National Cancer Society Malaysia

Giving Hope Celebrating Life

LUNG CANCER NETWORK MALAYSIA

ALK-POSITIVE NON-SMALL CELL LUNG CANCER

A comprehensive guide for newly diagnosed ALK+ve lung cancer patients and caregivers

Supported by:

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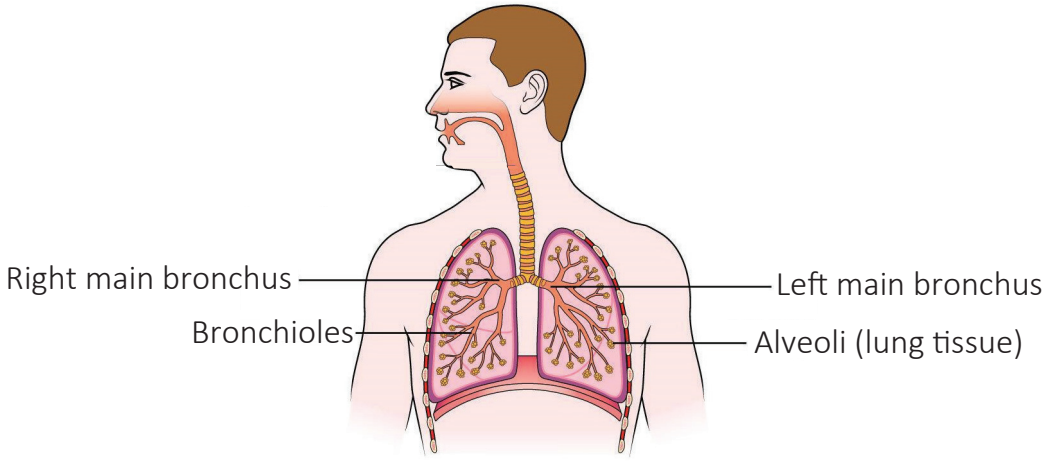
What is lung cancer?

- Cancer that starts in the lungs is called primary lung cancer. Lung cancer can occur in either the main airway (bronchus) or the tissue of the lung known as alveoli.[1]

- In Malaysia, lung cancer ranks as the third most prevalent cancer, making up 9.8% of all cancer cases.[2]



- Lung cancer can be broadly categorised into two different tissue groups, namely **small cell lung cancer** (SCLC) and **non-small cell lung cancer** (NSCLC).[3]

Lung Cancer

Small cell lung cancer (SCLC) 15-20%

- SCLC is typically caused by tobacco smoking and can spread quickly.[4]

Non - small cell lung cancer (NSCLC) 80-85%

- NSCLC often develops at a slower pace and may not show any symptoms until later on.[4]

References:
1. Lung cancer [Internet]. 2022 [Cited on 2023 Nov 20]. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer
2. Azizah AM, Hashimah B, Nirmal K, et. al. Summary of Malaysian National Cancer Registry Report (2012-2016) [Internet]. 2019 [cited 2023 Nov 21]. Available from: https://nci.moh.gov.my/index.php/ms/pengumuman/789-summary-of-malaysiannational-cancer-registry-report-2012-2016
3. What is lung cancer?: Types of lung cancer [Internet]. [Cited on 2023 Nov 20]. Available from: https://www.cancer.org/cancer/types/lung-cancer/about/what-is.html
4. NFCR. Small Cell Lung Cancer vs. Non-small Cell Lung Cancer: What's the Difference? [Internet] 2020 [Cited on 2023 Dec 12]. Available from: https://www.nfcr.org/blog/small-cell-lung-cancer-vs-non-small-cell-lung-cancer-whats-the-difference/

What is Non-Small Cell Lung Cancer (NSCLC)?

- NSCLC can be viewed in two ways, either from a **cell-type** viewpoint or a **gene mutation** viewpoint.

A. Cell-type Viewpoint[1]:

The three most common types of NSCLC from a cell-type viewpoint are:

Adenocarcinoma

- Most common form
- Starts in mucus-producing cells; often found in the outer part (periphery) of the lungs.

Squamous cell carcinoma

- Starts in cells that line the inside of the airways; usually found in the central part of the lungs.

Large cell carcinoma

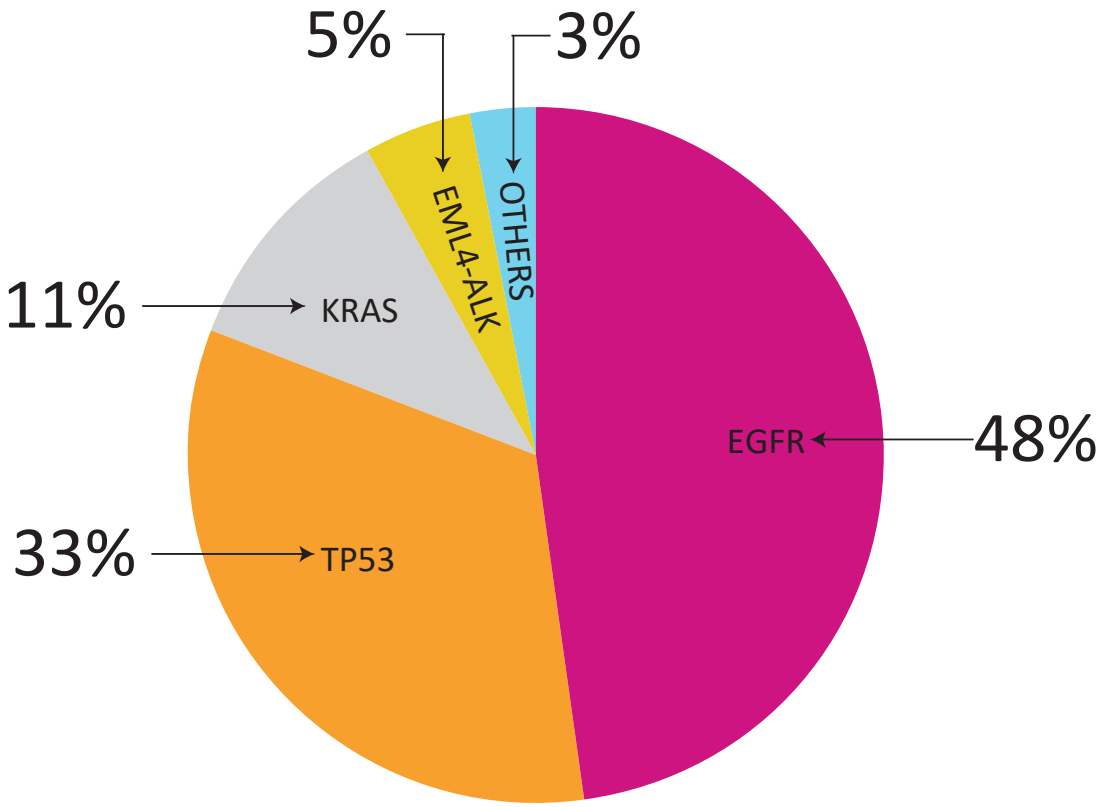
- Appears in any part of the lung and often grows and spreads quickly.

