Plain Language Summary of Publication

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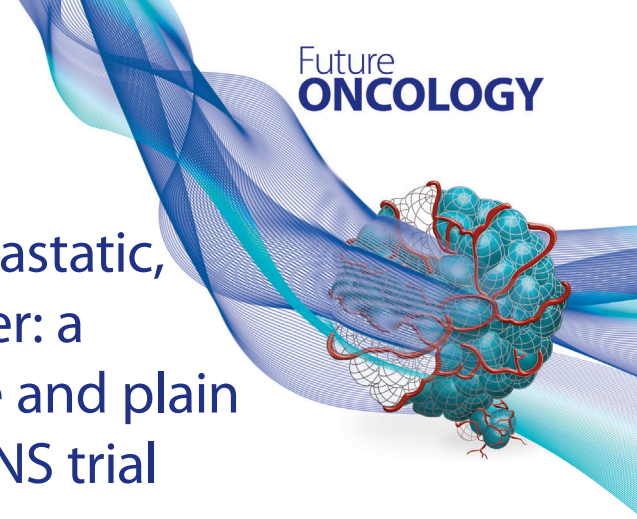

Darolutamide and survival in metastatic, hormone-sensitive prostate cancer: a patient and caregiver perspective and plain language summary of the ARASENS trial

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First draft submitted: 27 April 2022; Accepted for publication: 17 May 2022; Published online: 3 June 2022

Summary

What is this summary about?

This is a summary of a publication about the ARASENS trial, which was published in the *New England Journal of Medicine* in February 2022. The trial includes 1,306 men with a type of prostate cancer called metastatic, hormone-sensitive prostate cancer (also called mHSPC). In the trial, researchers wanted to learn if combining a treatment called **darolutamide** (also known by the brand name Nubeqa®) with two other medicines called androgen deprivation therapy (also called **ADT**) and **docetaxel** (brand name Taxotere®) could help treat patients with mHSPC better than **placebo** plus **ADT** and **docetaxel**. **ADT** with **docetaxel** is a treatment used for patients with mHSPC. **Darolutamide** is an approved treatment for a different type of prostate cancer called non-metastatic, castration-resistant prostate cancer (also called nmCRPC).

How to say (double-click on the icon to play sound)…
- **Darolutamide:** Dah-ruh-LOO-tuh-mide
- **Docetaxel:** Doe-suh-TAK-sul

What were the results?

The trial results showed that combining **darolutamide** with **ADT** and **docetaxel** increased the chance of survival and lowered the risk of death by 32.5% compared to combining **ADT** and **docetaxel** with **placebo** instead. Compared to patients who received the **placebo**, patients who received **darolutamide** had a delay in:
- their cancer becoming castration-resistant
- worsening pain
- having cancer-related bone fractures or related symptoms
- needing additional therapies for cancer

The percentage of trial patients who had medical problems during the trial, also called adverse events, was similar between trial patients who received **darolutamide** and those who received the **placebo**.

What do the results of the trial mean?

Combining **darolutamide** with **ADT** and **docetaxel** helped treat trial patients with mHSPC better than **placebo** with **ADT** and **docetaxel**. **Darolutamide** in combination with **ADT** and **docetaxel** could be a treatment option for patients with mHSPC. Patients should always talk to their doctors and nurses before making any decisions about their treatment. This summary also includes perspectives on the ARASENS trial and prostate cancer from 3 members of the patient community.

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Who is this summary for?

This summary is co-authored by members of the patient community and includes their perspectives to help patients and caregivers understand the results of the trial. It may also be helpful for patient advocates, the general public, and healthcare professionals, including those who are looking at treatment options for mHSPC.

What was the purpose of the ARASENS trial?

The purpose of the ARASENS trial was to learn if combining **darolutamide** with **ADT** and **docetaxel** could help treat patients with mHSPC better than **placebo** with **ADT** with **docetaxel**.

What is mHSPC and what are some possible treatments?

m – Metastatic
The cancer has spread to other parts of the body.

HS – Hormone-sensitive
Sometimes also called 'castration-sensitive'. The cancer can be treated with hormone therapy such as **ADT**.

PC – Prostate cancer
The cancer started in the prostate gland. 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 spread to other parts of the body.

