Cancer Association of South Africa (CANSA)

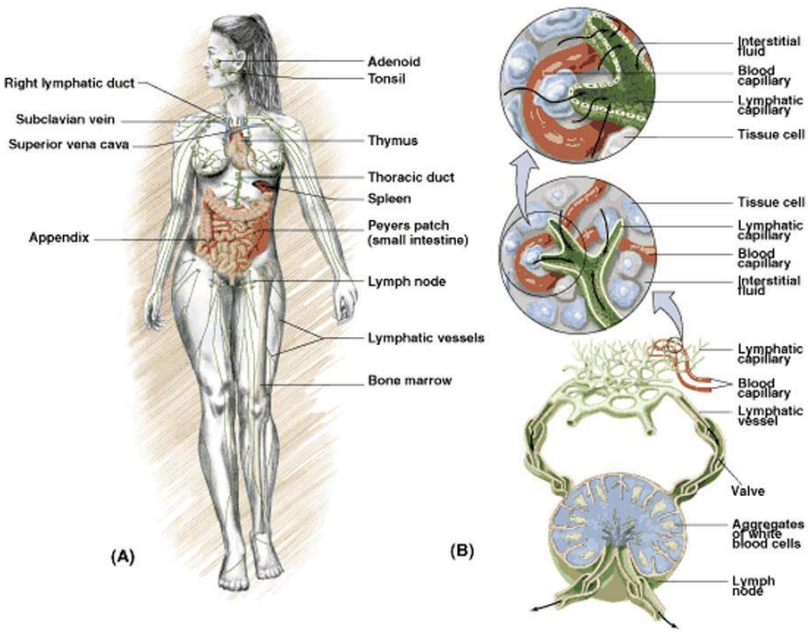
Research • Educate • Support

Fact Sheet on Follicular Lymphoma

Introduction

Lymphoma (also termed lymphatic cancer) is a type of cancer involving cells of the immune system, called lymphocytes. Just as cancer represents many different diseases, lymphoma represents many different cancers of lymphocytes -- about 35-60 different subtypes, in fact, depending upon which group of experts is categorizing the subtypes.

Lymphoma is a group of cancers that affect the cells that play a role in the immune system and primarily represents cells involved in the lymphatic system of the body.



[Picture Credit: Lymphatic system]

The lymphatic system is part of the immune system. It consists of a network of vessels that carry fluid called lymph, similar to the way that the network of blood vessels carry blood throughout the body. Lymph contains white blood cells called lymphocytes that are also present in blood and tissues. Lymphocytes attack a variety of infectious agents as well as many cells in the precancerous stages of development.

Lymph nodes are small collections of lymph tissue that occur throughout the body. The lymphatic system involves lymphatic channels that connect thousands of lymph nodes scattered throughout the body. Lymph flows through the lymph nodes, as well as through other lymphatic tissues including the spleen, the tonsils, the bone marrow, and the thymus gland.

These lymph nodes filter the lymph, which may carry bacteria, viruses, or other microbes. At infection sites, large numbers of these microbial organisms collect in the regional lymph nodes and produce the local swelling and tenderness typical of a localized infection. These enlarged and occasionally confluent collections of lymph nodes (so-called lymphadenopathy)

are often referred to as "swollen glands." In some areas of the body (such as the anterior part of the neck), they are often visible when swollen.

- Lymphocytes recognise infectious organisms and abnormal cells and destroy them. There are two major subtypes of lymphocytes: B lymphocytes and T lymphocytes, also referred to as B cells and T cells.

- B lymphocytes produce antibodies (proteins that circulate through the blood and lymph and attach to infectious organisms and abnormal cells). Antibodies essentially alert other cells of the immune system to recognize and destroy these intruders (also known as pathogens); the process is known as humoral immunity.

- T cells, when activated, can kill pathogens directly. T cells also play a part in the mechanisms of immune system control to prevent the system from inappropriate overactivity or underactivity.

- After fighting off an invader, some of the B and T lymphocytes "remember" the invader and are prepared to fight it off if it returns.

Cancer occurs when normal cells undergo a transformation whereby they grow and multiply uncontrollably. Lymphoma is a malignant transformation of either B or T cells or their subtypes.

