



Treatment considerations for patients with advanced squamous cell carcinoma of the lung: a plain language summary

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Summary

What is this article about?

This plain language summary reports the key points of a recent review article that discussed current treatment options for a type of cancer called squamous cell carcinoma (SCC) of the lung.

What is SCC of the lung?

SCC of the lung is a type of non-small-cell lung cancer (NSCLC for short) that is usually linked with smoking. It can be difficult to treat because it is often diagnosed after it has spread to other parts of the body.

What first-line treatment options are available for people with SCC of the lung?

Most patients receive a combination of chemotherapy and immunotherapy as their first-line treatment (the first treatment they receive after their diagnosis). Immunotherapy drugs have improved how long people with SCC of the lung can live for. However, for most patients, they eventually stop working. At this point, other second-line treatments are considered, meaning treatments patients receive after their first-line treatment is stopped due to side effects or because it no longer works.

What second-line treatment options are available to people with SCC of the lung?

Immunotherapy drugs were originally developed as second-line options after chemotherapy. However, immunotherapy drugs are now used with chemotherapies as first-line treatments. This has left a gap for second-line treatment options. There are some drugs available for second-line treatment, such as afatinib, which comes as a tablet, and docetaxel with or without ramucirumab, which is given as an infusion. Other potential treatments are being developed.

What emerging treatment options are being developed?

Some early clinical trials of potential treatments have shown promise, but more results are needed. Research into the genetic mutations linked with the development of SCC of the lung is also ongoing. It is hoped that this will help identify patients who might benefit from specific treatments.

Who should read this article?

People with SCC of the lung and their caregivers, patient advocates, and healthcare professionals, including those who are helping people learn about scientific discoveries and potential new therapeutic strategies.

How to say...

- **Afatinib:** aff-AT-in-ib
- **Carcinoma:** kar-sih-NOH-muh
- **Chemotherapy:** kee-mow-THEH-ruh-pee
- **Docetaxel:** dow-SUH-tak-sil
- **Immunotherapy:** im-mew-no-THEH-ruh-pee
- **Ramucirumab:** ra-mu-SIH-roo-mab
- **Squamous:** SKWAY-mus

Where can I find the original article on which this summary is based?

The original article discussed in this summary was written by Edgardo S. Santos and Estelamari Rodriguez. It is entitled 'Treatment Considerations for Patients With Advanced Squamous Cell Carcinoma of the Lung' and was published in *Clinical Lung Cancer* in September 2022. You can read the original article, which is freely accessible, at:

[https://www.clinical-lung-cancer.com/article/S1525-7304\(22\)00146-2/fulltext](https://www.clinical-lung-cancer.com/article/S1525-7304(22)00146-2/fulltext)

Who sponsored the review that this summary is based on?

The review was sponsored by the pharmaceutical company Boehringer Ingelheim Pharmaceuticals, Inc. (the manufacturers of afatinib).

What is SCC of the lung?

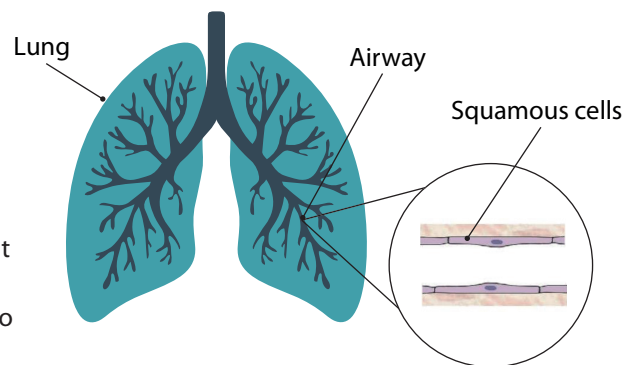
Squamous cell **carcinoma** (SCC for short) of the lung is a type of cancer that develops from thin, flat cells that line the airways, called squamous cells. These cells are sensitive to toxins, especially in cigarette smoke. Toxins can cause cells to multiply uncontrollably, leading to tumor development. Squamous tumor cells often spread to other parts of the body while the tumor is in early stages of development and before symptoms develop. Typical symptoms of SCC of the lung include:

- Chest pain
- Shortness of breath
- Persistent cough
- Bloody sputum (mucus coughed up from the lungs)
- Swelling of neck and face
- Hoarseness

SCC of the lung is an aggressive tumor type that, despite recent progress, has typically been difficult to treat because:

- Tumor characteristics differ greatly from person to person, so response to drugs tends to be variable
- People with SCC of the lung are often diagnosed after the tumor has spread to other parts of the body

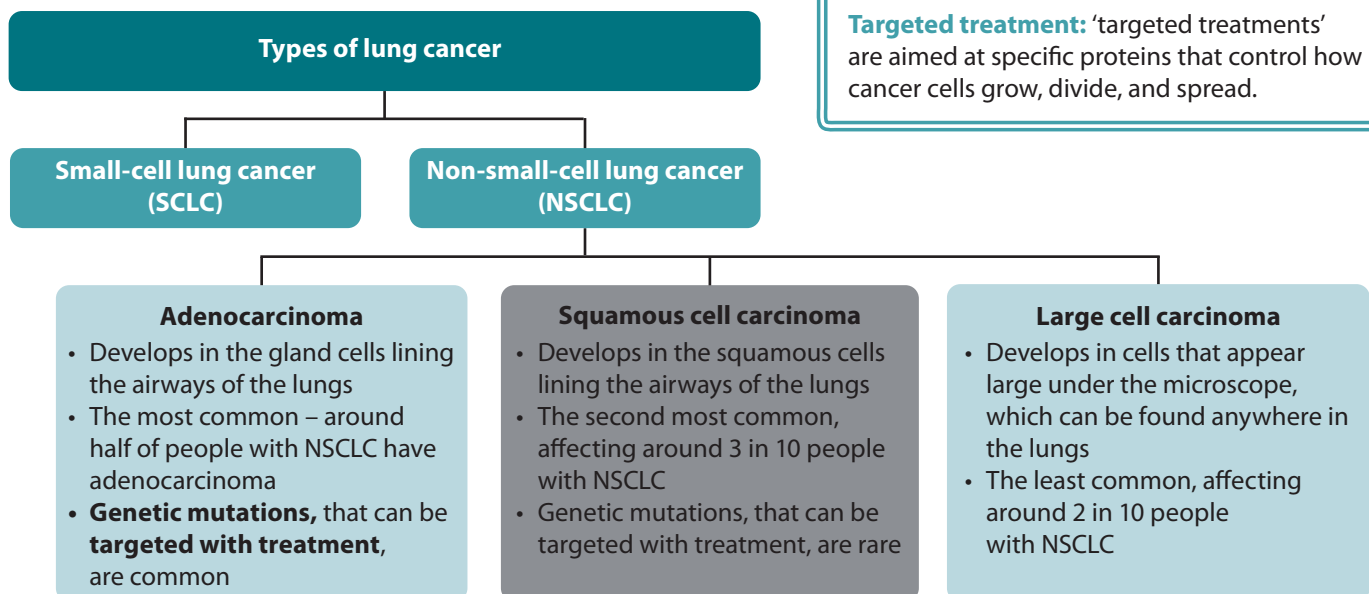
SCC of the lung is considered to have a poor prognosis. On average, only around 25% of people survive for 5 years after diagnosis, but recent improvements in treatment options are improving these statistics. SCC of the lung is the second most common type of non-small-cell lung cancer (NSCLC for short) after adenocarcinoma, which develops from a different type of cells in the airways of the lungs.



