Future ONCOLOGY

Plain Language Summary of Publication

Pralsetinib in patients with *RET* fusion–positive non-small-cell lung cancer: a plain language summary of the ARROW study

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Summary

What is this summary about?
This is a summary of a research study called ARROW, which tested a medicine called pralsetinib in patients with non-small cell lung cancer (NSCLC), thyroid cancer, and other advanced solid tumours caused by a change in a gene called *RET*. For the purposes of this summary, only patients with NSCLC with a change in *RET* called fusion (*RET* fusion+) are highlighted.

How to say (double click sound icon to play sound)...

- **Pralsetinib:** Pral-SEH-tih-nib

What were the results?
In total, 281 patients with *RET* fusion+ NSCLC had taken part in this study across the USA, Europe, and Asia. Patients were asked to take four pills (adding up to 400 mg) of pralsetinib each day and were checked for any changes in their tumours, as well as for any side effects. After an average of 8 months of treatment with pralsetinib, 72% of previously untreated patients and 59% of patients who had previously received chemotherapy had considerable shrinkage of their tumours. Among 10 patients with tumours which had spread to the brain (all of whom had received previous treatments), 70% had their tumours shrink greatly in the brain after treatment with pralsetinib.

Side effects: An unintended effect, suspected to be caused by the medicine.
Severe side effects: An unintended effect, suspected to be caused by the medicine, that needs medical attention.

On average, patients lived with little to no tumour growth for 16 months. In previously untreated patients, the most common severe side effects that were considered related to pralsetinib treatment were decreased white blood cells (neutrophils and lymphocytes), increased blood pressure, and an increase in a blood protein called creatine phosphokinase. In previously treated patients, the severe side effects were decreased white blood cells (neutrophils, lymphocytes, and leukocytes), increased blood pressure, and low levels of red blood cells. In both untreated and previously treated patients, the most common severe side effects that required hospital attention were lung inflammation/swelling causing shortness of breath (pneumonitis) and lung infection (pneumonia).

What do the results mean?
Overall, the ARROW study showed that pralsetinib was effective in shrinking tumours in patients with *RET* fusion+ NSCLC regardless of previous treatment history. The recorded side effects were expected in patients receiving this type of medicine.

Where can I find the original article?

The original article called "Safety and efficacy of pralsetinib in *RET* fusion–positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial" that was published in *Annals of Oncology* can be found at:
https://doi.org/10.1016/j.annonc.2022.08.002

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What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research. Pralsetinib is used to treat the condition under study that is discussed in this summary.

Who is this article for?

This summary is an overview of the original ARROW (NCT03037385) study article and was written to help healthcare professionals explain the results of the ARROW study.

Who sponsored the study?

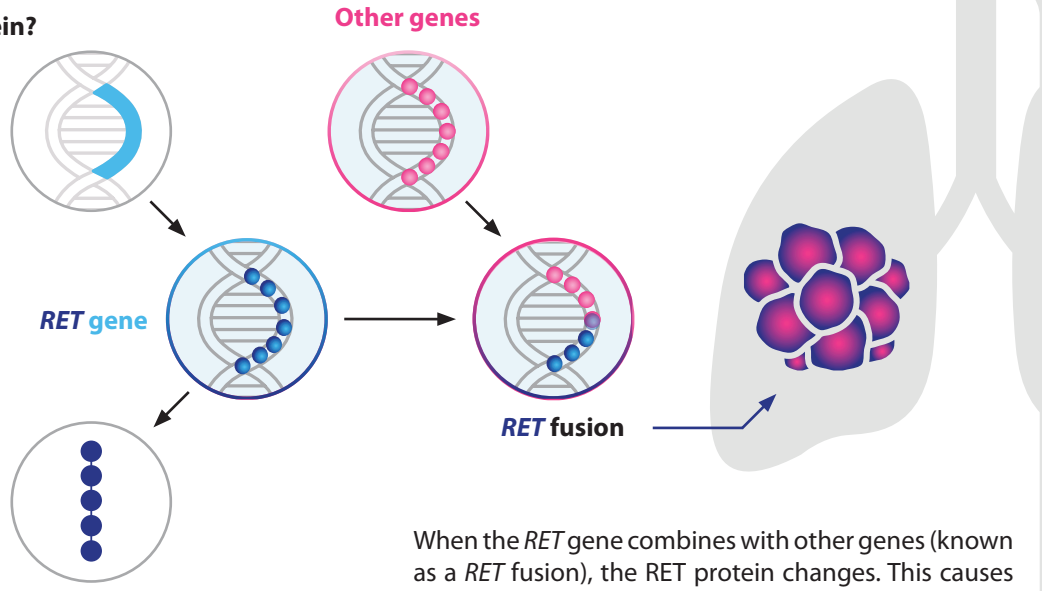
F. Hoffmann-La Roche, Ltd in partnership with Blueprint Medicines Corporation funded and were responsible for conducting this clinical study.

