoiding attendant toxicity. Over many years, we have continued to carry out preclinical and clinical studies of MoAbs targeting MM cells, tumor-host interactions, and cytokines as well as evaluated MoAb-based immunotoxin therapies<sup>1,10,11</sup> (Fig 1). For example, we identified CS-1 to be highly and uniformly expressed at the gene and protein levels in patient MM cells and then showed that targeting this antigen with elotuzumab was effective in preclinical models of MM in the BM milieu both *in vitro* and *in vivo*.<sup>13</sup> These promising data in turn led to a clinical trial of elotuzumab, which achieved stable disease in relapsed refractory MM but did not induce responses sufficient to warrant new drug development. Importantly, our preclinical studies showed that lenalidomide enhanced antibody-dependent cellular cytotoxicity triggered by elotuzumab,<sup>13</sup> providing the rationale for a combination clinical trial with promising results. This bedside-to-bench-and-back iterative process illustrates our trans-



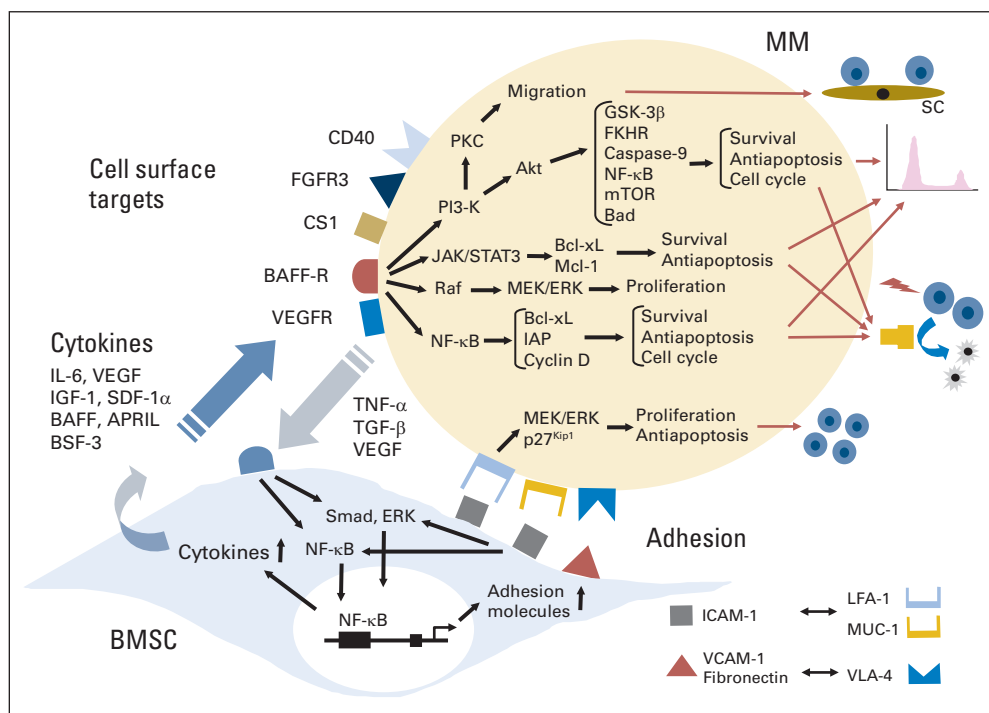
**Fig 1.** Monoclonal antibody therapeutic targeting of multiple myeloma (MM). Monoclonal antibodies evaluated in clinical trials mediate antibody-dependent cellular cytotoxicity (ADCC) or complement mediated cytotoxicity (CDC) as well as directly target growth or apoptotic signaling pathways. IL, interleukin. Data adapted.<sup>12</sup>

lational focus. An example of an immunotoxin clinical trial is that of CD138 linked to maytansinoid toxin DM, which is currently ongoing based on our promising data both *in vitro* and in xenograft models of human MM in mice.<sup>14</sup>

Our more recent focus in immune therapies has been on the development of vaccines. Vasair et al<sup>15</sup> have shown in murine MM and Rosenblatt et al<sup>16</sup> in human MM that vaccination with fusions of dendritic cells (DCs) with tumor cells allows for generation of T- and B-cell tumor-specific responses *in vitro* and *in vivo* preclinical models; derived recent clinical trials of MM-DC vaccinations to treat minimal residual disease posttransplantation are triggering host antitumor T-cell and humoral responses associated with high rates of complete response. An alternative strategy is the use of cocktails of peptides for vaccination. Specifically, we have shown that CS-1, XBP-1, and CD138 are functionally significant targets in MM cells and derived peptides from these antigens, which can be presented and trigger cytotoxic T lymphocyte responses in human leukocyte antigen A2-positive patients.<sup>17</sup> Ongoing clinical trials are evaluating vaccination with cocktails of these peptides in patients most likely to respond, with the goal of triggering immune responses with clinical significance.

We have also characterized the underlying immunodeficiency in patients with MM to design strategies to overcome it.<sup>18</sup> Our studies have demonstrated decreased help, increased suppression, pro-MM growth cytokines, and dysregulated immune-homeostasis, always with a view toward mechanism and clinical application. For example, the demonstration of increased TH-17 cytokines promoting MM cell growth set the stage for a related clinical trial of anti-interleukin-17 MoAb in MM.<sup>18</sup> In our studies of host accessory cells, we have shown that plasmacytoid DCs (pDCs) in patients with MM do not induce immune effector cells, as do normal pDCs, but instead promote tumor growth, survival, and drug resistance.<sup>19</sup> In preclinical studies, maturation of pDCs with CpG oligonucleotides both restores immune stimulatory function of pDCs and abrogates their tumor-promoting activity, setting the stage for a derived clinical trial.





**Fig 2.** Targeting growth, survival, and drug resistance of multiple myeloma (MM) cells in the bone marrow microenvironment. Novel therapies can target the MM cell surface, cytokines, host-tumor cell interactions, and signaling pathways within tumor and accessory cells. APRIL, A Proliferation-inducing ligand; BAFF, B-cell activating factor; BAFF-R, B-cell activating factor receptor; BCL, B-cell lymphoma; BM, bone marrow; BMSC, bone marrow stromal cell; BSF, B-cell stimulating factor; FGFR, fibroblast growth factor receptor; FKHR, forkhead in human rhabdomyosarcoma; GSK, glycogen synthase kinase; IAP, inhibitor of apoptosis; ICAM, intercellular adhesion molecule; IGF, insulin-like growth factor; IL, interleukin; JAK, janus kinase; LFA, lymphocyte function-associated antigen; mTOR, mammalian target of rapamycin; MUC, mucin; NF-κB, nuclear factor κB; PKC, protein kinase C; SC, stromal cell; SDF, stromal cell-derived factor; STAT3, signal transducer and activator of transcription 3; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGFR, vascular endothelial growth factor receptor; VLA, very late antigen. Data adapted.<sup>1</sup>

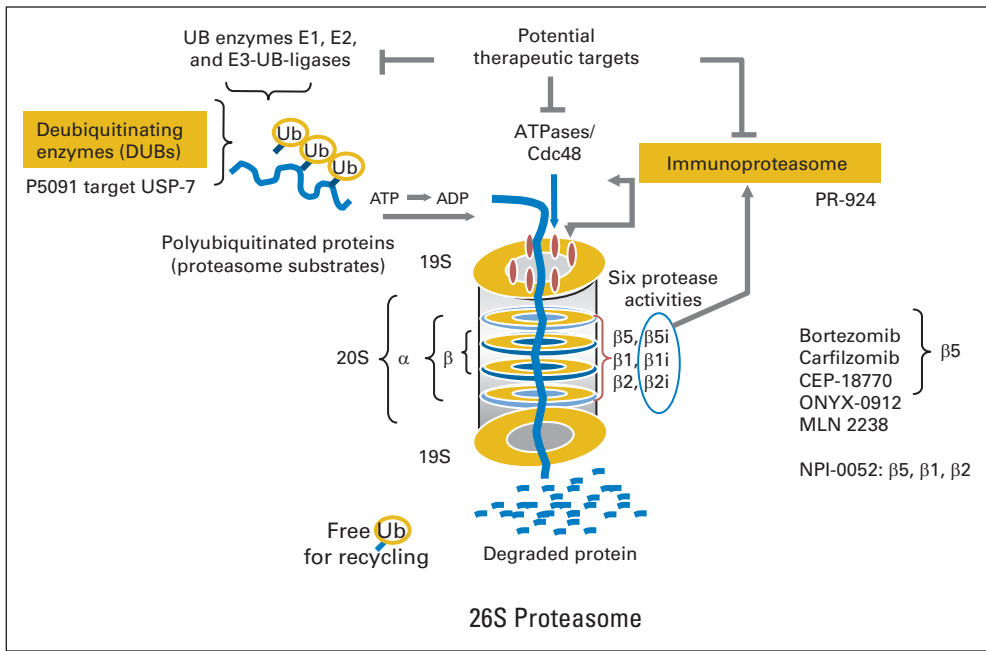
### THERAPIES TARGETING THE TUMOR IN ITS MICROENVIRONMENT

From the 1990s to the present, we have developed *in vitro* and *in vivo* models to define the role of MM-BM interactions in pathogenesis, identify novel targets, and validate novel targeted therapies. We have then gone on to translate multiple single and combination agents targeting the tumor and microenvironment from bench to bedside in clinical trials. We have also used oncogenomics to characterize pathogenesis, identify novel targets, predict response, and inform design of single-agent and combination clinical trials.

Specifically, we have developed models of MM in the BM microenvironment that have been useful in defining the role of tumor cell–BM accessory cell contact as well as cytokines in the BM milieu in conferring growth, survival, and drug resistance in MM<sup>1,20,21</sup> (Fig 2). Importantly, these models have allowed for the identification of agents that can overcome cell adhesion–mediated drug resistance to conventional therapies. The proteasome inhibitor bortezomib, for example, triggers MM cell cytotoxicity in the BM, whereas antitumor activity of dexamethasone is completely attenuated.<sup>22</sup> Both at gene transcript and proteasome activity levels, the ubiquitin proteasome cascade is upregulated by MM-BM binding, perhaps contributing to its enhanced activity in this context.<sup>23</sup> Bortezomib directly targets chymotryptic proteasome activity, inhibits growth and survival, induces apoptosis, upregulates heat shock proteins, inhibits DNA damage repair, and induces endoplasmic reticulum stress in MM cells; downregulates adhesion molecules on tumor and BM, thereby abrogating adhesion; and, importantly, targets the microenvironment to trigger antiangiogenesis as well as apoptosis of osteoclasts while promoting osteoblast differentiation.<sup>22,24–28</sup> It was rapidly translated from the bench to the bedside and received accelerated US Food and Drug Administration approval in 2003 for treatment of relapsed refractory

MM, followed by approval for relapsed MM and as initial therapy based on its superiority in randomized phase III clinical trials.<sup>29–31</sup> Most recently, promising data supporting bortezomib as consolidation and maintenance therapy have been emerging.