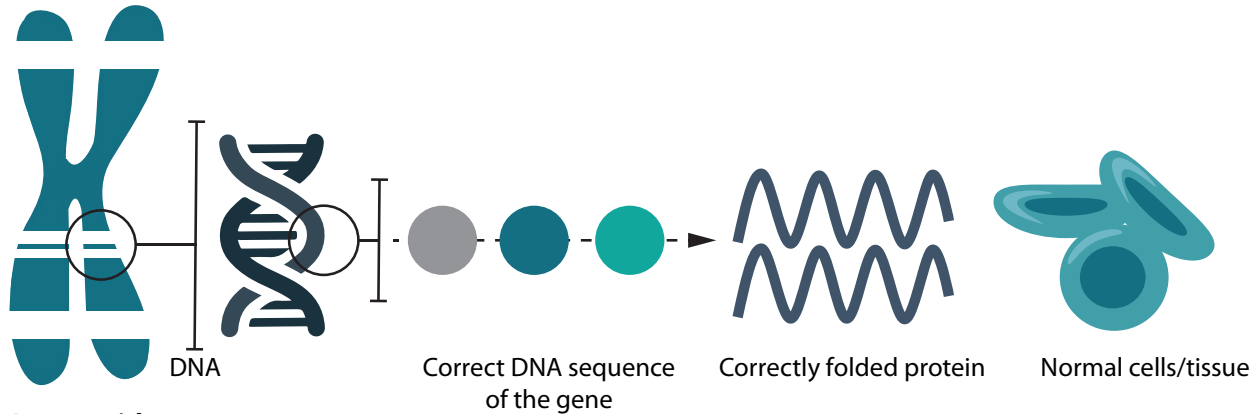
Carcinoma: is a type of cancer that starts in cells that line organs, such as the lungs.

Genetic mutations: changes to the DNA sequence of a gene, which can impact the structure and function of the protein that the gene produces.

Targeted treatment: 'targeted treatments' are aimed at specific proteins that control how cancer cells grow, divide, and spread.



Person without cancer



Person with cancer



Many lung cancers are caused by genetic mutations, where mistakes in the DNA sequence develop, either suddenly and without an obvious reason, or, for example, due to exposure to tobacco smoke. This can lead to mistakes in important proteins that control cell growth and turnover, sometimes leading to the formation of tumors.

Some genetic mutations can be treated with targeted drugs. For example, the gene for an important protein that helps control cell turnover, called epidermal growth factor receptor (EGFR), is mutated in around one or two in every 10 people with lung adenocarcinoma. Patients with *EGFR* mutations can be effectively treated with targeted drugs called EGFR tyrosine kinase inhibitors.















What first-line treatments are available for SCC of the lung?

A person with SCC of the lung may receive several different treatments over time. These are known as **'lines' of treatment**.

Given the lack of mutations that can be treated with targeted drug options for SCC of the lung, most people receive a combination of immunotherapy and chemotherapy (known as immunochemotherapy) or immunotherapy as their first-line treatment. Some patients are still treated with chemotherapy alone if, for example, they are at high risk of side effects from immunotherapy.

