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A Review on recent Anti-Cancer Agents and Drugs containing Pyrazole

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ABSTRACT

Cancer is not a single disease. It is a group of more than 200 different diseases. Cancer can be generally described as an uncontrolled growth and spread of abnormal cells in the body. Cells are basic units of life. All organisms are composed of one or more cells. Nor mally, cells divide to produce more cells only when the body needs them. Sometimes cells keep dividing and thus creating more cells even when they are not needed. When this happens; a mass of tissue forms. This mass of extra tissue is called a tumor. Tumors are found in all kinds of tissue, and can be benign or malignant.

Keywords: Cancer, Malignant tumor, Antineoplastic agents

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INTRODUCTION

How Cancers Develop and Spread:

Cancer develops only in cells with damaged genes (mutations).

Mutations can be inherited or caused by exposure to:

- Low-dose radiation
- Drugs
- Toxic chemicals
- Infection with certain viruses can cause mutations.
- Lifestyle plays a major role in cancer prevention.

Tumors:

a) Benign:

Benign tumors are not cancer. They usually can be removed and, in most cases, they do not come back. Most important, cells from benign tumors do not spread to other parts of the body. Cells from benign tumors stay together and often they are surrounded by a containing membrane. Benign tumors are not usually a threat to life.[1]

b) Malignant

Malignant tumors are cancer. Cancer cells can invade and damage tissues and organs near the tumor. Cancer cells also can break away from a malignant tumor and enter the lymphatic system or the bloodstream, which is how cancer can spread to other parts of the body. The characteristic feature of cancer is the cell's ability to grow rapidly, uncontrollably, and independently from the tissue where it started. The spread of cancer to other sites or organs in the body through the blood stream or lymphatic system is called metastasis. [2]

Malignant tumors generally can be classified in two categories.

Carcinomas: These cancers originate in the epithelium. The epithelium is the lining cells of an organ. Carcinomas are the most common type of cancer. Common sites of carcinomas are the skin, mouth, lung, breast, stomach, colon and uterus.

Sarcomas: Sarcomas are cancers of connective and supportive tissue (soft tissues) of all kinds. Sarcomas can be found anywhere in the body, and they often form secondary growths in the lungs. [3]

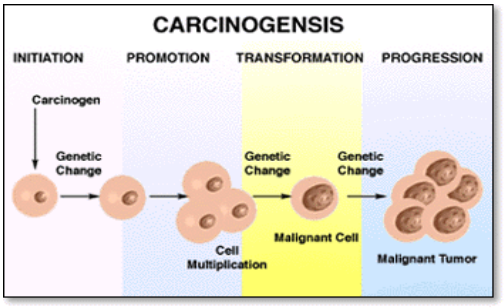


Figure 1: Process of cancer development

Anti-cancer agents:

Antineoplastic drugs: are most effective against rapidly dividing tumor cells. The main goal of Antineoplastic Agents is to eliminate the cancer cells without affecting normal tissues (the concept of differential sensitivity). In reality, all cytotoxic drugs affect normal tissues as well as malignancies - aim for a favorable therapeutic index.

Therapeutic Index = LD_{50} / ED_{50}

A therapeutic index is the lethal dose of a drug for 50% of the population (LD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50}).

Classification: [4]

A. Drug acting directly on cells (CYTOTOXIC DRUGS):

1. Alkylating agents: (Nitrogen mustards)

Mechlorethamines

Cyclophosphamide

Ifosfamide

Chlorambucil

Melphalan

Ethylenimine

Thio-TEPA

2. Alkyl sulfonates

Busulfan

Nitrosoureas

Carmustine

Lomustine

Triazine

Dacarbazine

3. Antimetabolites

a) Folate antagonist : Methotrexate

b) Purine antagonist : 6-mercaptopurine, 6-thioguanine, Azathioprine

c) Pyrimidine antagonist : 5-Fluorouracil Cytarabine (cytosine arabinoside)

4. **Vinca alkaloids:** Vincristine, Vinblastine

5. **Taxanes** : Paclitaxel, Docetaxel

6. **Epipodophyllo toxin:** Etoposide

7. **Camptothecin analogues:** Topotecan, Irinotecan

8. **Antibiotics:** Actinomycin (dactinomycin), Doxorubicin, Daunorubicin, Mitoxantrone, Bleomycins, Mitomycin C, Mithramycin (plicamycin)