However, not all MMs respond to bortezomib, and some tumors ultimately develop resistance. From the outset, we have therefore tried to identify gene signatures of response versus resistance to bortezomib in MM<sup>32</sup> as well as develop functional assays to better predict patients whose cancers are most likely to respond. For example, we developed a predictive model in which tumors like MM with high proteasome load and low proteasome capacity have high proteasome stress and are therefore susceptible to proteasome inhibition, whereas solid tumors with high proteasome capacity and low proteasome load are relatively resistant to proteasome inhibitors.<sup>33</sup> Importantly, bortezomib has opened a whole new area of preclinical and clinical experimentation in cancer targeting the ubiquitin proteasome cascade upstream of the proteasome with deubiquitinating inhibitors, selectively or more broadly targeting proteasome activity, and targeting the immunoproteasome (Fig 3). For example, our preclinical studies show that inhibitors of deubiquitinating enzymes upstream of the proteasome, such as USP-7 inhibitor P5091, inhibit human MM cell growth, and prolong host survival in a murine xenograft model. Carfilzomib, a next-generation, more potent intravenous inhibitor of chymotryptic activity, can overcome bortezomib resistance in preclinical and early clinical trials. Oral proteasome inhibitors targeting chymotryptic activity that have translated from the bench to bedside in phase I clinical trials include Onyx 0912, which triggers cytotoxicity against MM cell lines and patient cells, and MLN2238/9708, which has shown more potent preclinical activity against MM cells *in vivo* than bortezomib.<sup>34–39</sup> NPI-0052 targets chymotryptic, tryptic-like, and caspase-like activities and similarly shows clinical promise.<sup>38</sup> Finally, inhibitors of the immunoproteasome, such as the PR-924 inhibitor of



**Fig 3.** Proteasome: present and future therapies. Novel strategies of inhibiting the ubiquitin (Ub) proteasome cascade include deubiquitinating enzyme inhibitors upstream of the proteasome; selective or broader inhibitors of the chymotryptic, tryptic, and caspase-like activities; and immunoproteasome inhibitors. USP, Ub-specific peptidase.

the LMP-7 immunoproteasome subunit, also block MM growth in vitro and in vivo.<sup>40</sup>

Since the empiric observation that thalidomide had anti-MM activity in 1998, we have studied the IMiDs thalidomide, lenalidomide, and pomalidomide in our models of MM in the BM microenvironment. These agents directly trigger caspase 8–mediated apoptosis; decrease binding of tumor cells to BM; inhibit constitutive and MM cell binding–induced secretion of cytokines from BM; inhibit angiogenesis; and stimulate autologous natural killer, T, and natural killer–T cell immunity to MM cells.<sup>41–43</sup> Like bortezomib, lenalidomide was rapidly translated from the bench to the bedside. Our preclinical studies demonstrated increased responses when lenalidomide (which triggers caspase 8–mediated apoptosis) was combined with dexamethasone (which induces caspase 9–mediated apoptosis), and our phase I and II clinical trials both established the maximum-tolerated dose and confirmed the enhanced clinical efficacy of combined lenalidomide with dexamethasone, informing the design of phase III clinical trials leading to its US Food and Drug Administration/European Medicines Agency approval to treat relapsed MM.<sup>29,30,44–48</sup> Trials of lenalidomide as initial therapy in both transplantation candidate and elderly populations, as well as consolidation and maintenance therapy, are promising.<sup>49,50</sup> For example, maintenance lenalidomide has been shown to add years of progression-free survival in both newly diagnosed transplantation and nontransplantation candidates, further improving patient outcome. More recently, we and others have shown that the second-generation IMiD pomalidomide achieves remarkable and durable responses, with a favorable adverse effect profile, even in the setting of MM resistant to lenalidomide and bortezomib.<sup>51,52</sup>

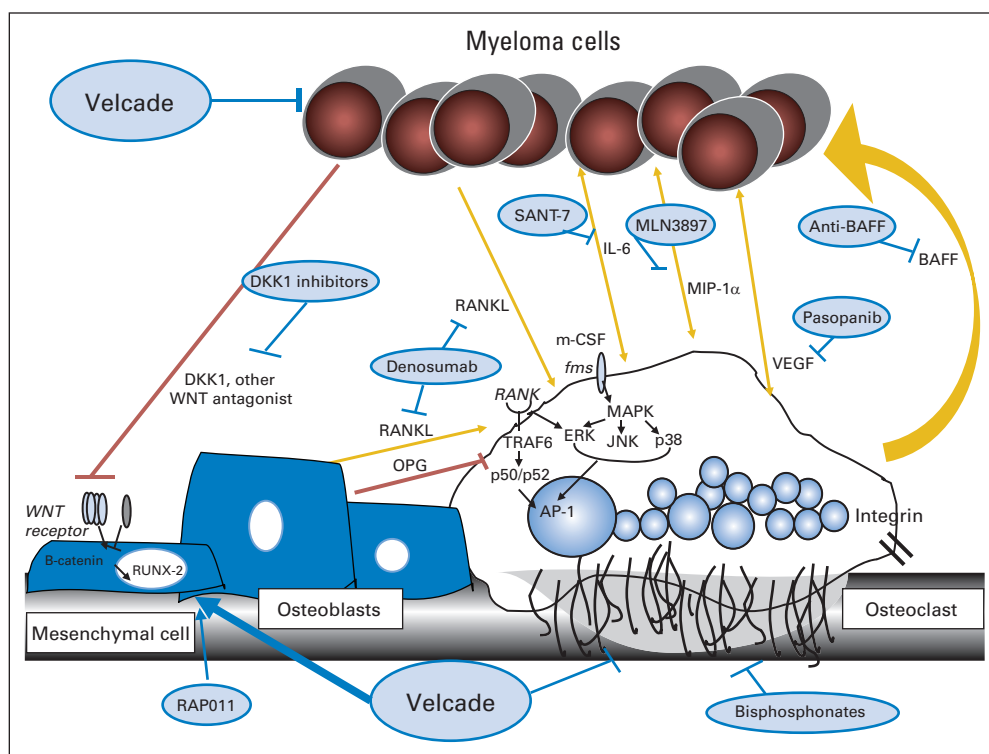
#### THERAPIES TARGETING ACCESSORY CELLS WITH ANTI-MM ACTIVITY

Bortezomib and lenalidomide are examples of targeting the tumor and also affecting the microenvironment, because both positively

affect bone disease in MM.<sup>28,53</sup> Conversely, we have also had a long-term interest in targeting the MM BM microenvironment, with the goal of also triggering MM responses (Fig 4). For example, MM cells secrete DKK-1, which downregulates osteoblast function via targeting Wnt signaling. In our preclinical murine xenograft models of human MM, the neutralizing anti-DKK-1 BHK880 MoAb not only triggers new bone formation but also inhibits MM cell growth,<sup>55</sup> and a derived clinical trial of BHK880 MoAb is ongoing. We have also shown that B-cell activating factor is elevated in the BM plasma of patients with MM and mediates osteoclastogenesis as well as tumor cell survival and drug resistance; importantly, anti-B-cell activating factor MoAb can neutralize these effects,<sup>56</sup> and a related clinical trial is ongoing. Most recently, targeting BTK in our preclinical models has not only blocked osteoclast formation and growth, thereby maintaining bone integrity, but also inhibited MM cell growth. These studies illustrate the principle that targeting cytokines or accessory cells in the tumor microenvironment can also affect MM cell growth, further validating the utility of our in vitro and in vivo model systems.

#### PRECLINICAL STUDIES TO INFORM COMBINATION TARGETED THERAPIES

We have also used functional oncogenomics to inform the design of novel combination therapies. For example, bortezomib was shown to inhibit DNA damage repair in vitro,<sup>26</sup> providing the rationale for its combination with DNA damaging agents to enhance or overcome drug resistance. Indeed, a large randomized phase III clinical trial of bortezomib versus bortezomib with pegylated doxorubicin showed prolonged progression-free and overall survival as well as increased extent and frequency of response,<sup>57</sup> leading to the US Food and Drug Administration approval of bortezomib with pegylated doxorubicin to treat relapsed MM. In a second example, we found heat shock protein 27 (Hsp 27) to be increased at transcript and protein levels in patient MM cells in the setting of bortezomib refractoriness. Our bedside-back-to-bench studies showed that overexpression of Hsp 27

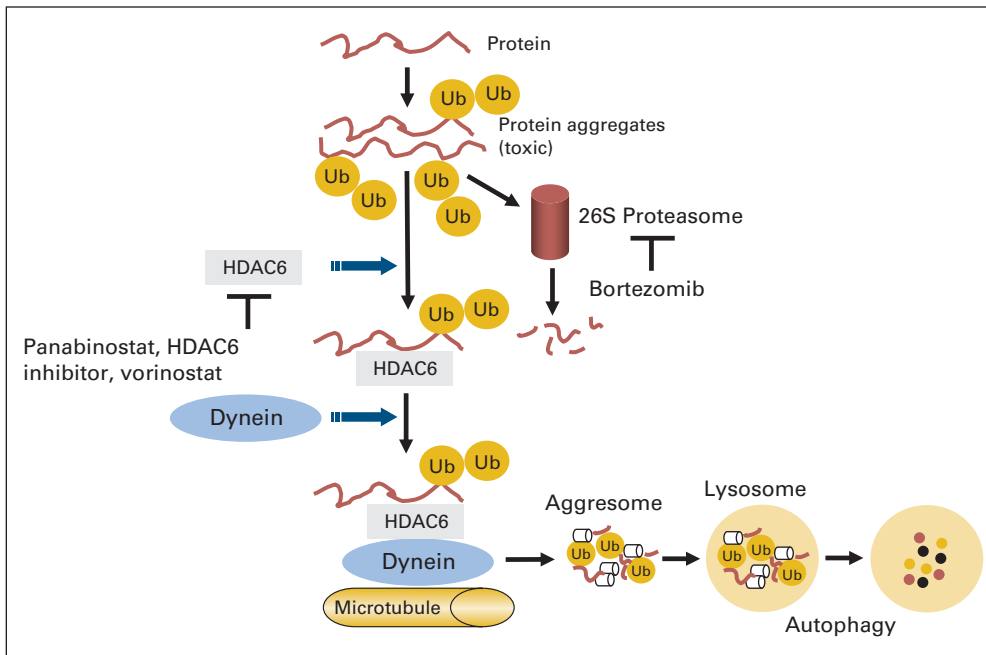


**Fig 4.** Targeting accessory cells in the multiple myeloma (MM) bone marrow microenvironment. Novel agents targeting cytokines mediating MM bone disease can also inhibit MM cell growth. BAFF, B-cell activating factor; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; m-CSF, macrophage colony-stimulating factor; MIP, macrophage inflammatory protein; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor  $\kappa$ B ligand; RUNX, runt-related transcription factor; SANT, super antagonist; TRAF, tumor necrosis factor receptor-associated factor; VEGF, vascular endothelial growth factor. Data adapted.<sup>54</sup>