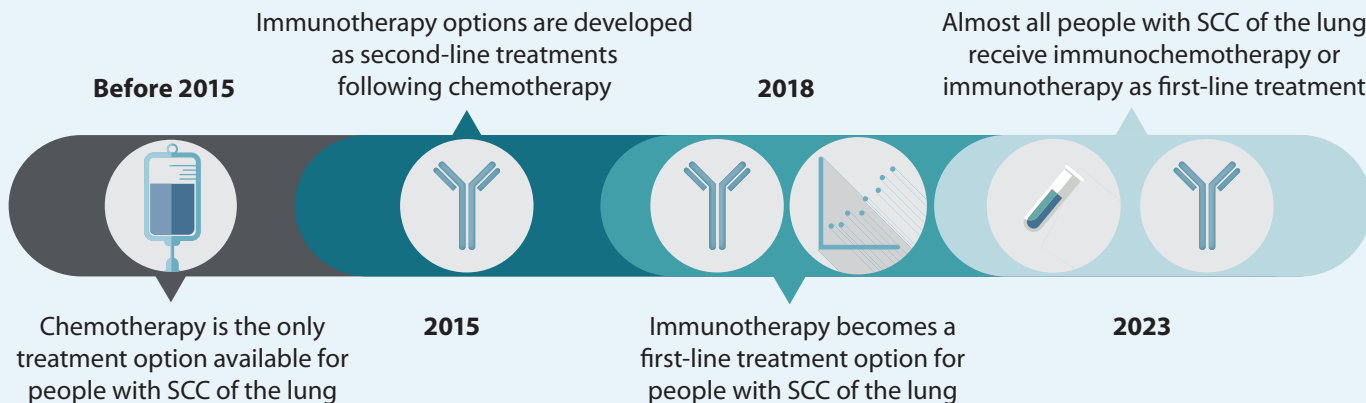
First-line: the treatment that a person receives first after their diagnosis.

Second-line: the treatment that a person receives after their first-line treatment is stopped due to side effects or because it no longer works.

Treatment	How it works	Examples	Most likely side effects
 <p>Chemotherapy</p>	<p>Uses chemicals that destroy cancer cells. There are many types of chemotherapy, and their side effects depend on which chemotherapy is given. It is usually given as an infusion into a vein (intravenously)</p>	 Carboplatin/paclitaxel  Carboplatin/nab-paclitaxel  Carboplatin/gemcitabine  Carboplatin/docetaxel	<ul style="list-style-type: none"> • Anemia • Bruising and bleeding • Fatigue (tiredness) • Hair loss • Infections • Loss of appetite • Sore mouth • Tingling of extremities
 <p>Immunotherapy</p>	<p>Helps the immune system to recognize and attack cancer cells. Immunotherapy (without chemotherapy) is only used when the amount of a protein called PD-L1 is present on tumor cells to a certain level. Different types of immunotherapy may be given in different ways (intravenously, etc.)</p>	 Pembrolizumab  Atezolizumab  Cemiplimab  Nivolumab + ipilimumab	<ul style="list-style-type: none"> • Diarrhea/constipation • Fatigue • Infusion-related reactions • Itchy skin • Nausea/vomiting • Rash • Thyroid disorders • Side effects related to the immune system
 <p>Immunochemotherapy</p>	<p>A treatment that combines immunotherapy and chemotherapy. Immunochemotherapy is not restricted to a certain level of PD-L1 on tumor cells</p>	 Pembrolizumab + carboplatin/paclitaxel  Pembrolizumab + carboplatin/nab-paclitaxel  Nivolumab/ipilimumab + carboplatin/paclitaxel	<ul style="list-style-type: none"> • Anemia • Blood disorders • Diarrhea/constipation • Fatigue • Hair loss • Infusion-related reactions • Nausea/vomiting

PD-L1: a protein that helps to control the body's immune responses, that can be found in higher-than-normal amounts on some types of cancer cells. The proportion of tumor cells that have PD-L1 on the cell surface can be given as a percentage.

Treatment choices for SCC of the lung have changed over time:

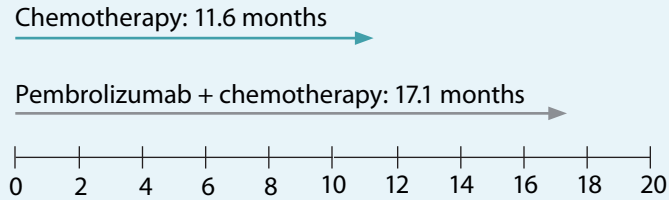


Evidence from a selection of studies

Study:
KEYNOTE-407
This trial was carried out in people with SCC of the lung only