ADT is sometimes also called "hormone therapy". **ADT** is a hormone therapy given as an injection under the skin, also called a subcutaneous injection. **ADT** is also now currently available to be taken as a pill by mouth. **ADT** lowers levels of testosterone, which is a type of androgen hormone. Androgen hormones are a group of sex hormones that typically give men their "male" characteristics like facial hair. Lowering testosterone levels can reduce or slow the growth of cancer cells.
ADT with **docetaxel** is one of the current standards of care in mHSPC.

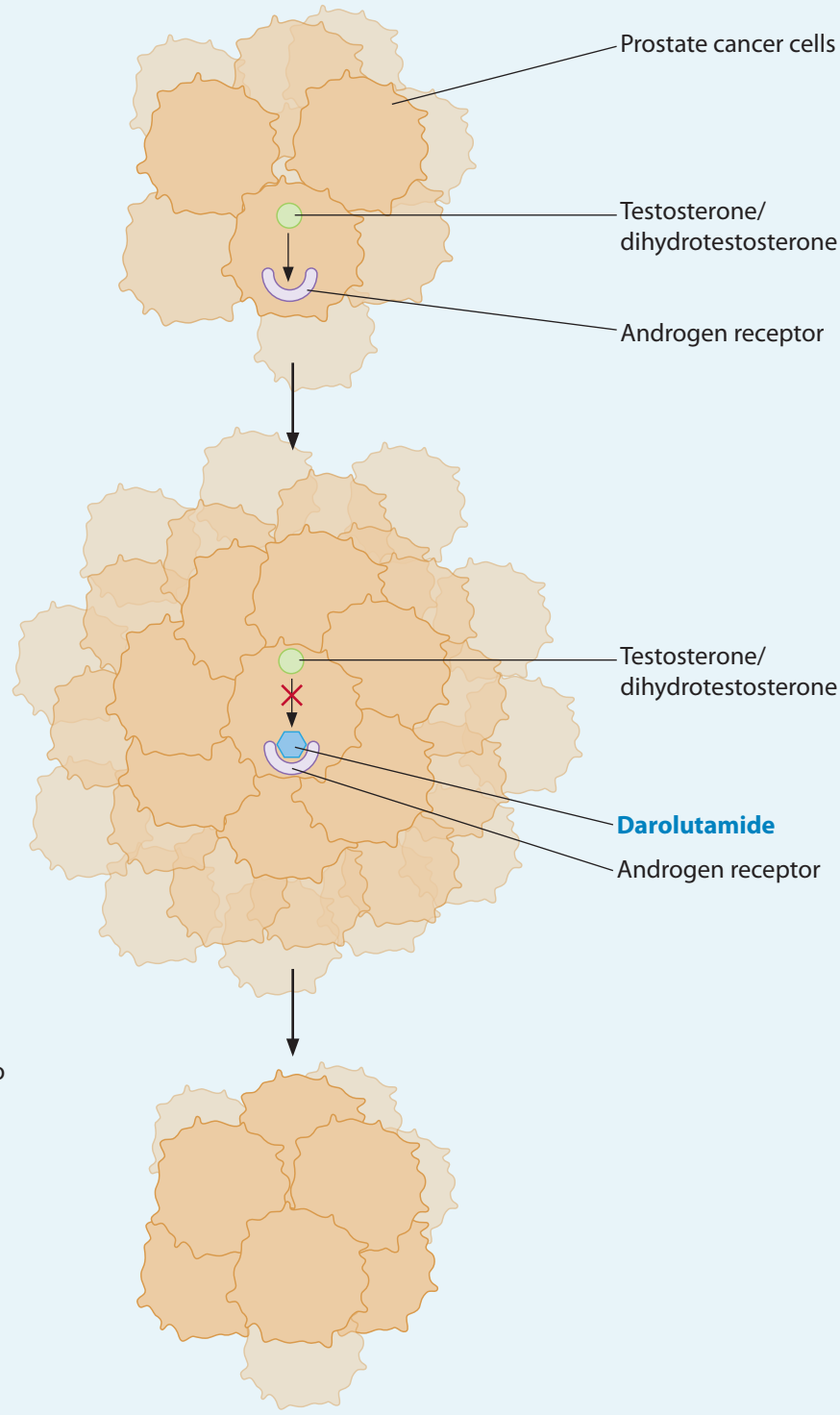
Docetaxel (brand name Taxotere®) is a type of chemotherapy used to treat many different types of cancer. It is given directly into a vein, also called an intravenous infusion or IV drip.
In the ARASENS trial, the researchers wanted to learn if adding a treatment called darolutamide could help treat patients with mHSPC better than ADT and docetaxel only.