References:
1. American Cancer Society. "What Is Lung Cancer?" [Internet]. Oct 2019 [Cited on 2023 Dec 28]. Available from: https://www.cancer.org/cancer/types/lung-cancer/about/what-is.html

What is Non-Small Cell Lung Cancer (NSCLC)? (continued)

B. Gene Mutation Viewpoint[1]:

- The four most common types of NSCLC from a gene mutation viewpoint and their percentages are visualised in the pie chart below:



- Gene mutations, also known as gene alterations or changes in a gene, can lead to NSCLC.[1]
- Different gene mutations can be found in various cases of NSCLC as shown in the pie chart.[2]
- For example, mutations in the ALK gene can be found in about 5% of patients with NSCLC.

References:
1. Cancer.Net.Lung Cancer - Non-Small Cell: Types of Treatment. [Internet] 2022. [Cited on 28 Dec 2023] Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/types-treatment
2. Dearden S, Stevens J, Wu YL, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). Annals of oncology. 2013 Sep 1;24(9):2371-6. Available from: https://www.sciencedirect.com/science/article/pii/S0923753419369431

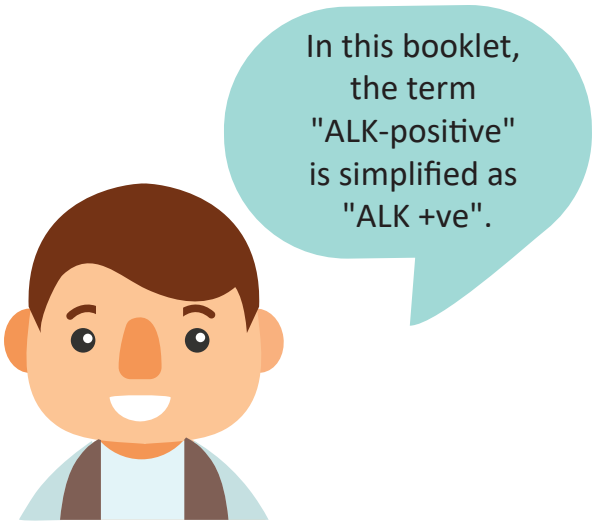
What is ALK +ve lung Cancer?

- ALK stands for **anaplastic lymphoma kinase.**
- It is a gene present in every individual.
- The ALK gene provides signals for making a protein named ALK receptor tyrosine kinase. This protein is important for the control of cell growth.
- Changes or mutations in ALK gene can potentially lead to cancer due to uncontrollable cell growth.[1]

What happens to the ALK gene for people diagnosed with ALK +ve lung cancer?

- ALK +ve lung cancer happens when a genetic mutation occurs and the ALK gene merges with another gene, most commonly the EML4 gene. This is known as EML4 - ALK fusion gene.[2]

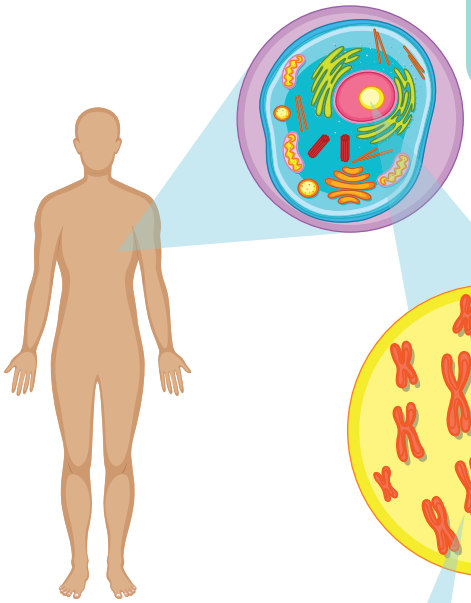
ALK +ve lung cancer is a subtype of non-small cell lung cancer (NSCLC). It accounts for **5%** of all NSCLC.[2]



References:
1. American Lung Association. ALK and Lung Cancer [Internet]. [cited 2023 Nov 20]. Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/symptoms-diagnosis/biomarker-testing/alk-lung-cancer#:~:text=ALK%2Dpositive%20lung%20cancer%20represents,to%20have%20a%20smoking%20history.
2. What is Alk-positive lung cancer? by the Alk Positive Community [Internet]. [cited 2023 Nov 20]. Available from: https://www.alkpositive.org/what-is-alk

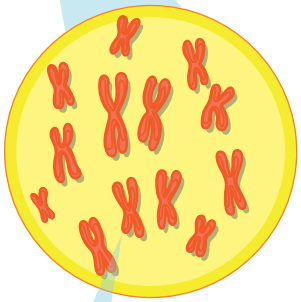
Cells

Cells are the basic unit of life. Humans are made up of trillions of cells, including neurons (nerve cells), bone cells, and skin cells. Cells comprise the nucleus, cytoplasm, and other organelles.[1]



