

## Plain Language Summary of Publication

# Darolutamide and survival in nonmetastatic, castration-resistant prostate cancer: a patient perspective of the ARAMIS trial

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### Summary

This is a summary of a publication about the ARAMIS (Androgen Receptor Antagonizing Agent for Metastasis-free Survival) trial, which was published in the *New England Journal of Medicine* in September 2020. The trial was in adult participants with nonmetastatic, castration-resistant prostate cancer (nmCRPC) who received a trial treatment called darolutamide (brand name Nubeqa®). Darolutamide is currently available as an oral treatment for adults with nmCRPC. The ARAMIS trial looked at darolutamide taken by mouth in 1509 participants from 36 countries with nmCRPC (prostate cancer that has not spread to other parts of the body and no longer responds adequately to initial hormone therapy). The trial showed that darolutamide in addition to hormone therapy increased the length of time that the trial participants were still alive for and lowered the risk of death by 31% compared with placebo (sugar pill) and hormone therapy. The participants who received darolutamide and hormone therapy also had longer time to worsening pain, needing chemotherapy, and having cancer-related bone fractures or symptoms related to cancer-related bone fractures compared with those who received placebo and hormone therapy during the trial. In general, the percentage of participants who experienced medical problems (referred to as adverse events) was similar between those who received darolutamide and those who received placebo, in addition to hormone therapy. This summary also includes insights and perspectives from a participant who was in the ARAMIS trial and from a prostate cancer patient advocate.

#### How to say....

• **Darolutamide:**  
Dah-ruh-LOO-tuh-mide

### Who should read this article?

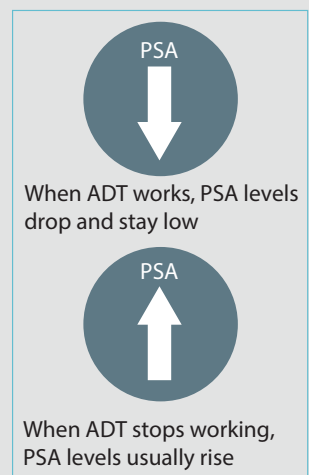
This summary is co-authored by patients and includes their perspectives to help patients and caregivers understand the results of the trial. It may also be helpful for patient advocates and healthcare professionals. This includes those who are looking for treatment options for patients with nmCRPC.

### What is nonmetastatic, castration-resistant prostate cancer (nmCRPC)?

- In patients with prostate cancer, the body cannot control the growth of abnormal prostate cells. The abnormal cells form tumors in the prostate gland and may also spread to other parts of the body.
- In patients with prostate cancer, doctors and researchers can use a protein in the blood to measure the cancer growth and response to therapy. This protein is called prostate specific antigen (PSA). PSA is produced by normal prostate cells, but tumor cells that are growing quickly can cause abnormal increases in PSA levels. So, high or increasing levels of PSA can mean the tumors are growing.

### What is nonmetastatic, castration-resistant prostate cancer (nmCRPC) cont.?

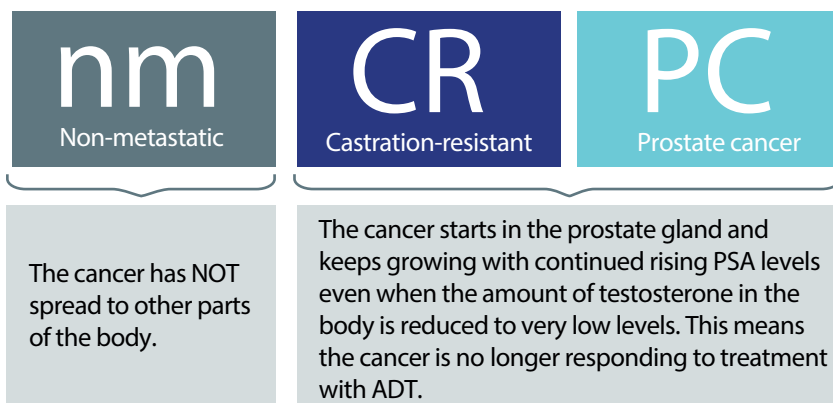
- Initially, high-risk prostate cancer is often treated by surgery or radiation, but sometimes PSA levels may still continue to rise or start to rise again for some patients after initial treatment. This is known as a relapse or recurrence. For these patients, prostate cancer is treated with a type of hormonal therapy called androgen-deprivation therapy (ADT).
- This therapy lowers testosterone hormone levels in the body, which reduces or slows the growth of the tumor cells.
- Nonmetastatic, castration-resistant prostate cancer (nmCRPC) is a type of prostate cancer that has not spread to other parts of the body and PSA levels continue to rise despite surgical or medical treatment (e.g., ADT) that lowers testosterone levels.
- The participants in the ARAMIS trial had nmCRPC.