Darolutamide (brand name Nubeqa®) is an available treatment taken as a pill by mouth. Results from another trial called the ARAMIS trial showed that **darolutamide** can help treat a different type of prostate cancer called non-metastatic, castration-resistant prostate cancer (nmCRPC). Results from the ARAMIS trial can be read here: https://www.nejm.org/doi/full/10.1056/NEJMoa2001342
and a summary of these results can be read here: https://www.futuremedicine.com/doi/10.2217/fon-2020-1291

How is darolutamide designed to work?

Darolutamide is designed to work by blocking signals from androgen hormones that can cause cancer cells to grow.

Prostate cancer cells have androgen receptors that respond to androgen hormones like testosterone. 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 cells to grow.



Darolutamide was designed to work by **blocking** signals from androgen hormones that can cause cancer cells to grow.

About the ARASENS trial

started in November 2016 and is still ongoing as of April 2022.

includes 1,306 patients with mHSPC.

Placebo-controlled
A placebo looks like a trial treatment but does not have any medicine in it. Researchers use a **placebo** to make sure the effects of the trial treatment are actually caused by the trial treatment. In this trial, in addition to **ADT** and **docetaxel**, about half of trial patients received a placebo and the other half received **darolutamide**.

Double-blinded
None of the trial patients, researchers, or doctors knew what treatment each patient received. This means they were "blind" to this information.

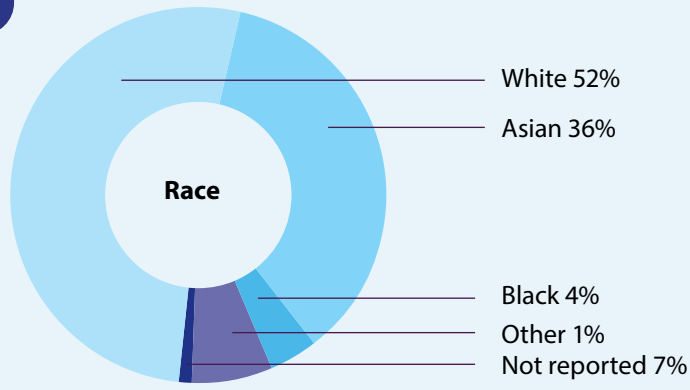
Randomized
Random chance was used by a computer to place trial patients into different equally sized groups. This is similar to flipping a coin.

