

# Targeted Therapies in Lung Cancer



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## Why this booklet?

- » To respond to your questions
- » To help you understand new opportunities you could have in your fight against lung cancer.

## Who is it addressed to?

- » Lung cancer patients
- » Patient family members and caregivers
- » All those people who want to know some more facts about lung cancer



***The information in this guide can't replace the medical advice. For information related to your situation, you must always consult your doctor.***

## Table of contents

🎯 What about Lung Cancer today?.....	5
🎯 How do targeted therapies work?.....	9
🎯 Molecular test .....	13
🎯 Targeted therapy biomarkers.....	17
🎯 Side effects.....	21
🎯 Glossary.....	23

## 🎯 What about lung cancer today?



Worldwide lung cancer is the leading cause of cancer deaths in men and women.

At diagnosis, the average age of patients is 60 years and tobacco consumption remains the major risk.

There is no currently a recognized and accepted method for an “*early diagnosis*” on the population and unfortunately this cancer is often diagnosed when the disease is at an advanced stage and surgery with radical intent can't be performed.

Although each case should be evaluated individually, for most patients with advanced-stage disease, pharmacological treatment is still the indication.

Over the past ten years there have been many advances in lung cancer field.

Nevertheless, it's important to be very critical of any information found on web and provided by newspapers and television.



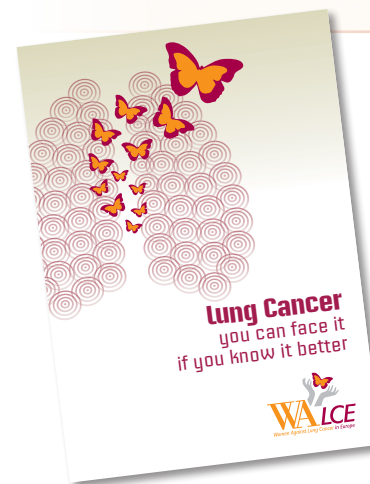
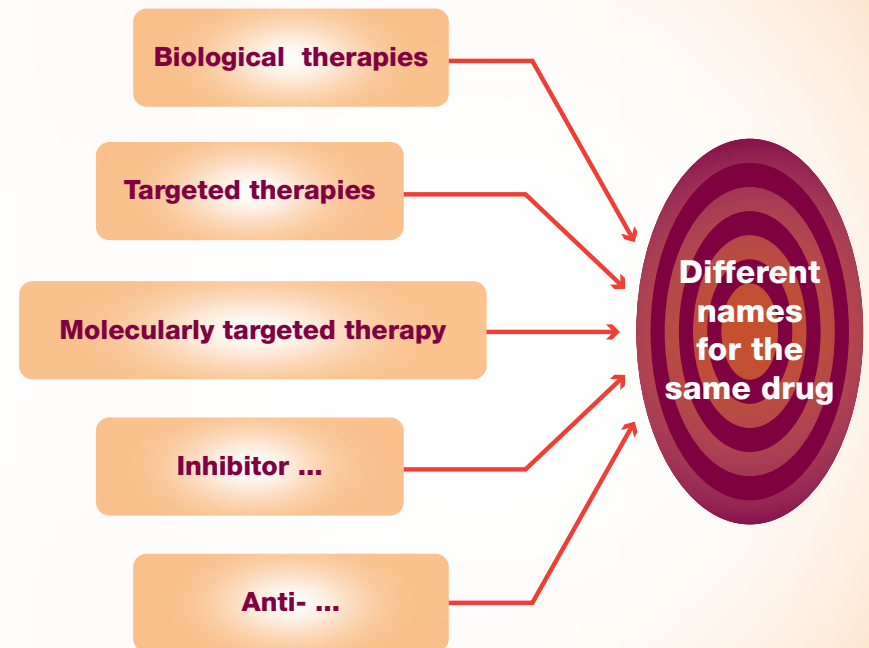
“New breakthroughs in lung cancer treatment” is a message that commonly circulates and which is sometimes difficult to explain to patients, their families and caregivers, but also to general public.

Frequently, it does not correspond to reality and may generate false hopes and disappointments.

For this reason, it should be discussed with the doctor in order to better understand the messages coming from the media.

