Protocol Plain Language Summary

A clinical study of pembrolizumab to treat hormone-sensitive metastatic prostate cancer (MK-3475-991)

Protocol title: A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (KEYNOTE-991)

Why is this study needed?

Researchers are looking for new ways to treat metastatic hormone-sensitive prostate cancer (mHSPC). mHSPC is prostate cancer that has spread to other parts of the body and can be treated by lowering testosterone (a hormone). **Androgen deprivation therapy (ADT)** and **enzalutamide** are hormone blocking treatments. They block the body from making hormones as a way of preventing the cancer from growing.

Researchers want to know if **pembrolizumab** can be used with **ADT** and **enzalutamide** to help treat mHSPC. **Pembrolizumab** is an immunotherapy, which is a treatment that helps the immune system fight cancer.

The goal of this study is to learn if people who receive pembrolizumab with enzalutamide and ADT live longer overall and without the cancer growing or spreading compared to people who receive placebo with enzalutamide and ADT.

Who will take part in this study?

About 1,232 people with mHSPC will be in this study. They will be male (assigned male at birth) and:

- Are 18 years or older
- Be willing to continue ADT
- Did not have another type of cancer in the past 3 years

What treatments are being given during the study?

All people in this study will receive enzalutamide and ADT. People take enzalutamide by mouth once a day until their cancer gets worse or the end of the study. People will receive ADT until their cancer gets worse or the end of the study.

People will also receive one of these treatments through a needle in a vein as an intravenous (IV) infusion once every 3 weeks for up to about 2 years:

- Pembrolizumab, the study medicine
- Placebo. A placebo looks like the study medicine but does not have any medicine in it. Using a placebo helps researchers better understand the real effects of the study medicine.

After a planned review of results, the researcher has decided not to continue the study except for people who may be receiving benefit from the study treatment. All people have stopped receiving pembrolizumab and placebo. People may have the option to stay on enzalutamide and ADT or their doctor may offer other medications.

How is this study designed?

People will have an equal chance of being assigned to one of these treatment groups:

- Pembrolizumab with enzalutamide and ADT

- Placebo with enzalutamide and ADT

Neither the people in the study nor the researchers will know which treatment a person receives (**double-blind** study).

People may have urine, blood, tumor, and imaging tests during the study. They will also have physical examinations and answer questions.

People may be in this study for up to 5 years.

What are the goals of this study and how will they be measured?

Main goal	How it will be measured
To learn if people who receive pembrolizumab with enzalutamide and ADT live longer overall and without cancer getting worse compared to people who receive placebo with enzalutamide and ADT	Researchers will measure: • **Radiographic progression-free survival (rPFS)**: the length of time from the start of the study until cancer grows or spreads (based on imaging tests), or death from any cause • **Overall survival (OS)**: the length of time that people live from the start of the study until death from any cause
Other goals	**How they will be measured**
To learn about the **time to the next treatment or death (TFST)** in people who receive pembrolizumab with enzalutamide and ADT compared to people who receive placebo with enzalutamide and ADT	**TFST** is the length of time from the start of the study until the start of a new cancer treatment or death
To learn about the **pain and bone health** of people who receive pembrolizumab with enzalutamide and ADT compared to people who receive placebo with enzalutamide and ADT	Researchers will measure the length of time from the start of the study until: • A person's pain worsens called **time to pain progression (TTPP)** • Bone-related events occur called **symptomatic skeletal-related event (SSRE)** such as certain treatments, surgeries, or broken bones
To learn about the **levels of prostate specific antigen (PSA)** in people who receive pembrolizumab with enzalutamide and ADT compared to people who receive placebo with enzalutamide and ADT. **PSA** is a protein in the blood. It may be higher in people with prostate cancer.	Researchers will measure these responses during the study: • **PSA response**: the number of people who have their PSA level go down by at least half when it is measured 2 times at least 3-weeks apart • **PSA undetectable**: the number of people whose PSA is too low to be measured • **PSA progression**: the length of time from the start of the study until the PSA goes up by a certain level
To learn how the **cancer responds** (gets smaller or goes away) in people who receive pembrolizumab with enzalutamide and ADT compared to people who receive placebo with enzalutamide and ADT	During the study, researchers will measure: • **Objective response rate (ORR)**: the number of people whose cancer responds to treatment • **Duration of response (DOR)**: the length of time from when the cancer first responds to treatment until the cancer grows, spreads, or death from any cause

	• **Radiographic soft-tissue progression**: the length of time from the start of the study until the cancer spreads to soft tissue (muscle, fat, blood vessels, or other tissue) • **Progression-free survival (PFS) 2**: the length of time from the start of the study until cancer grows or spreads, or death from any cause. This will be measured after a person has started a new treatment for cancer because the first treatment has stopped working.
To learn about the safety of pembrolizumab or placebo with enzalutamide and ADT and how well people tolerate the treatments	The number of people who: • Have an **adverse event (AE).** An AE is a health problem that happens or worsens during a study • Stop treatment due to an AE

What are the possible benefits and risks?

People may or may not benefit from the treatment received during the study. This study has an external group of experts that oversees the overall risk and benefit. If this group of experts decides that the study treatment is not safe or does not show benefit, the study can be stopped. More information about the benefits and risks is in the Investigator Brochure, Protocol, and Informed Consent documents.