conferred bortezomib resistance, whereas knockdown of Hsp 27 in bortezomib-resistant MM cells restored sensitivity.<sup>58</sup> Hideshima et al<sup>59</sup> then showed that p38 mitogen-activated protein kinase inhibitor decreased downstream Hsp 27 and thereby overcame bortezomib resistance in MM cell lines and patient cells, providing the rationale for a clinical trial of bortezomib and p38 mitogen-activated protein kinase inhibitor. Third, on the basis of hallmark cyclin D abnormalities in MM, Raje et al<sup>60,61</sup> have studied cyclin D kinase inhibitors, alone and in combination, in MM. Fourth, Ghobrial et al<sup>62</sup> have translated promising preclinical data of mammalian target of rapamycin inhibitor and bortezomib into derived clinical trials. Fifth, we showed that bortezomib triggers activation of Akt and that bortezomib with Akt inhibitor perifosine can sensitize or overcome resistance to bortezomib in preclinical models.<sup>63</sup> Our derived phase I and II trials of combination therapy showed durable responses even in the setting of bortezomib resistance, and a phase III clinical trial of bortezomib versus bortezomib with perifosine in relapsed MM is ongoing for US Food and Drug Administration approval. Sixth, we believe that protein homeostasis represents one of the most attractive novel therapeutic targets in MM (Fig 5). Specifically, we have shown that inhibition of the proteasome upregulates aggresomal degradation of protein and, conversely, that blockade of aggresomal degradation induces compensatory upregulation of proteasomal activity.<sup>66</sup> Most importantly, blockade of aggresomal and proteasomal degradation of proteins by histone deacetylase (HDAC) inhibitors (eg, vorinostat, panibinostat, tubacin) and proteasome inhibitors (eg, bortezomib, carfilzomib), respectively, triggers synergistic MM cell cytotoxicity in preclinical studies.<sup>64,66,67</sup> We are leading international phase I and II clinical trials combining HDAC inhibitors vorinostat or panibinostat with bortezomib, which have achieved responses in the majority of patients with relapsed bortezomib-refractory MM, as well as phase III clinical

trials for US Food and Drug Administration registration of these combinations. Excitingly, an HDAC 6 selective inhibitor causes acetylation of tubulin and more potently and selectively blocks aggresomal protein degradation; it mediates synergistic MM cytotoxicity when combined with bortezomib. This combination has been rapidly translated from our laboratory to the bedside, and clinical trials have been directed to achieve clinical efficacy without the adverse effect profile of fatigue, diarrhea, thrombocytopenia, and cardiac abnormalities attendant to the broader types 1 and 2 HDAC inhibitors.

To date, the most exciting combination from our preclinical studies is derived from the synergistic cytotoxicity induced by combined lenalidomide (caspase 8–mediated apoptosis) and bortezomib (caspase 9–mediated apoptosis) in models of MM cells in the BM milieu.<sup>68</sup> Richardson et al<sup>69</sup> led efforts to translate these findings into clinical trials in advanced MM, which showed that lenalidomide, bortezomib, and dexamethasone achieved 58% responses in relapsed refractory MM, often refractory to either agent alone. Most importantly, our center has shown that lenalidomide, bortezomib, and dexamethasone combination therapy for newly diagnosed MM achieves 100% responses, with 74% at least very good partial and 52% complete or near-complete responses.<sup>46</sup> Given these unprecedented results, a clinical trial is now evaluating whether high-dose therapy and stem-cell transplantation adds value in the context of this high extent and frequency of response to combined novel therapies. Therefore, the integration of combination novel-agent therapy, predicated on scientific rationale, is transforming the treatment paradigm in MM. Going forward, on the basis of these exciting results, we are now carrying out high-throughput drug screening to identify novel agents active against MM cells bound to BM stromal cells reflective of their microenvironment.



**Fig 5.** Blockade of ubiquitinated protein catabolism. Blockade of proteasomal and aggresomal breakdown using bortezomib and histone deacetylase (HDAC) inhibitors (panobinostat, vorinostat, HDAC6 selective inhibitor) mediate synergistic multiple myeloma cell cytotoxicity. Ub, ubiquitin. Data adapted.<sup>64-66</sup>

## ONCOGENOMIC STUDIES

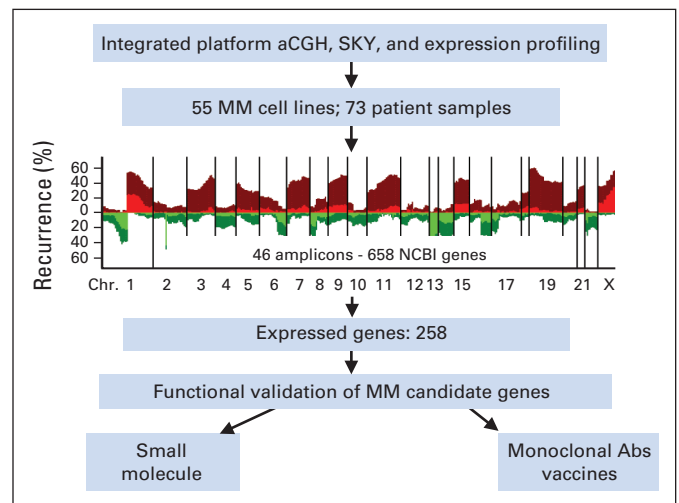
From the 1990s to the present, we have used oncogenomics to characterize MM pathogenesis, identify novel targets, predict response, and inform the design of single-agent and combination clinical trials. Our earliest studies profiled transcriptional changes occurring with transition from normal plasma cells to monoclonal gammopathy of undetermined significance to MM as well as identified gene and protein changes distinguishing patient MM cells from normal plasma cells in a syngeneic twin.<sup>70</sup> We have repeatedly used transcript profiling to identify signatures of response, initially with bortezomib and subsequently with multiple other single and combination therapies,<sup>32</sup> and most recently shown that microRNA profiling can also identify prognostic subgroups. Our DNA-based array comparative genomic hybridization studies have identified copy number alterations (CNAs) and suggested novel MM oncogenes or suppressor genes; once validated using knock-in and knockdown experiments in our models of MM cells in the BM milieu, these may serve as potential therapeutic targets<sup>71</sup> (Fig 6).

Single nucleotide polymorphism array has also identified CNAs and allowed for the development of novel prognostic models.<sup>72</sup> For example, recent single nucleotide polymorphism analyses of clinically annotated samples have identified CNAs, including increased 1q and 5q as sites for putative MM oncogenes as well as decreased 12p as a site of putative MM suppressor genes, to predict for clinical outcome.<sup>72</sup> Most importantly, as one of the founding centers of the Multiple Myeloma Research Consortium, we have participated in MM genome sequencing studies that have revealed mutated genes involved in protein homeostasis, nuclear factor  $\kappa$ B signaling, IRF4 and Blimp-1, and histone methylating enzymes, all consistent with MM biology.<sup>73</sup> These studies have also identified unexpected mutations, such as those in *BRAF* observed in melanoma, which may have short-term clinical application. Finally, our early studies now show continued evolution of genetic changes with progressive MM, strongly supporting the view

that personalized medicine in MM must include profiling patient tumor cells not only at diagnosis but also at time of relapse.

## FUTURE DIRECTIONS AND CONCLUSIONS

Our ongoing efforts include the development of immune (vaccine and adoptive immunotherapy) strategies, development of novel agents targeting the MM cell in the BM microenvironment, development of rationally based multiagent combination therapies, and use of



**Fig 6.** Oncogenomics to identify targeted therapies. Array comparative genomic hybridization (aCGH) of multiple myeloma (MM) cell lines and patient samples identifies amplicons with putative MM oncogenes. Profiling identifies transcribed genes, which are then functionally validated in overexpression and knockdown experiments in MM cells in the bone marrow microenvironment. Validated cell surface molecules can be targeted with monoclonal antibodies (Abs) or vaccines, whereas intracellular molecules are targeted with small molecule inhibitors. NCBI, National Center for Biotechnology Information; SKY, spectral karyotyping. Data adapted.<sup>71</sup>

genomics to improve both patient classification and allow for personalized medicine in MM. With this continued rapid evolution of progress, MM will be a chronic illness with sustained complete responses in a significant fraction of patients.

In closing, I want to gratefully acknowledge the laboratory and clinical researchers at our center and throughout the world with whom I have had the privilege to work over many years. Not only have we together had an impact on the natural history of MM, but the next generation of leaders in MM research is now in place to expedite progress even further. We not only share academic interests in MM but also treasure longstanding personal friendships. I am deeply grateful to the many funding organizations and individuals supporting our efforts over many years. None of this would have been possible without the loving support of my family. And most importantly, I have been honored to care for many extraordinary patients, who are truly my heroes and will always be the inspiration for all that we do.

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## AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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## Emerging Targeted Therapies for Breast Cancer

Ricardo H. Alvarez, Vicente Valero, and Gabriel N. Hortobagyi

See accompanying articles on page 3248 and 3256

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Corresponding author: Ricardo H. Alvarez, MD, The University of Texas M. D. Anderson Cancer Center, Department of Breast Medical Oncology, 1155 Herman P. Pressler, CPB5.3458, Houston, TX 77030-3721; e-mail: [ralvarez@mdanderson.org](mailto:ralvarez@mdanderson.org).

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### ABSTRACT

Increased understanding of the molecular events involved in cancer development has led to the identification of a large number of novel targets and, in parallel, to the development of multiple approaches to anticancer therapy. Targeted therapy focuses on specific molecules in the malignant cell signal transduction machinery, including crucial molecules involved in cell invasion, metastasis, apoptosis, cell-cycle control, and tumor-related angiogenesis. In breast cancer, two new targeted agents have recently been approved: lapatinib, directed against the human epidermal growth factor receptor 2 (HER2); and bevacizumab, directed against vascular endothelial growth factor (VEGF). Multiple other targeted agents are under evaluation in clinical trials, including inhibitors of the epidermal growth factor receptor (EGFR), dual EGFR and HER2 inhibitors, other VEGF or VEGF-receptor inhibitors, and agents that alter crucial signaling pathways, such as RAS/MEK/ERK; phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin; insulin-like growth factor/insulin-like growth factor receptor; poly (ADP-ribose) polymerase 1; and others. In this review, we present the most promising studies of these new targeted therapies and novel combinations of targeted therapies with traditional cytotoxic agents.

