Comparing cabozantinib and ramucirumab after treatment with sorafenib for patients with hepatocellular carcinoma

Date of summary: February 2021

The purpose of this summary is to help you understand the findings from a recent study

Cabozantinib and ramucirumab are approved drugs to treat a type of liver cancer called hepatocellular carcinoma, for patients in whom the liver cancer has kept growing (progressing) despite taking sorafenib, another anti-cancer drug.

Overall, the results of this study, which looks at data from two clinical trials, suggest that, compared with ramucirumab, cabozantinib can increase how long patients with liver cancer (hepatocellular carcinoma–type) live with their cancer without it progressing.

The results shown in this summary represent one analysis of two clinical trials. Please be aware that other studies, either alone or combined, may produce different results.

How to say the medical terms used in this summary:

Alpha-fetoprotein	<AL-fuh-FEE-toh-PROH-teen>
Cabozantinib	<KA-boh-ZAN-tih-nib>
Hepatocellular carcinoma	<heh-PA-toh-SEL-yoo-ler KAR-sih-NOH-muh>
Hepatocytes	<heh-PA-toh-sites>
Placebo	<pluh-SEE-boh>
Ramucirumab	<RA-myoo-SIR-yoo-mab>
Sorafenib	<sor-A-feh-nib>
Tyrosine kinase inhibitor	<TY-ruh-seen KY-nays in-HIH-bih-ter>

1 What was this study about?

- **In this study researchers looked at cabozantinib and ramucirumab as treatments for patients with hepatocellular carcinoma (HCC for short).**

What is HCC?

- HCC is the most common type of cancer that starts in the liver. The cancer develops from the main cells in the liver, called hepatocytes.
  - HCC occurs most often in patients with chronic liver disease.
- Patients living with liver cancer (HCC-type) may have increased levels of a protein called alpha-fetoprotein (AFP for short) in their blood.
  - AFP is made in the liver. Adults usually have low levels of AFP in their blood. High levels of AFP can help doctors to diagnose patients with HCC and predict how their disease may develop.

Which medicines did researchers look at?

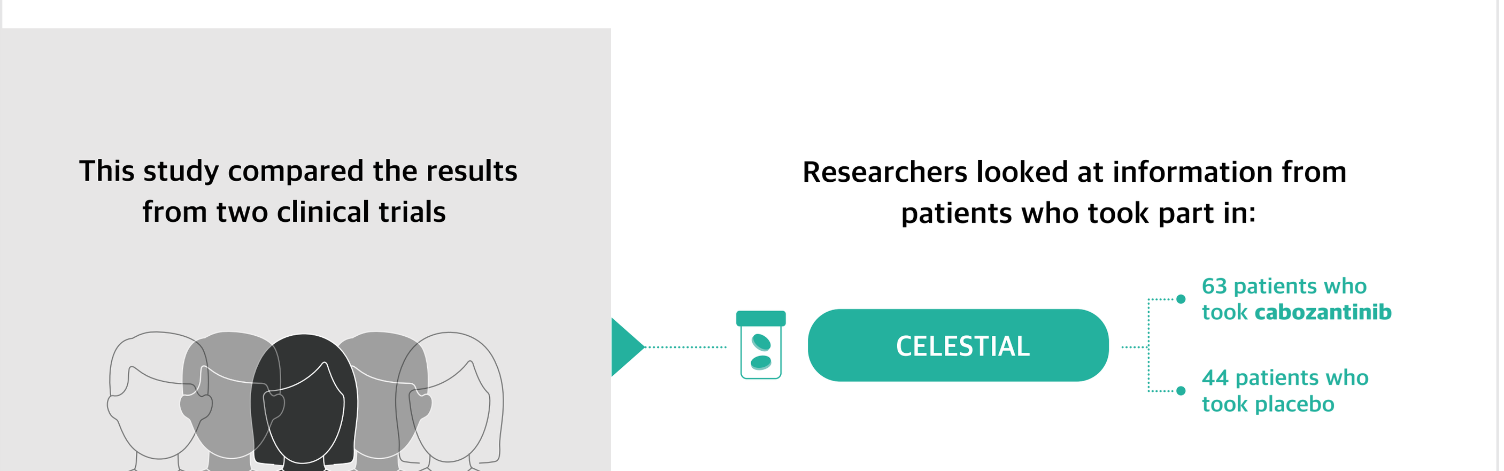
- Cabozantinib and sorafenib are a type of drug called a tyrosine kinase inhibitor.
  - Tyrosine kinases are proteins in the body that regulate how cells grow.
  - Tyrosine kinase inhibitors work by blocking tyrosine kinases in cancer cells, which can help to stop them from growing.
- Cabozantinib is taken as a tablet, once daily.
- Ramucirumab is a type of drug called an antibody.
  - Ramucirumab works by binding to a specific protein on cancer cells called vascular endothelial growth factor receptor.
  - This stops the cancer cells from forming the new blood vessels that they need to survive and grow.
- Patients receive ramucirumab every 2 weeks through a drip into their vein (known as an intravenous infusion).
  - Ramucirumab is only approved to treat patients living with liver cancer (HCC-type) who have high levels of AFP in their blood.