- As the abnormal cells multiply, they may collect in one or more lymph nodes or in other lymph tissues such as the spleen

- As the cells continue to multiply, they form a mass often referred to as a tumour

- Tumours often overwhelm surrounding tissues by invading their space, thereby depriving them of the necessary oxygen and nutrients needed to survive and function normally

- In lymphoma, abnormal lymphocytes travel from one lymph node to the next, and sometimes to remote organs, via the lymphatic system.

While lymphomas are often confined to lymph nodes and other lymphatic tissue, they can spread to other types of tissue almost anywhere in the body. Lymphoma development outside of lymphatic tissue is called extranodal disease.
(eMedicine Health).

Types of Lymphoma
Lymphomas fall into one of two major categories:
- Hodgkin's lymphoma (HL, previously called Hodgkin's disease)
- Non-Hodgkin’s Lymphoma (NHL, all other lymphomas)

These two types occur in the same places, may be associated with the same symptoms, and often have similar appearance on physical examination. However, they are readily distinguishable via microscopic examination.

Hodgkin's lymphoma develops from a specific abnormal B lymphocyte lineage. NHL may derive from either abnormal B or T cells and are distinguished by unique genetic markers. There are five subtypes of Hodgkin's lymphoma and about 30 subtypes of non-Hodgkin's lymphoma. Because there are so many different subtypes of lymphoma, the classification of lymphomas is complicated (it includes both the microscopic appearance as well as genetic and molecular markers).

Many of the NHL subtypes look similar, but they are functionally quite different and respond to different therapies with different probabilities of cure. HL subtypes are microscopically distinct, and typing is based upon the microscopic differences as well as extent of disease.

World Health Organization Classification System of Lymphoma Types

Over the years, various classification systems have been used to differentiate lymphoma types including the Rappaport Classification (used until the 70's), the Working Formulation, the National Cancer Institute Working Formulation, and the Revised European-American Lymphoma Classification (REAL).

The WHO classification has its origins in the 1850s. The first edition, known as the International List of Causes of Death, was adopted by the International Statistical Institute in 1893. The ICD is the international standard diagnostic classification. It is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. These records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States.

The older Rappaport, Working Formulation, and REAL categories are described in a separate section for reference. This might be helpful if a patient's records state some of the classifications of older lymphoma types.

Hodgkin's lymphoma

- Lymphocytic-histiocytic predominance
- Nodular sclerosis
- Mixed cellularity
- Lymphocytic depletion
- Hodgkin's, unspecified

Follicular (nodular) non-Hodgkin's lymphoma

- Small cleaved cell, follicular
- Mixed small cleaved and large cell, follicular
- Large cell, follicular
- Other follicular non-Hodgkin's lymphoma types
- Follicular non-Hodgkin's lymphoma, unspecified
    - Nodular non-Hodgkin's lymphoma NOS

Diffuse non-Hodgkin's lymphoma

- Small cell (diffuse)
- Small cleaved cell (diffuse)
- Mixed small and large cell (diffuse)
- Large cell (diffuse)
    - Reticulum cell sarcoma

- Immunoblastic (diffuse)
- Lymphoblastic (diffuse)
- Undifferentiated (diffuse)
- Burkitt's tumour (Burkitt's lymphoma)
- Other diffuse non-Hodgkin's lymphoma types
- Diffuse non-Hodgkin's lymphoma, unspecified

Peripheral and cutaneous T-cell lymphomas

- Mycosis fungoides
- Sézary's disease
- T-zone lymphoma
- Lymphoepithelioid lymphoma
  - Lennert's lymphoma
- Peripheral T-cell lymphoma
- Other and unspecified T-cell lymphomas

Other and unspecified types of non-Hodgkin's lymphoma

- Lymphosarcoma
- B-cell lymphoma, unspecified
- Other specified types of non-Hodgkin's lymphoma
  - Malignant:
    - reticuloendotheliosis
    - reticulosis
  - Microglioma
- Non-Hodgkin's lymphoma, unspecified type
  - Lymphoma NOS
  - Malignant lymphoma NOS
  - Non-Hodgkin's lymphoma NOS