9. **Miscellaneous:** Hydroxyurea, L-Asparaginase, Cisplatin

B. Drugs altering hormonal milieu

1. **Glucocorticoids:** Prednisolone

2. **Estrogens:** Fosfestrol, Ethinylestradiol

3. **Antiestrogen:** Tamoxifen

4. **Antiandrogen:** Flutamide

5. **5-Alpha reductase inhibitor:** Finasteride

6. **GnRH Analogues:** Naferelin, Goserelin

7. **Progestins:** Hydroxyprogesterone acetate

Chemotherapy: classification based on the **mechanism of action:**

Antimetabolites: Drugs that interfere with the formation of key biomolecules including nucleotides, the building blocks of DNA.

Genotoxic Drugs: Drugs that alkylate or intercalate the DNA causing the loss of its function.

Plant-derived inhibitors of mitosis: These agents prevent proper cell division by interfering with the cytoskeletal components that enable the cell to divide.

Plant-derived topoisomerase inhibitors: Topoisomerases unwind or religate DNA during replication. [5]

Cell cycle specificity of Anti-Neoplastic Agents:

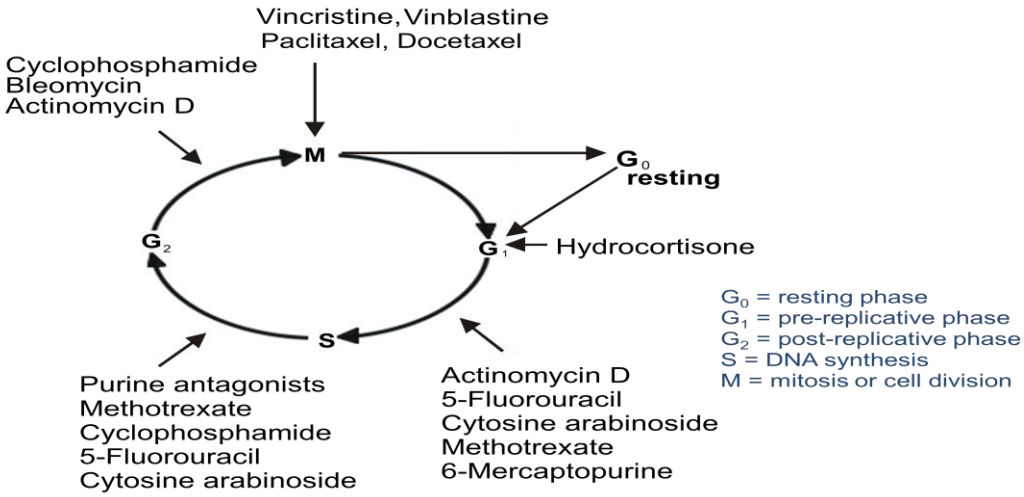
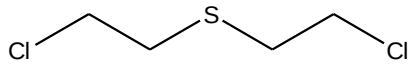


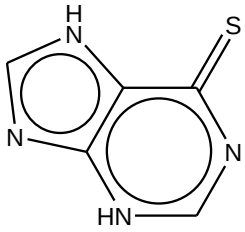
Figure 2: Cell cycle specificity of Anti-Neoplastic Agents

DEVELOPMENTS LEADING IMPROVEMENT IN ANTI CANCER MOIETY

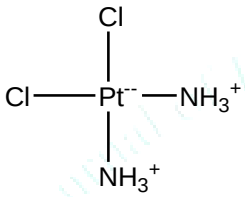
Sulfur mustard gas-offensive weapon by Germans during World War I, destroyed the blood's white cells, leading to discovery of drugs used in leukaemia therapy.



6-Mercaptopurine was really the first effective leukemic drug for which Hitchings and Elion shared the Nobel Prize in 1988.