This guide is designed to make it as clear as possible the role of targeted therapies, their mechanism of action, their efficacy and who may benefit from.

- 1. Targeted therapies may *not* replace the chemotherapy.**
- 2. Targeted therapies are “selective therapies” because they identify and attack cancer cells.**
- 3. Targeted therapies may have side effects, although they don’t affect the body the same way that chemotherapy does.**
- 4. Targeted therapies don’t work for everyone.**
- 5. Targeted therapies may significantly improve the survival and quality of life of patients with a specific molecular alteration.**



We advise you to consult the booklet:  
**“Lung Cancer:  
you can face it if you know it better”**

## 🎯 How do targeted therapies work?



### What are targeted therapies?

Targeted therapies don't belong to the group of chemotherapy.

They are called in this way because they act against specific *molecular targets*, which are more prevalent in cancer cells, such as **protein** or an **enzyme**.

In other cases, the target of the drug may be the formation of new blood vessels that carry oxygen and nutrients to the tumor (**neovascularization**).

Some of these drugs have more than one molecular target at the same time (*multi-target*).



## How do you take targeted therapies?

In some case they may be administered intravenously as chemotherapy (by infusion) or may be taken orally (tablets/capsules). Some of these therapies is used alone, some in combination with other treatments, such as chemotherapy.



## What role do targeted therapies have?

Their role is to interfere with cancer cell growth and proliferation, sometimes blocking the signalling process, sometimes slowing them down.

It is as if these drugs lighted on the red light of a traffic light and the cells were not able to keep on growing. In some case the tumor size decreases, in others, it may remain the same, without growing or generating metastases.

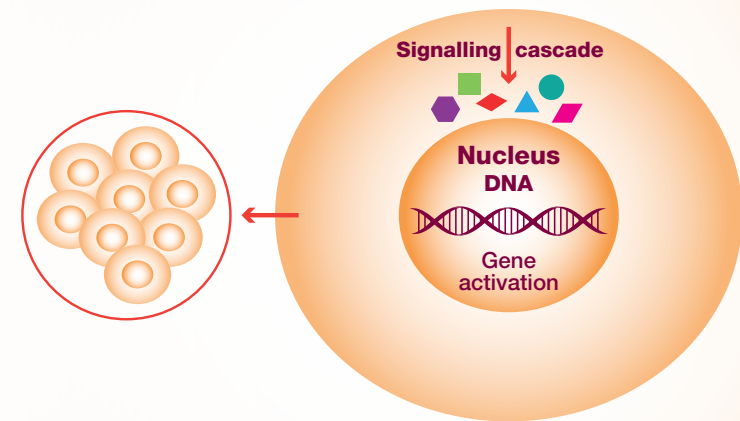


## What are the targets in targeted therapies?

Some drugs block some specific **protein kinase**, linked to cell-surface **receptors** or to the intracellular portion.

**Protein kinases** regulate the enzymatic activity and are crucial in the signal transduction.

An hyperactive kinase confers an aberrant, **ligand**-independent, not regulated stimulus to cancer cells. These drugs are **tyrosine kinase inhibitors** and are generally administered as oral tablets.