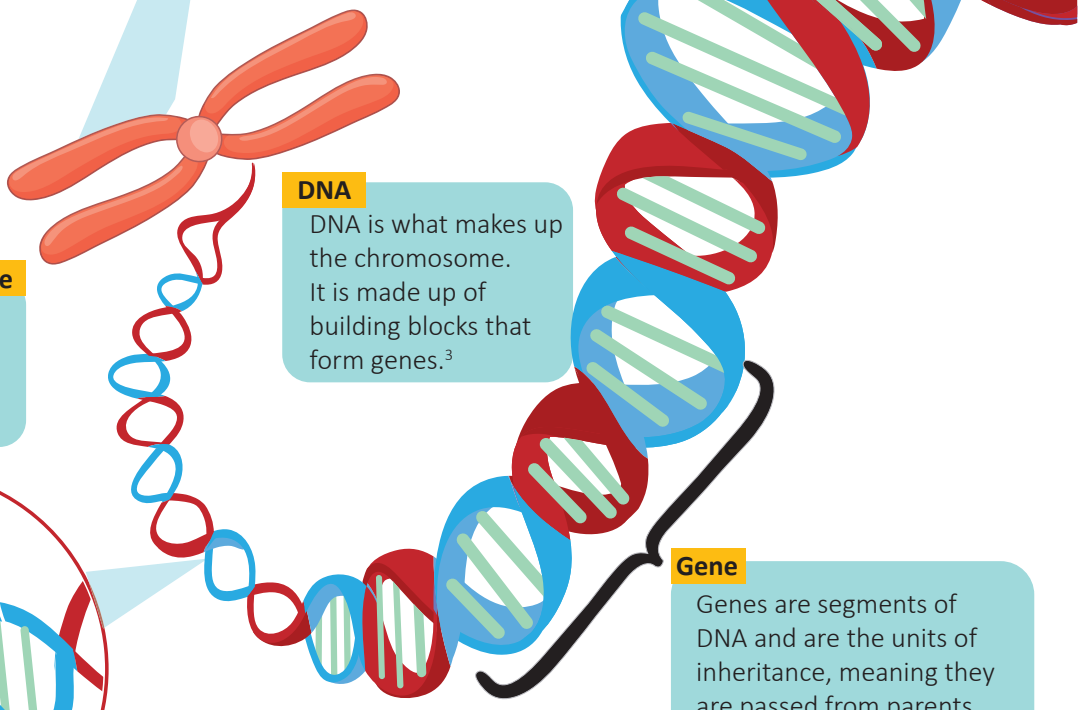
Chromosome

In the nucleus, there are chromosomes. Chromosomes are units of Deoxyribonucleic Acid (DNA) that contain genetic material.[2]



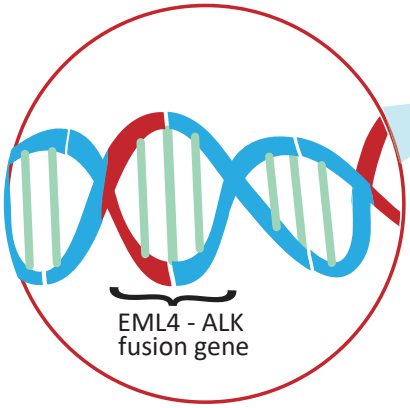
DNA

DNA is what makes up the chromosome. It is made up of building blocks that form genes.[3]



EML4 - ALK Fusion Gene

The ALK gene merges with the EML4 gene to form the EML4- ALK fusion gene.[5]



Gene

Genes are segments of DNA and are the units of inheritance, meaning they are passed from parents to children. Genes carry the information that is necessary to produce proteins that ultimately make us unique, be it physically or biologically.[4]

References:

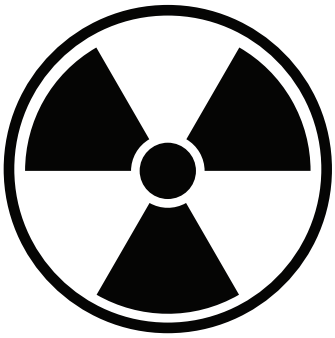
1. Cell [Internet]. Bethesda, MD (USA): National Human Genome Research Institute, National Institutes of Health. Updated on 24th January 2024. Cited on 31st January 2024. Available from: https://www.genome.gov/genetics-glossary/Cell
2. Chromosome [Internet]. Bethesda, MD (USA): National Human Genome Research Institute, National Institutes of Health. Updated on 24th January 2024. Cited on 31st January 2024. Available from: https://www.genome.gov/genetics-glossary/Chromosome
3. DNA [Internet]. Bethesda, MD (USA): National Human Genome Research Institute, National Institutes of Health. Updated on 24th January 2024. Cited on 31st January 2024. Available from: ttps://www.genome.gov/genetics-glossary/DNA
4. Gene [Internet]. Bethesda, MD (USA): National Human Genome Research Institute, National Institutes of Health. Updated on 24th January 2024. Cited on 31st January 2024. Available from: https://www.genome.gov/genetics-glossary/Gene
5. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009;27(26):4247-4253. doi:10.1200/JCO.2009.22.6993

Who is at risk for ALK +ve lung cancer?

- These changes are not inherited and therefore **cannot be passed down from parent to child.**

- Some are triggered by environmental factors such as exposure to tobacco smoke, be it via direct inhalation or through secondhand smoke, or exposure to air pollutants, high-temperature cooking fumes, industrial chemicals or radiation.

  In some cases, lung cancer can occur randomly without a clear cause.[1,2]



People who are at higher risk for ALK+ve lung cancer[2,3]:

- Female gender
- Younger age of onset (50 and below)
- Never-smokers or light smokers

References:
1. Lung cancer risk factors: Smoking & lung cancer [Internet]. 2024 [cited 2024 Mar 12]. Available from: https://www.cancer.org/cancer/types/lung-cancer/causes-risks-prevention/risk-factors.html
2. Xue Y, Jiang Y, Jin S, Li Y. Association between cooking oil fume exposure and lung cancer among Chinese nonsmoking women: a meta-analysis. OncoTargets and therapy. 2016 May 19:2987-92.
3. What is Alk-positive lung cancer? by the Alk Positive Community [Internet]. [cited 2023 Nov 20]. Available from: https://www.alkpositive.org/what-is-alk

What are the signs and symptoms of lung cancer?

- The common symptoms of ALK +ve NSCLC are the same as those of any lung cancer.[1]
- However, many patients may have no signs or symptoms in the early stages of the disease.