Malignant immunoproliferative diseases

- Waldenström's macroglobulinaemia
- Alpha heavy chain disease
- Gamma heavy chain disease
  - Franklin's disease
- Immunoproliferative small intestinal disease
  - Mediterranean disease
- Other malignant immunoproliferative diseases
- Malignant immunoproliferative disease, unspecified
  - Immunoproliferative disease NOS

Multiple myeloma and malignant plasma cell neoplasms

- Multiple myeloma
  - Kahler's disease
  - Myelomatosis
  - Excludes: solitary myeloma
- Plasma cell leukemia
- Plasmacytoma, extramedullary
  - Malignant plasma cell tumour NOS
  - Plasmacytoma NOS

- Solitary myeloma

Lymphoid leukaemia

- Acute lymphoblastic leukaemia
  - Excludes: acute exacerbation of chronic lymphocytic leukaemia
- Chronic lymphoblastic leukaemia
- Subacute lymphocytic leukaemia
- Prolymphocytic leukaemia
- Hairy-cell leukaemia
  - Leukaemic reticuloendotheliosis
- Adult T-cell leukaemia
- Other lymphoid leukaemia
- Lymphoid leukaemia, unspecified

Myeloid leukaemia

- Includes:
  - granulocytic
  - myelogenous
- Acute myeloid leukaemia
  - Excludes: acute exacerbation of chronic myeloid leukaemia
- Chronic myeloid leukaemia
- Subacute myeloid leukaemia
- Myeloid sarcoma
  - Chloroma
  - Granulocytic sarcoma
- Acute promyelocytic leukaemia
- Acute myelomonocytic leukaemia
- Other myeloid leukaemia
- Myeloid leukaemia, unspecified

Monocytic leukaemia

- Includes: monocytoid leukaemia
- Acute monocytic leukaemia
  - Excludes: acute exacerbation of chronic monocytic leukaemia
- Chronic monocytic leukaemia
- Subacute monocytic leukaemia
- Other monocytic leukaemia
- Monocytic leukaemia , unspecified

Other leukaemias of specified cell type

- Acute erythraemia and erythroleukaemia
  - Acute erythraemic myelosis
  - Di Guglielmo's disease
- Chronic erythraemia
  - Heilmeyer-Schöner disease
- Acute megakaryoblastic leukaemia
  - leukaemia :
    - megakaryoblastic (acute)
    - megakaryocytic (acute)

- Mast cell leukaemia
- Acute panmyelosis
- Acute myelofibrosis
- Other specified leukaemia s
    - Lymphosarcoma cell leukaemia

Leukaemia of unspecified cell type

- Acute leukaemia of unspecified cell type
    - Blast cell leukaemia
    - Stem cell leukaemia
- Chronic leukaemia of unspecified cell type
- Subacute leukaemia of unspecified cell type
- Other leukaemia of unspecified cell type
- leukaemia , unspecified

Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue

- Letterer-Siwe disease
    - Nonlipid:
        - reticuloendotheliosis
        - reticulosis
- Malignant histiocytosis
    - Histiocytic medullary reticulosis
- Malignant mast cell tumour
    - Malignant:
        - mastocytoma
        - mastocytosis
    - Mast cell sarcoma
        - Excludes: mast cell leukaemia
        - mastocytosis (cutaneous)
- True histiocytic lymphoma
- Other specified malignant neoplasms of lymphoid, haematopoietic and related tissue
- Malignant neoplasm of lymphoid, haematopoietic and related tissue, unspecified