Median overall survival

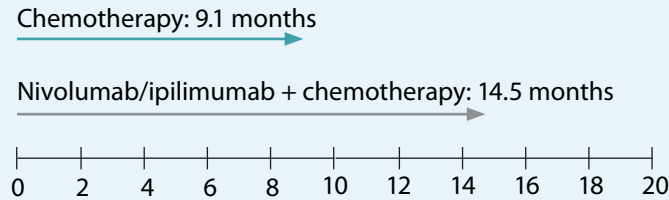


Result:
Overall, patients with SCC of the lung who were given pembrolizumab + chemotherapy survived longer than those given chemotherapy alone

Study:
CheckMate 9LA
This trial was carried out in people with NSCLC, the analysis of people with SCC of the lung is presented



Median overall survival



Result:
Overall, patients with SCC of the lung who were given nivolumab/ipilimumab + chemotherapy survived longer than those given chemotherapy alone

The introduction of immunochemotherapy and immunotherapy as first-line treatment options has improved survival times for people with SCC of the lung compared to chemotherapy alone. This has been shown in several clinical studies.

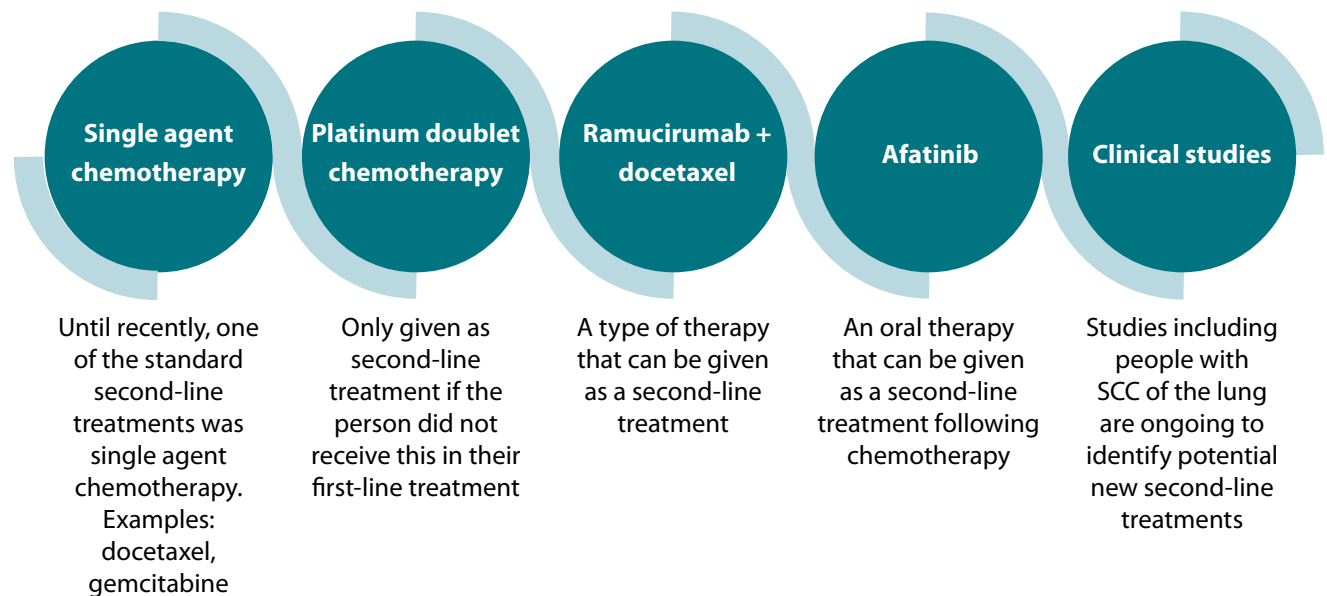
Eventually, immunochemotherapy or immunotherapy stops working for most people. When this happens, people will usually receive a second-line treatment.

Median: the middle number of a set of numbers.

Overall survival: the time a patient with advanced SCC of the lung could expect to live from the start of treatment.

What second-line treatment options are available for people with SCC of the lung?

