# Targeted therapy in cancer

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## Abstract

The historical use of chemotherapy relied on the systemic use of cytotoxic agents to disrupt mitosis in rapidly dividing cancer cells, with foreseeable dose-limiting haematological toxicities. Targeted therapies affect specific cellular molecular mechanisms promoting cancer cell survival and proliferation, enabling treatment tailored to specific tumour characteristics. The key pathways include the hormonal axis, growth factor receptor-mediated tyrosine kinases and cellular immune system. Monoclonal antibodies can target extracellular ligands or cell surface growth factor receptors. Tyrosine kinase inhibitors prevent signal transduction from the intracellular portion of the receptors. Immune checkpoint inhibiting antibodies facilitate immune recognition and destruction of cancer cells by cytotoxic T cells. Various agents are used to reduce hormone synthesis or block activation of intracellular hormone receptors. These newer agents have a different pattern of adverse effects, but offer an improved therapeutic ratio for many patients. The highly targeted mechanism of activity means that an individualized pre-treatment characterization of the patient's tumour molecular profile is increasingly needed.

**Keywords** Cancer; immunotherapy; monoclonal antibodies; targeted therapy; tyrosine kinase inhibitors

## What's new?

**Immune checkpoint targets (immunotherapy)**

- Tumours evade recognition and destruction by the immune system (immunosurveillance) through several immune-inhibition mechanisms
- The monoclonal antibodies ipilimumab (against CTLA-4) and nivolumab (against PD-1) block two distinct pathways of T cell inhibition. This up-regulates the immune response and allows the recognition and destruction of tumour cells
- Ipilimumab and nivolumab have demonstrable efficacy in both malignant melanoma and lung cancer

## Introduction

The mainstay of cancer treatment since the development of chemotherapeutic agents in the 1940s has been cytotoxic drugs. (See *Principles of Systemic Anticancer Therapy* on pages 20–24 and *Cytotoxic Chemotherapy: Clinical Aspects* on pages 25–29 of this issue.) Cytotoxics affect cellular mitosis and broadly work in three different ways:

- disruption of DNA structure – platinum agents such as cisplatin cause inter- and intrastrand DNA adducts; alkylating agents such as cyclophosphamide cause DNA alkylation
- prevention of DNA synthesis – the pyrimidine analogue 5-fluorouracil blocks the synthesis of the nucleoside thymidine; antifolate drugs such as methotrexate inhibit the enzyme dihydrofolate reductase needed for purine and pyrimidine synthesis
- disruption of microtubules – the taxanes docetaxel and paclitaxel stabilize microtubules, preventing mitosis; vinca alkaloids (e.g. vinorelbine, vincristine) prevent microtubule formation.

As these treatments are given systemically, their action of mitotic inhibition is not limited to cancer cells, particularly profound effects being seen on the haematopoietic system, often with resulting neutropenia or pancytopenia.[1]

Targeted therapy conversely seeks to selectively affect cancer cells based on specific molecular characteristics. Targets for therapy are diverse but involve cellular growth, proliferation and, more recently, immune evasion. (See *Biology of Cancer* on pages 1–5 of this issue.)

The clinical aim with targeted therapy, as with conventional cytotoxics, can be curative, for example neoadjuvant (to downstage the tumour before surgery), adjuvant (given after surgery to reduce risk of relapse) or palliative (to improve quality of life or survival). Targeted therapies can be given concurrently with both chemotherapy and radiotherapy, for example docetaxel and trastuzumab for breast cancer, and cetuximab and radiotherapy for head and neck cancer.

## Development of targeted therapy

The initial advances in cancer targeted therapy were made with haematological malignancies. The first cancer-targeted therapy was the monoclonal antibody rituximab, an antibody to the B cell antigen CD20, used to treat B cell non-Hodgkin's lymphoma (Table 1).[2]

Investigations into the molecular biology of chronic myeloid leukaemia (CML) demonstrated that the BCR-ABL translocation between chromosomes 9 and 22 of the Philadelphia chromosome, found in the majority of cases, produced a constitutively active tyrosine kinase. Tyrosine kinases are involved in signal transduction, which in CML leads to a constitutive activation of proliferation signals. Following identification of the underlying pathological mechanism, imatinib was developed specifically to block this fusion tyrosine kinase; it has demonstrated significant survival benefit in CML.[3] The same tyrosine kinase is involved in the development of the rare gastrointestinal stromal tumours (GISTs); imatinib was found to be highly active for GISTs and rapidly became the standard of care.