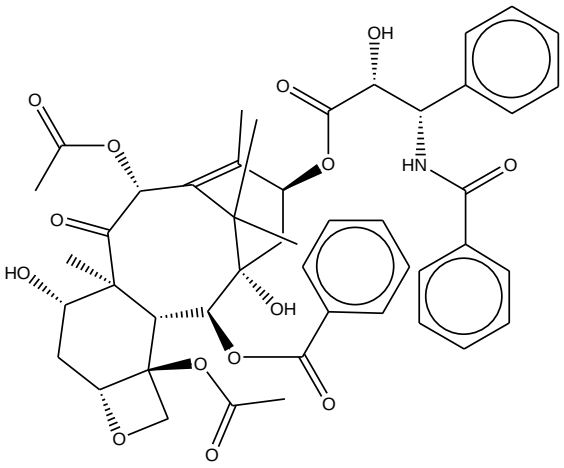


Unlike, many cancer drugs available today, Cisplatin interferes with the growth of cancer cells by binding to DNA and interfering repair mechanism. [6]

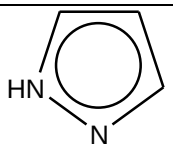


Cisplatin is now THE GOLD STANDARD against which new medicines are compared.

Taxol , generically called Paclitaxel became effective drug for treating ovarian, breast and certain forms of lung cancers.



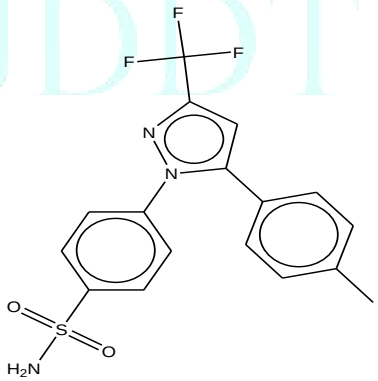
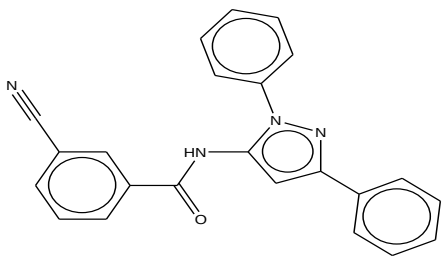
Characteristics of Pyrazole: [7]

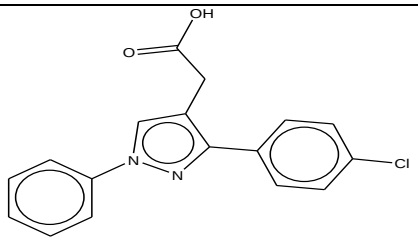
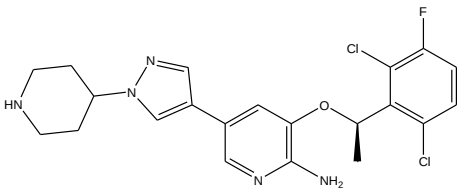
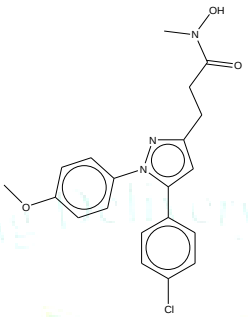
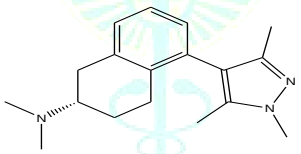
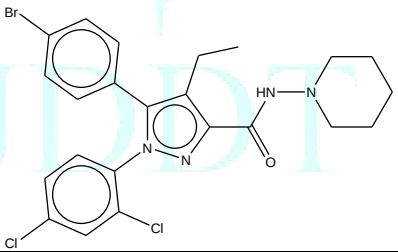
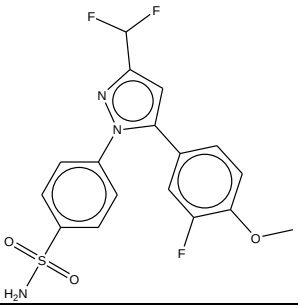
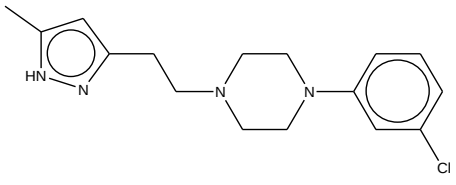
Structure	
IUPAC Name	1,2-diazole
Molecular Formula	$C_3H_4N_2$
Molecular Weight	68.08