### What is darolutamide?

Prostate cells have a protein called an androgen receptor that responds to testosterone. Testosterone is a type of hormone known as an androgen. Inside the prostate cell, testosterone is converted to a slightly different version of the hormone, called dihydrotestosterone. When dihydrotestosterone attaches to the androgen receptor, it creates a signal that causes the cell to grow.

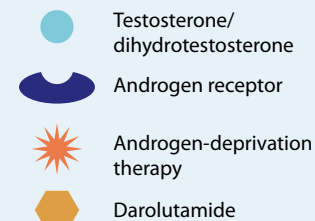
Darolutamide was designed to attach to androgen receptors and block the testosterone and dihydrotestosterone signal, slowing the tumor growth.



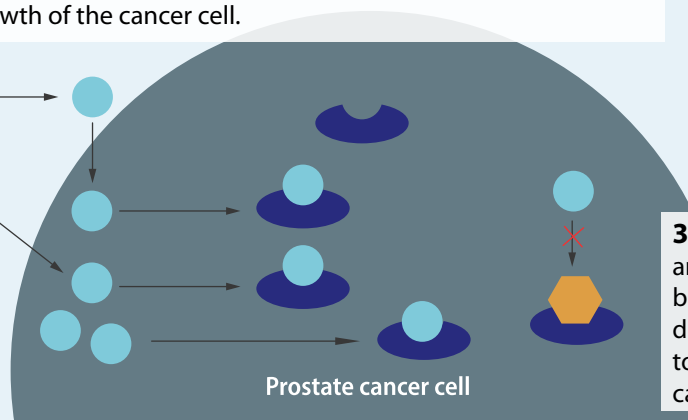
### Why was the trial needed?

Because nmCRPC doesn't respond as effectively to ADT anymore, further treatment options that work in different ways are needed for patients with nmCRPC to help control the growth of their tumors. This can help patients live longer and improve their quality of life.

2. Androgen-deprivation therapy lowers the levels of testosterone/dihydrotestosterone in the body. Having less testosterone/dihydrotestosterone attaching to androgen receptors helps slow the growth of the cancer cell.



1. Testosterone/dihydrotestosterone attaches to androgen receptors in prostate cancer cells and delivers a signal that can cause the cancer cell to grow.



3. Darolutamide attaches to androgen receptors to block the testosterone/dihydrotestosterone signal to slow the growth of the cancer cell.

### Who took part in the trial?

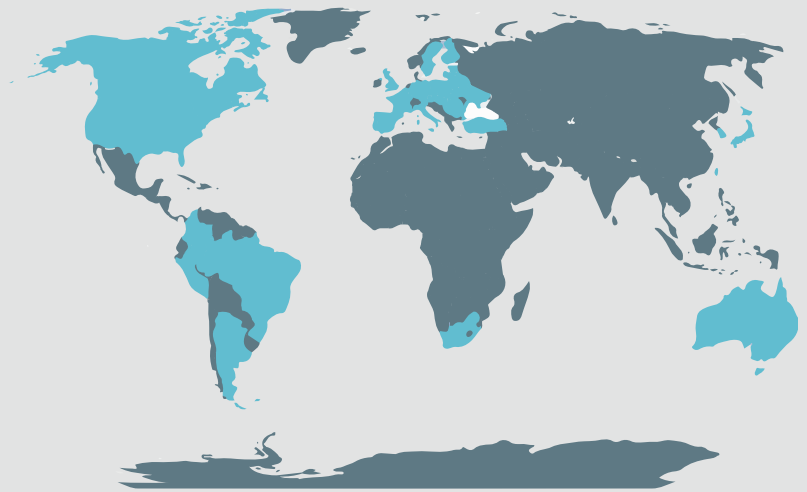
The ARAMIS trial included 1509 participants who were 48–95 years old. Out of the 1509 participants, 1194 were White, 52 were Black or African American and 193 were Asian. The trial included participants from 36 countries:

### All of the participants:

- had nmCRPC
- were already receiving ADT
- had a PSA blood level of at least 2.0 ng/ml
- had PSA levels that doubled every 10 months or less (known as doubling time)
- were able to move around easily or were otherwise fully active

Participants were not able to join the trial if they had metastatic prostate cancer. This includes tumors that had grown beyond the prostate that were measurable on bone scans and CT or MRI scans. Participants who had metastatic tumors in their pelvic lymph nodes that were smaller than 2 cm could still join the trial.

Argentina	France	Russian Federation
Australia	Germany	Serbia
Austria	Hungary	Slovakia
Belarus	Israel	South Africa
Belgium	Italy	South Korea
Brazil	Japan	Spain
Bulgaria	Latvia	Sweden
Canada	Lithuania	Taiwan
Colombia	Peru	Turkey
Czech Republic	Poland	Ukraine
Estonia	Portugal	United Kingdom
Finland	Romania	United States

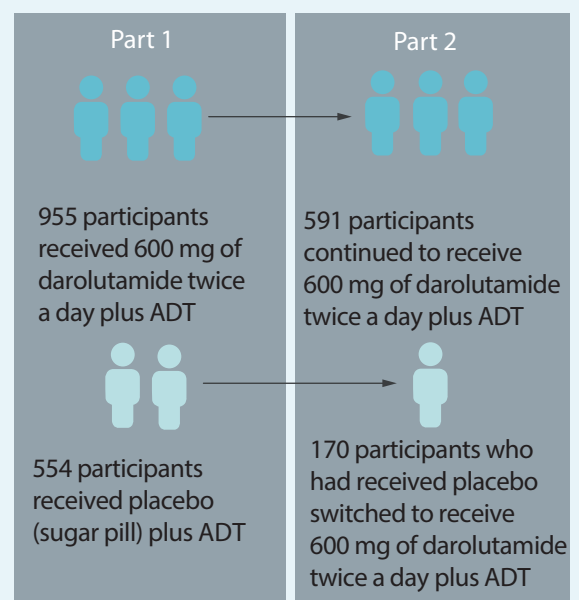


### What happened in the trial?

- The ARAMIS trial began in September 2014 and ended in September 2018.
- The trial had two parts. During both parts, all of the participants continued to receive their regular ADT.

In **Part 1**, participants received either darolutamide or placebo (sugar pill) as tablets taken by mouth twice a day, plus their regular ADT. The dose of darolutamide was 600 mg twice a day, or 1200 mg in total. In Part 1, 955 participants received darolutamide plus ADT and 554 participants received placebo plus ADT.

In **Part 2**, participants in either the darolutamide or placebo group could continue in the trial to receive darolutamide plus their regular ADT. The dose of darolutamide was the same as in Part 1. In Part 2, 591 participants from the darolutamide group continued receiving darolutamide and ADT and 170 participants from the placebo group switched to receive darolutamide and ADT. The rest of the participants either stopped receiving trial treatment altogether or switched to other therapies.



### What was the purpose of this trial?

The main questions the researchers wanted to answer at the end of the trial that are included in this summary were:

- Did darolutamide affect how long the participants survived?
- Did darolutamide affect how long it took for participants to have worsening pain?
- Did darolutamide affect how long it took for participants to need chemotherapy?
- Did darolutamide affect how long it took for participants to have cancer-related bone fractures or symptoms related to cancer-related bone fractures?

For more information about the questions that the researchers in this trial wanted to answer, please refer to the websites listed at the end of this summary.