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### INTRODUCTION

Although numerous systemic agents are available to treat metastatic breast cancer (MBC), most tumors eventually become unresponsive to systemic therapy. In recent years, several targeted agents have become available that have improved the outcomes of patients with solid tumors. One of these agents, trastuzumab (Herceptin; Genentech, South San Francisco, CA), a monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), has proven effective in the treatment of women with HER2-positive breast cancer.<sup>1-4</sup> Other targeted agents are also showing promise in breast cancer treatment. Two—lapatinib (Tykerb; GlaxoSmithKline, Research Triangle Park, NC), a selective, reversible dual inhibitor of the epidermal growth factor receptor (EGFR; HER1) and HER2, and bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF)—have recently been approved by the US Food and Drug Administration for patients with certain types of breast cancer.<sup>5,6</sup> However, most targeted agents that have shown promise against breast cancer are still in preclinical or early clinical testing. Here, we review the most current information regarding the emerging targeted therapies for breast cancer. We excluded trastuzumab from this review, because its role in breast cancer is well established.

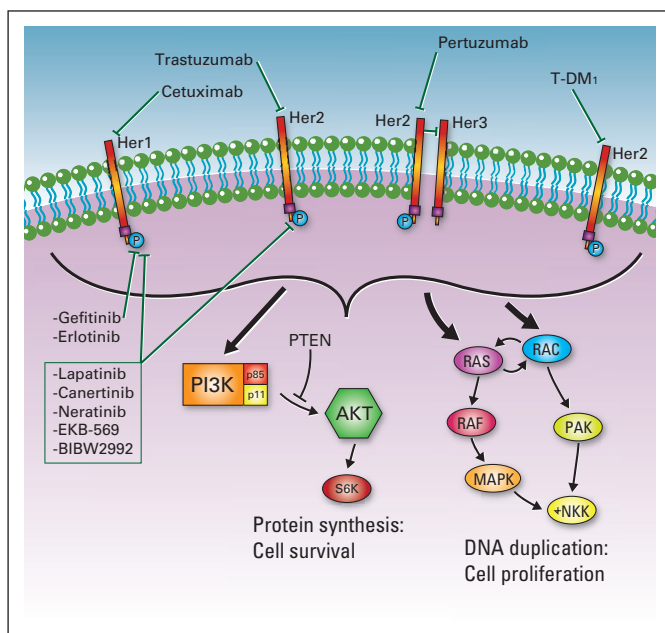
### EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY

EGFR is a transmembrane growth factor receptor tyrosine kinase (TK) frequently expressed in epithelial tumors. In breast cancer, EGFR plays a major role in promoting cell proliferation and malignant growth (Fig 1).<sup>7</sup> EGFR and HER2 are frequently overexpressed in breast cancer, and such overexpression is associated with aggressive clinical behavior and poor clinical outcome.<sup>8-11</sup> In addition, EGFR overexpression was found in half of triple-receptor-negative (TRN) breast tumors but in only approximately 15% of unselected tumors.<sup>12</sup>

### Pure EGFR Inhibitors: Gefitinib and Erlotinib

Gefitinib (Iressa; AstraZeneca, Macclesfield, Cheshire, United Kingdom) is a small molecule that reversibly inhibits EGFR TK autophosphorylation and inhibits downstream signaling.<sup>13,14</sup> In a phase I, dose-escalation study in 88 patients with multiple solid tumors, the dose-limiting toxicities (DLTs) at 1,000 mg/d were grade 3 diarrhea and grade 3 somnolence.<sup>15</sup> The most frequent drug-related adverse effects were acne-like rash and diarrhea.

Multiple phase II studies of single-agent gefitinib and gefitinib plus chemotherapy or hormonal therapy



**Fig 1.** Epidermal growth factor receptor (EGFR) family. The EGFR family is composed of four homologous receptors: ERBB1 (EGFR/HER1), ERBB2 (HER2/*neu*), ERBB3 (HER3), and ERBB4 (HER4). The three receptors are implicated in the development of cancer; the role of ERBB4 is less clear. Six different ligands, known as EGF-like ligands, bind to EGFR. After ligand binding, the ERBB receptor becomes activated by dimerization between two identical receptors (ie, homodimerization) or between different receptors of the same family (ie, heterodimerization). Dimerization leads to phosphorylation of several intracellular catalytic substrates, including members of the Ras/Raf/mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol-3-kinase (PI3K)/Akt/PTEN family, and other important signaling pathways that regulate apoptosis, protein synthesis, and cellular proliferation. The morphology of the extracellular domain of four EGFRs is almost identical; however, they vary considerably in the functional activity. For instance, ERBB3 lacks inherent kinase function but can heterodimerize with other ERBB receptors. Indeed, the ERBB2-ERBB3 dimer, which is considered the most active ERBB signaling dimer, is fundamental for ERBB2-mediated signaling in tumors with ERBB2 amplification.

for breast cancer have been completed (Appendix Table A1, online only). Single-agent gefitinib showed minimal clinical benefit (CB). Although the studies of combination therapy were not randomized, gefitinib did not significantly improve overall response rate and time to treatment failure on a chemotherapy regimen.

More recently, an exploratory analysis of two randomized, phase II trials comparing anastrozole or tamoxifen plus gefitinib versus anastrozole or tamoxifen plus placebo was published.<sup>16</sup> In both trials, endocrine-therapy-naïve patients had longer progression-free survival (PFS) with hormonal therapy plus gefitinib.

Erlotinib (Tarceva; OSI Pharmaceuticals, Melville, NY) is a small molecule that reversibly inhibits the EGFR TK and prevents receptor autophosphorylation.<sup>17</sup> Preclinical studies have demonstrated that both erlotinib and gefitinib inhibit breast cancer proliferation in vitro, and the greatest effects are in HER2-positive cell lines.<sup>14</sup>

In a clinical trial of erlotinib monotherapy in patients with MBC, the main adverse effects were acneiform rash, diarrhea, and asthenia.<sup>18</sup> One of 69 patients had a partial response (PR). Several trials of erlotinib in combination with drugs known to be active in breast cancer were recently conducted. In a dose-escalation study of erlotinib plus capecitabine and docetaxel in patients with MBC, the overall response rate was 67%; two patients had a complete response, and 12 had a

PR.<sup>19</sup> The regimen was generally well tolerated; manageable skin and gastrointestinal problems were the most common treatment-related adverse effects. Several other preliminary studies of erlotinib combined with docetaxel,<sup>20</sup> vinorelbine plus capecitabine,<sup>21</sup> and bevacizumab<sup>22</sup> have been reported.

On the basis of data from a preclinical mouse xenograft model, patients with stages I to IIIA invasive breast cancer were treated with erlotinib 150 mg/d orally for 6 to 14 days until the day before surgery.<sup>23</sup> Ki67 expression was reduced in estrogen-receptor-positive tumors but not in tumors that overexpressed HER2 or were TRN.

### TRASTUZUMAB-DM1

Trastuzumab-DM1 is the first antibody-drug conjugate that is based on trastuzumab. Trastuzumab-DM1 consists of trastuzumab linked to an antimicrotubule drug, maytansine (also known as DM1). Trastuzumab-DM1 showed activity in a xenograft model of HER2-positive, trastuzumab-resistant tumors.<sup>24</sup> A phase I study of trastuzumab-DM1 in heavily pretreated patients with HER2-overexpressing MBC showed clinical activity, with thrombocytopenia as the DLT, at a dosage of 4.8 mg/kg every 3 weeks. The recommended dosage for phase II studies was 3.6 mg/kg every 3 weeks.<sup>25</sup> In a recent preliminary report of a phase II study of trastuzumab-DM1 in 112 patients with HER2-overexpressing MBC in whom treatment with trastuzumab, lapatinib, or both had failed to show promising activity, the independent review panel confirmed an overall response rate of 25% (28 patients) and a CB rate of 34% (38 patients).<sup>26</sup>

Two phase III studies of trastuzumab-DM1 are ongoing. One study tests the activity of trastuzumab-DM1 versus standard therapy with lapatinib-capecitabine as second-line therapy for patients with HER2-positive MBC. The other study tests docetaxel plus trastuzumab versus single-agent trastuzumab-DM1 as first-line therapy for HER2-positive MBC.

### EGFR INHIBITORS PLUS AGENTS TARGETING OTHER PATHWAYS

Inhibition of EGFR/HER1 phosphorylation by anti-EGFR agents does not always correlate with antitumor effects. This suggests that tumor proliferation may be controlled by alternate growth factors in the presence of EGFR inhibitors and that the antitumor activity of anti-EGFR agents may be improved by combining them with therapies targeting other signal transduction pathways.<sup>27</sup> However, several studies in patients with breast cancer who were treated with these compounds as single agents showed disappointing results.<sup>28</sup>

### Dual EGFR and HER2 Inhibitors

Interest in the role of EGFR in HER2-amplified tumors was renewed with the advent of dual TK inhibitors (TKIs) that interact with several EGFR members. Of these, lapatinib (Tykerb) is the agent that has been studied most extensively (Table 1). Other dual EGFR-HER2 inhibitors studied for breast cancer include cetuximab, canertinib, neratinib, and pertuzumab (Table 2).