What did the researchers want to find out?

- Researchers wanted to compare how well cabozantinib and ramucirumab work in patients with HCC and high levels of AFP who have previously taken sorafenib.
  - These two medicines were investigated in different clinical trials.
  - Directly comparing results between clinical trials can be difficult because patients taking part in the trials can often have different characteristics, such as age and sex, and different disease characteristics at the start of the study, such as levels of AFP.
  - Researchers can use statistical methods to balance out some differences between trials so that they can look at the results from two different trials together.
  - In this study, researchers used a type of analysis that allowed them to compare outcomes from different trials even though there were differences in the patients taking part. This is known as a "matching-adjusted indirect comparison."
- **This summary describes the safety and effects of cabozantinib and ramucirumab in patients with liver cancer (HCC-type) and high levels of AFP who have previously taken sorafenib. Researchers looked at:**
  - How long patients lived with their cancer overall (known as overall survival).
  - How long patients lived with their cancer without it progressing (known as progression-free survival).
  - Any side effects that patients experienced with cabozantinib or ramucirumab.
    - During clinical trials, patients are asked to report if they feel unwell or notice anything different about their bodies. If the trial doctor thinks these feelings or changes may be related to the treatment patients are taking, it is called a side effect.

2 Who took part in this study?

- Researchers looked at information from patients living with liver cancer (HCC-type) who had taken part in one of two previous trials that compared:
  1. Cabozantinib versus placebo (in the CELESTIAL trial), or
  2. Ramucirumab versus placebo (in the REACH-2 trial).
- A placebo does not contain any active ingredients but looks like the trial medicine.
- Researchers used similar approaches in both trials to look at similar outcomes, but there were some differences between the patients taking part.
  - One of the main differences between the trials was that REACH-2 only included patients with high AFP levels. CELESTIAL included patients with any AFP level.
- In this study, researchers identified 11 patient characteristics that they thought might influence the effect of cabozantinib and ramucirumab on liver cancer (HCC-type), such as age, for how long patients had taken sorafenib previously, and their AFP levels.
- Next, they used mathematical models to match these characteristics of patients between the trials to make them similar.
  - This meant that results from the two trials could be compared more fairly.
- Finally, researchers compared the overall and progression-free survival and side effects in patients who took cabozantinib with patients who received ramucirumab.
- As an extra check, the researchers repeated the whole process without mathematically matching the patients based on their AFP levels.
  - This was because it wasn't possible to match the AFP levels of the CELESTIAL and REACH-2 populations exactly in the main analysis and the researchers wanted to know if this might affect the results.
  - If a difference in AFP level was important, then the results for the analysis that had matched patients on AFP levels would be different from the analysis that had not.