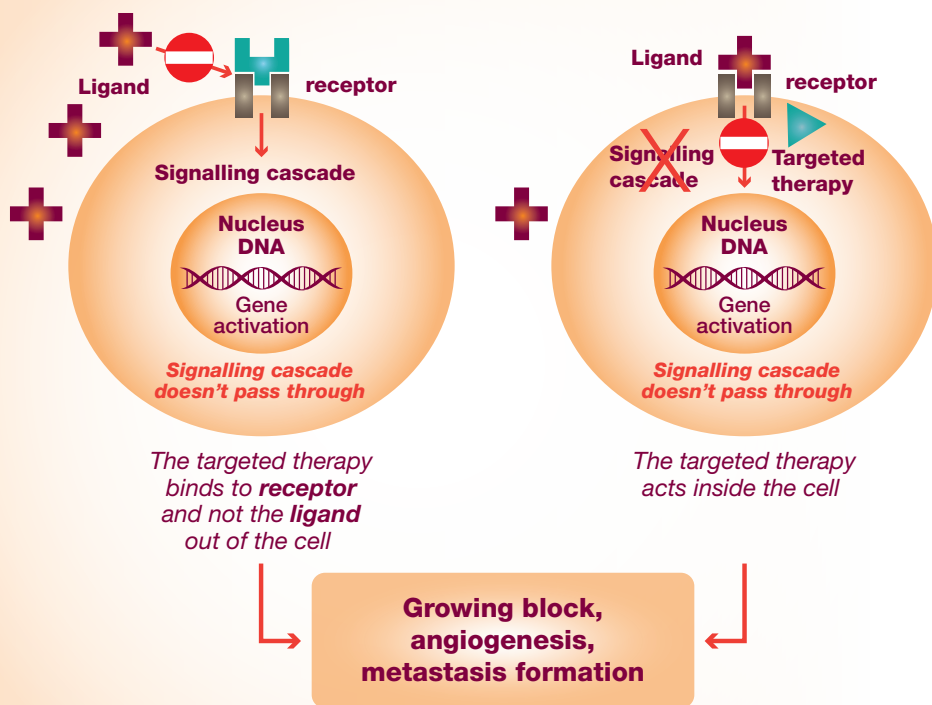
Other new drugs can bind to receptors located to cell surface (there are much more into cancer cells than normal ones).

These receptors are mostly activated by binding of specific **ligands** (also called **growth factors**). Upon activation by **growth factor ligands** in the cells, a cascade of molecular events lead to cellular proliferation.

Preventing the reciprocal binding may block the cell proliferation.

It is crucial to switch the signal off and block the formation of new blood vessels (**angiogenesis**) and cancer growth. Monoclonal antibodies act in this way and are administered through a drip into a vein (*intravenous infusion*) or subcutaneous.

## How do targeted therapies act?



## Molecular tests



## Which patients may benefit from targeted therapies?

Not all lung cancer patients may benefit from these therapies. It depends on the presence or absence of tumor's features (for example, **mutations** in some DNA's genes).

Over the years, several tumor markers were discovered. They could be considered as cancer cell fingerprints and just as no two fingerprints are alike, neither are molecular fingerprints. The information contained in your unique molecular fingerprint gives your oncologist or treating physician insights into how to personalize your lung cancer treatment plan.

In the last few years several targeted therapies were developed to act on specific molecular targets that are associated with cancer. Only a small percentage of patients (ie those with *specific features*) may currently receive these drugs. Even if it is not a rule, most of lung cancer patients with gene's mutations have never smoked or having been a mild smoker.





## How are these tumors diagnosed?

When there is a reasonable suspicion of cancer, a biopsy is necessary and the most common methods are the CT guided biopsy or the bronchoscopy, but the situation should be individually evaluated to determine the best procedure. The analysis of the tissue removed in a biopsy determines the exact nature of the tumor (*histology*).

These alterations are very common in lung adenocarcinomas, but other targets are being to be defined in other cancer subtypes. There are *molecular tests* that are currently available to identify the molecular profile of the disease (the targets, also called biomarkers) and which are performed on the same material used for 1<sup>st</sup> biopsy. When this material is not sufficient, it may be necessary to repeat the biopsy to obtain more tissue for molecular testing.

## How is my tumor tissue for molecular testing obtained?

One of your doctors will do a biopsy to get a tissue sample from your tumor. Biopsies can be performed in a number of ways. It is important to get a big enough piece of tumor tissue to do molecular testing.

Fine needle aspiration (FNA) biopsy may not provide enough tissue for molecular testing, so your oncologist may recommend one of the following methods for biopsy:

- Core needle biopsy performed by an interventional radiologist
- Bronchoscopy performed by a pulmonologist
- **Lymph node** biopsy performed by an interventional radiologist or pulmonologist
- **Mediastinoscopy** performed by a thoracic or general surgeon
- Computed tomography (CT), fluoroscopy, ultrasound, or MRI-guided core needle biopsy performed by an interventional radiologist or pulmonologist
- Video-assisted thoracoscopic surgery performed by a thoracic surgeon
- Electromagnetic Navigational Bronchoscopy® (ENB™) performed by a pulmonologist or thoracic surgeon