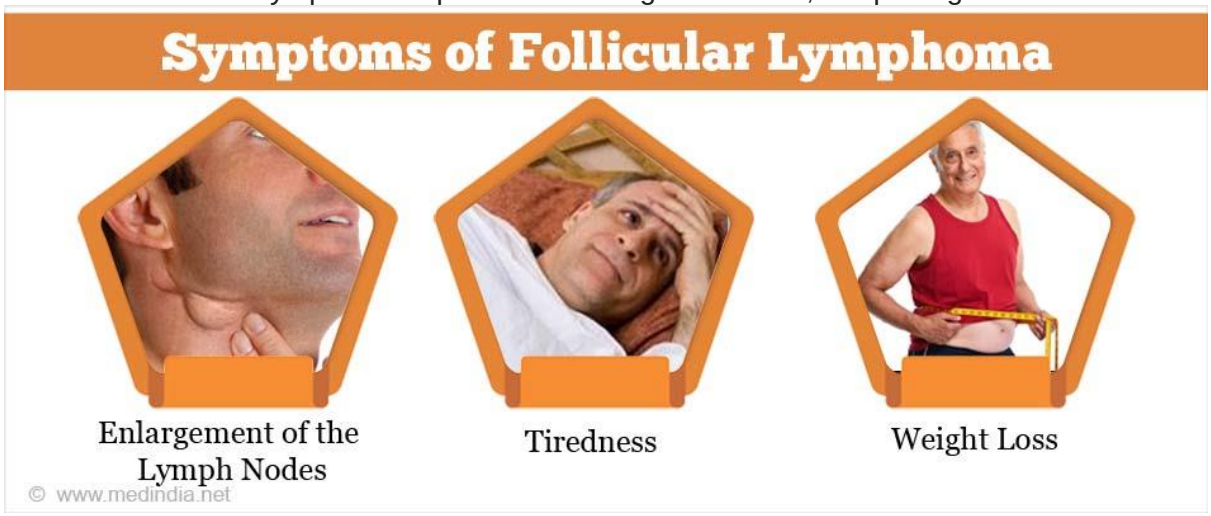
(Lymphomainfo.net)

Follicular Lymphoma (FL)

Follicular lymphoma (FL) is a type of non-Hodgkin lymphoma. It develops when the body makes abnormal B-lymphocytes – the lymphoma cells. (B-lymphocytes are white blood cells that fight infection). The lymphoma cells build up in lymph nodes.

Follicular lymphoma is slow-growing and does not always need to be treated straight away. When treatment is needed, it usually involves a combination of chemotherapy and a monoclonal antibody called rituximab. Some people may have radiotherapy. You may be invited to join a clinical trial looking at new ways of treating follicular lymphoma. You can talk about this with your haematology doctor. (MacMillan Cancer Support).

Signs and Symptoms of Follicular Lymphoma (FL)
The most common symptom is a painless swelling in the neck, armpit or groin.



[Picture Credit: Symptoms]

Other symptoms may include:

- tiredness
- weight loss
- night sweats
- high temperatures (fevers).

(MacMillan Cancer Support).

Incidence of Follicular Lymphoma (FL) in South Africa
According to the National Cancer Registry of 2012, the following number of Non-Hodgkin's Lymphoma cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	933	1:206	2,53%
Asian males	29	1:222	3,39%
Black males	555	1:274	4,76%
Coloured males	79	1:212	1,81%
White males	271	1:121	1,35%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	797	1:311	2,12%
Asian females	21	1:333	1,96%
Black females	500	1:401	3,03%
Coloured females	70	1:272	1,68%
White females	206	1:179	1,30%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	32	46	134	208	199	146	105	49
Asian males	1	0	2	4	7	5	5	2
Black males	24	33	108	158	127	53	22	9
Coloured males	3	5	9	12	18	12	11	6
White males	4	8	12	30	44	74	62	31

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	17	50	144	188	141	106	92	44
Asian females	0	0	2	4	6	3	4	0
Black females	11	39	120	156	81	37	27	10
Coloured females	2	3	8	14	9	13	14	6
White females	4	8	13	12	43	49	47	26

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Diagnosis of Follicular Lymphoma (FL)