Recurrent chest infections

Prolonged coughing that worsens or does not improve

Unexplained weight loss

Difficulty in breathing

Coughing up blood

Continuous and unexplained tiredness

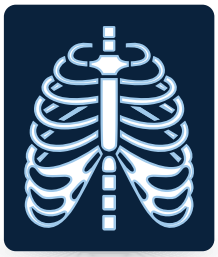
Chest pain

Wheezing

References:
1. Centers for Disease Control and Prevention. Lung Cancer: What Are the Symptoms?[Internet]. 2021[cited 2023 November 22]. Available from: https://www.cdc.gov/cancer/lung/basic_info/symptoms.htm

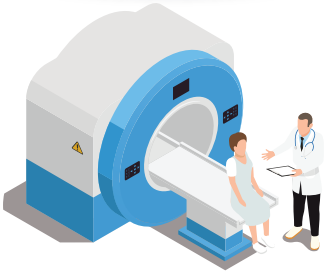
How do I check if I have lung cancer?

- To look for evidence of lung cancer, your doctor will examine you and order imaging tests to check for masses in your lungs.[1,2,3,4]



Chest X-ray (including artificial intelligence enabled chest x-ray)

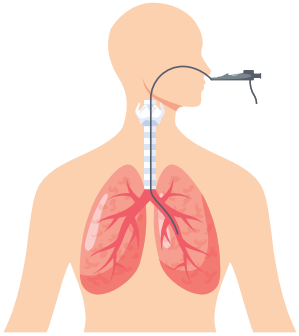
It is usually used as an initial lung imaging tool. If anything suspicious is found (e.g. mass or nodules), the doctor might request for more specific tests.



Low-Dose CT Scan (Gold standard imaging tool)

It is used to diagnose lung cancer. It is a non-contrast scan with minimal radiation. No prior fasting or blood test required.

Biopsy: CT-guided / Bronchoscopic / Thoracoscopic approach



A small amount of tissue will be extracted from the lung or the nearby lymph nodes, both of which will be sent for examination under a microscope. Sometimes this is done from the outside with an x-ray guided needle (CT-guided biopsy), through a scope in the airway (bronchoscopy), or via a scope inserted through a small chest incision to access the space between the chest wall and the lung (thoracoscopy).

Immunohistochemical and Molecular Testing

These tests help to determine the:

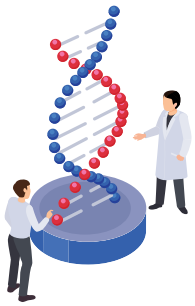
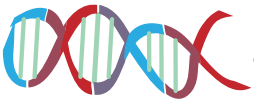
1. Origin of the cancer – To differentiate if this is a primary lung cancer or a secondary cancer from another part of the body that has metastasized to the lung.

2. Biology of the cancer - To determine the best treatment or drugs to offer, doctors analyse the genetic profile of the cancer.

References:
1. Health Harvard Publishing. Lung cancer overview [Internet]. 2023 Mar 31 [cited on 2023 Dec 28]. Available from: https://www.health.harvard.edu/a_to_z/lung-cancer-overview-a-to-z
2. American Cancer Society. Can Lung Cancer Be Found Early? [Internet]. 2023 Nov 1 [cited on 2023 Dec 28]. Available from: https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/detection.html
3. Mayo Clinic. Lung cancer – Diagnosis [Internet]. 2022 Mar 22 [cited on 2023 Dec 28]. Available from: https://www.mayoclinic.org/diseases-conditions/lung-cancer/diagnosis-treatment/drc-20374627
4. K.M. Kerr, F. López-Ríos. Precision medicine in NSCLC and pathology: how does ALK fit in the pathway?.Annals of Oncology.2016. Suppl 3:iii16-iii24. doi: 10.1093/annonc/mdw302.

How do I check if I have ALK +ve lung cancer?

- Molecular testing should be carried out at initial biopsy. It detects the **ALK gene rearrangement**. Examples of molecular testing are as follow[1]:

		Price Range
	**Next-generation Sequencing (NGS):** A large number of possible biomarkers are searched for at one time using a machine.	$$$$
	**Fluorescence In Situ Hybridization (FISH):** Genetic rearrangements are visualised using dual colours.	$$$$
	**Immunohistochemistry (IHC):** Detect ALK fusion proteins.	$$$$
	**Liquid Biopsy:** Searches for tumour DNA in blood.	$$$$

Price Range:

$$ - Between RM 10 – RM 99

$$$ - Between RM 100 – RM 999

$$$$ - Between RM 1,000 – RM 9,999

*Prices in Malaysia as of the time of publication

References:
1. Nathany S, Sharma M, Batra U. Testing modalities for Alk-driven lung cancer: A narrative review. Cancer Research, Statistics, and Treatment. 2023;6(3):432–9. doi:10.4103/crst.crst_252_23

I'm diagnosed with ALK +ve lung cancer, what is next?

- A healthcare team for treating ALK +ve lung cancer commonly consists of a doctor who treats cancer (oncologist), a doctor who treats lung conditions (a pulmonologist or a cardiothoracic surgeon), an oncology nurse, and others.[1]

- The choice of treatment depends on various factors[2]:

The stage of the cancer

Patient's preference or wishes

The patient's overall health fitness

The presence of any additional mutations

References:
1. Get to know your lung cancer care team [Internet]. 2021 [cited 2023 Dec 8]. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/lung-cancer/get-to-know-your-lung-cancer-care-team
2. American Cancer Society. Understanding Your Options and Making Treatment Decisions [Internet]. Chicago IL, US; [Last updated 2021 May 13; cited on 2024 Apr 19]. Available from: https://www.cancer.org/cancer/managing-cancer/making-treatment-decisions/making-decisions.html

What are the treatment options for lung cancer?

- Treatment options for lung cancer include surgery, radiotherapy, chemotherapy, immunotherapy or targeted therapy. The choice of treatment depends on the stage of the disease (early or advanced stage).

- **Chemotherapy**

  Chemotherapy can be the main type of treatment for lung cancer, or it can be used alongside surgery, radiotherapy, and immunotherapy.[1] It is used to target and kill fast-multiplying cells. Chemotherapy uses the bloodstream to travel around the body to reach cancer cells.[1]

  There are two ways in which chemotherapy is administered[1]:

1. Intravenous

Intravenous or IV chemo involves delivering cancer-treating medication directly into the bloodstream using a needle inserted into a vein.

2. Oral Chemotherapy

Prescribed drugs are taken by mouth in the form of pills or tablets.