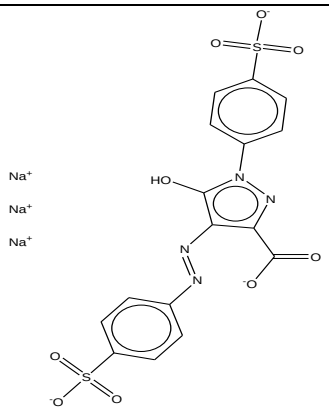
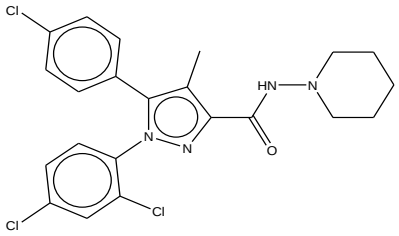
CHEMISTRY OF PYRAZOLE

Pyrazole is the organic compound with the formula $C_3H_3N_2H$. It is a heterocycle characterized by a 5-membered ring of three carbon atoms and two adjacent nitrogen centres. Pyrazoles are also the class of compounds that have the ring C_3N_2 with adjacent nitrogen centres.

Table 1: Drugs containing pyrazole moiety [8]

S.No.	Name	Structure	Biological activity
1.	Celecoxib		NSAIDs
2.	CDPPB		Antipsychotic effects
3.	Lonazolac		NSAIDs

			
4.	Crizotinib		Anti-cancer
5.	Tepoxalin		NSAIDs
6.	AS-19		$5HT_7$ receptor agonist
7.	Surinabant		Cannabinoid receptor type 1 antagonist
8.	Deracoxib		NSAIDs
9.	Mepiprazole		Minor tranquilizer
10.	Tartrazine		Azo dye primarily used

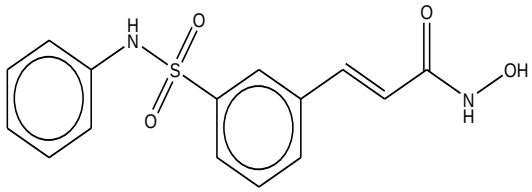
			as a food coloring.
11.	Rimonabant		Anorectic antiobesity drug

RECENT DEVELOPMENT ON ANTI CANCER AGENTS [9]

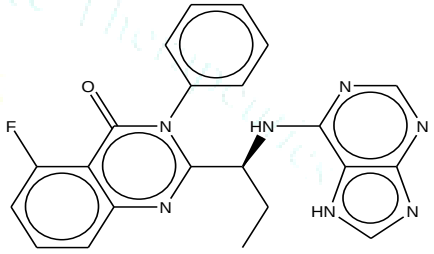
Chemotherapyis the use of anti-cancer of drugs. Anti-cancer drugs destroy cancer cells by stopping growth or multiplication at some point in their life cycles. Drugs may be administered intravenously (into a vein), orally (by mouth), by injection into a muscle, topically (applied to the skin) or in other ways, depending on the drug and the type of cancer. Chemotherapy is often given in cycles of alternating treatment and rest periods.

Recent Drugs: [10]

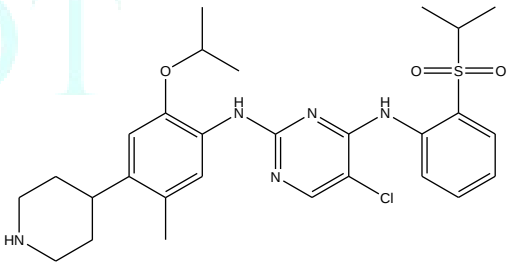
Belinostat is experimental drug candidate under development by TopoTarget for the treatment of hematological malignancies and solid tumors. It is a histone deacetylase inhibitor.In 2007 preliminary results were released from the Phase II clinical trial of intravenous belinostat in combination with carboplatin and paclitaxel for relapsed ovarian cancer. Final results in late 2009 of a phase II trial for T cell lymphoma were encouraging.