### What were the overall results of the trial?

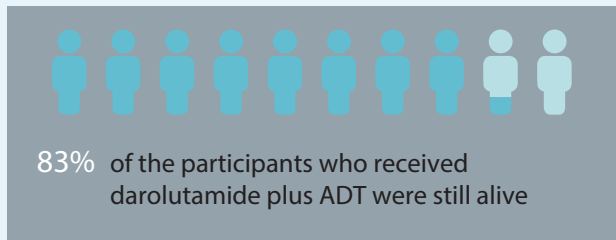
The main results from Part 1 were published in the *New England Journal of Medicine* in February 2019. Those results showed that darolutamide increased the length of time that the trial participants were still alive for without the cancer spreading to other parts of the body. This is known as metastasis-free survival. It also showed that the medical problems (referred to as adverse events) occurred in a similar percentage of participants who received darolutamide plus ADT as in those who received placebo plus ADT. Information on where to find that article is included at the end of this summary.

Below is a summary of the final results at the end of the trial after Part 2 was completed. A full report of the trial results can be found on the websites listed at the end of this summary. For privacy and confidentiality, this summary and the full published report do not identify participants individual results.

### Did darolutamide affect how long the participants survived?

Yes. Overall, the researchers found that treatment with darolutamide plus ADT increased the length of time that the trial participants were still alive for and reduced the risk of dying by 31% compared with placebo plus ADT.

The results after 3 years of receiving trial treatment were:



This is also known as “overall survival” and is a common question that researchers try to answer in clinical trials for cancer.

### Did darolutamide affect how long it took for participants to have worsening pain during the trial?

Yes. The researchers found that treatment with darolutamide plus ADT delayed the time to worsening pain and reduced the risk by 35% compared with treatment with placebo plus ADT.

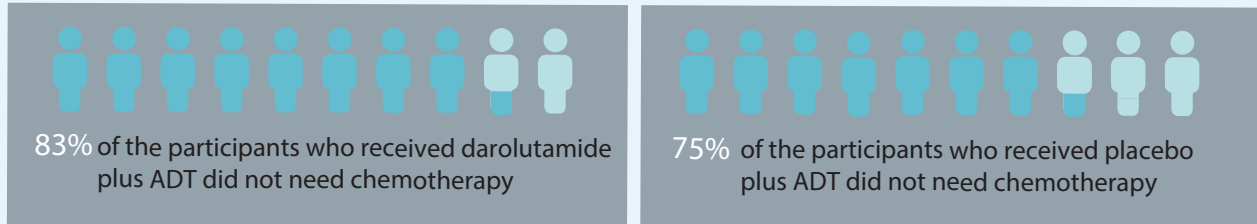
The results after 3 years of receiving trial treatment were:



### Did darolutamide affect how long it took for participants to need chemotherapy?

Yes. The researchers found that treatment with darolutamide plus ADT delayed the time to needing chemotherapy and reduced the risk of receiving chemotherapy by 42% compared with treatment with placebo plus ADT.

The results after 3 years of receiving trial treatment were:

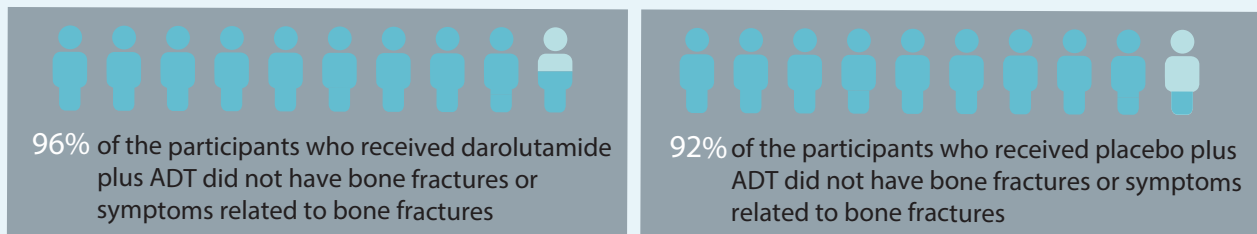


### Did darolutamide affect how long it took for participants to have cancer-related bone fractures or symptoms related to cancer-related bone fractures?

Yes. The researchers found that treatment with darolutamide plus ADT delayed the time to having cancer-related bone fractures or symptoms related to cancer-related bone fractures and reduced the risk by 52% compared to treatment with placebo plus ADT.