What is *RET* fusion+ non-small cell lung cancer?

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. In a small number of patients with NSCLC (1–2%), this cancer is caused by a change in a gene called *RET* (*RET* fusion+), for which standard medicines have limited treatment benefits.

What is a *RET* gene/protein?

A **gene** is a specific section of DNA which provides the body with instructions on how to make proteins that are essential for life.



RET is a protein involved in how cells in the body become different, grow, move, and survive.

When the *RET* gene combines with other genes (known as a *RET* fusion), the RET protein changes. This causes cells to rapidly grow to form tumours.

How is *RET* fusion+ NSCLC treated?

Before the ARROW study, the standard treatment for patients with previously untreated *RET* fusion+ NSCLC was chemotherapy with or without another type of medicine called immunotherapy. However, these treatments do not target the root cause of cancer in patients with *RET* fusion+ NSCLC (changes in the RET protein).

Testing for changes in the RET protein is important. By finding changes in the RET protein early, therapies that target these changes can be used, increasing the chances of long-term survival.

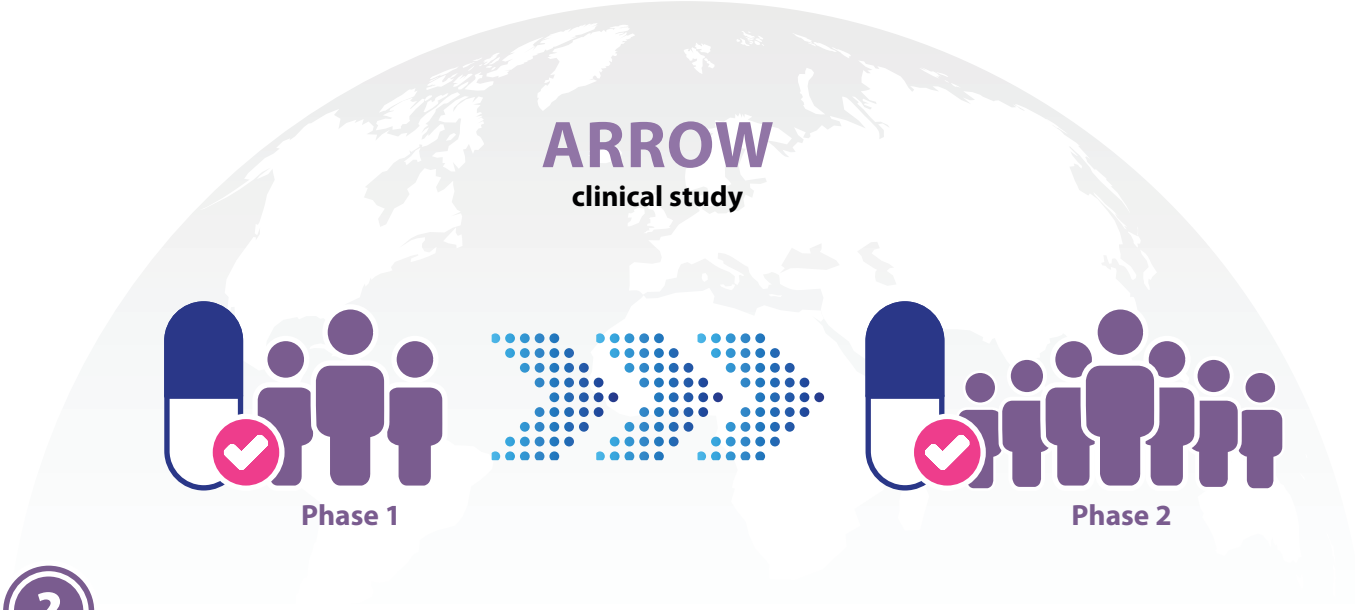
What is pralsetinib?

