Protocol Plain Language Summary

Clinical study of pembrolizumab alone and with other treatments in people with bladder cancer (MK-3475-057)

Protocol Title: A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) and Pembrolizumab in Combination with Other Investigational Agents in Subjects with High-risk Non-muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy

Why is this study needed?

Researchers are looking for new ways to treat people with **high-risk non-muscle invasive bladder cancer** (**HR NMIBC**). **NMIBC** is cancer in the tissue that lines the inside of the bladder but has not spread to the bladder muscle or outside of the bladder. **High-risk** means cancer may have a high chance of getting worse or coming back after treatment.

The standard treatment for HR NMIBC is **transurethral resection of the bladder tumor (TURBT) followed by** Bacillus Calmette-Guerin (BCG). **BCG** is a type of immunotherapy that is injected into your bladder as a liquid. However, BCG does not work to treat HR NMIBC in some people. **Immunotherapy** is a treatment that helps the immune system fight cancer.

Researchers want to know if **pembrolizumab** given alone (Groups A and B) or with either **vibostolimab** or **favezelimab** (Group C) can help treat HR NMIBC that did not get better or go away with BCG. BCG, pembrolizumab, vibostolimab, and favezelimab are immunotherapies.

The goal of this study is to learn if more than 20 percent (1 out of every 5) of people who receive pembrolizumab in Groups A and B have no signs of cancer in their body and how long people stay cancer free after treatment. Researchers also want to learn how many people who receive pembrolizumab with either vibostolimab or favezelimab have no signs of cancer in their body after 1 year.

Who will take part in this study?

About 320 people with HR NMIBC will be in this study (260 people in Groups A and B and 60 people in Group C). They will be ages 18 years and older and:

- BCG did not work to treat HR NMIBC
- Cannot have or do not want to have surgery to remove their bladder
- Do not have cancer that has spread into the bladder muscle or to other parts of the body

What treatments are being given during the study?

People will receive 1 of 3 treatments:

- Pembrolizumab alone
- Vibostolimab with pembrolizumab
- Favezelimab with pembrolizumab

People will receive treatment through a needle into a vein as an intravenous (IV) infusion every 3 weeks for up to 2 years.

How is this study designed?

People will be assigned to 1 of 3 groups based on whether or not the cancer is **carcinoma-in-situ (CIS).** CIS is bladder cancer that appears flat and is only in the inner layer (surface) of the bladder. CIS is not raised and is not growing toward the center of the bladder.

Group	CIS	Treatment
Group A	Have CIS	Pembrolizumab alone
Group B	Do not have CIS	Pembrolizumab alone
Group C	Have CIS	People will be assigned by equal chance to receive either: • Vibostolimab with pembrolizumab • Favezelimab with pembrolizumab

Both the people in the study and the researcher will know which study treatment a person is getting (open label).

During the study, people will give tumor, blood, and urine samples, have a cystoscopy (procedure that uses a thin tube with a camera to see inside the bladder and the urethra), imaging tests, physical examinations, and answer sets of questions (Groups A and B only) about their health and their ability to perform daily tasks.

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 goals	How they will be measured
To learn how HR NMIBC **responds** (cancer gets smaller or goes away) to pembrolizumab alone in Groups A and B and with either vibostolimab or favezelimab in Group C	Researchers will measure: • **Complete response rate (CRR):** the number of people whose high risk NMIBC goes away. This will be measured in Group A at about 3 months and in Group C at 1 year of treatment. • **Disease-free survival (DFS):** DFS is the length of time that people are HR NMIBC free after starting treatment until the cancer comes back or death from any cause. Researchers will measure the DFS in Group B at 1 year.
To learn about **safety** of pembrolizumab alone in Groups A and B and with either vibostolimab or favezelimab in Group C and how well people **tolerate** the treatments	The number of people who: • Had an **adverse event (AE).** An AE is a health problem that happens or worsens during a study • Stopped treatment due to an AE
Other goals	**How they will be measured**
To learn how any bladder cancer **responds** to pembrolizumab in Group A	Researchers will measure how any bladder cancer responds during the study: • **CRR** of any bladder cancer
To learn how HR NMIBC and any bladder cancer **responds** to pembrolizumab in Group A	Researchers will measure how HR NMIBC and any bladder cancer responds during the study: • **Duration of response (DOR)**: the length of time from when the cancer first responds to treatment until the cancer grows or spreads, or death from any cause. DOR will be measured in all people and people with PD-L1 at multiple time points. PD-L1 is a type of protein found on cancer cells that can help the cancer hide from the body's immune system. • **CRR** in people with PD-L1

	• **Progression-free survival (PFS)**: PFS is the length of time from the start of treatment until cancer worsens, spreads into the bladder muscle or to another part of the body, or death from any cause. PFS will be measured in all people and people with PD-L1. • **Overall survival (OS)** in people with PD-L1: the length of time that people live from the start of the study until death from any cause
To learn how any bladder cancer **responds** to pembrolizumab in Group B	Researchers will measure how any bladder cancer responds during the study: • **DFS**
To learn how HR NMIBC and any bladder cancer **responds** to pembrolizumab in Group B	Researchers will measure how HR NMIBC and any bladder cancer responds during the study: • **DFS** at 3 months, 6 months, 1 year, and overall in people with PD-L1 • **PFS** in people with PD-L1 • **OS** in people with PD-L1
To learn how any bladder cancer **responds** to pembrolizumab with either vibostolimab or favezelimab in Group C	Researchers will measure how any bladder cancer responds during the study: • **DOR** for HR NMIBC • **CRR** at 3 months, 6 months, and overall • **PFS** • **OS**

What are the possible benefits and risks?

Clinical studies may have benefits and risks. People may benefit because the study medicine may treat HR NMIBC or stop it from getting worse. There may be risks because the study medicine may not work or may cause health problems.

This study has a group of experts for Groups A and B, separate from the researchers, who oversee the benefits and risks. If they decide that the study medicine is not safe or doesn't show benefit, the study can be stopped. More information about the benefits and risks is in the protocol.