About the patients in the ARASENS trial

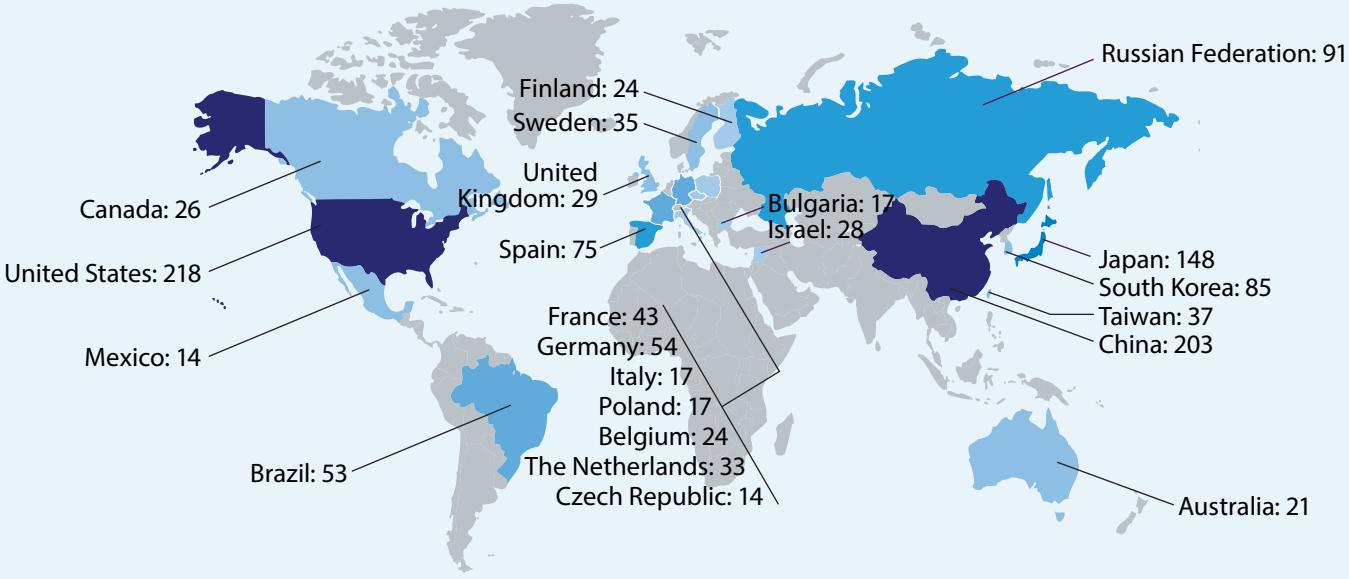
41–89 years
age range

67 years
median age

The median is the middle number in a list of numbers organized from lowest to highest.



Number of patients from 23 countries



In order to be included in the ARASENS trial...

all the patients have:

- confirmed metastatic prostate cancer.
- prostate cancer that could be treated with ADT and docetaxel.
- a score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) test.
  The ECOG test measures how much cancer is affecting a patient's ability to complete daily activities. Scores range from 0 to 5, with higher scores meaning higher disability.
- healthy enough bone marrow, liver and kidneys.

all the patients do not have:

- prior treatment with certain hormone therapies, immunotherapies, or chemotherapies.
- prior treatment with radiation therapies within 2 weeks of starting the trial.
- previous metastatic cancer of a different type, unless it was treated and controlled well enough.
- any disorder of the stomach or gut that would affect the way the trial treatment is absorbed by the body.

What happened in the ARASENS trial?

1,306
patients were split into 2 groups

651
patients were put into the **darolutamide** group and received these treatments:

Docetaxel
6 cycles of 75 mg per 1 square meter of body-surface area on day 1 and every 21 days

ADT
As prescribed, throughout the entire trial

Darolutamide
600 mg taken twice a day, throughout the entire trial

655
patients were put into the **placebo** group and received these treatments:

Docetaxel
6 cycles of 75 mg per 1 square meter of body-surface area on day 1 and every 21 days

ADT
As prescribed, throughout the entire trial

Placebo
Taken twice a day, throughout the entire trial

The patients received **darolutamide** or the **placebo**, in addition to **ADT** and **docetaxel,** until any of the following happened:

- Their cancer got worse
- They had a change in chemotherapy
- They had treatment effects that were too toxic
- They or their doctor decided to stop treatment for a different reason

What were the results?

The purpose of the ARASENS trial was to learn if combining **darolutamide** with **ADT** and **docetaxel** could help treat patients with mHSPC better than **placebo** with **ADT** and **docetaxel**.

The researchers wanted to learn the answers to several questions to determine if combining **darolutamide** was working better than the **placebo**. To answer these questions, the researchers collected data from the trial patients until October 2021.

They compared the results of the patients who received **darolutamide** to the patients who received the **placebo**. The results below were similar in all race groups.

Below are the answers to these questions.

Compared to the **placebo**, did adding **darolutamide** to **ADT** and **docetaxel** help…

		Risk reduction	After 4 years of receiving trial treatment
trial patients live longer?	Yes	Overall, treatment with **darolutamide** increased the chance of survival and reduced the risk of dying by **32.5%** compared to the **placebo**.	 **62.7%** of patients in the **darolutamide group** were still alive  **50.4%** of patients in the **placebo group** were still alive

			As of October 2021
delay castration-resistant cancer? When prostate cancer becomes castration-resistant, it means it is no longer responding to treatment with ADT and the growth of cancer cells may increase.	Yes	Overall, treatment with **darolutamide** increased the length of time patients continued to respond to ADT and didn't require treatment change. It also reduced the risk of cancer becoming castration-resistant by **64%** compared to the **placebo**.	 **35%** of patients in the **darolutamide group** had castration-resistant cancer  **60%** of patients in the **placebo group** had castration-resistant cancer

delay worsening pain? Severity of pain was measured using a survey called the Brief Pain Inventory (Short Form) that was completed by trial patients.	Yes	Overall, treatment with **darolutamide** increased the length of time patients remained alive without worsening of pain and reduced the risk of pain becoming worse by **21%** compared to the **placebo**.	 **34%** of patients in the **darolutamide group** had worsening pain  **38%** of patients in the **placebo group** had worsening pain

delay cancer-related bone fractures or symptoms related to bone fractures?