- **Immunotherapy**

  Immunotherapy uses the body's immune system to fight cancer by changing how the immune system functions and helping it to find and attack cancer cells.[2]

- **Targeted Therapy**

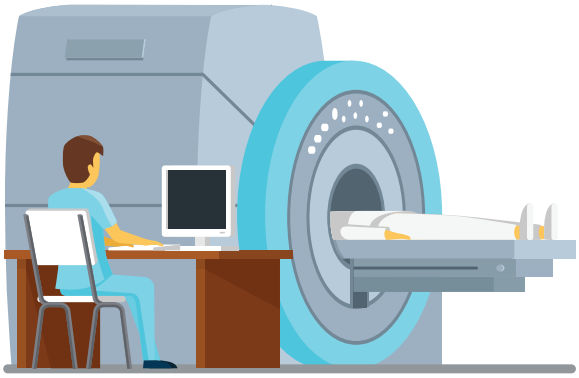
  Targeted therapy is a type of cancer treatment that targets proteins involved in regulating how cancer cells grow, divide, and spread.[3]

References:
1. American Cancer Society. Chemotherapy for Lung Cancer [Internet]. Chicago IL, US; [Last updated 2022 Nov 22; cited on 2023 Dec 28]. Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/treatment/types-of-treatment/lung-cancer-surgery
2. American Cancer Society. What is Immunotherapy? [Internet]. Chicago IL, US; [Last updated 2019 December 27; cited on 2024 March 28]. Available from: https://www.cancer.org/cancer/managing-cancer/treatment-types/immunotherapy.html
3. National Cancer Institute. Targeted Therapy to Treat Cancer [Internet].[Last updated 2022 May 31; cited on 2024 March 28]. Available from: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies

What are the treatment options for lung cancer? (continued)

Radiotherapy

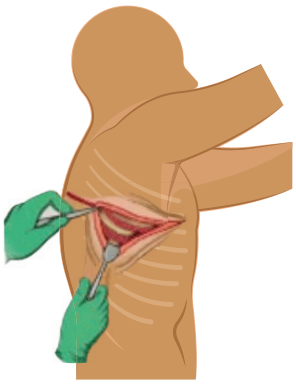
Radiotherapy uses high-energy x-rays to kill cancer cells. It can also be used to relieve symptoms caused by cancer.[1]



Surgery

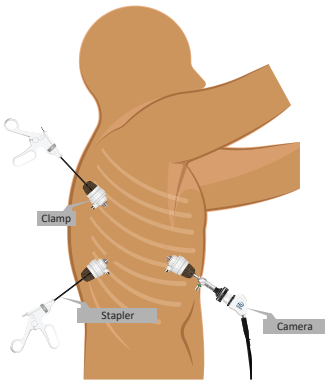
Lung cancer surgery is considered for certain patients based on the type, location, and stage of their cancer. The goal is to cure by removing the tumour, surrounding lung tissue, and nearby lymph nodes. This approach is favoured when the cancer is localised and unlikely to have spread, offering the best chance of a cure and long-term survival.

There are two surgical approaches commonly used[2]:



1. Thoracotomy

This is a side chest incision along the curve of the ribs, involving the division of chest wall muscles. A tool is used to spread between two ribs, granting the surgeon access to the lung. The muscles are then stitched together when the incision is closed.



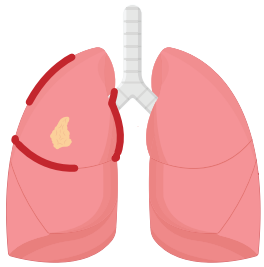
2. Minimally invasive surgery

This method involves making one to four small chest incisions, inserting a camera and operating instruments for thoracoscopy or video-assisted thoracoscopic surgery (VATS), and may involve the assistance of a surgical robot.

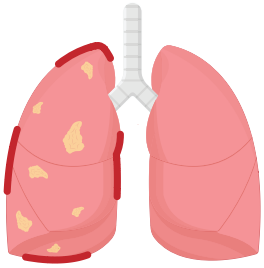
References:
1. American Cancer Society. Radiation Therapy for Lung Cancer [Internet]. Chicago IL, US; [Last updated 2022 Nov 17; cited on 2023 Dec 28]. Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/treatment/types-of-treatment/radiation-therapy
2. American Cancer Society. Lung cancer surgery [Internet]. Chicago IL, US; [Last updated 2022 Nov 17; cited on 2023 Dec 28]. Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/treatment/types-of-treatment/lung-cancer-surgery

What are the treatment options for lung cancer? (continued)

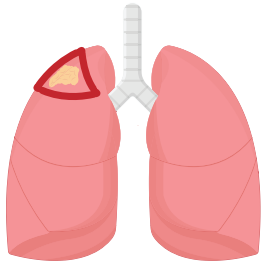
- Types of lung resections include surgery that may remove all or part of a lung.[1]



Lobectomy
One lobe of a lung is removed



Pneumonectomy
One whole lung is removed



Segmentectomy or wedge resection
Only part of a lobe is removed. It can be performed if the lesion is detected early, at a size of less than 2cm.