**Table 1.** Phase II and III Trials of Lapatinib for Treatment of Breast Cancer

Study and Author	No. of Patients	Type of Study	Patient Population	Lapatinib Dose (mg/d)	Combination Therapy	Response (%)			Patient Outcome
						PR	CR	CB	
Lapatinib single agent									
Blackwell et al <sup>29</sup>	78	Phase II	HER2 positive and Tz refractory	1,250-1,500	—	5.1	0	9	All patients had KPS > 70%. Efficacy outcomes: TTP was 15.3 weeks, and PFS was 15.3 weeks (range, 9.7 to 16.3 weeks). AE: skin rash (47%), diarrhea (46%), and nausea (31%)
Burstein et al <sup>30</sup>	229	Phase II	A, T, and Cap refractory	1,500					
Arm A	140				HER2 positive and Tz refractory	4	0		76% of patients had received four or more lines of therapy. HER2-positive patients: response rate was 4.3% and 1.4% by investigator and independent assessment, respectively.
Arm B	89				HER2 negative	0	0		No response rate observed in HER2 negative. Independent review assessment of median TTP and PFS were similar in HER2 positive and HER2 negative (9.1 weeks and 7.6 weeks, respectively). AE: diarrhea (54%), skin rash (30%), nausea (24%)
Gomez et al <sup>31</sup>	138	Phase II	HER2 positive; first-line treatment	1,500 once daily v 500 twice daily	—	24	0	31	Median TTP was 7.9 weeks (1,500 mg once a day, 7.9 weeks; 500 mg twice daily, 7.9 weeks), and median duration of response was 28.4 weeks (1,500 mg once a day, 27.6 weeks; 500 mg twice daily, 29 weeks). AE: diarrhea, rash, pruritus, and nausea. No significant difference in efficacy between dosing schedules.
Lapatinib in combination with chemotherapy, hormone therapy, and targeted therapy									
Geyer et al <sup>5</sup>	324	Randomized, phase III	HER2 positive and A, T, and Cap refractory						The median TTP for L + Cap v Cap were 8.4 months and 4.4 months (HR, 0.49; 95% CI, 0.34 to 0.71; <i>P</i> < .001), respectively. The median PFS for L + Cap v Cap were 8.4 and 4.1 months (HR, 0.47; 95% CI, 0.33 to 0.67; <i>P</i> < .001). Most common AEs were gastrointestinal toxicity: diarrhea, 60% v 39%; nausea, 44% v 42%; and vomiting, 26% v 24% for L + Cap compared with Cap alone, respectively. AE: grade 4 toxicity diarrhea in two patients (1%) in the L + Cap arm.
Arm A	163			1,250	Cap 2,000 mg/d for 14 days	35	1	44	
Arm B	161				cap 2,500 mg/d for 14 days	23	0	29	

(continued on following page)

Targeted Therapies in Breast Cancer

Table 1. Phase II and III Trials of Lapatinib for Treatment of Breast Cancer (continued)

Study and Author	No. of Patients	Type of Study	Patient Population	Lapatinib Dose (mg/d)	Combination Therapy	Response (%)			Patient Outcome
						PR	CR	CB	
Di Leo et al <sup>32</sup>	579	Randomized, phase III	HER2 negative or HER2 UT						There were no significant differences in TTP, EFS, or OS between treatment arms, although differences in ORR were noted. In 86 patients (15%) with HER2-positive, treatment with P + L resulted in statistically significant improvements in TTP, EFS, ORR, and CB compared with P + Pl.
Arm A				1,500	P 175 mg/m <sup>2</sup> every 3 weeks	30	5	40.5	
Arm B				Pl	P 175 mg/m <sup>2</sup> every 3 weeks	23	2	32	
Johnston et al <sup>33</sup>	1,286	Randomized, phase III	Hormone receptor positive, HER2 negative; or hormone receptor positive, HER2 positive	Arm A:	Let 2.5 mg daily	NA	NA	NA	Hormone receptor positive/HER2 negative: no significant treatment benefit on PFS (HR, 0.90; 95% CI, 0.77 to 1.05; <i>P</i> = .188).
Arm A				1,500	Let 2.5 mg daily	NA	NA	NA	Subgroup analysis of patients who had HER2 negative and lower expression of ER (H-score < 160) had significant improvement in median PFS (13.6 months v 6.6 months; HR, 0.65; 95% CI, 0.47 to 0.9; <i>P</i> < .005) when are treated with L + Let. <sup>34</sup>
Arm B				Pl					Overall, 219 of 1,286 patients were hormone receptor positive/HER2 positive. The PFS was 8.2 v 3 months for L + Let v Let alone (HR, 0.71; <i>P</i> = .019). Significant improvement in CB rate (29% to 48%; <i>P</i> = .003) for the combination arm.
O'Shaughnessy et al <sup>35</sup>	296	Randomized, phase III	HER2 positive					13.2	The primary and secondary end points were PFS and CB rate at 24 weeks. The combination of L and Tz demonstrated synergy and improved the median PFS: 12 v 8.4 weeks (HR, 0.73; 95% CI, 0.6 to 1; <i>P</i> = .008); CB rate, 25% v 13% (HR, 2.1; 95% CI, 1.1 to 4.2; <i>P</i> = .01) compared with L as a single agent, respectively. There were no significant differences in ORR or OS.
Arm A			A, T, Cap, and Tz refractory	1,500	—				
Arm B				1,000	Tz: 2 mg/kg weekly after 4 mg/kg loading dose			25.2	

Abbreviations: PR, partial response; CR, complete response; CB, clinical benefit; HER2, human epidermal growth factor receptor 2; Tz, trastuzumab; KPS, Karnofsky performance status; TTP, time to tumor progression; PFS, progression-free survival; AE, adverse event; A, anthracyclines; T, taxanes; Cap, capecitabine; L, lapatinib; HR, hazard ratio; UT, untested; EFS, event-free survival; OS, overall survival; ORR, overall response rate; P, paclitaxel; Pl, placebo; Let, letrozole; NA, not available; ER, estrogen receptor.

Table 2. Dual EGFR and HER2 Inhibitors

Agent	Drug Class	Mechanism of Action	Study Comments
Cetuximab (Erbix)	mAb	Binds to the extracellular domain of EGFR <sup>36</sup>	<p>A phase I, dose-escalation study of cetuximab and P in patients with MBC showed that two of six patients in the second cohort (cetuximab 100 mg/m<sup>2</sup>) developed DLT effects, in the form of grade 3 rash. Ten patients were evaluable for response; two experienced SD, and eight experienced PD.<sup>37</sup></p> <p>Preliminary results were reported from a randomized trial in which patients with TRN MBC refractory to one to three lines of chemotherapy were randomly assigned to CP plus cetuximab v cetuximab alone.<sup>38</sup> Cetuximab alone was well tolerated and had an RR of 6%. This arm was closed for insufficient activity, and the cetuximab-plus-CP arm had 18% RR and 27% CB.</p> <p>A preliminary report in patients with MBC treated with irinotecan plus CP v the same regimen plus cetuximab showed that cetuximab did not improve antitumor activity, PFS, or OS but increased toxicity.<sup>39</sup> However, on subset analysis, the addition of cetuximab increased the overall RR associated with irinotecan plus CP in TRN breast cancer.</p>
Canertinib	TKI	Irreversible inhibitor of all EGFR family	<p>Preclinical activity was documented in mouse xenografts model, including breast cancer.<sup>40,41</sup></p> <p>A phase I study in heavily pretreated patients on canertinib, including patients with breast cancer, showed MTD doses of 225 mg three times a week and 250 mg with a 7-day on, 7-day off schedule.<sup>42</sup></p> <p>In phase I and phase II studies, the most common adverse effects were gastrointestinal toxicity and rash.<sup>43,44</sup> Compared with oral delivery, intravenous delivery produced fewer gastrointestinal adverse events and increased bioavailability three-fold.<sup>45</sup></p> <p>A phase I study of canertinib plus docetaxel in patients with advanced solid tumors<sup>46</sup> resulted in a recommended phase II dose of canertinib 50 mg/d plus docetaxel 75 mg/m<sup>2</sup>.</p>
Neratinib	TKI	Irreversible inhibitor of EGFR and HER2 <sup>47</sup>	<p>In a phase I/II study in MBC patients who were HER2 positive and who experienced progression on Tz therapy, 45 patients were treated with neratinib 160 mg or 240 mg daily plus Tz.<sup>48</sup> Among 33 evaluable patients, the objective RR was 27% (95% CI, 13% to 46%), and median PFS was 19 weeks (95% CI, 15 to 32 weeks).</p> <p>In a phase II study, patients with stage IIIB to IV, HER2-positive MBC were assigned to arm A (n = 65) if they had received Tz and to arm B (n = 66) if they had not received Tz or another HER2-targeting drug, and patients received neratinib 240 mg daily.<sup>49</sup> The primary end point, median PFS, was 23 weeks (95% CI, 16 to 39 weeks) for arm A and 40 weeks (95% CI, 32 to 55 weeks) for arm B. RR for arms A and B were 26% and 56%, respectively, and CB rates were 36% and 68%, respectively. One fourth of the patients required dose reductions; grade 3 diarrhea was seen in five patients (19%).</p>
Pertuzumab (Omnitarg; Genentech)	mAb	Bind different HER2 epitope of the HER2 than Tz, blocking heterodimerization of HER2 with EGFR and <i>ErbB3</i> <sup>50</sup>	<p>In HER2-positive breast cancer cell lines, Tz plus pertuzumab increased apoptosis and cell growth arrest compared with Tz alone.<sup>51</sup> A two-stage, phase II study of pertuzumab plus Tz in patients with previously treated (including with adjuvant Tz), HER2-positive MBC showed that, of 66 patients evaluable for response, five experienced CR, 11 had PR, and 17 had SD for approximately 6 months.<sup>52</sup> Thirty-three (50%) of 66 patients had CB. There were no clinical cardiac events and no occurrences of decrease in LVEF greater than 10%.</p> <p>Patients are currently being enrolled on a phase III study of pertuzumab plus Tz as first-line treatment for HER2-positive MBC (CLEOPATRA study).</p>

Abbreviations: mAb, monoclonal antibody; EGFR, epidermal growth factor receptor; P, paclitaxel; MBC, metastatic breast cancer; DLT, dose-limiting toxicity; SD, stable disease; PD, progressive disease; TRN, triple-receptor negative; CP, carboplatin; RR, response rate; CB, clinical benefit; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; HER2, human epidermal growth factor receptor 2; Tz, trastuzumab; CR, complete response; PR, partial response; LVEF, left ventricular ejection fraction; CLEOPATRA, Clinical Evaluation of Pertuzumab and Trastuzumab.

## LAPATINIB

Lapatinib is a selective, reversible, dual EGFR-HER2 inhibitor. Lapatinib has a slower rate of dissociation from EGFR than erlotinib and gefitinib, which results in prolonged target-site downregulation.<sup>53</sup>

Lapatinib plus capecitabine was approved by the US Food and Drug Administration on March 13, 2007, for the treatment of patients with advanced or HER2-overexpressing MBC previously treated with an anthracycline, a taxane, and trastuzumab.<sup>5</sup> In a phase I study of lapatinib in heavily pretreated patients with EGFR- and HER2-positive MBC, no DLT was found<sup>54</sup>; the most common adverse effects were diarrhea and rash, and there were no grade 4 toxic effects. Four of

59 evaluable patients with trastuzumab-resistant disease, including two with inflammatory breast cancer, had a PR, and all of these patients had high expression of activated phosphorylated HER2. Phase II trials of single-agent lapatinib have shown modest CB rates in patients with HER2-positive breast cancer (Table 1).