Yes

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

Overall, treatment with **darolutamide** increased the length of time it took for patients to have cancer-related bone fractures and related symptoms. It also reduced the risk of fractures and related symptoms by **29%** compared to the **placebo**.

15% of patients in the **darolutamide group** had cancer-related bone fractures or symptoms related to bone fractures

17% of patients in the **placebo group** had cancer-related bone fractures or symptoms related to bone fractures

delay the need for additional therapies for cancer?

Yes

Overall, treatment with **darolutamide** increased the length of time it took for patients to need additional therapies for cancer and reduced the risk of needing additional therapies for cancer by **61%** compared to the **placebo**.

34% of patients in the **darolutamide group** needed additional therapies for cancer

60% of patients in the **placebo group** needed additional therapies for cancer

delay worsening of cancer-related physical symptoms?

No

Severity of cancer-related symptoms was measured using a survey called the Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17 Item Version questionnaire that was completed by trial patients.

Overall, treatment with **darolutamide** did not increase the length of time it took for the patients' cancer-related physical symptoms to become worse and did not reduce the risk of worsening cancer-related physical symptoms compared to the **placebo**.

54% of patients in the **darolutamide group** had worsening cancer-related physical symptoms

47% of patients in the **placebo group** had worsening cancer-related physical symptoms

delay opioid use for 7 or more days in a row?

Opioid medication is used to control pain.

Not sure

The researchers could not answer this question because of the way they designed the trial. They designed the trial so that each question they wanted to answer was ranked by importance. If the researchers concluded that the answer to a question is "No" based on the trial results, then they did not analyze the results of the remaining ranked questions. Designing the trial this way helps make sure the results are as accurate as possible. This question was ranked the lowest, and the answer to the question ranked above it was "No." So, the researchers did not analyze the results for this question.

14% of patients in the **darolutamide group** had used opioids for 7 or more days in a row

18% of patients in the **placebo group** had used opioids for 7 or more days in a row

How many trial patients had adverse events?

In this summary, any medical problem that happened during the trial is referred to as an "adverse event". Adverse events are considered serious when they lead to death, put the patient's life at risk, require hospitalization, cause disability, or are medically important.

Adverse events **may or may not be related** to the trial treatments. This is why adverse events are not the same as "side effects". Side effects are known to be related to a treatment. It takes a lot of research to know for sure if an adverse event is related to a treatment.

Overall, the percentage of patients who had adverse events was similar between the **darolutamide group** and the **placebo group**. The combination of **darolutamide** with **ADT** and **docetaxel** did not result in more toxic effects than the combination of **placebo** with **ADT** and **docetaxel**. Many of the most common adverse events happened more often earlier on in the trial when patients were receiving **docetaxel**.

Percentage of trial patients who…	Darolutamide group	Placebo group
had an adverse event	99.5%	98.9%
had a serious adverse event	44.8%	42.3%
stopped receiving **darolutamide** or the **placebo** because of an adverse event	13.5%	10.6%
stopped receiving **docetaxel** because of an adverse event	8.0%	10.3%

What grade 3 or 4 adverse events did more than 2.0% of trial patients have?

Adverse events are categorized into 5 different groups based on severity:

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
adverse events are mild and will probably not impact daily activities	adverse events are not considered dangerous but may impact some daily activities	adverse events may impact more basic daily activities like eating or getting dressed and require medical attention	adverse events probably require hospitalization	adverse events cause death

The table below shows the grade **3** or **4** adverse events that happened in **more than 2.0%** of patients during the trial.

Adverse event	Darolutamide group	Placebo group
Low levels of neutrophils, a type of white blood cell that helps the body fight infections (neutropenia)	33.7%	34.2%
A fever and low levels of neutrophils (febrile neutropenia)	7.8%	7.4%
High blood pressure (hypertension)	6.4%	3.2%
Not having enough healthy red blood cells (anemia)	4.8%	5.1%
An infection in the lungs called pneumonia	3.2%	3.1%
Diabetes and high blood sugar levels (hyperglycemia)	2.8%	3.7%
Increased levels of alanine aminotransferase (ALT), a sign of liver inflammation	2.8%	1.7%
Increased levels of aspartate aminotransferase (AST), a sign of liver damage	2.6%	1.1%
Weight gain	2.1%	1.2%
Urinary tract infection	2.0%	1.8%

What adverse events of interest did the trial patients have?

Previous research has shown that treatment with **ADT** can be associated with specific adverse events. The researchers wanted to learn if the patients 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 the trial.

