Protocol Plain Language Summary

A clinical study of pembrolizumab, lenvatinib, and belzutifan in people with certain cancers (MK-6482-016)

Protocol Title: An Open-label, Multicenter, Phase 2 Study to Evaluate the Efficacy and Safety of Pembrolizumab Plus Lenvatinib in Combination With Belzutifan in Multiple Solid Tumors

Why is this study needed?

Researchers are looking for new ways to treat people with certain cancers:

- **Hepatocellular carcinoma (HCC)**
- **Non microsatellite instability-high** (**MSI-H) or deficient mismatch repair (dMMR) colorectal cancer (CRC)**. MSI-H or dMMR means a person's body is less able to repair DNA.
- **Pancreatic ductal adenocarcinoma (PDAC)**
- **Biliary tract cancer (BTC)**
- **Non MSI-H/dMMR endometrial cancer (EC)**
- **Esophageal squamous cell carcinoma (ESCC)**

Pembrolizumab is an immunotherapy, which is a treatment that helps the immune system fight cancer. **Lenvatinib** is a targeted therapy, which is a treatment that works to control how specific types of cancer cells grow and spread. **Belzutifan** is a study medicine designed to block a protein that helps tumors grow and survive.

The goal of this study is to learn if pembrolizumab, lenvatinib, and belzutifan are safe and well tolerated when given together. Researchers also want to learn if people who receive pembrolizumab, lenvatinib, and belzutifan have the cancer get smaller or go away.

Who will take part in this study?

About 240 people with HCC, MSI-H/dMMR CRC, PDAC, BTC, EC, or ESCC will be in the study. They will be 18 years old and older and:

- Be able to provide a tumor sample
- Not have certain heart diseases

What treatments are being given during the study?

People will receive 2 or more of these treatments:

- **Pembrolizumab –** given every 6 weeks through a needle into a vein as an intravenous (IV) infusion
- **Lenvatinib –** taken once a day by mouth as tablets or capsules
- **Belzutifan –** taken once a day by mouth as tablets or capsules

People will take lenvatinib and belzutifan until the cancer gets worse or they don't tolerate it. People will receive pembrolizumab for up to 2 years.

How is this study designed?

People will be placed into different groups based on the type of cancer they have. The treatment people receive will depend on the group they are in.

Types of cancer	Treatments
• HCC • CRC • PDAC • BTC • EC • ESCC that was not previously treated with immunotherapy	Everyone will receive pembrolizumab, lenvatinib, and belzutifan
• ESCC that was previously treated with immunotherapy and it stopped working	People will have an equal chance of receiving either: • Pembrolizumab, lenvatinib, and belzutifan • Pembrolizumab and lenvatinib

The study will have 2 parts:

- **Part 1**: Researchers will give people with certain types of cancer different dose levels (amounts) of lenvatinib and belzutifan, and one dose level of pembrolizumab. Researchers will review the safety of each dose level and how well people tolerate it. This will help choose the dose levels for Part 2.
- **Part 2**: People with all types of cancer will receive the dose levels chosen in Part 1.

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 imaging tests, have physical examinations, and answer questions about how they are feeling and their ability to perform daily tasks. A person 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 if pembrolizumab, lenvatinib, and belzutifan are **safe** and how well people **tolerate** them	The number of people who: • Had a **dose limiting toxicity (DLT)** in Part 1. A DLT is a medical problem related to study medicine that prevents giving a higher dose. • Had an **adverse event (AE).** An AE is a health problem that happens or worsens during a study. • Stopped treatment due to an AE
To learn about the **objective response rate (ORR)** of people who receive pembrolizumab and lenvatinib, with or without belzutifan	**ORR** is the number of people whose cancer responds to treatment during the study. **Responds** means cancer gets smaller or goes away.

Other goals	How they will be measured
To learn about the **response** of people who receive pembrolizumab and lenvatinib, with or without belzutifan	Researchers will measure responses 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 • **Disease control (DC):** the number of people whose cancer gets smaller, goes away, or stays the same after at least 6 weeks of treatment • **Progression-free survival (PFS):** the length of time from the first dose of belzutifan until a person's cancer grows or spreads, or death from any cause • **Overall survival (OS):** the length of time from the first dose of belzutifan until death from any cause

To learn if pembrolizumab and lenvatinib are **safe** and how well people **tolerate** them	The number of people who: • Had an AE • Stopped 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. More information about the benefits and risks is in the Investigator Brochure, Protocol, and Informed Consent documents.