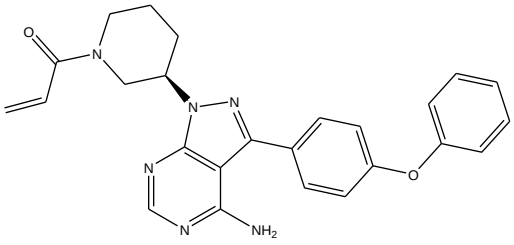
Idelalisib a drug under investigation for the treatment of chronic lymphocytic leukaemia. The substance acts as a phosphoinositide 3-kinase inhibitor; more specifically, it blocks P110δ, the delta isoform of the enzyme phosphoinositide 3-kinase.**Approval by the FDA** On 25 July 2014, the FDA granted Idelalisib approval to treat different types of leukemia.Idelalisib is a second line drug for patients whose chronic lymphocytic leukemia (CLL) has relapsedThe FDA is also granted Idelalisib approval to treat patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL).



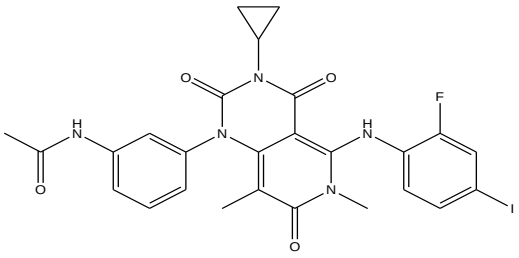
Ceritinib is a drug for the treatment of lung cancer. It is an ALK inhibitor. It was approved in April 2014 by the Food and Drug Administration for the treatment of ALK-positive metastatic non-small cell lung cancer (NSCLC) following treatment with crizotinib. [11]



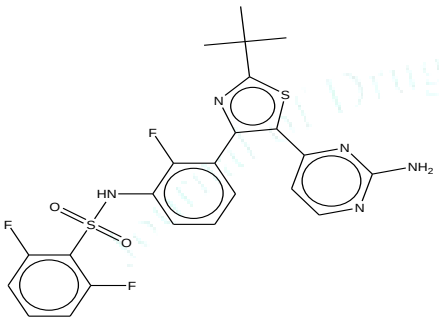
Ibrutinib is an anticancer drug targeting B-cell malignancies. It was approved by the US FDA in November 2013 for the treatment of mantle cell lymphoma and in February 2014 for the treatment of chronic lymphocytic leukemia. It is an orally-administered, selective and covalent inhibitor of the enzyme Bruton's tyrosine kinase (BTK).



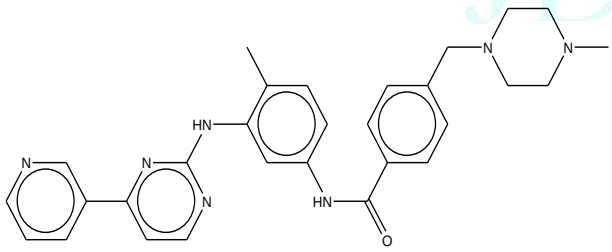
Trametinib is a cancer drug. It is a MEK inhibitor drug with anti-cancer activity. It inhibits MEK1 and MEK2. In May 2013, trametinib was approved as a single-agent by the Food and Drug Administration for the treatment of patients with V600E mutated metastatic melanoma. Trametinib had good results for metastatic melanoma carrying the BRAF V600E mutation in a phase III clinical trial. In this mutation. [12]



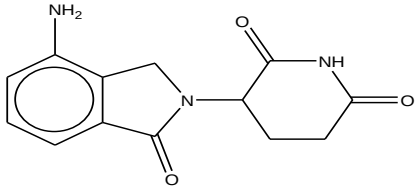
Dabrafenib is a drug for the treatment of cancers associated with a mutated version of the gene *BRAF*. Dabrafenib acts as an inhibitor of the associated enzyme B-Raf, which plays a role in the regulation of cell growth. The Food and Drug Administration approved dabrafenib as a single agent treatment for patients with BRAF V600E mutation-positive advanced melanoma on May 30, 2013.