- Diagnosis is primarily based on a combination of laboratory, radiologic, and pathologic evaluations
    - Patients with FL typically present with superficial lymph nodes of small to medium size, which sometimes go unnoticed by the patient
        - Primary mediastinal involvement is uncommon
        - Patients may present with B symptoms or symptoms from the slow growth of lymphoma in deep areas of the body such as the infradiaphragmatic territories
        - 50% to 60% of cases have bone marrow involvement
    - Essential laboratory workup parameters include a complete blood count, serum lactate dehydrogenase (LDH) levels, and beta-2-microglobulin (B2M) levels
    - Initial radiologic imaging studies should include positron emission tomography–computed tomography (PET–CT)
- Pathologic testing includes morphologic evaluation and immunophenotyping
    - Excisional diagnostic biopsy is critical to avoid false-negative results and inaccurate histologic classification
    - When a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and fine-needle aspiration (FNA) biopsies in conjunction with ancillary techniques such as immunohistochemistry (IHC), flow cytometry, polymerase chain reaction (PCR), and fluorescence in situ hybridization (FISH) may be sufficient for diagnosis
    - FNA or core needle biopsy alone is generally not suitable for the initial diagnosis of lymphoma
- Two methods used for immunophenotyping are paraffin section IHC and cell surface marker analysis by flow cytometry
- In addition, techniques to assess the cytogenetics of the lymphoma cells may be helpful in determining whether a genetic rearrangement, such as a chromosomal translocation t(14;18) involving the *BCL-2*gene, has occurred

(Biooncology).

Grading and Staging of Folllicular Lymphoma (FL)

Grading of Follicular Lymphoma:

- Grading based on percent of large cells
  - Grade 1, under 25%
  - Grade 2, 25-50%
  - Grade 3, over 50%

- Based on highest grade area present
  - If two discrete patterns present, lymphoma may be considered composite

- WHO recommendation (Mann-Berard) entails counting 20 hpf using 40x objective
  - Record mean number of large noncleaved cells
  - Using the table below
    - Grade 1 is at the low cutoff or below
    - Grade 2 is above the low cutoff to the high cutoff
    - Grade 3 is above the high cutoff

Microscope Type	Eyepiece	Low Cutoff	High Cutoff
American Optical	10x	5	15
American Optical	15x	4	12
Olympus	10x	7	20
Olympus	15x	4	12
Nikon	10x	7	20
Nikon	15x	4	12

    - Modifications for other microscopes from Warnke *et al*. AFIP Fascicle

  - Reproducibility of the Mann-Berard method is subject to:
    - Interobserver consistency in recognition of large noncleaved cells
    - Variations in slide thickness and staining
    - We prefer the simpler percentage based scheme given above

While staging is linked to prognosis, it does not usually determine therapy

- Therapy is usually determined by clinical signs and symptoms
  - Most staging is radiographic
  - Pathologic staging is usually limited to bone marrow and biopsy of other sites to confirm clinical evidence of involvement
  - Staging laparotomy is not generally indicated

- 40-70% present as stage III or IV

Ann Arbor Staging System

- Stage I
  - I if involvement of a single lymph node region
  - IE if involvement of a single extralymphatic organ or site
- Stage II
  - II if two or more lymph node regions on same side of diaphragm
  - IIE if localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm
- Stage III
  - III if Involvement of lymph node regions on both sides of the diphragm
  - IIIS if spleen involved

        - IIIE if extralymphatic site involved
- Stage IV
    - Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement

- Systemic Symptoms in 6 months preceding admission
    - Fever, night sweats, 10% weight loss
    - A = absent
    - B = present

- Extranodal sites are also designated
    - M+ = marrow
    - L+ = lung
    - H+ = liver
    - P+ = pleura
    - O+ = bone
    - D+ = skin and subcutaneous tissue

- Although originally designed for Hodgkin lymphoma, the Ann Arbor System is also used for non-Hodgkin lymphomas.

The pathology report should contain the following information:

- Diagnosis in the World Health Organization (WHO) classification
    - Equivalent diagnosis in other classifications used by relevant clinicians

- Results of supplementary studies if performed
- Relationship to other specimens from the same patient
- Information relevant to staging if available

(Stanford medicine).

Treatment of Follicular Lymphoma (FL)

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumour. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

Follicular lymphoma (FL) is the most common *indolent* (slow- growing) form of NHL, accounting for approximately 12 percent of all B-cell NHLs. Common symptoms of FL include enlargement of the lymph nodes in the neck, underarms, abdomen, or groin, as well as fatigue, shortness of breath, night sweats, and weight loss. Often, patients with FL have no obvious symptoms of the disease at diagnosis.