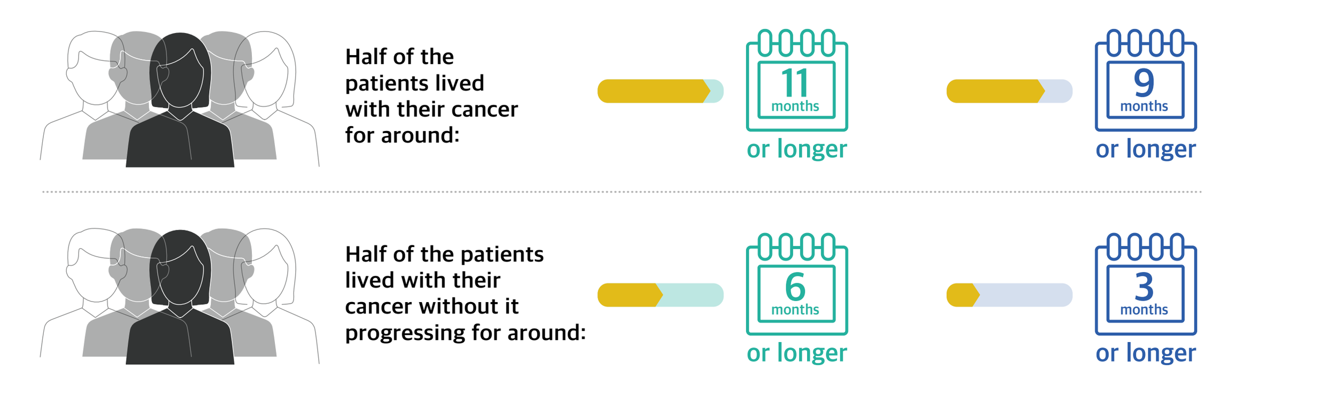


This study compared the results from two clinical trials
Researchers looked at information from patients who took part in:
CELESTIAL
63 patients who took cabozantinib
44 patients who took placebo
REACH-2
197 patients who received ramucirumab
95 patients who received placebo

To take part, patients had to have HCC, have taken sorafenib previously, and have high levels of AFP in their blood (at least 400 nanograms/milliliter). A nanogram is one thousand-millionth of a gram.

3 What were the results of this study?

How well did cabozantinib and ramucirumab work?

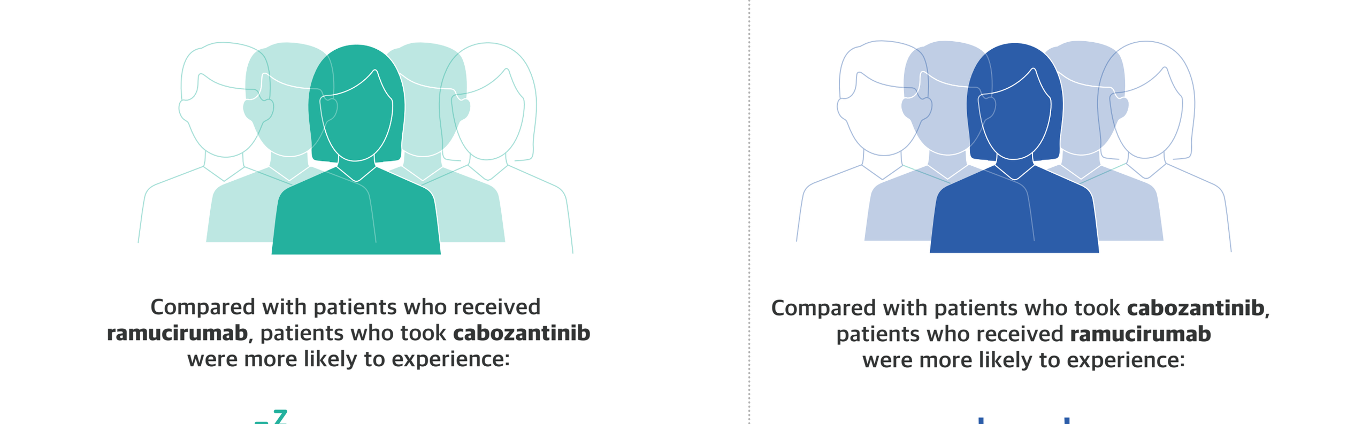


In studies of patients with cancer, researchers usually measure the time when half of the patients who started treatment are still alive, or how long half of the patients live without their cancer progressing. This is called the median time, which is the middle value in a set of measurements, and in this case, the middle patient. This allows researchers to compare averages when some of the patients in a study are still alive.