Prostate cancer and treatment with ADT can be associated with bone thinning and increased risk of fractures because of changes in hormone levels.

The results after 3 years of receiving trial treatment were:



During the trial, the researchers also found that treatment with darolutamide plus ADT reduced the need for cancer-related surgeries or additional cancer treatments compared with treatment with placebo plus ADT.

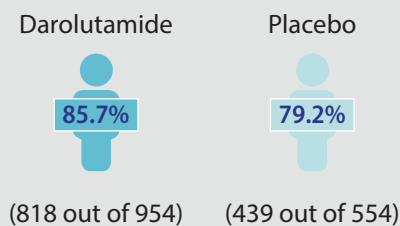
### What were the most common medical problems?

In this summary, medical problems are referred to as adverse events. Adverse events are considered serious when they lead to death, put the participant's life at risk, require hospitalization, cause disability or may require treatment to prevent one of these from happening.

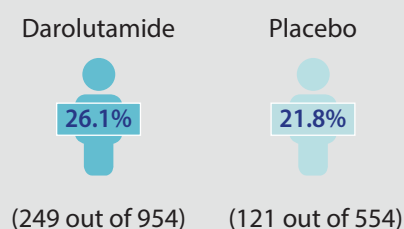
Researchers looked at the adverse events that happened in:

- 954 participants who received darolutamide plus ADT (one participant did not receive darolutamide as planned)
- 554 participants who received placebo plus ADT

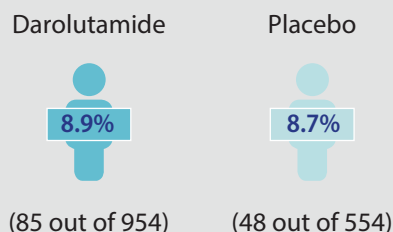
### How many participants had adverse events?



### How many participants had serious adverse events?



### How many participants stopped receiving trial treatment because of adverse events?



### What were the adverse events that were most likely to affect participants' daily lives?

	Darolutamide (out of 954)	Placebo (out of 554)
<b>Feeling more tired than usual (fatigue)</b>	13.2% (126)	8.3% (26)
<b>High blood pressure (hypertension)</b>	7.8% (74)	6.5% (36)
<b>Bone fractures</b>	5.5% (52)	3.6% (20)
<b>Falls</b>	5.2% (50)	4.9% (27)
<b>Rash</b>	3.1% (30)	1.1% (6)
<b>Mental fatigue, also known as brain fog (mental impairment)</b>	2.0% (19)	1.8% (10)

