Protocol Plain Language Summary

A clinical study of belzutifan with standard treatment and pembrolizumab combined with quavonlimab and lenvatinib to treat kidney cancer (MK-6482-012)

Protocol Title: An Open-label, Randomized Phase 3 Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Belzutifan (MK-6482) and Lenvatinib (MK-7902), or MK-1308A in Combination with Lenvatinib, versus Pembrolizumab and Lenvatinib, as First-line Treatment in Participants with Advanced Clear Cell Renal Cell Carcinoma (ccRCC)

Why is this study needed?

Researchers are looking for new ways to treat advanced clear cell renal carcinoma (ccRCC). **ccRCC** is the most common type of kidney cancer. Advanced means the cancer has spread in the body or cannot be removed with surgery.

Standard treatment for advanced ccRCC includes immunotherapy and targeted therapy. **Immunotherapy** is a treatment that helps the immune system fight cancer**. Targeted therapy** is a treatment that works to control how specific types of cancer cells grow and spread. **Pembrolizumab**, an immunotherapy, and **lenvatinib**, a targeted therapy, in combination are one standard treatment.

Researchers want to learn about 2 study medicines. **Belzutifan** (study medicine) is a targeted therapy. **Pembrolizumab combined with quavonlimab**, also called **MK-1308A** (another study medicine) is a combination of 2 immunotherapies.

The goal of this study is to learn if people who receive belzutifan plus pembrolizumab and lenvatinib or pembrolizumab combined with quavonlimab and lenvatinib live longer overall and live longer without the cancer growing or spreading compared to people who receive standard treatment alone.

Who will take part in this study?

About 1,653 people with advanced ccRCC will be in the study. They will be at least 18 years old and:

- Have not been treated for advanced ccRCC in the past year
- Do not have another cancer that is growing or needed treatment in the past 3 years

What treatments are being given during the study?

People will receive one of these treatments:

- Belzutifan (study medicine) and standard treatment (pembrolizumab and lenvatinib)
- Pembrolizumab combined with quavonlimab (study medicine) and lenvatinib
- Standard treatment alone: pembrolizumab and lenvatinib

People will receive pembrolizumab combined with quavonlimab or pembrolizumab alone through a needle into a vein as an intravenous (IV) infusion-every 6 weeks. People will take belzutifan and lenvatinib by mouth once a day.

How is this study designed?

People will have an equal chance of being assigned to 1 of 3 groups:

- **Group 1** will receive **belzutifan and standard treatment**
- **Group 2** will receive **pembrolizumab combined with quavonlimab and lenvatinib**
- **Group 3** will receive **standard treatment alone**

Both the people in the study and the researcher will know which study treatment 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 and their ability to carry out daily tasks. A person may be in this study for up to 6 years.

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

Main goals	How they will be measured
To learn if the **progression-free survival (PFS)** of people in Group 1 and Group 2 is longer than those in Group 3	**PFS** is the length of time from the start of treatment until the cancer grows or spreads, or death from any cause. Researchers will compare: • Group 1 to Group 3 • Group 2 to Group 3
To learn if the **overall survival (OS)** of people in Group 1 and Group 2 is longer than those in Group 3	**OS** is the length of time that people live from the start of study treatment assignment until death from any cause. Researchers will compare: • Group 1 to Group 3 • Group 2 to Group 3

Other goals	How they will be measured

To learn about the **cancer response** to treatment	During the study, researchers will measure:
	• **Overall Response Rate (ORR),** is the number of people whose cancer responds to treatment (gets smaller or goes away) in:
	  ○ Group 1 to group 3
	  ○ Group 2 to Group 3
	• **Duration of Response (DOR),** is the length of time from when the cancer first responds to treatment until the cancer grows, or spreads, or death from any cause

To learn about the **safety** and how well people **tolerate** treatment in Group 1 and 2 compared to Group 3	During the study, the number of people who: • Have an **adverse event (AE)** – an AE is a health problem that happens or worsens • 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 which means the cancer may or may not get smaller or go away. 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.