## LAPATINIB PLUS CAPECITABINE

The pivotal trial that led to regulatory approval of lapatinib showed that lapatinib plus capecitabine increased PFS compared with capecitabine alone in patients with locally advanced or metastatic HER2-positive breast cancer not controlled by previous treatment with

anthracyclines, taxanes, and trastuzumab.<sup>5</sup> The study was closed prematurely, because the first interim analysis showed that the addition of lapatinib was associated with a 51% reduction in the risk of disease progression. The median times to progression for patients treated with lapatinib plus capecitabine and for patients treated with capecitabine plus placebo were 8.4 months and 4.4 months, respectively (hazard ratio, 0.49; 95% CI, 0.34 to 0.71;  $P < .001$ ; Appendix Fig A1, online only). Eleven patients in the capecitabine group had progressive CNS metastasis compared with four in the combination-therapy group ( $P = .10$ ). One third of women with HER2-positive MBC who receive trastuzumab develop CNS metastasis.<sup>55</sup> Small molecules, such as lapatinib, can cross the blood-brain barrier. In a recent phase II study of patients with HER2-positive breast cancer and brain metastasis, rates of objective response, defined as  $\geq 50\%$  reduction in the volume of the brain lesion(s), were 6% for patients treated with lapatinib and 20% for patients treated with lapatinib and capecitabine; furthermore, 21% of the patients treated with lapatinib alone and 40% of the patients treated with combination therapy experienced at least a 20% volumetric reduction in their CNS lesion(s).<sup>56</sup>

Concerns have been voiced about the potential cardiotoxicity of lapatinib, but a recent pooled analysis of 3,689 lapatinib-treated patients revealed low rates of cardiac toxic effects. These effects were mostly asymptomatic decreases in left cardiac ejection fraction.<sup>57</sup>

Preclinical studies showed a synergistic interaction between lapatinib and trastuzumab in HER2-overexpressing breast cancer cell lines and tumor xenografts.<sup>58</sup> Preliminary results of a randomized, phase III trial of lapatinib with or without trastuzumab in patients with heavily pretreated HER2-positive MBC demonstrated synergy and improved median PFS with combination therapy.<sup>35</sup> Ongoing are a large trial of lapatinib plus trastuzumab as adjuvant therapy (the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization [ALTTO] trial) and a small trial of lapatinib plus trastuzumab as primary systemic therapy (the Neo-ALTTO trial) in patients with HER2-positive, early-stage breast cancer.

### LAPATINIB PLUS HORMONAL AGENTS

Evidence is accumulating that signaling interplay between the estrogen receptor, HER2, EGFR, and insulin-like growth factor (IGF) 1 receptor plays a role in the acquired resistance to hormonal therapies.<sup>59,60</sup> In a preclinical model, lapatinib restored tamoxifen sensitivity in hormone-receptor-positive, tamoxifen-resistant breast cancer.<sup>61</sup> Several studies investigating lapatinib plus hormonal agents are planned.

In the EGF30008 trial, a phase III study of letrozole with or without lapatinib in postmenopausal patients with hormone-receptor-positive, HER2-positive MBC, the combination therapy resulted in a 29% reduction in the risk of disease progression ( $P = .019$ ), and the median PFS improved from 3.0 to 8.2 months.<sup>33</sup> Ongoing is a large, European, phase II study of letrozole with or without lapatinib as neoadjuvant therapy in patients with hormone-sensitive, HER2-negative, operable breast cancer (the LET-LOB study).<sup>62</sup> Lapatinib is also active in patients with newly diagnosed inflammatory breast cancer, both alone and with paclitaxel.<sup>63</sup>

### PERTUZUMAB

The discovery of the crucial role of ERBB3 in mediating signaling with different dimers and blocking ERBB2-dependent signaling through the phosphatidylinositol-3-kinase (PI3K)–Akt pathways provides an excellent opportunity for the development of TKIs with specific activity against ERBB3.<sup>64</sup> Because ERBB3 lacks intrinsic kinase activity, though, the generation of specific HER3-directed TKIs is challenging. Pertuzumab is an ERBB2 antibody that inhibits ERBB3 signaling by blocking ligand-induced HER2-to-HER3 heterodimerization. Preclinical observation in several breast cancer cell lines suggested that interfering with the ERBB3 component may be more relevant than inhibition of EGFR in HER2-amplified breast cancer cell lines.<sup>65</sup> In patients with ovarian cancer, high levels of ERBB3 correlated with shorter overall survival than *ERBB2* overexpression.<sup>66</sup>

### NERATINIB

Recent preliminary data showed impressive antitumor activity in patients with trastuzumab-pretreated, *HER2*-amplified breast cancer after treatment with neratinib, a highly selective irreversible inhibitor of EGFR and ERBB2. Mature data are awaited, and more studies are underway.

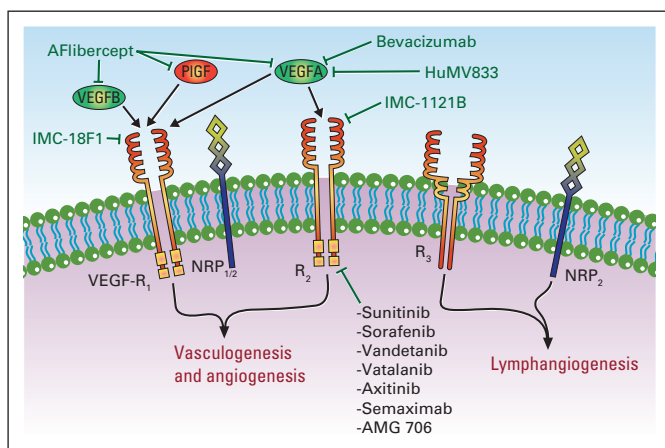
### NEW-GENERATION ANTI-HER2 TYROSINE KINASES

A new generation of anti-HER2 TKs is being developed. Among these new agents are EKB-569 and BIBW 2992, which are currently being studied in clinical trials.<sup>67,68</sup> The bispecific (ertumaxomab)<sup>69</sup> and trispecific antibodies that target ERBB2 are also under investigation.

The therapeutic armamentarium against the EGFR family, especially HER2-positive disease, has grown in the past decade. Results from the clinical trials highlight the potential of combination anti-HER2 therapies that might be superior to single-agent strategies. For instance, combination of both anti-HER2 therapies—lapatinib and trastuzumab—in patients in whom trastuzumab failed is superior to lapatinib alone.<sup>35</sup> Coexpression of both estrogen receptor and HER2 are reported in approximately 50% of patients with breast cancer; preclinical data suggest that *HER2* overexpression confers intrinsic resistance to hormonal therapy. However, new clinical evidence reveals that the combination of anti-HER2 and hormonal therapy could be considered the treatment of choice at this time.<sup>33,70</sup>

### VEGF INHIBITORS

Angiogenesis plays an essential role in breast cancer development, invasion, and metastasis.<sup>71</sup> Agents that block the VEGF pathway have been shown to effectively inhibit tumor angiogenesis and growth in preclinical tumor models (Fig 2; Appendix Fig A2, online only). Studies in early-stage breast cancer show that elevated VEGF expression is associated with decreased relapse-free survival and overall survival in patients with both lymph-node-positive and lymph-node-negative disease.<sup>73,74</sup> Several drugs that target VEGF ligands or receptors have now emerged into the clinic (Appendix Table A2, onlineonly).



**Fig 2.** Vascular endothelial growth factor (VEGF) family. The VEGF family comprises seven secreted glycoproteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factors (PlGFs) -1 and -2. Free VEGF members exert effects by binding a variety of cell-surface receptors, including VEGF receptor 1 (a 180-kDa transmembrane protein also called fms-like tyrosine kinase-1 or Flt-1), and VEGF receptor 2 (a 200-kDa transmembrane protein also called kinase insert domain-containing receptor, or KDR). A third structurally related tyrosine kinase receptor is the 180-kDa VEGFR-3, which is expressed broadly on endothelial cells during early embryogenesis but which becomes restrictive to endothelial cells of adult lymphatic tissues and is necessary for adult lymphangiogenesis. Two additional VEGF receptors, neuropilin 1 (NRP-1) and neuropilin 2 (NRP-2), have also been recently implicated in VEGF-mediated vascularization and lymphangiogenesis.<sup>72</sup>

### Bevacizumab

On February 22, 2008, the US Food and Drug Administration approved bevacizumab (Avastin; Genentech) plus paclitaxel as first-line therapy in patients with MBC. An early phase I/II, dose-escalation trial of single-agent bevacizumab in 75 patients with MBC showed a response rate of 6.7%.<sup>75</sup> Hypertension was the most common adverse effect, and it occurred in 22% of patients. Headache associated with vomiting was seen in four patients at a dose of 20 mg/kg and was considered the DLT.

The trial that resulted in US Food and Drug Administration approval of bevacizumab for breast cancer was the Eastern Cooperative Oncology Group trial ECOG 2100, in which 680 patients with previously untreated locally recurrent breast cancer or MBC received paclitaxel 90 mg/m<sup>2</sup> on days 1, 8, and 15 with or without bevacizumab 10 mg/kg on days 1 and 15 in 4-week cycles until progression occurred.<sup>6</sup> Most patients (96%) had HER2-negative disease. The primary end point, median PFS, was significantly better with combination therapy (11.8 v 5.9 months; hazard ratio, 0.60; 95% CI, 0.43 to 0.62;  $P \leq .001$ ). The PFS benefit observed with bevacizumab was independent of patient age, number of metastatic sites, previous adjuvant taxane use, disease-free interval after adjuvant therapy, and hormone receptor status. The overall response rate was also better with combination therapy, at 36.9% with combination therapy versus 21.2% without ( $P < .001$ ). Bevacizumab was not associated with an increased risk of death; however, an audit of the trial by a group of experts revealed several occurrences of small bowel perforation that had not been attributed to bevacizumab.

The US Food and Drug Administration decision to grant accelerated approval of bevacizumab plus paclitaxel on the basis of the observed PFS benefit generated much debate. Overall survival is universally accepted as the most reliable cancer end point, but PFS is not

recognized by many investigators as an important surrogate end point in patients with MBC. However, demonstrating in a clinical trial that a drug improves overall survival requires larger numbers of patients and a prolonged period of time. Since the US Food and Drug Administration approved of bevacizumab for MBC, several other anticancer drugs have been approved by using PFS as a primary end point.

Several phase III studies of bevacizumab combined with different chemotherapy agents have been reported (Table 3). Mature data from four studies<sup>6,77,80,81</sup> demonstrated an improvement in PFS when bevacizumab was added to chemotherapy. Bevacizumab as neoadjuvant therapy is under investigation in a large study by the National Surgical Adjuvant Breast and Bowel Project (NSABP-B40), and bevacizumab as maintenance therapy in patients with TRN breast cancer is being investigated in the Bevacizumab Adjuvant Therapy in Triple-Negative Breast Cancer (BEATRICE) trial. There are two large, ongoing, randomized, phase III trials of bevacizumab as adjuvant therapy: ECOG 5103, which compares chemotherapy versus chemotherapy plus bevacizumab, and the Bevacizumab and Trastuzumab Adjuvant Therapy in HER2-Positive Breast Cancer (BETH) trial, which compares chemotherapy with docetaxel, carboplatin, and trastuzumab with or without bevacizumab for HER2-amplified breast cancer.