Current second-line treatment options for SCC of the lung are:






Other than standard chemotherapy options, patients may be treated with afatinib, docetaxel (with or without ramucirumab), or may join a clinical trial of an investigative treatment.

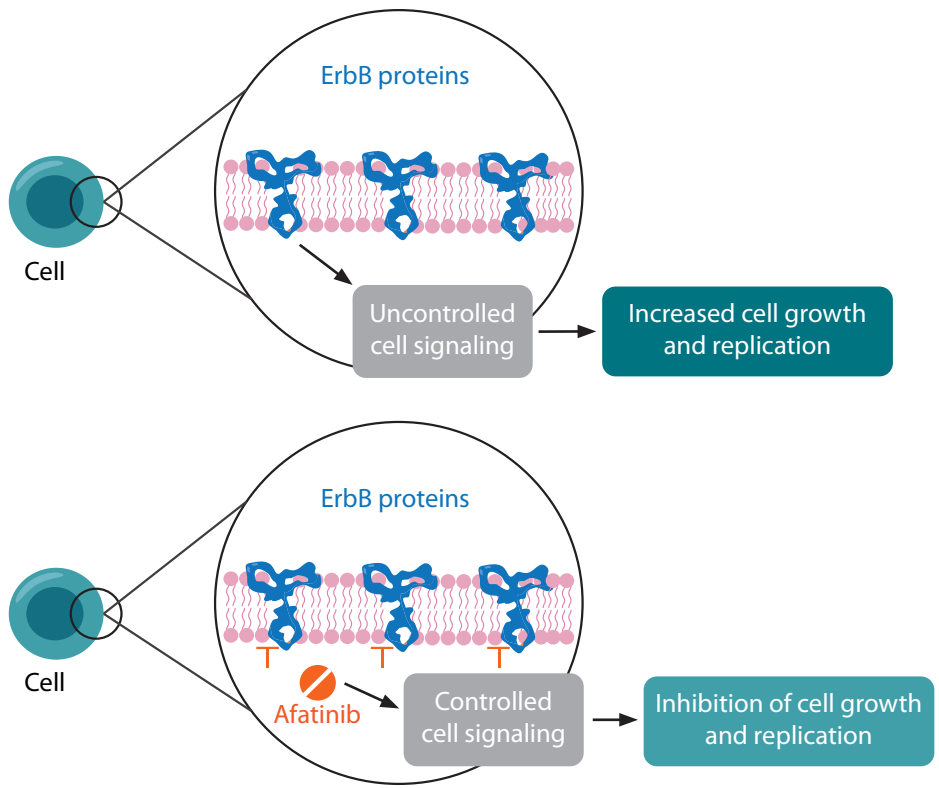
1 Afatinib

Afatinib is an oral drug used in the treatment of lung cancer. Results from the Phase 3 LUX-Lung 8 trial described below show that side effects were considered acceptable by the investigators in SCC of the lung.

The LUX-Lung 8 clinical trial

-  People with SCC of the lung received afatinib or erlotinib (a drug that works in a similar way to afatinib but was developed earlier) after first-line chemotherapy
-  People who received afatinib survived longer (7.9 months) than those who received erlotinib (6.8 months)
-  The most common side effects with afatinib were diarrhea, rash, acne, fatigue, and sore mouth. 27% of people had to have their dose of afatinib reduced and 20% had to stop taking afatinib due to side effects

Afatinib is a type of targeted therapy that blocks the activity of proteins, called ErbB receptors (one of which is EGFR), that are involved in the growth and spread of cancer cells.



However, LUX-Lung 8 was carried out at a time when immunochemotherapy was not widely used as first-line treatment. Currently, no **randomized controlled clinical trials** have been done to find out whether afatinib helps people live longer after the most up-to-date drugs are used first. On the other hand, one **retrospective study** has been carried out in people treated in 'real-world' clinical practice.