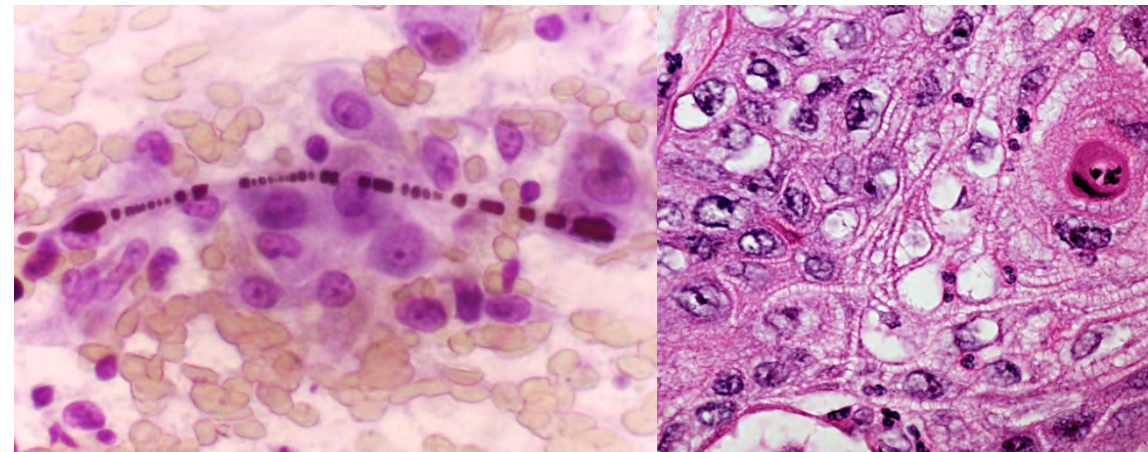
## What does this mean for cancer patients?

It means that these changes or mutations may be targeted by certain drugs that are currently available or may identify that a patient is eligible for a clinical trial. This technology will help your doctor to create your personal treatment plan.



## Where will my tissue be tested?

A Clinical Laboratory Improvement Amendments certified laboratory, most commonly referred to as a CLIA certified laboratory, will usually test the tumor tissue. If your hospital does not have a lab that offers the molecular testing, your oncologist will ask that the tissue be sent to another lab.



## What material is used to perform molecular tests?

These tests require a good quality and a sufficient quantity of material, since multiple procedures need to be performed. Sometimes some preparation contains only few cells, which is not adequate for the test. In this case your oncologist will discuss with you the opportunity to have another biopsy.

## How long does it take to get my results?

Your oncologist will get the results of the molecular testing within 3 to 10 business days. Your oncologist may call you with the results or discuss them with you at your next appointment. Either way, your oncologist will discuss the results and treatment options that may be appropriate for you based on those results.



## Who does perform molecular tests?

Biologists and **pathologists** perform these exams, and your oncologist acts as an intermediary.

- **An appropriate biopsy is important to perform molecular tests**
- **Not all lung cancers should be tested**
- **These tests are best used in patients with adenocarcinoma**
- **Sometimes the oncologist may require a new biopsy, because the previous one had not enough material**

## Targeted therapy biomarkers



### What biomarkers are used in the clinical practice?

The biomarkers currently used in routine clinical practice and associated to treatments considered “standard” are:

- » **EGFR** gene mutation (Epidermal Growth Factor Receptor)
- » **ALK** gene rearrangement (Anaplastic Lymphoma Kinase)

Their presence in patients with lung adenocarcinoma allows the use of a targeted treatment.

### Numbers and names

1	E	B	C	U	A	L	K	I
A	T	G	2	O	5	6	7	Y
9	Q	S	F	X	D	H	Z	M
0	8	P	4	R	3	N	V	J

### What specific information is obtained from my molecular testing and how does it determine my personalized treatment?

Different molecular tests are done depending on the laboratory where the tissue is sent. Many major cancer centers at teaching hospitals can perform molecular testing. Most labs will test the tissue from your tumor for at least four specific genetic mutations, EGFR, KRAS, EML4-ALK and BRAF.