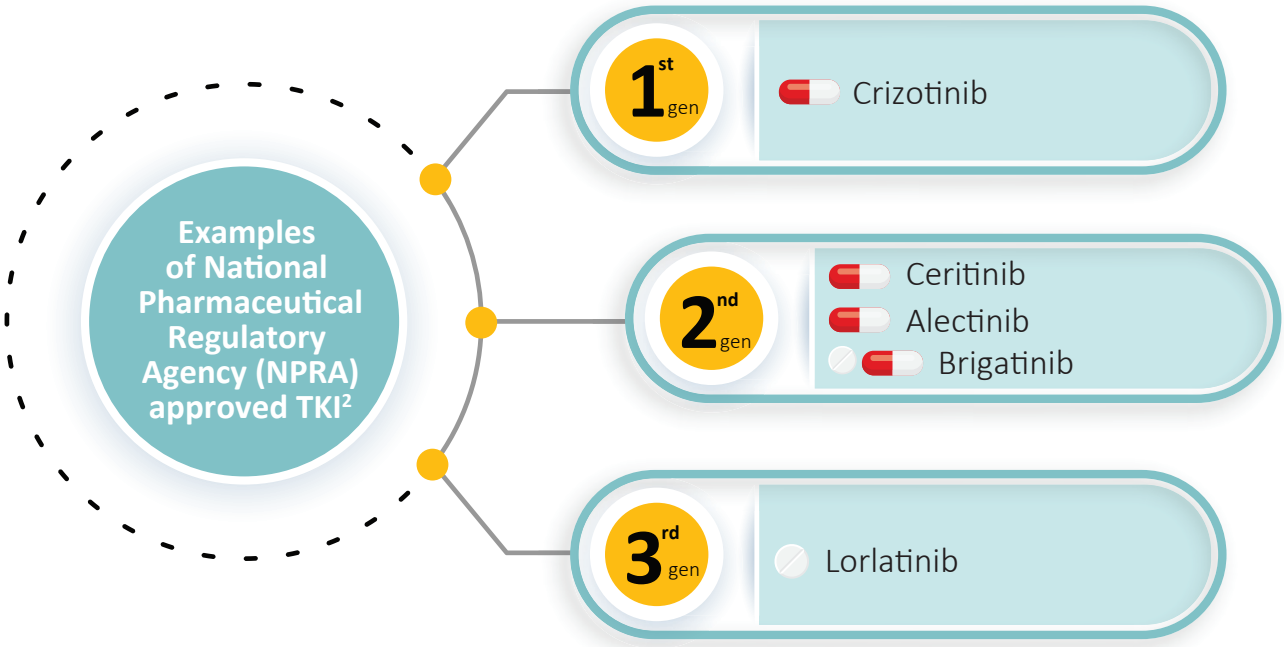
References:
1. American Cancer Society. Lung cancer surgery [Internet]. Chicago IL, US; [Last updated 2022 Nov 17; cited on 2023 Dec 28]. Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/treatment/types-of-treatment/lung-cancer-surgery

What are the treatment options for ALK +ve lung cancer?

- Currently, one approach for treating ALK +ve non-small cell lung cancer (NSCLC) involves targeted therapy.[1]

- **Tyrosine kinase inhibitors (TKIs)** or **ALK inhibitors** are an example of targeted therapy for ALK +ve NSCLC.[1]

- By administering ALK inhibitors, the drug blocks signals from reaching the receptors, preventing further growth and spread of cancer cells while sparing healthy cells from harm.[1]



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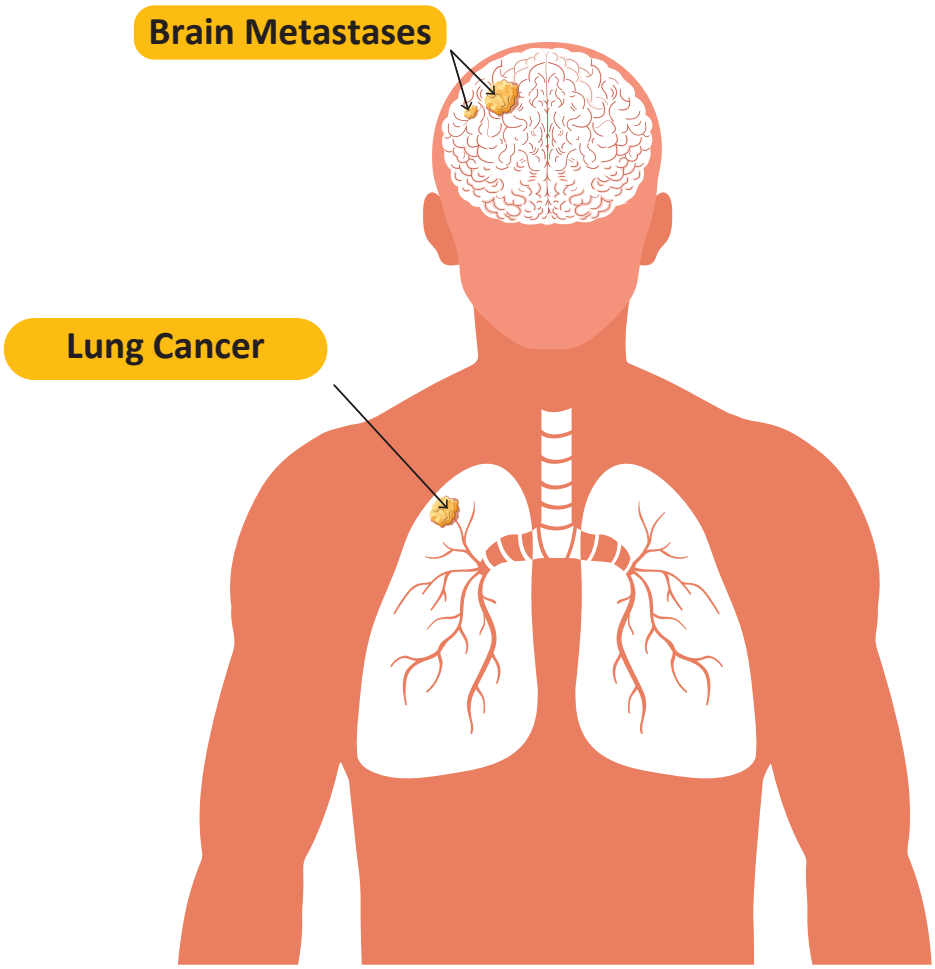
1. What is Alk-positive lung cancer? understanding diagnosis: LCFA [Internet]. 2022 [cited 2023 Nov 21]. Available from: https://lcfamerica.org/lung-cancer-info/types-lung-cancer/alk-positive-lung-cancer/#1572536052547-0f2e7123-c8e8
2. Cicin I, Martin C, Haddad CK, Kim S-W, Smolin A, Abdillah A, et al. ALK TKI therapy in patients with ALK-positive non-small cell lung cancer and brain metastases: A review of the literature and local experiences. Critical Reviews in Oncology/Hematology. 2022;180:103847. doi:10.1016/j.critrevonc.2022.103847

What are the treatment options for ALK +ve lung cancer? (continued)

- Brain metastasis, where the primary cancer spreads to the brain, is associated with poor prognosis, a high symptom burden, and subsequently, a decreased quality of life.[1,2]
- Newer ALK inhibitors are especially useful for targeting brain metastases, which studies have shown develop in more than 50% of ALK +ve lung cancer cases. [3,4]
- Thus, with these newer ALK inhibitors, patients may be able to avoid undergoing brain radiotherapy.[5]