In the retrospective real-world study (you can see the results below), people had already been given either afatinib or follow-up chemotherapy, and the researchers were looking back at their medical records. Real-world studies provide useful information on how treatments work in everyday clinical practice. Physicians used electronic medical records to identify people with SCC of the lung who could be included in the study. The study did not compare afatinib with follow-up chemotherapy, but researchers looked at people's outcomes with each treatment.

Randomized controlled clinical trials: trials in which participants are divided by chance into separate groups where they are given different treatments. The results are then compared.

Retrospective studies: studies in which participants are identified based on drugs they have received. Their clinical records from the past are then analyzed to assess how well the drugs worked and what the side effects were.

EGFR genetic mutations: changes in the gene for epidermal growth factor receptor (*EGFR*), which is often mutated in certain types of cancer.

Real-world study of afatinib after immunochemotherapy



200 people with SCC of the lung who received first-line pembrolizumab + chemotherapy were included in the study:

- 99 people were treated with afatinib as their second-line treatment (including 35 with tumors made up of different types of cells, called 'mixed histology', and 39 with **EGFR genetic mutations**)
- 101 people were treated with chemotherapy as their second-line treatment (including 3 with mixed histology, and 5 with *EGFR* genetic mutations)



The average time on treatment with afatinib was:

- 7.3 months overall
- 8.1 months for those with tumor characteristic typical of other types of tumors
- 7.4 months for those with *EGFR* genetic mutations

The average time on treatment with chemotherapy was 4.2 months overall



In people treated with afatinib:

- The most common side effects were diarrhea, skin rash, tiredness, nausea, and inflamed and sore mouth
- 6 people had severe side effects related to the immune system, but all 6 also had severe immune-related side effects during initial immunochemotherapy treatment

No people treated with chemotherapy had side effects linked to the immune system



In the context of other studies, this study suggests that afatinib is effective after immunochemotherapy, and that the side effects can be managed, without too many severe side effects related to the immune system

In patients with SCC of the lung, afatinib is currently the only oral chemotherapy-free treatment option after platinum-based chemotherapy and immunotherapy.

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Docetaxel + ramucirumab

Docetaxel + ramucirumab is a combination treatment, which is given by intravenous infusion and is approved for the treatment of SCC of the lung after chemotherapy. This approval was supported by the results of the Phase 3 REVEL trial:

The REVEL clinical trial



People with NSCLC (25% with SCC of the lung) were given ramucirumab + docetaxel or docetaxel alone after first-line chemotherapy



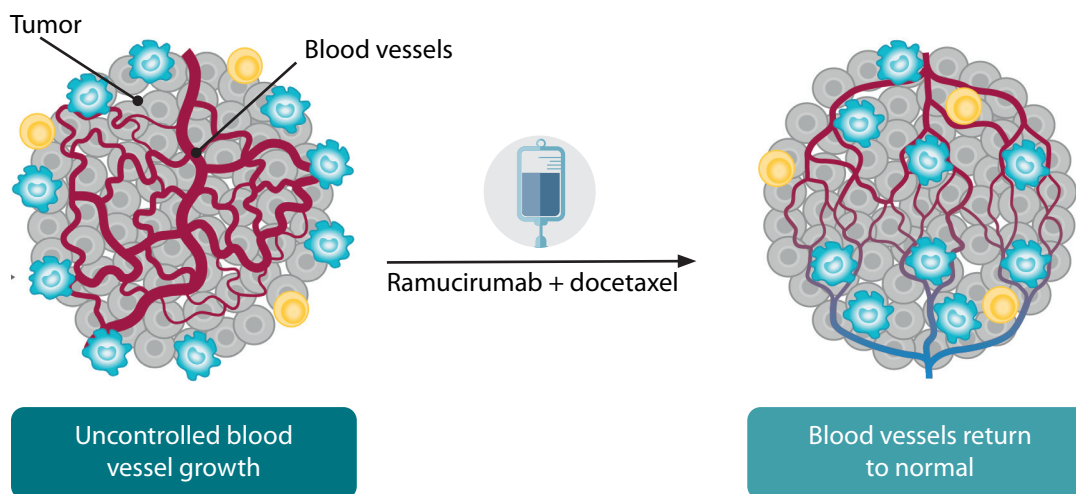
People who were given ramucirumab + docetaxel survived longer (9.5 months) than those who were given docetaxel alone (8.2 months)