Adverse event of interest	Darolutamide group	Placebo group
Feeling more tired than usual (fatigue)	33.1%	32.9%
Hot flushes	20.4%	21.7%
Rash	16.6%	13.5%
Diabetes and high blood sugar levels (hyperglycemia)	15.2%	14.3%
High blood pressure (hypertension)	13.7%	9.2%
Heart disorders (cardiac arrhythmia, coronary artery disorder, or heart failure)	10.9%	11.7%
Bone fracture	7.5%	5.1%
Falls	6.6%	4.6%
Mental fatigue, also called brain fog (mental impairment disorder)	3.5%	2.3%
Weight loss	3.4%	5.4%
Depression	3.2%	3.7%
Swollen breast tissue (gynecomastia)	3.2%	1.5%
Brain does not get enough blood (cerebral ischemia)	1.2%	1.2%
Seizure	0.6%	0.2%

What do the results mean?

In this trial, combining **darolutamide** with **ADT** and **docetaxel** helped treat trial patients with mHSPC better than **placebo** with **ADT** and **docetaxel**.

Trial patients in the **darolutamide group** lived longer than those in the **placebo group**. **Darolutamide** helped trial patients live longer than those who received the **placebo**, even though trial patients who received the **placebo** often had life-prolonging treatments later on once their cancer got worse.

Trial patients in the **darolutamide group** had a delay in their cancer becoming castration-resistant, worsening pain, having cancer-related bone fractures or related symptoms, and needing additional therapies for cancer compared to those in the **placebo group**.

The percentage of trial patients who had adverse events was similar between the darolutamide group and the **placebo group**. The combination of **darolutamide** with **ADT** and **docetaxel** did not result in more toxic effects than the combination of **placebo** with **ADT** and **docetaxel**.

Darolutamide in combination with **ADT** and **docetaxel** could be a treatment option for patients with mHSPC. Patients should always talk to their doctors and nurses before making any decisions about their treatment.

What does the ARASENS trial mean for the patient community?

"Prostate cancer (PC) patients need treatment options, especially patients who are metastatic (prostate cancer outside the prostate). The ARASENS study offers yet one more potential option for patients who are metastatic, yet still 'hormone sensitive' (responsive to ADT/hormone treatments).

As an advocate for 20 years, I'd like to take this time to encourage patients to stay involved in their care, especially if they are metastatic. Shared Decision Making is a valid term in medicine, and it means you share the decisions with your doctors and nurses – and they share the decisions with you. I speak from personal experience, with my husband's diagnosis of metastatic PC in the year 2000, and a PSA of 7,096. He lived for 13 years, greatly because of our involvement in his treatment decisions. I wrote an article about this in 2013, titled "Understanding Survival Statistics".

Remember that every man's prostate cancer is different, but Antonov, *et al.*, published a case study in 2019 titled "Unexpected Long-Term Survival in an Adult Patient with Metastatic Prostate Cancer". I would encourage everyone to read this article as it illustrates a case study of long-term survival in a metastatic PC patient, age 87 at last report.

Remember that new treatment options are still on the horizon, because many clinical studies are still underway as we speak. New treatment options are something we cannot measure today, so we cannot factor them into any current data, including survival. The ARASENS study offers one more treatment option, and patients, caregivers, and advocates will continue to watch for more options over time.

Stay involved in your care. Look up the phrase "Shared Decision Making" and see what inspires you. Even the best data will never measure everything, including the power you may have in your own cancer journey."

– J Manarite, Prostate cancer patient caregiver

"The results of the ARASENS study bring a number of significant benefits to patients with metastatic, hormone-sensitive prostate cancer when compared to the existing standard treatments. Patients at this stage of their prostate cancer journey are most interested in treatments that will extend their lives with minimal impact on their quality of life.

Darolutamide, as demonstrated by the ARASENS study, provides a 32.5% decrease in the risk of dying and increases the length of time for the cancer to become castration-resistant by 64%. These are real benefits that all patients can celebrate. While the decrease in the risk of dying is most appealing, delaying castration-resistant disease prolongs the time when patients will have to transition to harsher treatments and the associated reductions in their quality of life. We as patients would like to see prostate cancer become a chronic disease as opposed to one that we die from, and these two factors from the successful ARASENS study provides another step towards achieving this goal.