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1. Guérin A, Sasane M, Zhang J, Culver KW, Dea K, Nitulescu R, Wu EQ. Brain metastases in patients with ALK+ non-small cell lung cancer: clinical symptoms, treatment patterns and economic burden. Journal of medical economics. 2015 Apr 3;18(4):312-22.
2. Ali A, Goffin JR, Arnold A, Ellis PM. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. Current Oncology. 2013 Aug;20(4):300-6.
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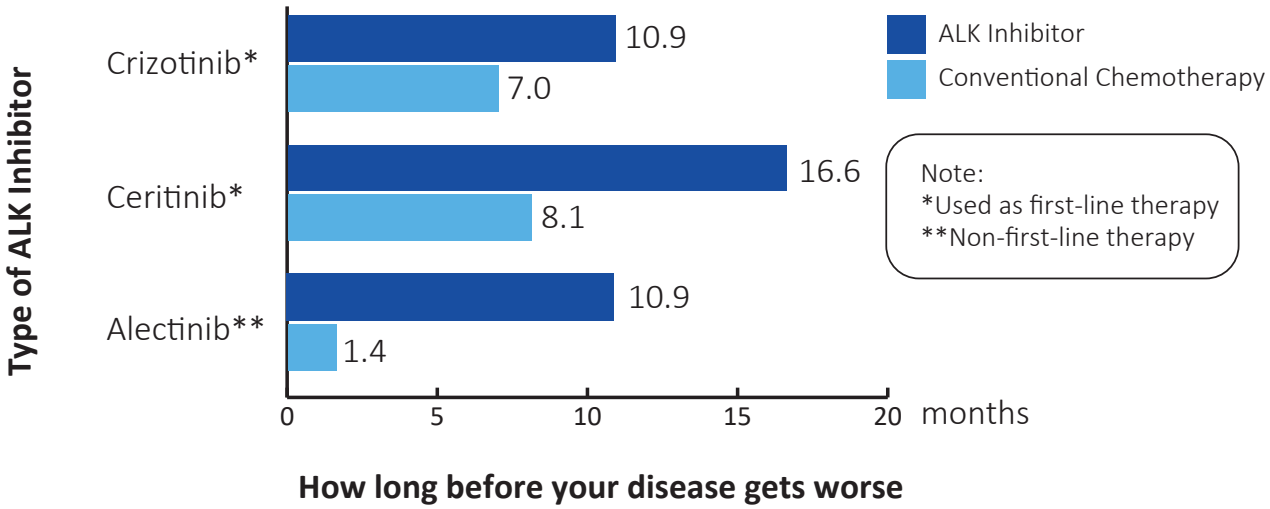
5. Agarwal JP, Tibdewal A, Mohanty S, Mummudi N. Radiotherapy of brain metastasis from lung cancer in limited resource settings. Journal of Thoracic Disease. 2021 May;13(5):3308.

What is targeted therapy for ALK +ve lung cancer?

- When using ALK inhibitors in comparison to chemotherapy for treatment, how long does it take before your disease gets worse?[1,2]



Remark: The data on each ALK inhibitor should not be directly compared as data are taken from different individual studies.

In general, when compared to conventional chemotherapy, people on ALK inhibitors take longer before their disease worsens. With the advent of ALK inhibitors about two decades ago, ALK +ve lung cancer patients are now living much longer (7 years and beyond).[3] Hence, the trajectory of the disease is changing into a chronic one.

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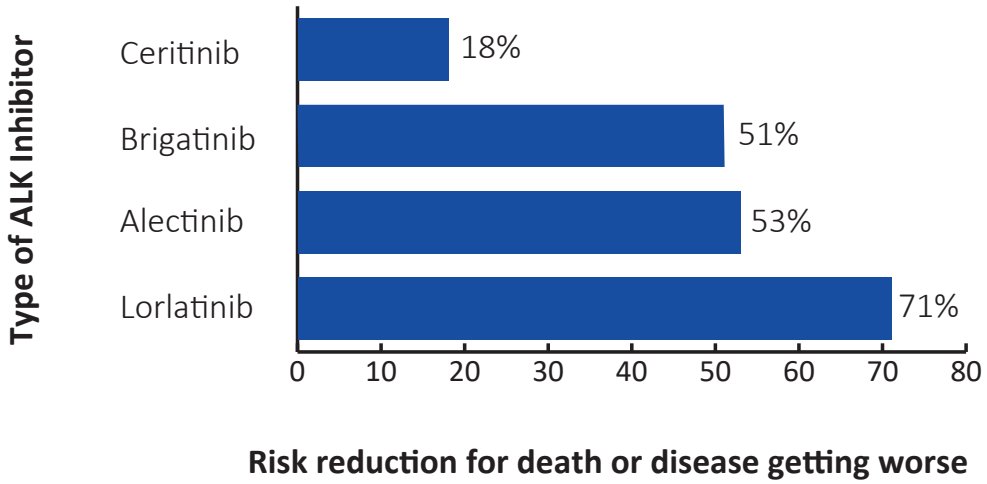
What is targeted therapy for ALK +ve lung cancer? (continued)

- When using other ALK inhibitors in comparison to crizotinib, how much can your risk of death or disease worsening be lowered?[1.2.3.4,5]



Remark: The data on each ALK inhibitor should not be directly compared as data are taken from different individual studies.

Ultimately, the decision on which ALK inhibitor to use should be made collaboratively between you and your physician.

References:
1. Bearz A, De Carlo E, Del Conte A, Spina M, Da Ros V, Bertoli E, Revelant A, Stanzione B, Tirelli U. The Change in Paradigm for NSCLC Patients with EML4–ALK Translocation. International Journal of Molecular Sciences. 2022 Jun 30;23(13):7322.
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How is targeted therapy for ALK +ve lung cancer used?

Below are examples of how targeted therapy is used for different cases of ALK +ve lung cancer.

Case study 1

A 60-year-old lady presented with a chronic cough for three months. She is a non-smoker and has diabetes mellitus. The chest x-ray shows a large mass. The Computer Tomography (CT) of the thorax, abdomen, and pelvis showed large, multiple mediastinal lymphadenopathy. The biopsy and molecular testing confirmed it as adenocarcinoma with ALK+ve. Hence, she was started on an **ALK inhibitor**. She responded very well, and a repeated CT scan showed good response to the treatment. She has been well for the past 18 months.

