Protocol Plain Language Summary

A clinical study of pembrolizumab and enfortumab vedotin with or without other immunotherapies in people with urothelial cancer (MK-3475-04B)

Protocol Title: A Phase 1/2 Randomized, Umbrella Study to Evaluate the Safety and Efficacy of Pembrolizumab Plus Enfortumab Vedotin (EV) in Combination With Investigational Agents Versus Pembrolizumab Plus EV, as First-Line Treatment for Participants With Advanced Urothelial Carcinoma (KEYMAKER-U04): Substudy 04B

Why is this study needed?

Researchers are looking for better ways to treat people with **advanced urothelial carcinoma (UC)**. **UC** is cancer in the:

- **Bladder**, which is the organ that stores urine
- **Renal pelvis**, which is a funnel-shaped part of the kidney that collects urine
- **Ureter**, which is the tube that connects each kidney to the bladder
- **Urethra**, which is the tube which carries urine from the bladder out from the body

Advanced means the cancer has spread to other parts of the body.

Researchers want to learn if the study medicines **enfortumab vedotin (EV)** and **pembrolizumab** combined with certain immunotherapies can treat UC. **Immunotherapy** is a treatment that helps the immune system fight cancer. Pembrolizumab is an immunotherapy. EV is a **targeted therapy**, which is a treatment that works to control how specific types of cancer cells grow and spread.

The goals of this study are to learn about the:

- Safety of the study medicines and how well people tolerate them
- The **cancer response** to treatment (it gets smaller or goes away)

Who will take part in this study?

Up to about 390 people with urothelial cancer will be in this study. They will be at least 18 years old and:

- Will provide a tissue sample of the urothelial cancer
- Have not had certain treatments in the past

What treatments are being given during the study?

Everyone will receive **EV** through a needle into a vein as an intravenous (IV) infusion. They will receive EV twice every 3 weeks until the cancer gets worse or they don't tolerate it.

Everyone will also receive one of these treatments as an IV infusion:

- **Pembrolizumab**
- **MK-4280A**, which is pembrolizumab with **favezelimab**, an immunotherapy
- **MK-7684A**, which is pembrolizumab with **vibostolimab**, an immunotherapy

People will receive pembrolizumab, MK-4280A, or MK-7684A once every 3 weeks for up to 2 years.

How is this study designed?

This study may have 2 parts. In Part 1, people will be assigned to one of these groups:

- **Group A** will receive EV and MK-4280A
- **Group B** will receive EV and MK-7684A
- **Group C** will receive EV and pembrolizumab

In Part 2, more people could be added to 2 or 3 of the groups above, depending on the results from Part 1.

Both the people in the study and the researcher will know which study medicines a person is getting (**open-label study**). During the study, people will give urine and blood samples, have tumor and imaging tests, have physical examinations and answer questions about how they are feeling. People may be in this study for about 4 years.

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

Main goals	How they will be measured
To learn the **objective response rate (ORR)** of people in Groups A, B, and C in Part 1	**ORR** is the number of people whose cancer **responds** to treatment during the study
To learn if the study medicines are **safe** 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 a study • Stopped treatment due to an AE • Had a **dose-limiting toxicity (DLT)** during the first 3 weeks of treatment. A DLT is a medical problem related to the study medicine that may prevent researchers from giving the same or higher dose
To learn the **progression free survival (PFS)** of people in Groups A, B, and C after Part 2	**PFS** is the length of time from when the person starts in the study until the cancer grows or spreads, or death from any cause

Other goals	How they will be measured
To learn about the **cancer response** of people in Groups A, B, and C	During Part 1, researchers will measure: • PFS • **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 After Part 2, researchers will measure: • **Overall survival (OS)**: the length of time that people live from the start of treatment until death from any cause • ORR • DOR
To learn about the **health-related quality of life (HRQoL)** of people in Groups A, B, and C in Part 1 and 2	People will answer sets of questions to measure their HRQoL, including questions about their overall health and their ability to carry out daily tasks. Researchers will measure: • Change in the scores during the study • The time from the start of the study until people's QoL gets worse

What are the possible benefits and risks?

People may or may not benefit from the treatment received during the study. More information about the benefits and risks is in the Protocol.