Today, the incidence of patients being initially diagnosed with metastatic disease has increased rapidly, making the ARASENS study very timely for all prostate cancer patients. African American men who are most impacted by prostate cancer, with higher incidence and death rates and historically with more advanced disease, could potentially benefit significantly from darolutamide treatment for metastatic, hormone-sensitive prostate cancer."

– T Farrington, Prostate cancer patient

"I was diagnosed in March of 2017 with a Gleason score of 4+3 and was blindsided with the news. Did not know who to turn to for guidance and I was scared. I was overwhelmed trying to get educated on the internet. I was fortunate enough to find www.ANCAN.org who helped me and other men in the same position navigate our disease and teach us how to be our own best advocates. Once I calmed down, I was able to understand the research and how much progress has been made with respect to cutting edge treatments. The more information (especially written in layman's terms) I have the more confident I feel I can live a normal life without fear."

– D Muslin, Prostate cancer patient

Who sponsored the ARASENS trial?

The ARASENS trial was funded Bayer and Orion Pharma.

Where can readers find more information on this trial?

The original publication discussed in this summary called: "Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer" was published in the *New England Journal of Medicine* in February 2022. You can read the original article at: https://www.nejm.org/doi/full/10.1056/NEJMoa2119115

The full name of the ARASENS trial is: A Randomized, Double-blind, Placebo Controlled Phase III Study of Darolutamide (ODM-201) Versus Placebo in Addition to Standard Androgen Deprivation Therapy and Docetaxel in Patients with Metastatic Hormone Sensitive Prostate Cancer.

You can read more about the ARASENS trial on the following websites:
- Enter the trial number **NCT02799602** into the "Other terms" search field at www.clinicaltrials.gov.
- Enter the EudraCT identifier **2015-002590-38** into the search field at www.clinicaltrialsregister.eu. Click "Home & Search" to find the search option.

If you were a trial patient and have questions about the results of this trial and darolutamide, please speak with the doctor or staff at your trial site.

Educational resources

- Read more about prostate cancer on the Prostate Cancer Foundation website at: https://www.pcf.org/guide/prostate-cancer-patient-guide/
- Most countries throughout the world have dedicated national prostate cancer agencies and foundations. These organizations provide explanations, treatment options, educational resources, and support for people interested in maintaining prostate health and assistance following a prostate cancer diagnosis. Ask your doctors and nurses or community support group to direct you to these organizations.

Acknowledgments

The authors would like to thank the patients in the ARASENS trial and their family members and caregivers. They would also like to thank the trial staff who cared for and supported the patients in the trial. Without all of these people working together, clinical studies could not move forward.

Medical writing and editorial assistance in the development of this summary were provided by Kimbra Edwards, PhD and Scott Finger of the Center for Information & Study on Clinical Research Participation (CISCRP), a non-profit organization focused on educating and informing the public about clinical research participation. Medical writing and editorial assistance was supported by Bayer.

Financial & competing interests disclosure

MR Smith reports receiving consulting fees from Amgen, Astellas Pharma, Bayer, Eli Lilly and Company, Janssen Biotech, and Pfizer. M Hussain reports receiving consulting fees from Bayer, Daiichi Sankyo Company, Janssen Global Services, LLC, and Novartis, as well as honorarium from AstraZeneca and travel support from Bayer. F Saad reports receiving honoraria from Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen Global Services, LLC, Merck, Myovant sciences, Pfizer, and Sanofi Pasteur Inc. K Fizazi reports receiving consulting fees paid to his institution from Amgen, Astellas Pharma, AstraZeneca, Bayer, Clovis Oncology, Inc., Janssen Biotech, MSD, Novartis, Pfizer, and Sanofi-Aventis U.S. LLC, as well as consulting fees from Orion Corporation and CureVac. CN Sternberg reports receiving consulting fees from Astellas Pharma, AstraZeneca, Bayer HealthCare Pharmaceuticals Inc., Bristol Myers Squibb Company, Genentech, Incyte Corporation, Medscape Oncology, Merck, Merck Sharp & Dohme Corporation, Pfizer, Sanofi, and Genzyme US Companies, and Uro Today. ED Crawford reports receiving consulting fees from Astellas Pharma, Carden Jennings, Janssen Biotech Inc., MDx, and TOLMAR Pharmaceuticals, Inc., as well as for data and safety monitoring for Bayer HealthCare Pharmaceuticals Inc., and has optical biopsy intellectual property. B Tombal reports receiving consulting fees from Bayer HealthCare Pharmaceuticals Inc. 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.