Case study 2

A 52-year-old man who is an ex-smoker with a history of 13 pack-years, presented with shortness of breath on exertion and a dry cough for the past 4 months. He underwent a chest x-ray, CT Thorax scan, PET-CT scan, endobronchial ultrasound biopsy. He received a final diagnosis of locally advanced lung adenocarcinoma, stage IIIB with ALK+ve.

He underwent concurrent chemoradiation and achieved a partial response. Unfortunately, brain metastasis was noted during a routine brain MRI. He underwent radiosurgery for all lesions with an adequate response in brain disease followed by **ALK inhibitor** tablets. He tolerates the **ALK inhibitor** well with minimal side effects, and so far, the repeated radiological images show a partial response. His condition has remained stable for the past 22 months.

The cases above illustrate how different ALK inhibitors are used in two different cases of ALK +ve lung cancer provided by healthcare professionals for educational purpose only. Discuss with your doctor if ALK inhibitors are suitable for you.

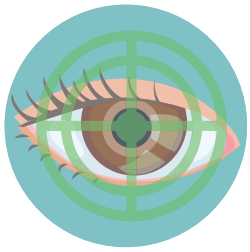
What are the potential side effects of using ALK inhibitors?

- Different ALK inhibitors can cause different side effects and it varies from person to person. Here are some commonly reported side effects of ALK inhibitors[1]:

Nausea and vomiting

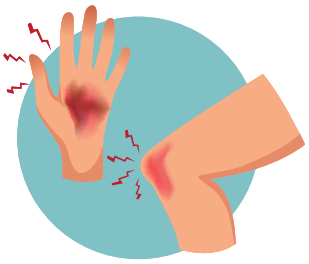
Diarrhea

Constipation

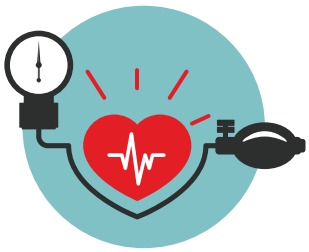


Changes in vision

Fatigue



Swelling in hand or feet



Hypertension

Peripheral numbness

Remember, everyone reacts differently to medications, so you might not experience every side effect listed.[2] It is crucial to discuss any concerns you have with your doctor.

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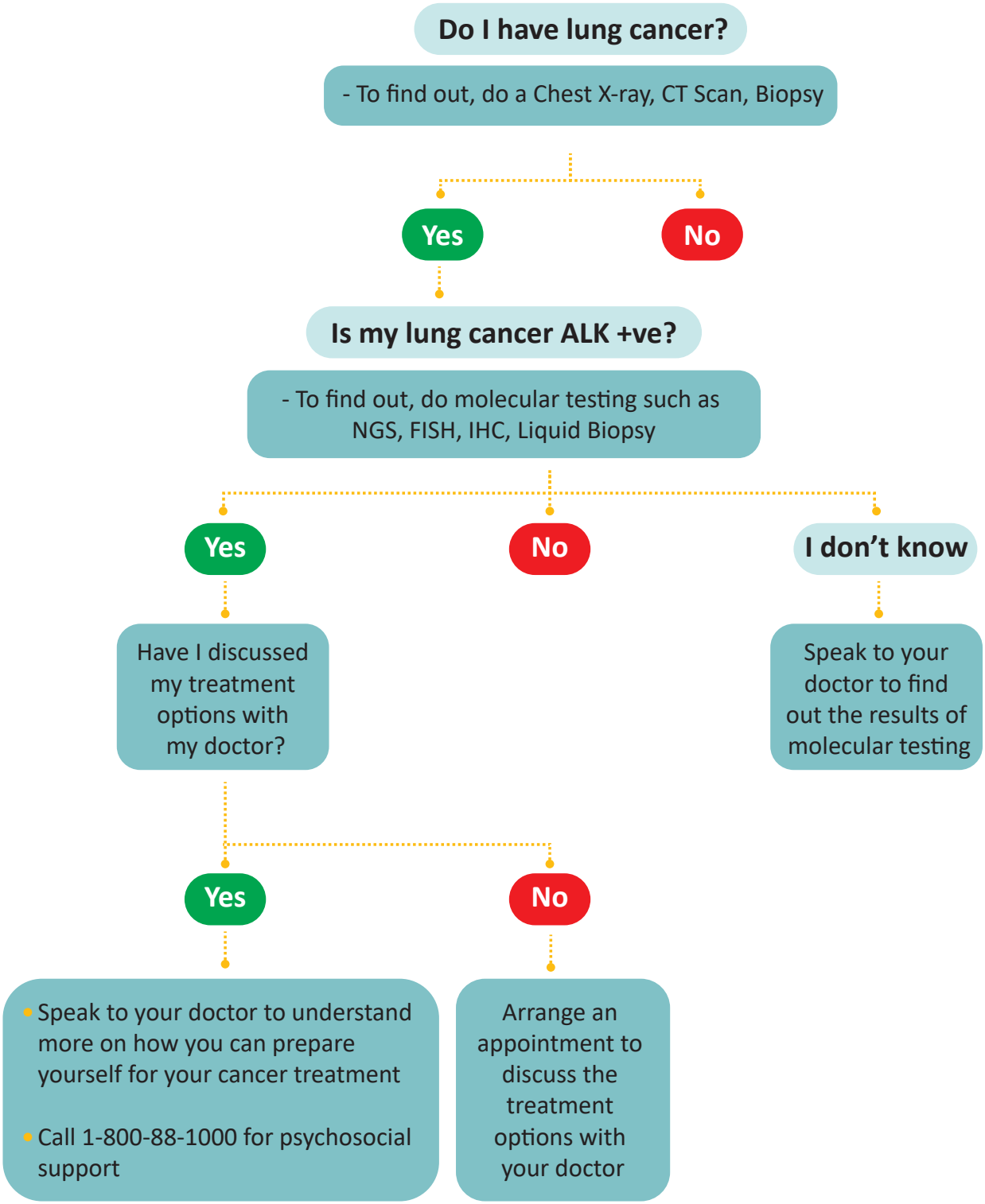
Do I have ALK +ve lung cancer? A snapshot view of what to do



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