Pralsetinib is a type of medicine called a tyrosine kinase inhibitor that specifically blocks RET proteins that have undergone changes in the *RET* gene. RET inhibitors stop the altered RET proteins in cancer cells, causing them to die and tumours to shrink, thus increasing the chances of long-term survival.

Pralsetinib was designed to work against "normal" RET proteins and RET proteins that have gone through gene changes.

What is the ARROW clinical study?

ARROW is a global phase 1 and phase 2 study that is being carried out to look at how well pralsetinib works in patients with cancers that are caused by changes in the RET protein.



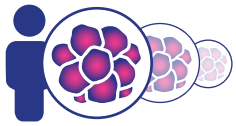
What does phase 1 mean?

A phase 1 clinical study is the first step of testing a new treatment in humans. It involves a small number of people and focuses on how safe the medicine is, what the side effects are, what the best dose is, and what the best timing of treatment is.

What does phase 2 mean?

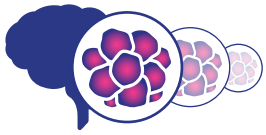
A phase 2 clinical study tests the new treatment in patients with a specific type of disease (for example, cancer). It involves a larger number of patients than a phase 1 clinical study and tests if patients improve after taking the medicine (for example, seeing if a tumour shrinks). Phase 2 studies can also give more information on how the new treatment affects the body.

What did the ARROW clinical study assess?



What was the proportion of patients whose tumours shrank and how much did the tumours shrink by?

This is known as best overall response and is assessed using ***RECIST v1.1***



For patients whose cancer spread to the brain, did these brain tumours shrink?

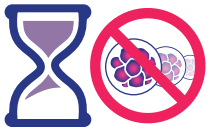
This is known as intracranial response rate (assessed using ***RECIST v1.1***)

Did any side effects occur while on pralsetinib treatment?

A side effect is a medical problem that occurs after treatment. In clinical studies, these are known as adverse events

How long did the tumour respond to treatment without it growing or spreading?

This is known as duration of response (assessed using ***RECIST v1.1***)



How long did patients live without their cancer getting worse?

This is known as progression-free survival (assessed using ***RECIST v1.1***)

How long did patients who were treated with pralsetinib live?

This is known as overall survival

What does *RECIST v1.1* measure?

Response Evaluation Criteria in Solid Tumours version 1.1 (***RECIST v1.1***) is used to see how well cancers respond to treatment. To assess this, the diameter of the tumour is measured before and after treatment to see whether it has grown in size.

Overall response rate	Complete response	Partial response	Stable disease	Disease progression
The proportion of patients whose tumor has either gone away or shrunk (complete response or partial response)	Tumor has gone away	Tumor has shrunk by at least one third of its original size	No major change in the size of the tumor	Tumor has increased by at least a fifth of its original size, or there are new tumors

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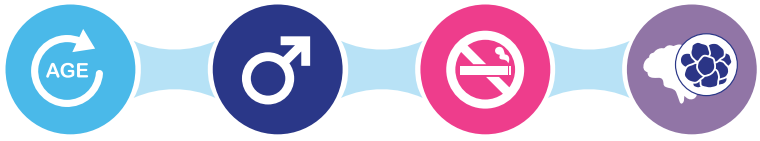
Who took part in the study?

To be involved in this study, patients needed to:

- Be 18 years or older
- Have cancer that has spread to nearby tissues or to other places in the body
- Have changes in the *RET* gene (fusions or mutations)
- Have a good-to-moderate level of functioning (ability to care for themselves and perform routine daily activities)
- Have measurable disease

281 patients with *RET* fusion+ NSCLC took part in the study, and were started on four pills (adding up to 400 mg) of pralsetinib each day. This included **previously untreated patients** and **patients with prior treatment**.

233 of these patients were included in the analysis that looked at the **efficacy** of pralsetinib.



Patients ages were between 26 and 87 years old

48% were male

62% had never smoked

37% had or currently have cancer that spread to the brain

Efficacy: The capacity of a medicine to produce an effect in a controlled setting (such as a clinical trial).

Follow-up: Checking on the progress of a patient at a later, specified date since their last appointment.

Previously untreated patients

Due to encouraging initial results in previously untreated patients, changes were made to include more patients who had not received treatment for *RET* fusion+ NSCLC before.

As of 6 November 2020, 110 patients with *RET* fusion+ NSCLC were still on pralsetinib treatment (average **follow-up**: 17.1 months).