The most common side effects with docetaxel + ramucirumab were related to the digestive system and the blood. Most of these side effects were manageable with dose adjustments or supportive care

Docetaxel is a type of chemotherapy and ramucirumab is an **anti-angiogenic agent**, which blocks the development of blood vessels that support the growth of tumor cells.

Anti-angiogenic agent: a treatment that prevents the growth of new blood vessels.



Evidence from a few limited studies involving people with SCC of the lung suggests that docetaxel + ramucirumab could be effective as a second-line treatment after platinum-based chemotherapy and immunotherapy.

Real-world studies of ramucirumab + docetaxel after immunochemotherapy or immunotherapy



Several real-world studies have assessed ramucirumab + docetaxel in people with NSCLC following immunochemotherapy or immunotherapy. These studies included people with SCC of the lung



People with NSCLC given ramucirumab + docetaxel lived for 7.5–20.9 months from the start of second-line treatment



This suggests that ramucirumab + docetaxel is an effective treatment for SCC of the lung after immunochemotherapy or immunotherapy

What does the future hold for the treatment of SCC of the lung?

Targeting genetic mutations

There is a lot of research taking place to identify genetic mutations that could be targeted with existing or potential new targeted therapies.

- The **NCCN** Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) recommend molecular testing be considered in all patients with **metastatic** NSCLC squamous cell carcinoma
- It is important that people with SCC of the lung are tested for genetic mutations that are treatable now, for example *EGFR*, or by any new treatment options

Testing potential drug targets

The LUNG-MAP **umbrella trial** aims to identify potential drug targets in SCC of the lung. People were recruited to sub-studies (different parts of a main clinical trial that ask separate research questions) based on their personal characteristics, or those of their tumors.

- One of the sub-studies suggests that the combination of ramucirumab (anti-angiogenic) and pembrolizumab (immunotherapy) might be a promising option for people with SCC of the lung

NCCN: a not-for-profit alliance of 32 leading US cancer centers devoted to patient care, research, and education.

Metastatic: cancer that has spread to other parts of the body.

Umbrella trial: a trial that subdivides people with the same disease into different groups depending on certain characteristics. Each group receives a different drug based on the likelihood that they will benefit from that treatment.

LUNG-MAP umbrella trial sub-study S1800A



136 people with NSCLC (including SCC) received either:

- Ramucirumab + pembrolizumab
- Ramucirumab + docetaxel
- Alternative chemotherapy treatments after first-line immunochemotherapy



People with NSCLC who received ramucirumab + pembrolizumab had a median overall survival of 14.5 months. This survival benefit appeared to be particularly strong in those with SCC of the lung



This suggests that ramucirumab + pembrolizumab should be investigated as a treatment for SCC of the lung in further studies

What are the key points of this review and what do they mean?

- SCC of the lung develops from abnormal squamous cells lining the airways of the lung
- While rapid advances in first-line immunotherapy have revolutionized treatment options for SCC of the lung, fewer potential second-line treatment options are available
- The limited evidence available supports afatinib or ramucirumab + docetaxel as second-line treatment options for SCC of the lung after immunochemotherapy
- Afatinib is available as an oral medication with a well-documented safety profile that does not need to be combined with chemotherapy
- Many other potential second-line treatment options are being assessed. Early results from some of the options, such as ramucirumab + pembrolizumab, look encouraging
- It is essential that people with SCC of the lung are tested for genetic mutations. Research into potential target genetic mutations is ongoing

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