A clinical study of pembrolizumab to treat breast cancer (MK-3475-756)

Protocol Title: A Randomized, Double-Blind, Phase III Study of Pembrolizumab versus Placebo in Combination with Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy for the Treatment of High-Risk Early-Stage Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2–) Breast Cancer (KEYNOTE-756)

Why is this study needed?

Researchers are looking for new ways to treat people with **high-risk early-stage breast cancer** that is **estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-)**:

- **High-risk** means the cancer may have a high chance of getting worse or coming back after treatment
- **Early-stage** means the cancer is in the breast and/or lymph nodes around the breast
- **ER positive** means the cancer cells have proteins that attach to estrogen (a hormone) which help the cancer to grow and spread
- **HER2 negative** means the cancer cells have zero or only a low amount of a protein called HER2

The **standard treatment** for ER+/HER2- breast cancer is chemotherapy before surgery (**neoadjuvant treatment**) and then hormone therapy after surgery (**adjuvant treatment**). **Chemotherapy** is medicine that destroys cancer cells or stops them from growing. **Hormone therapy** can block or lower the levels of certain hormones to slow the growth and spread of cancer cells.

Pembrolizumab (the study medicine) 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 and chemotherapy before surgery have fewer cancer cells in the breast tissue and/or lymph nodes removed with surgery compared to those who receive placebo and chemotherapy. A **placebo** looks like the study medicine but has no study medicine in it. Using a placebo helps researchers better understand the effects of a study medicine.

Another goal of this study is to learn if people who receive pembrolizumab and standard treatment live longer:

- without the cancer growing, spreading, or coming back
- without developing a new type of cancer

Who will take part in this study?

About 1,240 people with high-risk early-stage ER+/HER2- breast cancer will be in this study. They will be at least 18 years old and:

- Have breast cancer that has not spread to body parts outside the breast or lymph nodes near the breast
- Have not received treatment for breast cancer

What treatments are being given during the study?

Everyone in the study will receive the **standard treatment** of chemotherapy before surgery and hormone therapy after surgery. People will also receive one of these treatments:

- **Pembrolizumab**, the study medicine, given once every 3 weeks before and after surgery
- **Placebo**, given once every 3 weeks before and after surgery

People will receive chemotherapy once a week then once every 2 or 3 weeks. People will take the researchers choice of hormone therapy daily by mouth as a tablet. All other treatments will be given through a needle into a vein as an (IV) infusion.

People may also receive radiation therapy after surgery, based on local guidelines. **Radiation therapy** is a treatment that uses beams of intense energy (similar to X-rays) to shrink or get rid of tumors.

A type of hormone therapy may also be given as a monthly injection to people who have not yet reached menopause. **Menopause** is a natural stage in life where the body makes less hormones.

How is this study designed?

This study has 2 parts. People will have an equal chance to be assigned to 1 of 2 groups:

Group	Part 1: Before surgery	Part 2: After surgery
A	Pembrolizumab and chemotherapy for 6 months	Pembrolizumab for about 6 months and hormone therapy for up to 10 years
B	Placebo and chemotherapy for 6 months	Placebo for about 6 months and hormone therapy for up to 10 years

During the study, people will give urine, blood, and tumor samples, have tumor and imaging tests, and answer questions about how they are feeling and their ability to carry out daily tasks. Neither the people in the study nor the researchers will know which treatment a person is taking (double-blind study).

Researchers will follow up with people until they are no longer alive, they no longer want to be in the study, or the study ends. A person may be in this study for about 12 years.

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

Main goals	How they will be measured
To compare the **pathological complete response (pCR)** of people who receive pembrolizumab and chemotherapy to those who receive placebo and chemotherapy	The number of people who have pCR**. pCR** means that there are no signs of cancer in the breast tissue and/or lymph nodes removed during surgery.
To compare the **event-free survival (EFS)** of people who receive pembrolizumab and standard treatment to those who receive placebo and standard treatment	**EFS** is the length of time people live from the start of treatment until: • The cancer grows or spreads and cannot be removed with surgery • The cancer comes back after surgery • A new, different type of cancer develops • Death from any cause
Other goals	**How they will be measured**
To compare the **overall survival (OS)** of people who receive pembrolizumab and standard treatment to those who receive placebo and standard treatment	**OS** is the length of time that people live from the start of treatment until death from any cause.

To compare the **pCR**, **EFS** and **OS** of people whose tumors have a certain protein on the cancer cells	During the study, the **pCR**, **EFS** and **OS** will be measured in people whose tumors have PD-L1. **PD-L1** is a type of protein found on cancer cells that can help the cancer hide from the body's immune system.
To compare the **pCR** of people who receive pembrolizumab and chemotherapy to those who receive placebo and chemotherapy	**pCR** will be measured differently than in the main goal.
To learn about the **safety** and how well people **tolerate** pembrolizumab and standard treatment	During the study, researchers will measure: • The number of people who have an **adverse event (AE)** – An AE is a health problem that happens or worsens • The types of AE's people have • How severe the AE's are • The number of people who stop treatment due to an AE
To learn about people's **health-related quality of life (HRQoL)**	People will answer questions to measure their **HRQoL.** The questions are about their overall health and their ability to carry out daily tasks. Researchers will measure: • The change in the scores during the study • The length of time from the start of treatment until HRQoL gets worse

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 will oversee 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.