### Aflibercept

Aflibercept is a soluble decoy receptor protein that consists of a fusion of the second immunoglobulin domain of the VEGF receptor-1 (VEGFR-1) and the third immunoglobulin domain of the human VEGFR-2 with the constant region of human immunoglobulin G<sub>1</sub>.<sup>78</sup> Aflibercept recognizes the entire VEGF family that binds to VEGFR-1 and VEGFR-2, including placental growth factor, and possesses higher affinity for VEGF than bevacizumab in vitro. Aflibercept potently inhibited tumor growth, metastasis formation, and ascites formation in several murine tumor models.<sup>79</sup>

A phase II trial of aflibercept 4 mg/kg every 21 days in patients with MBC who had received fewer than two regimens for MBC was stopped early, after the first stage was completed with 21 patients, as there were no objective responses, and because the median PFS was 2.4 months.<sup>82</sup>

### MONOCLONAL ANTIBODIES TARGETING PORTIONS OF VEGFR

Several monoclonal antibodies, including HuMV833, IMC-1121B, and IMC-18F1, have been designed to target selected portions of VEGFR.<sup>83-85</sup> These agents are under investigation in clinical trials.

### MULTIKINASE INHIBITORS THAT INHIBIT VEGFRS

#### Sunitinib

Sunitinib malate (Sutent; Pfizer, New York, NY) is an oral TKI that targets several receptor TKs, including VEGFR-1, VEGFR-2, and VEGFR-3; platelet-derived growth factor receptor- $\alpha$  (PDGFR- $\alpha$ ) and PDGFR- $\beta$ ; c-Kit; and colony-stimulating factor-1 receptor.<sup>86</sup> In a phase I study in which patients with solid tumors received sunitinib 15 to 59 mg/m<sup>2</sup>, six of 28 patients had a PR.<sup>87</sup> The most common adverse effects were fatigue, hypertension, and skin manifestations. In a phase II trial in 64 patients with MBC previously treated with anthracyclines and taxanes who received sunitinib at a starting dose of 50 mg once daily for 4 weeks of a 6-week cycle, seven patients (11%) had a PR,

Targeted Therapies in Breast Cancer

Table 3. Phase III Trials of Bevacizumab in Breast Cancer

Trial	No. of Patients	Patient Population	Bevacizumab Dose	Combination Therapy	End Point	Benefit in Anti-VEGF Therapy	Study Primary Results
AVF2119 <sup>76</sup>	462	PT MBC	15 mg/kg every 3 weeks	Cap 2,500 mg/m <sup>2</sup> /d from day 1 to day 14	PFS	No	Bev and Cap significantly increased the ORR compared with Cap as a single agent (9.1% v 19.8%; <i>P</i> = .001), but not PFS (4.2 v 4.0 months; HR, 0.98). No significant differences were found in the incidence of diarrhea, hand-foot syndrome, and serious bleeding episodes between treatment groups.
ECOG 2100 <sup>6</sup>	722	FL MBC	10 mg/kg every 2 weeks	P 90 mg/m <sup>2</sup> on days 1, 8, and 15	PFS	Yes	Bev and P significantly prolonged PFS compared with P alone (median, 11.8 v 5.9 months; HR for progression, 0.60; <i>P</i> < .001) and increased ORR (36.9% v 21.2%). No differences in OS between the two groups (median 26.7 v 25.5 months; HR, 0.88; <i>P</i> = .16). AE: grade 3 or 4 hypertension (14.8% v 0%; <i>P</i> < .001), proteinuria (3.6% v 0%; <i>P</i> < .001), headache (2.2% v 0%; <i>P</i> = .008), and cerebrovascular ischemia (1.9% v 0%; <i>P</i> = .02) were more common in patients receiving the combination treatment.
AVADO <sup>80</sup>	736	FL MBC	7.5 mg/kg every 3 weeks or 15 mg/kg every 3 weeks	D 100 mg/m <sup>2</sup> every 3 weeks	PFS	Yes	In unstratified analysis, patients receiving Bev had significantly longer PFS compared with the D monotherapy group (Bev at 7.5 mg/kg: median PFS, 8.7 v 8.0 months; HR, 0.79; <i>P</i> = .0318; Bev at 15 mg/kg: median PFS, 8.8 v 8.0 months; HR, 0.72; <i>P</i> = .0099). ORR improved with the addition of Bev. Bev 7.5 mg/kg, 55% v 44% ( <i>P</i> = .0295); Bev 15 mg/kg 63% v 44% ( <i>P</i> < .001) The study was not powered to find differences in OS.
RIBBON1 <sup>81</sup>	1,237*	FL MBC	15 mg/kg every 3 weeks	Cap, taxanes (Nab-Pac and D), anthracycline	PFS	Yes	The median follow up was 15.6 months in the Cap cohort and 19.2 months in the taxanes and anthracycline cohort. The addition of Bev to Cap, taxanes, or anthracycline-based chemotherapy resulted in statistically significant improvement in PFS.
MO19391 <sup>77</sup>	2,027*	HER2 negative MBC or HER2 positive if previous Tz	10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks	Taxane-based chemotherapy	Safety	Yes	Median follow up was 7.4 months; approximately 75% of patients received taxanes, and 25% were treated with non-taxane regimens (Cap and VNR). Safety and efficacy of Bev plus D or P was similar to results of ECOG2100 and AVADO.

Abbreviations: VEGF, vascular endothelial growth factor; PT, pretreated; MBC, metastatic breast cancer; Cap, capecitabine; PFS, progression-free survival; Bev, bevacizumab; ORR, overall response rate; HR, hazard ratio; ECOG2100, Eastern Cooperative Oncology Group trial 2100; FL, first line; P, paclitaxel; OS, overall survival; AE, adverse event; AVADO, Avastin and Docetaxel; D, docetaxel; RIBBON1, Regimens in Bevacizumab for Breast Cancer; Nab-Pac, Nab-paclitaxel; HER2, human epidermal growth factor receptor 2; Tz, trastuzumab; VNR, vinorelbine.

\*Currently enrolling patients.

and three patients had stable disease for more than 6 months, for an overall CB rate of 16%.<sup>88</sup> Objective responses occurred in three of 20 patients with TRN tumors and in three of 12 patients with HER2-positive tumors. Grade 3 fatigue and hand-foot syndrome occurred in 14% and 9% of patients, respectively; one third of patients experienced grade 3 neutropenia. In a phase II, randomized study, 46 patients with HER2-negative MBC were randomly assigned to receive paclitaxel 90 mg/m<sup>2</sup> weekly and bevacizumab 10 mg/kg every 2 weeks with or without sunitinib 25 mg daily for 21 days as

first-line chemotherapy.<sup>89</sup> Sunitinib was associated with high rates of dose modification and treatment discontinuation because of toxic effects—including neutropenia, febrile neutropenia, and fatigue—that led to closure of the study.

Sunitinib also was studied in combination with metronomic dosing of cyclophosphamide and methotrexate in patients with MBC.<sup>90</sup> Fifteen patients were treated in three sunitinib dose cohorts: 12.5 mg/d, 25 mg/d, and 37.5 mg/d. Three patients developed grade 3 neutropenia, and five developed mucositis. One patient had a PR at

week 14, and one patient had stable disease for 47 weeks. Enrollment continues.

### Sorafenib

Studies of sorafenib (Nexavar; Bayer/Onyx Pharmaceuticals, West Haven, CT) have mainly focused on optimizing dosing to maximize activity against Ras.<sup>91</sup> In preclinical studies, daily sorafenib significantly inhibited tumor growth and microvessel density in an MDA-MB-231 breast cancer xenograft model.<sup>92</sup> A phase I study showed a favorable toxicity profile of sorafenib 400 mg twice daily in patients with advanced solid tumors.<sup>93</sup>

In a two-stage, phase II study of sorafenib 300 mg twice daily in patients with MBC refractory to anthracyclines and taxanes, the median number of cycles was 2, and dose reductions were necessary because of dermatitis/skin rash ( $n = 3$ ), hand-foot syndrome ( $n = 2$ ), and hypertension ( $n = 1$ ).<sup>94</sup> One of 20 patients eligible for efficacy evaluation had a PR that lasted 3.6 months. The study was closed after the first stage because of lack of sufficient response.

### Vandetanib

Vandetanib (Zactima; AstraZeneca) is a potent inhibitor of kinase insert domain-containing receptor (VEGFR-2), VEGFR-3, and EGFR/HER1.<sup>95</sup> A phase I dose-finding study established a dose of 300 mg daily.<sup>96</sup> A phase II study in 46 patients with MBC refractory to anthracyclines and taxanes showed no objective responses.<sup>97</sup> The authors hypothesized that the lack of activity could be related to inadequate blood concentration of vandetanib. Most patients achieved a plasma concentration greater than the 50% inhibitory concentration; however, adverse effects commonly seen with VEGF inhibitors (eg, hypertension, headache, thrombosis) and EGF inhibitors (eg, severe rash) were not seen.

### Vatalanib

Vatalanib is an oral inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 and of other related kinases.<sup>98</sup> A phase I study in patients with advanced solid tumors established that the maximum-tolerated dose was 750 mg twice daily, whereas the biologically active dose was greater than 1,000 mg twice daily.<sup>99</sup> The Hoosier Oncology Group recently finished accruing patients for a phase I/II study of vatalanib plus trastuzumab in patients with newly diagnosed, HER2-overexpressing MBC.<sup>100</sup>

### Axitinib

Axitinib is a potent small-molecule TKI of all known VEGFRs, PDGFR- $\beta$ , and c-Kit.<sup>101</sup> The initial phase I study in patients with solid tumors showed a 10% PR rate.<sup>102</sup> Fewer than 10% of the patients experienced grade 3 or 4 toxic effects; hypertension was the most common adverse effect and was reported in 22 patients (61%), 11 of whom had grade 3 or 4 hypertension. The incidence and severity of hypertension were dose related. Other DLTs observed were stomatitis (6%) and hemoptysis (3%).

In 2007, preliminary findings were reported from a phase II multicenter, randomized, double-blind, placebo-controlled trial of docetaxel (80 mg/m<sup>2</sup> every 3 weeks) alone or with axitinib (5 mg twice daily) in 168 patients with chemotherapy-naïve MBC.<sup>103</sup> The overall response rate was 40% with docetaxel plus axitinib and was 23% with docetaxel plus placebo ( $P = .038$ ); the median time to treatment failure was 9 months with docetaxel plus axitinib and was 6.3 months

for docetaxel plus placebo ( $P = .012$ ). Grades 3 and 4 adverse effects were more common with axitinib: febrile neutropenia (16%  $\nu$  7%), fatigue (13%  $\nu$  5%), stomatitis (13%  $\nu$  2%), diarrhea (11%  $\nu$  0%), and hypertension (5%  $\nu$  2%).