### What adverse events of interest did the participants have?

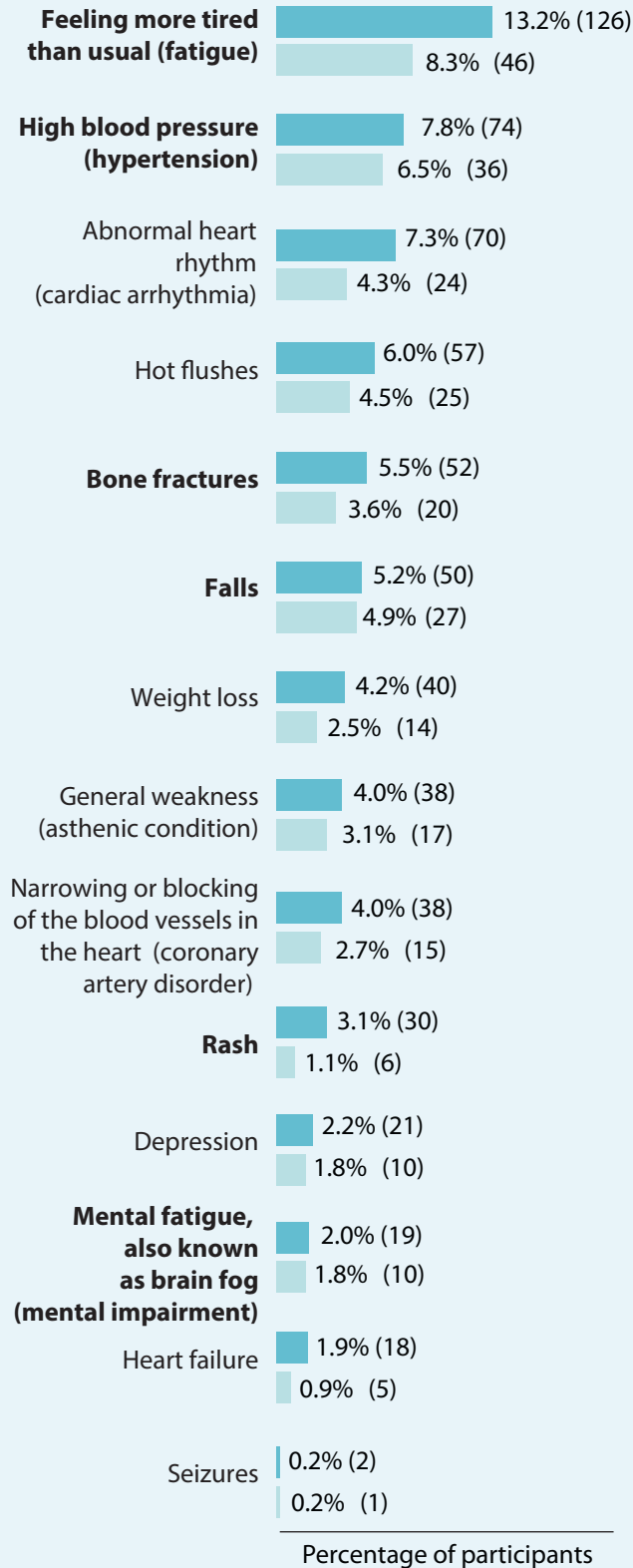
Previous research has shown that treatment with ADT can be associated with specific adverse events. The researchers wanted to learn if the participants in this trial also had similar adverse events when darolutamide was taken with ADT. These are called adverse events of interest.

The table below shows the adverse events of interest that happened during Part 1 of the trial. There are six adverse events of interest that affect participants' daily lives and are highlighted in bold.

The percentage of participants who experienced medical problems (adverse events) was similar between treatment groups. In these final results after a longer period of time, darolutamide plus ADT showed less than a 2% difference compared with placebo plus ADT for most adverse events that impact participants' daily lives including: high blood pressure, falls, bone fractures, brain fog and rash. Feeling more tired than usual (fatigue) was the only adverse event that happened in more than 10% of participants who received darolutamide plus ADT.



### Adverse events of interest that happened during Part 1



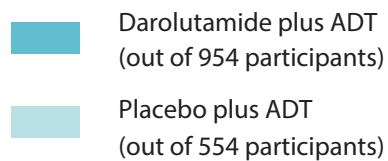
### What do the results of this trial mean?

The results from this trial showed that, compared with those who received placebo (sugar pill) plus ADT:

- Darolutamide plus ADT increased the length of time that the trial participants were still alive for and reduced the risk of death by 31%. This is known as overall survival.
- Participants who received darolutamide plus ADT also had longer time to worsening pain, needing chemotherapy, and having cancer-related bone fractures or symptoms related to bone fractures during the trial.
- The percentage of participants who experienced medical problems (referred to as adverse events) was similar between treatment groups. No new medical problems were seen in this trial that weren't seen in previous trials.

### Glossary

- ADT: Androgen-deprivation therapy
- ARAMIS: Androgen Receptor Antagonizing Agent for Metastasis-free Survival
- CT: Computed tomography
- FDA: US Food and Drug Administration
- MRI: Magnetic resonance imaging
- nmCRPC: Nonmetastatic, castration-resistant prostate cancer
- PSA: Prostate-specific antigen



## What does this trial mean for the patient community?

“ *New therapies to treat prostate cancer in men are being developed rapidly. Without men who are prepared to participate in clinical studies and new treatments, the progress in overall disease management is slowed.*