**EGFR:** The EGFR gene produces a protein called epidermal growth factor receptor. In 10%-15% of Caucasian patients with non-small cell lung cancer (NSCLC), the EGFR gene is mutated. Nearly 50% of the lung cancers resulting from EGFR

mutation happen in people who have never smoked. There are three drugs that are commonly used to treat lung cancer - **gefitinib** (Iressa™), **erlotinib** (Tarceva®) and **afatinib** (Giotrif®), that has already been approved in Europe, but not yet in all the countries. Researchers have found that EGFR genetic mutation tumors are sensitive to **gefitinib** (Iressa™) and **erlotinib** (Tarceva®) - that is, the growth of EGFR tumors may be slowed by these drugs.

**EML4-ALK:** If molecular testing shows that your tumor does not have mutations in the EGFR or KRAS genes, the pathologist will look for another abnormality called an EML4-ALK fusion gene. This mutation occurs when two genes (EML4 and ALK) become fused into a form that changes the way the original genes function. The EML4-ALK abnormality is found in nearly 5% of patients with non-small cell lung tumors. The drug used to treat patients with this mutation is **crizotinib** (Xalkori®).

### Future of molecular testing

Other genetic biomarkers and mutations that are currently being studied could provide additional specific treatments for non-small cell lung cancer.

*For these mutations targeted therapies are available only in **CLINICAL TRIALS**.*



### Some examples:

**KRAS:** The KRAS gene is mutated in about 25% of people with NSCLC. Tumors with the KRAS mutation are resistant to the drugs for EGFR that will not work for these tumors.

*By doing molecular testing, your doctor will be able to determine if your tumor is sensitive or resistant to these drugs.*

**BRAF:** The fourth identified mutation, BRAF, occurs in about 3% of people with lung cancer. This mutation seems to happen most often in patients who are either current smokers or who smoked in the past. The BRAF mutation produces a protein that transmits signals within a cell to its interior. In a cancer tumor, this signal can cause cells to divide and cancer to grow. The research on this mutation is looking for ways to block the signal and slow the spread of cancer.

**ROS1:** This is a mutation that occurs in 1% of people with lung cancer.

**MET:** This mutation occurs in 4-7%.

**HER2:** common mutation in breast cancer. It occurs in 1-2% of people with NSCLC.

**PIK3CA, RET, FGFR, PI3K, PDGFR, DDR2.**

### What if the biopsy does not produce enough tissue to test for all the known genetic mutations?

Only a small number of lung cancer patients are currently tested using molecular testing.

There are three common genetic mutations (EGFR, ALK and KRAS) with known effective treatments.

*If the doctor does not get enough tissue to test for all genetic markers, ask your doctor to at least test for these three.*

## 🎯 Side effects



One piece of information that often come from newspapers and websites is that targeted therapies don't have side effects.

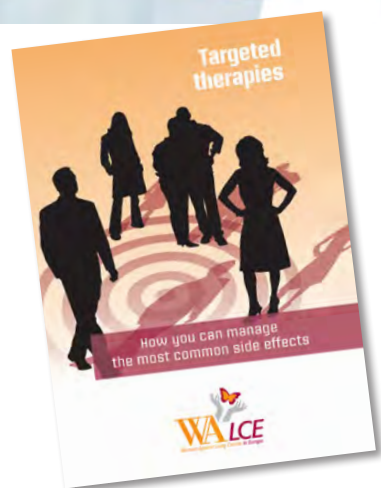
This is not entirely correct since even targeted therapies can cause toxicity, although different from those related with chemotherapy.

These new molecules have revolutionized the quality of life of patients, in most cases they result in very few problems and side effects are generally moderate or infrequent. But it's crucial to remember that each patient may react differently to the same drug, so it is important to talk with your oncologist.

The most common side effects related to targeted therapies are: dry skin with rashes and itching, conjunctivitis, nausea, diarrhea, blurred vision and liver function.



Your health care team will be able to list and explain how to treat them, sometimes with minimal doses of symptomatic medication, sometimes with resolution of symptoms without any specific treatment.



**We advise you to consult the booklet:**  
**“Targeted Therapies  
how you can manage  
the most common side effects”**

## Glossary



**Afatinib (Giotrif):** multiple tyrosine kinase inhibitor, used to treat NSCLC (mostly adenocarcinoma) with EGFR mutation. Currently on the market only in some countries. Its formulation is in tablet form.