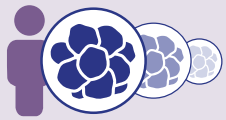
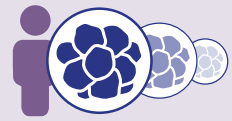
About *RET* mutations

Certain *RET* mutations are another type of change that can cause tumours to form in specific tumour types such as thyroid cancer.

What is measurable disease?

In order to know whether a medicine works in clinical studies, it is important to measure the size of the tumour before and after treatment. The ARROW study included patients whose tumours were measurable (with imaging procedures called computerized tomography or magnetic resonance imaging scans) from the start.

What were the overall results of the study?

All patients had measurable disease at baseline and a post-baseline assessment	 Overall response rate	 Duration of response at 12 months	 Tumour shrinkage	 Progression-free survival
Patients who were previously untreated	**72%**	**54%**	**100%**	**13 months**
Patients who were previously treated with chemotherapy	**59%**	**68%**	**97%**	**16.5 months**
Patients who were previously treated with other treatment	**73%**	**56%**	**Not available**	**12.8 months**
Patients with brain tumours	**70%**	**36%**	**100%**	**Not available**
Progression-free survival data were not available due to the low total number of patients with measurable brain tumours (10 in total)	The majority of patients had their tumours shrink greatly on pralsetinib treatment. This means that their tumours decreased by at least a third of their original size (complete response or partial response)	At least half of patients were estimated to still be responding after 12 months of pralsetinib treatment. This was true in approximately a third of patients with shrinkage of brain tumours	Tumours shrank in almost all patients treated with pralsetinib	On average, patients' cancers remained controlled without worsening for at least 13 months

Baseline: The initial conditions and measurements of participants, done at the start of the clinical trial.

75%
overall survival

In all patients, 75% were estimated to still be alive after 12 months.

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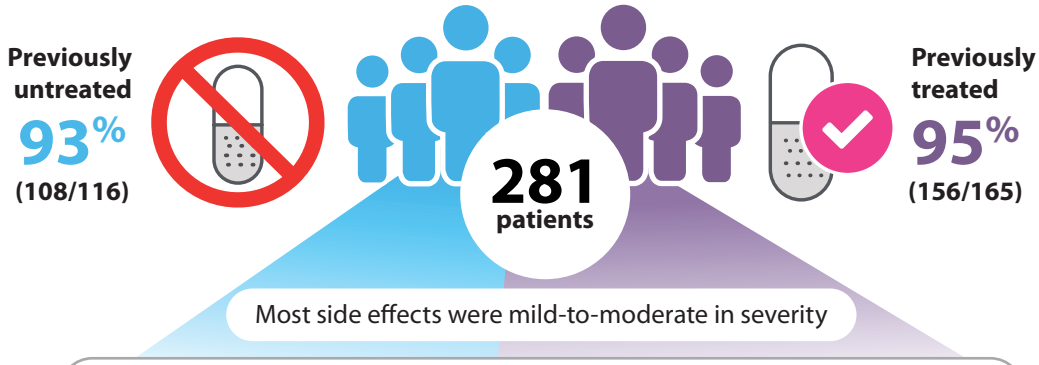
How many patients experienced side effects?



Most side effects were mild-to-moderate in severity

7% (20/281) of patients stopped pralsetinib treatment because of side effects

One previously untreated patient died due to a lung infection (pneumonia) which was considered related to pralsetinib

What were the most common side effects?

Previously untreated patients		Previously treated patients
50/116 43%	Low level of neutrophils (a type of white blood cell)	47% 78/165
45/116 39%	Low level of leukocytes (white blood cells)	31% 51/165
37/116 32%	Low level of red blood cells	43% 71/165
45/116 39%	Increase in aspartate aminotransferase (protein that indicates liver injury)	42% 69/165
37/116 32%	Increase in alanine aminotransferase (protein that indicates liver injury)	28% 47/165
35/116 30%	Constipation	23% 38/165

What were the most common severe, life-threatening, or disabling side effects?

Previously untreated patients		Previously treated patients	
21/116 18%	Low level of neutrophils (a type of white blood cell)	22% 36/165	
12/116 10%	High blood pressure	13% 22/165	
10/116 9%	Low level of lymphocytes (a type of white blood cell)	8% 14/165	
10/116 9%	Increase in creatine phosphokinase (protein that could indicate muscle injury) in the blood	5% 8/165	
8/116 7%	Low level of leukocytes (white blood cells)	8% 14/165	
5/116 4%	Low level of red blood cells	28% 30/165	
3/116 3%	Low level of platelets (cell fragments in the blood that form clots to prevent bleeding)	5% 8/165	

Which severe side effects most commonly required hospital attention?