*Participation in a clinical study of a new drug with limited side effects and a positive outcome brings a great sense of relief and renewed hope for the future. There is a strong sense of belonging among patients facing a common health challenge. We are in this patient community together. Participation in a clinical trial for a new drug or treatment has the potential to greatly help an individual. More importantly, if this leads to positive outcomes for men with prostate cancer, then that is a contribution worth making. In my case, being eligible to enter the ARAMIS trial was entirely due to my treating oncologist being aware of suitable studies and putting my name forward. Recent developments in scanning technologies and more sensitive radionuclides have increased the detection of smaller metastases but participants of the ARAMIS trial were admitted using the current conventional scans. The introduction of more advanced scanning techniques is a welcome addition to prostate cancer diagnosis and treatment. After five years in the ARAMIS trial, I have been very pleased to see the positive outcomes of the trial which has given me hope for a continued good quality of life for the foreseeable future.*

”

– I Blue

“ *Clinical trials are life.*

*Very simply, for us patients, clinical trials are our life force.*

*The only way we, as patients, can know that treatments will get better, that we will be able to live longer despite our cancer, that we will be able to make sound treatment decisions based on science and facts, is by supporting and encouraging participation in clinical trials.*

*When my prostate cancer recurred fourteen years ago, the only available treatments were hormone therapy (ADT), chemotherapy, and two radiopharmaceutical drugs that didn't offer any life extension. Today, there are over seven new FDA-approved treatments, all of which hold the promise of being able to extend and improve my life.*

*This new and promising landscape of treatments became available to me through drug discovery, development, and clinical trials.*

*Our researchers, scientists, and clinicians work together with pharmaceutical companies to do the discovery and development work, but it is entirely up to us patients to take this work to the next step, to participate in clinical trials.*

*Clinical trials not only let us know if an investigational treatment will work, they also provide us with an opportunity to receive the most “cutting edge” treatments years before they might otherwise become available. In many instances, without clinical trials, we might not be alive to have ever received treatment!*

*Clinical trials have become so advanced. Today we evaluate if a new potential treatment extends our life. We are often asking if this new treatment will also improve the quality of our life. For me, improving the quality of my life is just as important as extending it.*

”

– J Nowak

### Who sponsored this study?

Bayer HealthCare and Orion Pharma sponsored this trial. Both sponsors, together with the first author and other researchers in the ARAMIS trial, developed the trial design.



**Where can readers find more information on this trial?**

The main results from Part 1 of the ARAMIS trial entitled 'Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer' were published in the *New England Journal of Medicine* in 2019. You can read the original article at: [www.nejm.org/doi/full/10.1056/NEJMoa1815671](http://www.nejm.org/doi/full/10.1056/NEJMoa1815671)

The original article discussed in this summary entitled 'Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide' was published in the *New England Journal of Medicine* in 2020. You can read the original article at: [www.nejm.org/doi/full/10.1056/NEJMoa2001342](http://www.nejm.org/doi/full/10.1056/NEJMoa2001342)

The full name of the ARAMIS trial is: A multinational, randomised, double-blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer.

You can read more about the ARAMIS trial on the following websites:

- Enter the study number **NCT02200614** into the search field at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- Enter the EudraCT identifier **2013-003820-36** into the search field at [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)

If you were a trial participant and have questions about the results of this trial and darolutamide (brand name Nubeqa®), please speak with the doctor or staff at your trial site.

**Educational resources**

Read more about prostate cancer on the Cancer.Net website at:

[www.cancer.net/cancer-types/prostate-cancer/introduction](http://www.cancer.net/cancer-types/prostate-cancer/introduction)

Read more about advanced prostate cancer in the 2020 NCCN guidance for patients at:

[www.nccn.org/patients/guidelines/content/PDF/prostate-advanced-patient.pdf](http://www.nccn.org/patients/guidelines/content/PDF/prostate-advanced-patient.pdf)

Most countries throughout the world have dedicated national prostate cancer agencies and foundations. These websites provide explanations, treatment options, educational resources and support for people interested in maintaining prostate health and assistance following a prostate cancer diagnosis. Ask your health provider or community support group to direct you to these.

**Financial & competing interests disclosure**

K Fizazi is the primary trial investigator for ARAMIS and reports receiving consulting fees, honoraria, and travel support from Janssen, consulting fees and honoraria from Bayer, Astellas Pharma, and Sanofi, consulting fees from Orion Pharma, consulting fees, paid to his institution, from CureVac, AstraZeneca, ESSA Pharma, and Roche, and consulting fees, paid to his institution, and travel support from Amgen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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