**ALK (Anaplastic Lymphoma Kinase):** is a tyrosine kinase receptor encoded by the ALK gene. Alterations of this gene are often associated with the development of some cancers such as lung cancer.

**Clinical trials:** type of clinical research evaluating the therapeutic efficacy of a new drug on patients.

**EGFR (Epidermal Growth Factor Receptor):** is a growth factor receptor that induces cell differentiation and proliferation upon activation through the binding of one of its ligands. The receptor is located at the cell surface, where the binding of a ligand activates a tyrosine kinase in the intracellular region of the receptor.

**Growth factor:** a protein able to stimulate the proliferation and the improvement of the cell.

**Enzyme:** is a protein that speeds up chemical reactions in the body. Without enzymes, metabolism would not be able to generate products at a sufficient speed for the needs of the cell and the whole organism.

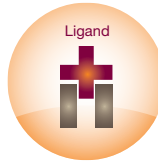
**Erlotinib (Tarceva):** tyrosine kinase inhibitor used to treat lung cancer. Currently on the market. Its formulation is in tablet form.

**Gefitinib (Iressa):** tyrosine kinase inhibitor used to treat NSCLC (mostly adenocarcinoma) with mutation of the EGFR gene. Currently on the market. Its formulation is in tablet form.

**Histology:** is the study of the microscopic anatomy of cells and tissues of plants and animals. It is commonly performed by examining cells and tissues

by sectioning and staining, followed by examination under a light microscope or electron microscope.

**Ligand:** substance able to bind and form a complex with a biomolecule (i.e. receptor) to serve a biological purpose.



**Lymph node:** the lymph nodes are small glands that make white blood cells (lymphocytes), which fight infection. Lymph nodes may trap the germs that are causing an infection. Cancer often spreads to lymph nodes.

**Mediastinoscopy:** is a surgical procedure that enables visualization of the contents of the mediastinum, usually for the purpose of obtaining a biopsy .

**Metabolism:** the set of life-sustaining chemical transformations within the cells of living organisms. The word metabolism can also refer to all chemical reactions that occur in living organisms, including digestion and the transport of substances into and between different cells.

**Mutation:** genes are segments of DNA located on chromosomes. A gene mutation is defined as an alteration in the sequence of nucleotides in DNA. This change can affect a single nucleotide pair or larger gene segments of a chromosome.

**Monoclonal antibody (Ab):** a type of protein made in the laboratory that can locate and bind to substances in the body, including tumor cells

**Neovascularization:** formation of new blood vessels that cancer cells need in order to grow.



**Pathologist:** is a specialist in anatomical pathology, a medical specialty, who works to identify and analyze the changes induced by disease in organs and tissues usually removed by biopsy or during surgery. He makes the diagnosis of disease based on the macroscopic examination of tissue.



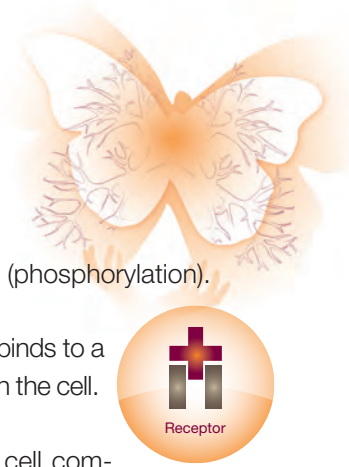
**Protein:** a molecule made up of aminoacids that are needed for the body to function properly.

**Protein kinase:** is a kinase enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation).

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

**Tyrosine kinase inhibitors:** a drug that interferes with cell communication and growth and may prevent tumor growth.

**Xalkori (Crizotinib):** tyrosine kinase inhibitor used to treat NSCLC (mostly adenocarcinoma) with translocation of ALK. Currently on the market. Its formulation is in tablet form.



**Notes**

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**Notes**



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# Notes

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## **WALCE (Women Against Lung Cancer in Europe)**

is a non-profit organization founded in 2006 with the primary aim to raise women's awareness about the increased rate of lung cancer's incidence in female gender.

Our mission is to **support** and **advocate** for lung cancer patients, their families and caregivers and to **educate** and **circulate information** in terms of prevention, diagnosis and therapy.



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