Over time, some patients with FL may eventually develop a transformed lymphoma, which is often more aggressive and usually requires more intensive types of treatment.

Treatment Options - there are various treatment options for FL based on the severity of associated symptoms and the rate of cancer growth. If patients show no or very few symptoms, physicians may recommend not to treat the disease right away, an approach referred to as "active surveillance" (also known as "watchful waiting"). Studies have shown that patients who are managed with an active surveillance approach have survival outcomes similar to those who are treated early in the course of their disease. With this strategy, patients' overall health and disease are monitored through regular check-up visits and various evaluations, such as laboratory and imaging tests. Active treatment is started if the patient begins to develop lymphoma-related symptoms or there are signs that the disease is progressing based on testing during follow- up visits.

FL is generally very responsive to radiation and chemotherapy. Radiation alone can provide a long-lasting remission in some patients with limited disease. In more advanced stages, physicians may use one or more chemotherapy drugs or the monoclonal antibody rituximab (Rituxan), alone or in combination with other agents.

Monoclonal antibodies can act more directly than chemotherapy agents by targeting particular markers found on tumour cells and recruiting immune cells to promote tumor destruction, which can increase response to treatment. Common combination regimens include:

- R-Bendamustine (rituximab and bendamustine)
- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
- R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone)

Some monoclonal antibodies can also be used as maintenance therapy for up to two years to prolong remission for patients with no signs of lymphoma.

Another treatment sometimes used for FL is radioimmunotherapy (RIT) using an agent such as yttrium-90 ibritumomab tiuxetan (Zevalin), which is a radioactive particle connected to an antibody that targets cancer cells.

After treatment, many patients can go into a remission that lasts for years; however, this disease should be considered a lifelong condition. Thus *relapse* (returns after treatment) and in some cases *refractory* (does not respond to treatment) disease can occur. For patients with relapsed FL, the same management choices as listed above may be utilised, or additional therapies may be successful in providing another remission.

For some patients with relapsed FL, high-dose chemotherapy followed by stem cell transplantation may be an option.

Treatments Under Investigation - many treatments are currently being tested in clinical trials for patients who are newly diagnosed or have relapsed/refractory FL. For patients who have not previously received treatment for FL, therapies under investigation include various combinations of several agents: rituximab, lenalidomide (Revlimid), bendamustine (Treanda), ofatumumab (Arzerra), bortezomib (Velcade), ibrutinib (Imbruvica), duvelisib, TGR1202, obinutuzumab (Gazyva), atezolizumab (Tecentriq), and pembrolizumab (Keytruda). Other combinations of treatment modalities, including immunochemotherapy, radioimmunotherapy, and stem cell transplantation are also under investigation and may help patients achieve prolonged remission. It is critical to remember that today's scientific research is continuously evolving. Treatment options may change as new treatments are

discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged.
(Lymphoma Research Foundation).

Novel Kinase Inhibitor Approved as Third-line Therapy for Follicular Lymphoma (FL)
The FDA announced that it approved a kinase inhibitor known as copanlisib (Aliqopa) for adults with relapsed follicular lymphoma who have received at least two prior systemic therapies.

Copanlisib is a pan-Class I phosphatidylinositol-3-kinase (PI3K) inhibitor with predominant inhibitory activity against PI3K-α and PI3K-δ isoforms, according to drugmaker Bayer Healthcare.

Options are limited for [relapsed] patients and today's approval provides an additional choice for treatment, filling an unmet need for them.

Approval of copanlisib was based primarily on an open-label trial enrolling 104 patients with follicular non-Hodgkin B-cell lymphoma, in which 59% obtained complete or partial responses with median duration of 12.2 months.

The drug comes with a range of adverse effects. Serious potential toxicities include hyperglycaemia, hypertension, pneumonitis, neutropenia, and skin reactions. The drug may induce foetal abnormalities and should not be taken by pregnant or breastfeeding women.

Bayer had received priority review, orphan drug, and accelerated approval designations from the FDA. The latter requires the firm to conduct additional studies to confirm copanlisib's clinical benefit.
(Medpage Today).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

<u>Types of Clinical Trials</u>
Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer
Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.
Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene

mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Medical Disclaimer

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