Protocol Plain Language Summary

Clinical study of pembrolizumab in people with muscle invasive bladder cancer (MK-3475-905)

Protocol title: A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Participants who are Cisplatin-Ineligible or Decline Cisplatin with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)

Why is this study needed?

Researchers are looking for new ways to treat a type of bladder cancer called muscle-invasive bladder cancer (MIBC). **MIBC** is cancer in the bladder muscles that has not spread outside of the bladder. **Standard treatment** for MIBC is having surgery to remove the bladder.

Researchers want to know if adding **pembrolizumab** with or without **enfortumab vedotin** to standard treatment can help treat MIBC. Pembrolizumab is an **immunotherapy**, which is a treatment that helps the immune system fight cancer**.** Enfortumab vedotin is a **targeted therapy**, which is a treatment that works to control how specific types of cancer cells grow and spread.

The goal of this study is to learn if pembrolizumab with or without enfortumab vedotin can help people live longer without their cancer growing, spreading, or coming back.

Who will take part in this study?

About 608 people with MIBC will be in this study. They will be at least 18 years old and:

- Can't receive or don't want to receive cisplatin. Cisplatin is a **chemotherapy**, which is a type of medicine that destroys cancer cells or stops them from growing.
- Do not have MIBC that has spread to other parts of their body (metastatic).

What treatments are being given during the study?

People may receive one or both of these treatments through a needle into a vein as an intravenous (IV) infusion:

- **Pembrolizumab**, a study medicine, given every 3 weeks
- **Enfortumab vedotin**, a study medicine, given once a week for 2 out of every 3 weeks

Everyone will receive **standard treatment**, which is surgery to remove the bladder and nearby lymph nodes. **Lymph nodes** are small, bean-shaped organs that are part of the immune system.

How is this study designed?

People will be placed into 1 of 3 treatment groups:

- **Group A** will receive pembrolizumab for about 2 months, then have surgery. After surgery, people will receive pembrolizumab for about 10 months.
- **Group B** will only have surgery (standard treatment)
- **Group C** will receive pembrolizumab and enfortumab vedotin for about 2 months, then have surgery. After surgery, people will receive pembrolizumab for about 10 months and enfortumab vedotin for about 4 months.

Both the people in the study and the researcher will know which study treatment a person is getting (**open-label study**). People will give urine and blood samples, have tumor and imaging tests, have physical examinations, and answer questions during the study. Researchers will follow up with people until they are no longer alive, no longer want to be in the study or the study ends.

A person could be in the study for up to about 8 years.

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

Main goal	How it will be measured
To compare the **event-free survival (EFS)** of people in Groups B and C	The length of time until any of the following: • The surgery to remove the bladder can't happen because the cancer gets worse • The person doesn't have the surgery • The surgery doesn't remove all the cancer • The cancer grows, spreads, or comes back • Death from any cause
Other goals	**How they will be measured**
To compare the **cancer response** between people in Groups B to those in Groups A and C	Researchers will measure: • **EFS** - Measured for people in Groups A and B • **Overall survival** - The length of time that people live from the start of treatment until death from any cause • **Pathologic complete response** - The number of people whose tumors and lymph nodes that were removed during surgery have no signs of living cancer cells • **Disease-free survival** - The length of time that people live and are cancer free after starting treatment • **Pathologic down staging** - The number of people whose tumors and lymph nodes that were removed during surgery have less cancer cells
To learn about the **safety** of pembrolizumab and enfortumab vedotin with standard treatment and how well people **tolerate** them	The number of people who: • Had an **adverse event** (**AE**) - an AE is a health problem that happens or worsens during the study • Stopped treatment due to an AE • Had health problems during surgery

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 who 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.