Protocol Plain Language Summary

A clinical study of different treatments for kidney cancer (MK-3475-03A)

Protocol title: A Phase 1b/2 Study of Immune and Targeted Combination Therapies in Participants with RCC (KEYMAKER-U03): Substudy 03A

Why is this study needed?

Researchers are looking for ways to treat people with advanced or metastatic **clear cell renal cell carcinoma (ccRCC). ccRCC** is the most common type of kidney cancer. **Advanced** means cancer has spread outside the kidney. **Metastatic** means cancer has spread to other parts of the body.

Researchers want to learn if different treatment combinations can treat ccRCC.

The goals of this study are to learn:

- About the safety of the treatment combinations
- How well people tolerate the treatments
- How many people have ccRCC that **responds** (cancer gets smaller or goes away) to the treatments

Who will take part in this study?

About 400 people with advanced or metastatic ccRCC will be in the study. They will be ages 18 years and older and:

- Have not received treatment for advanced or metastatic ccRCC
- Do not have certain heart conditions

What treatments are being given during the study?

People will receive 2 or 3 of these treatments:

- **Pembrolizumab** – an immunotherapy. An **immunotherapy** is a treatment that helps the immune system fight cancer.
- **MK-1308A** – a combination of the 2 immunotherapies pembrolizumab and quavonlimab
- **MK-4280A** – a combination of the 2 immunotherapies pembrolizumab and favezlimab
- **MK-7684A** – a combination of the 2 immunotherapies pembrolizumab and vibostolimab
- **Lenvatinib** – a targeted therapy**.** A **targeted therapy** is a treatment that works to control how specific types of cancer cells grow and spread.
- **Belzutifan** – a targeted therapy

People will receive immunotherapy treatments through a vein by intravenous (IV) infusion every 3 or 6 weeks. They will receive immunotherapy treatments for up to 2 years, or until the cancer gets worse or people do not tolerate the treatments.

People will take lenvatinib and belzutifan by mouth 1 to 3 times a day until the cancer gets worse or people do not tolerate the treatments.

How is this study designed?

People will be assigned by chance to one of these treatment groups:

- **Group A**: MK-1308A and lenvatinib
- **Group B**: MK-4280A and lenvatinib
- **Group C**: Pembrolizumab, belzutifan, and lenvatinib
- **Group D**: MK-7684A and belzutifan
- **Group E**: Pembrolizumab and lenvatinib

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This study has 2 parts.

Part 1: Researchers will test the safety of belzutifan or lenvatinib when given with other treatments in Groups A, B, C, and D in a small group of people. Researchers will give these people one dose (amount) of belzutifan or lenvatinib. They will lower the dose if people do not tolerate the first dose.

Researchers will review the safety of the combinations before giving them to more people in Part 2.

Part 2: People in every group will receive their assigned treatments.

Both the people in the study and the researchers will know which study treatment a person is getting (called an open-label study).

People may have urine, blood, tumor, and imaging tests during the study. They will also have physical examinations and tests to check their heart (electrocardiograms or ECGs).

People may be in this study for about 3 and a half years.

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

Main goals	How they will be measured
To learn about the **safety** of the treatments in all Groups and how well people **tolerate** them during Parts 1 and 2	The number of people who: • Have an **adverse event (AE).** An AE is a health problem that happens or worsens during a study • Stop treatment due to an AE • Have a **dose-limiting toxicity (DLT)** during the first 3 weeks of treatment in Parts 1 and 2. A DLT is a medical problem related to study treatment that prevents researchers from giving a higher dose
To learn about the **objective response rate (ORR)** for people in all Groups during Part 2	**ORR** is the number of people whose cancer responds to treatment during the study
Other goals	**How they will be measured**
To learn about the **cancer response** for people in all Groups during Part 2	Researchers will measure these cancer responses: • **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 • **Progression-free survival (PFS)** is the length of time from when the person starts the study until the cancer grows or spreads, or death from any cause • **Overall survival (OS)** is the length of time from when the person starts the study until death from any cause
To learn about the **clinical benefit rate (CBR)** for people in all Groups during Part 2	**CBR is** the number of people whose cancer gets smaller, goes away, or stays the same for at least 6 months

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.