## RAS/MEK/ERK PATHWAY INHIBITORS

The Ras superfamily of GTPases act as crucial regulatory switches coordinating a variety of biologic functions. These proteins are classified in five families: Ras, Rho, Rab, Sar1/Arf, and Ran.<sup>104</sup> Although fewer than 5% of breast cancers have *ras* mutations, hyperactivation of the Ras protein in breast cancer has been described.<sup>105</sup> Overexpression of Rho was associated with locoregional and distant metastasis of breast cancer<sup>106</sup> and also inflammatory breast cancer.<sup>107</sup>

Tipifarnib (Zarnestra; Johnson & Johnson, New Brunswick, NJ), a farnesyltransferase inhibitor, inhibited the growth of MCF-7 breast cancer cell xenografts in a dose-dependent manner.<sup>108</sup> In a phase I trial, single-agent tipifarnib was administered at doses up to 1,300 mg twice daily for 5 days every 2 weeks without significant toxicity.<sup>109</sup> The authors recommended that the tipifarnib dose for phase II trials be 500 mg twice daily for 5 consecutive days followed by 9 days of rest.

In a phase II study of tipifarnib in patients with hormone-sensitive MBC who experienced progression during second-line hormonal therapy, 10% of patients had a PR, and 25% had CB.<sup>110</sup> The main adverse effects were neutropenia, thrombocytopenia, and neurotoxic effects. In another study, tipifarnib was combined with dose-dense doxorubicin and cyclophosphamide as neoadjuvant therapy for patients with locally advanced breast cancer; after four cycles, patients underwent surgery.<sup>111</sup> Five of 32 patients had at least 50% farnesyltransferase inhibition in the primary tumor, as revealed by serial biopsies during treatment, and seven of 21 patients had a pathologic complete response. These data are interesting, because pathologic complete response occurred in patients with estrogen-receptor–positive tumors.

In a randomized, phase II study in 120 patients with MBC who experienced antiestrogen therapy failure, addition of tipifarnib to letrozole did not improve the objective response rate.<sup>112</sup> However, in another phase II study in patients with no prior therapy for MBC, tipifarnib combined with fulvestrant resulted in a CB rate of 51.6%.<sup>113</sup>

## PI3K/AKT/ MAMMALIAN TARGET OF RAPAMYCIN PATHWAY INHIBITORS

The PI3K signaling pathway is crucial to many aspects of key cellular functions, including growth, proliferation, survival, angiogenesis, and motility.<sup>114</sup> Recent studies indicate that, in patients with cancer, amplification, mutation, and translocation that result in activation are more common in the PI3K/AKT/ mammalian target of rapamycin (mTOR) pathway than in any other pathway.<sup>115</sup> Activating mutation of PI3K has been described in approximately 40% of primary breast tumors, which suggests the importance of PI3K in breast cancer tumorigenesis.<sup>116</sup> Three mTOR antagonists are being studied for breast cancer treatment<sup>117</sup>: everolimus, a mammalian target of rapamycin inhibitor with better oral availability than sirolimus; temsirolimus, a water-soluble ester of sirolimus; and deforolimus (AP23573), a non-rapamycin analog prodrug that has been tested in phase I and II

clinical trials and that shows promising results in several tumor types, including sarcoma. All three agents have shown activity against breast cancer in preclinical studies.<sup>118,119</sup> Phase I studies of everolimus<sup>120</sup> and temsirolimus<sup>121</sup> showed good adverse effect profiles.

### Everolimus

Everolimus (Cetican; Novartis Pharma AG, Basel, Switzerland) was developed in an attempt to improve the pharmacokinetic characteristics of sirolimus, particularly to increase oral bioavailability. In a phase II, randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with operable estrogen-receptor-positive breast cancer,<sup>122</sup> everolimus plus letrozole was associated with a significantly higher clinical response rate (68% v 59%;  $P = .0616$ ).

### Temsirolimus

Temsirolimus (Torisel; Wyeth, Philadelphia, PA) is a water-soluble ester of sirolimus with antitumor activity in preclinical breast cancer models.<sup>119</sup> In a phase I study in patients with advanced malignancies treated with weekly intravenous temsirolimus (7.5 to 220 mg/m<sup>2</sup>), the DLT was thrombocytopenia.<sup>121</sup>

In a phase II study in previously treated patients with locally advanced breast cancer or MBC treated with weekly intravenous temsirolimus (75 mg or 250 mg), 13.8% of patients had CB. The most common adverse effects were mucositis, maculopapular rash, and nausea.<sup>123</sup> Preliminary results of a large, phase II study of temsirolimus plus letrozole or letrozole alone showed similar rates of CB for the two approaches (82% and 83% for continuous and intermittent temsirolimus, respectively, and 79% for letrozole alone)<sup>124</sup> but suggested that PFS might be longer for combination therapy.<sup>125</sup>

In a phase III study, more than 1,200 postmenopausal patients with estrogen-receptor-positive MBC suitable for first-line therapy were randomly assigned to letrozole with or without temsirolimus.<sup>126</sup> The trial was terminated early after interim analysis demonstrated a lack of additional benefit with the combination therapy. Studies of temsirolimus in combination with other drugs are ongoing.

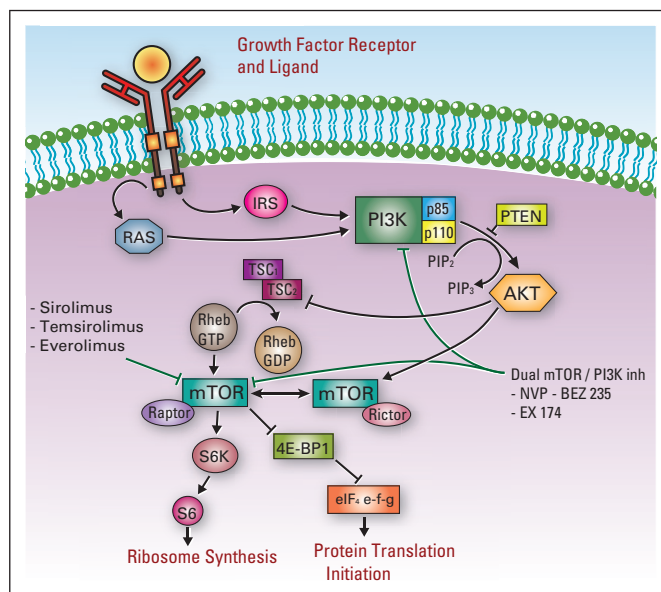
## INSULIN-LIKE GROWTH FACTOR INHIBITORS

The IGF system involves a complex regulatory network composed of two receptors, two ligands, and IGF-binding proteins. Several monoclonal antibodies (CP-751,856, AMG 479, and IMC-A12)<sup>127-129</sup> are in early clinical development in the treatment of breast cancer.

## POLY (ADP-RIBOSE) POLYMERASE 1 INHIBITORS

Poly (ADP-ribose) polymerase 1 (PARP-1) is a critical enzyme in cell proliferation and DNA repair. Multiple PARP-1 inhibitors have been tested preclinically as potentiators of chemotherapy and radiotherapy.<sup>130</sup> A preliminary analysis of a randomized, phase II study of gemcitabine plus carboplatin with or without the PARP-1 inhibitor BSI-201 in patients with TRN MBC showed a higher objective response rate and longer PFS and overall survival with BSI-201<sup>131</sup> (Fig 3; Appendix Fig A3, online only).

Olaparib (AZD2281) is a novel PARP inhibitor with significant activity in patients with breast, ovarian, and prostate cancer with



**Fig 3.** The mammalian target of rapamycin (mTOR) signaling network. mTOR is a highly conserved pathway that regulates cell proliferation and metabolism in response to environmental factors. The growth factor receptor is linked with mTOR signaling via the phosphatidylinositol-3-kinase (PI3K)/Akt family. *PTEN* plays an important role in this pathway; loss of *PTEN* function through mutation, deletion, or epigenetic silencing results in increased activation of Akt and mTOR. The mTOR proteins regulate activities of the translational regulators 4E-BP1 and p70S6 kinase (S6K). mTOR antagonists have been developed to inhibit mTORC1 (raptor).

*BRCA1* or *BRCA2* mutation.<sup>132</sup> A phase I study showed that 12 of 19 patients had CB, and nine patients had PR by Response Evaluation Criteria in Solid Tumors (RECIST). A preliminary report of a single-arm, phase II study in patients with *BRCA*-deficient breast cancer treated with olaparib was recently published.<sup>133</sup> Nine of 24 patients who received 400 mg daily of olaparib had PR by RECIST; 19% of patients experienced grade 3 or 4 toxic effects, including fatigue (11%), nausea (2%), and vomiting (5.5%). Several phase II studies of other PARP inhibitors (ie, ABT-888, AGO14699, and MK4827) are underway.

## FUTURE DIRECTIONS

The past decade has also been one of dramatic changes in breast cancer treatment, including increasing use of targeted therapy. However, despite great enthusiasm for targeted therapy, these agents have exhibited only anecdotal or modest activity when used as single agents in unselected patients. In addition, selection of patients for targeted therapy remains a challenge, because we lack reliable biomarkers to predict activity for most of the targeted agents.

The development of new drugs in oncology faces multiple challenges in this new molecular era. The final major contribution to the transformation of breast cancer treatment has been not a technical or pharmacologic revolution but rather a transformation in the way we think about the disease and its treatment. Continued application of old paradigms of drug evaluation (on the basis of response rates and toxicity) to new targeted therapies may be inappropriate, because neither tumor response nor toxicity is a useful surrogate for dose selection or efficacy. We need a better understanding of the molecular



biology of signaling pathways, and we need to discover new biomarkers that we can use to select the optimal dose of targeted agents for phase II clinical studies.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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#### AUTHOR CONTRIBUTIONS

**Conception and design:** Ricardo H. Alvarez  
**Financial support:** Gabriel N. Hortobagyi  
**Administrative support:** Vicente Valero, Gabriel N. Hortobagyi  
**Collection and assembly of data:** Ricardo H. Alvarez, Gabriel N. Hortobagyi  
**Data analysis and interpretation:** Ricardo H. Alvarez, Vicente Valero, Gabriel N. Hortobagyi  
**Manuscript writing:** Ricardo H. Alvarez  
**Final approval of manuscript:** Ricardo H. Alvarez, Vicente Valero, Gabriel N. Hortobagyi

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