- The average length of time that patients who took cabozantinib lived with their cancer without it progressing was nearly double that of patients who received ramucirumab.
- The average length of time that patients lived with their cancer overall was similar for cabozantinib and ramucirumab according to the statistical tests that were carried out.
- The results were similar for the main analysis and for the "extra check analysis" that didn't match patients based on their AFP levels.
  - This reassured the researchers that, although the populations weren't exactly matched on AFP levels in the main analysis, they could still be confident in the results.
- For patients who received placebo in the two trials, there was no difference in how long they lived with their cancer overall, or without it getting worse.
  - This meant that the statistical adjustments had worked because the patients who were given placebo in the trials weren't actually receiving an active drug and so, without any treatment, no difference in the time to progression of their cancer, or in their survival, would be expected.

What were the side effects of cabozantinib and ramucirumab?

- Researchers looked at side effects that patients reported in both trials. This study looked at side effects that were experienced by 5 or more patients out of every 100 patients.
  - Some side effects were reported in the CELESTIAL trial only, or the REACH-2 trial only, so they could not be compared in this study.



Compared with patients who received ramucirumab, patients who took cabozantinib were more likely to experience:
High or very high blood pressure
Extreme tiredness and lack of energy (fatigue)
Very high blood levels of an enzyme called AST, which is a sign of liver damage, cancer, and other diseases
Diarrhea
Compared with patients who took cabozantinib, patients who received ramucirumab were more likely to experience:
Increased levels of protein in their urine

- The number of patients who stopped their treatment because of side effects was similar for cabozantinib and ramucirumab.

4 What were the main conclusions of this study?

- In this study, researchers used a type of mathematical approach that can help to compare the results from two trials when the patients taking part in the trials are a little different, which makes a direct comparison of the results difficult.
- Comparing results in this way is not as accurate as comparing treatments within the same trial because it cannot account for all of the differences between the trials, or the patients taking part.
  - This may mean that the results are less reliable.
- Patients living with liver cancer (HCC-type) and high levels of AFP in their blood who had previously taken sorafenib lived longer (almost twice as long) without their cancer progressing if they took cabozantinib compared with those who received ramucirumab.
  - Overall, the length of time that patients lived with their cancer was similar, regardless of whether they took cabozantinib or received ramucirumab.
- Some side effects, such as high blood pressure, were more likely to be experienced by patients who took cabozantinib than by those who received ramucirumab.
  - Researchers have suggested that, in some cases, these side effects may be linked to the treatment working well.
- The number of patients who stopped their treatment because of side effects was similar for cabozantinib and ramucirumab.
- These results may help doctors to decide how best to treat patients living with liver cancer (HCC-type) and high levels of AFP who have taken sorafenib previously.

5 Who sponsored this study?

This study was sponsored by Ipsen.

6 Where can you find further information?

The full title of this article is: Comparative efficacy of cabozantinib and ramucirumab after sorafenib for patients with hepatocellular carcinoma and alpha-fetoprotein ≥ 400 ng/mL: A matching-adjusted indirect comparison

- You can access the full article here: https://doi.org/10.1007/s12325-021-01700-2

Trial identification numbers:

- For a full report on the CELESTIAL and REACH-2 clinical trials, please visit **ClinicalTrials.gov** and search for trial numbers NCT01908426 (for CELESTIAL) and NCT02435433 (for REACH-2).
- For more information about hepatocellular carcinoma and currently available treatments, please speak to a healthcare professional.
- If you have any questions about this study, please contact the sponsor, Ipsen, at: **www.ipsenmedicalinformation.com**

We thank all of the patients who took part in this study. Without their support, advances in treatments for medical conditions would not be possible.

We would also like to thank the laypeople who took the time to review this document to make it easier for a general audience to read.

Summary prepared by Katy Beck, PhD, CMPP, at Envision Pharma Group.

Plain language services were funded by Ipsen.

Adis PEER-REVIEWED PLAIN LANGUAGE SUMMARY OPEN ACCESS