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## Brief timeline of drug development

1997 — Rituximab approved for B cell non-Hodgkin's lymphoma
*First targeted cancer antibody*
1998 — Trastuzumab approved for HER2-positive metastatic breast cancer
*First targeted solid tumour antibody*
2001 — Imatinib approved for chronic myeloid leukaemia
*First small molecule targeted at cancer*
2003 — Gefitinib approved for the treatment of non-small cell lung cancer (NSCLC)
*First targeted solid tumour small molecule*
2004 — Bevacizumab approved for the treatment of colorectal cancer
2004 — Erlotinib approved for NSCLC
2005 — Sorafenib approved for renal cell carcinoma (RCC)
2007 — Sunitinib approved for RCC
2007 — Lapatinib approved for breast cancer
2009 — Pazopanib + everolimus approved for RCC
2010 — Denosumab approved to reduce bone-related adverse events
2011 — Crizotinib approved for anaplastic lymphoma kinase rearranged lung cancer
2011 — Ipilimumab approved for advanced melanoma
*First solid tumour immunotherapy*
2011 — Abiraterone approved for prostate cancer
2013 — Trastuzumab—emtansine (TDM-1) approved for breast cancer
2014 — Nivolumab approved for melanoma
2015 — Nivolumab approved for squamous NSCLC

* US Food and Drug Administration approval dates.
Adapted from Targeted Therapy Timeline, available at http://www.cancerprogress.net/timeline/targeted-drugs (American Society of Clinical Oncology (ASCO), 2015).

**Table 1**

The development of imatinib as an inhibitor of BCR-ABL has served as the paradigm for the development of tyrosine kinase inhibitors (TKIs) for solid tumours, for example against the epidermal growth factor receptor (EGFR) pathway in lung cancer. This paradigm for rational drug design based on the underlying pathological mechanisms driving individual cancers is the template for the development of modern cancer therapeutics.

## Types of agent

**Tyrosine kinase inhibitors**, such as erlotinib, gefitinib and afatinib (Table 2), are orally active small molecules that act intracellularly to prevent downstream signal transduction from activated growth factor receptors.[4] They have demonstrable efficacy in non-small cell lung cancers (NSCLCs) harbouring activating EGFR mutations.

**Monoclonal antibodies** utilize the specificity of the fragment antigen-binding region of the antibody to target specific therapeutic epitopes. Modern antibodies are either chimeric mouse—human or fully human, with the latter felt to be less immunogenic.[5] They target either extracellular ligands (the compounds that activate the receptor), for example bevacizumab on vascular endothelial growth factor (VEGF), or the cell surface receptors themselves, for instance cetuximab on EGFR (Figure 1). Bevacizumab and cetuximab have demonstrated efficacy in colorectal cancers.[5] Similarly to chemotherapy, they are usually delivered by intravenous infusion.

**Antibody drug conjugates** combine a monoclonal antibody with a cytotoxic to deliver the cytotoxic directly to the targeted cells. The antibody targets and binds to a specific extracellular receptor, leading to internalization of the complex, thus delivering the cytotoxic payload only to those cells expressing the targeted receptor. TDM-1 is a conjugate of trastuzumab and the cytotoxic emtansine and has been shown to improve survival in patients with metastatic human epidermal growth factor 2 receptor (HER2) positive breast cancer.

**Immune checkpoint inhibitors** are monoclonal antibodies that target key regulatory points in the cellular immune system such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1 (PD-1). As with growth factor-targeting antibodies, they target either the receptor (e.g. the anti-CTLA-4

## Small molecule targets

| Name | Pathway | Type of agent | Disease | Reference |
|---|---|---|---|---|
| Erlotinib | EGFR | TKI | EGFR-mutated NSCLC | 3 |
| Afatinib | EGFR | TKI | EGFR-mutated NSCLC | 9 |
| Lapatinib | EGFR + HER2 | TKI | HER2-positive breast cancer | 12 |
| Sorafenib | VEGFR | TKI | Clear cell renal cell carcinoma | 13 |
| Crizotinib | ALK | TKI | ALK-translocated NSCLC | 14 |
| Abiraterone | Androgen | Ligand synthesis inhibitor | Castrate-resistant metastatic prostate cancer | 8 |
| Vemurafenib | BRAF | Enzyme inhibitor | BRAF V600E-mutated malignant melanoma | 15 |

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor 2 receptor; NSCLC, non-small cell lung carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

**Table 2**