Lung inflammation/swelling causing shortness of breath (pneumonitis)

Previously untreated patients	Previously treated patients
5%	5%
6 patients	8 patients

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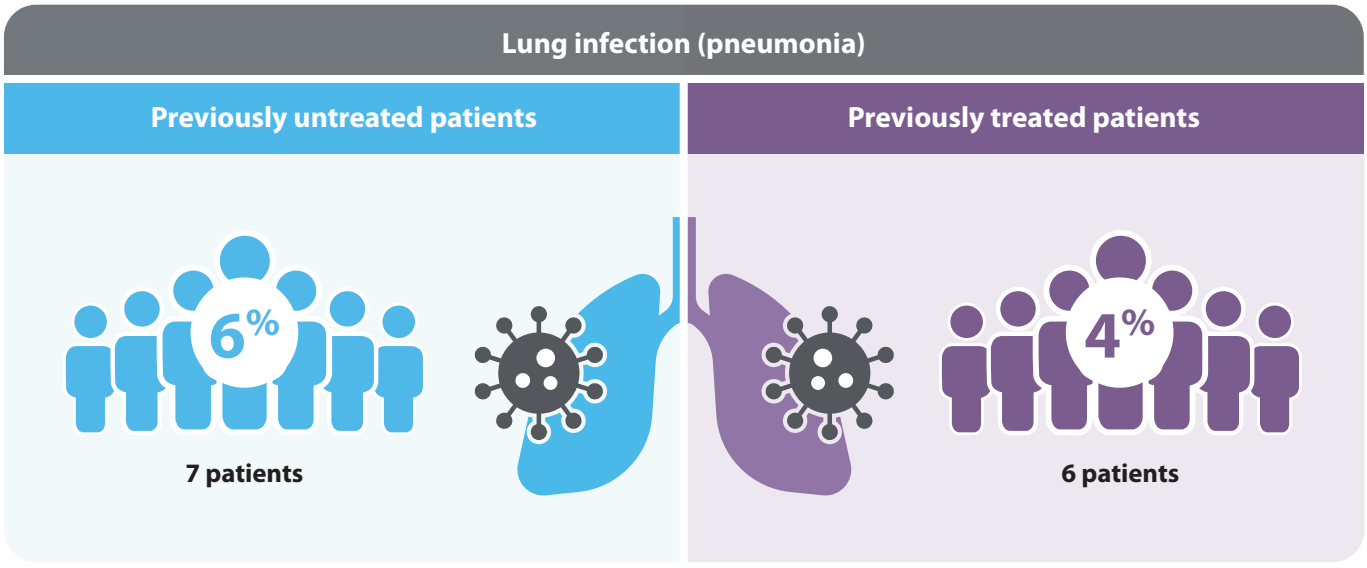

What do the results of this study mean?

The ARROW study involved patients with *RET* fusion+ NSCLC, including those who had not previously been treated for their cancer

A large proportion of patients who received pralsetinib had their tumours shrink, including the brain tumours of patients who had cancer that spread to the brain

Generally side effects were mild-to-moderate and manageable

A large-scale study called AcceleRET Lung is currently underway to check the efficacy and safety of pralsetinib compared with the standard treatment in previously untreated patients with *RET* fusion+ NSCLC

Where can readers find more information?

This is a plain language summary of the free-to-access original publication called: "Safety and efficacy of pralsetinib in *RET* fusion–positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial" and was published in *Annals of Oncology*. The original article can be found at: https://doi.org/10.1016/j.annonc.2022.08.002

The full name of the ARROW (NCT03037385) trial is, "Phase 1/2 Study of the Highly-selective RET Inhibitor, Pralsetinib (BLU-667), in Participants With Thyroid Cancer, Non-Small Cell Lung Cancer, and Other Advanced Solid Tumors (ARROW)." This study was started in March 2017, and has an estimated completion date of December 2023.

To find out more about the ARROW trial, please visit:

- https://clinicaltrials.gov/ct2/show/NCT03037385
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-004390-41

To find out more about the AcceleRET Lung trial, please visit:

- https://www.clinicaltrials.gov/study/NCT04222972
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-005269-15

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