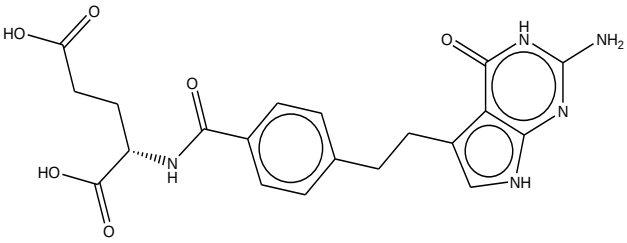
Imatinib is a tyrosine-kinase inhibitor used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML). imatinib works by preventing a tyrosine kinase enzyme, in this case BCR-Abl, from phosphorylating subsequent proteins and initiating the signalling cascade necessary for cancer growth and survival, thus preventing the growth of cancer cells and leading to their death by apoptosis. [13]



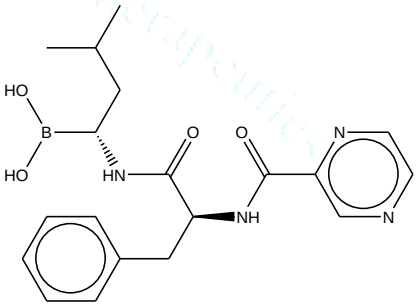
Lenalidomide is a derivative of thalidomide introduced in 2004. It was initially intended as a treatment for multiple myeloma, for which thalidomide is an accepted therapeutic treatment. Lenalidomide has also shown efficacy in the class of hematological disorders known as myelodysplastic syndromes (MDS). Lenalidomide has significantly improved overall survival in myeloma.



Pemetrexed is chemically similar to folic acid and is in the class of chemotherapy drugs called folate antimetabolites. It works by inhibiting three enzymes used in purine and pyrimidine synthesis—thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). By inhibiting the formation of precursor purine and pyrimidine nucleotides, pemetrexed prevents the formation of DNA and RNA, which are required for the growth and survival of both normal cells and cancer cells. [14]



Bortezomib) is the first therapeutic proteasome inhibitor to be tested in humans. It is approved in the U.S. for treating relapsed multiple myeloma and mantle cell lymphoma. In multiple myeloma, complete clinical responses have been obtained in patients with otherwise refractory or rapidly advancing disease. The boron atom in bortezomib binds the catalytic site of the 26S proteasome.



Siltuximab is a chimeric (made from human and mouse proteins) monoclonal antibody. It binds to interleukin-6.Siltuximab has been investigated for the treatment of metastatic renal cell cancer, prostate cancer, and Castleman's disease, among other types of cancer. It has undergone a phase I clinical trial in patients With B-cell non-Hodgkin's lymphoma, multiple myeloma, or Castleman's disease. Encouraging results have been reported from a phase II trial for relapsed or refractory multiple myeloma. On April 23, 2014, Siltuximab was FDA approved under the brand name of Sylvant for the treatment of patients with multicentric Castleman's disease (MCD) who do not have human immunodeficiency virus (HIV) or human herpesvirus-8 (HHV-8). [15]

Ramucirumab is a fully human monoclonal antibody (IgG1) developed for the treatment of solid tumors. Ramucirumab is being tested in several phase III clinical trials for the treatment of metastatic gastric adenocarcinoma, non-small cell lung cancer, among other types of cancer. On September 26, 2013 the manufacturer Eli Lilly announced that its Phase III study for ramucirumab failed to hit its primary endpoint on progression-free survival among women with metastatic breast cancer. On April 21, 2014, the FDA approved ramucirumab in treating stomach cancer. [16]

Ofatumumab is a fully human monoclonal antibody (for the CD20 protein) which appears to inhibit early-stage B lymphocyte activation. It is FDA approved for treating chronic lymphocytic leukemia that is refractory to fludarabine and alemtuzumab. Its only indication that has

received regulatory approval is Chronic lymphocytic leukaemia (CLL). It first received FDA approval for this indication on the 26th of October 2009, MHRA approval on the 19th of April 2010, EMA approval on the 14th of June 2010 and Health Canada approval on the 13th of August 2012. [17]

Rituximab was approved by the U.S. Food and Drug Administration in 1997 to treat B-cell non-Hodgkin lymphomas resistant to other chemotherapy regimens. Rituximab, in combination with CHOP chemotherapy, is superior to CHOP alone in the treatment of diffuse large B-cell lymphoma and many other B-cell lymphomas. In 2010 it was approved by the European Commission for maintenance treatment after initial treatment of follicular lymphoma. [18]

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