Protocol Plain Language Summary

A clinical study of pembrolizumab with standard treatment in people with bladder cancer (MK-3475-676)

Protocol Title: A Phase 3, Randomized, Comparator-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Bacillus Calmette-Guerin (BCG) in Participants with High-risk Non-muscle Invasive Bladder Cancer (HR NMIBC) that is either Persistent or Recurrent Following BCG Induction or that is Naïve to BCG Treatment (KEYNOTE-676)

Why is this study needed?

Researchers are looking for new ways to treat people with a type of bladder cancer called **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 NMIBC may have a high chance of getting worse or coming back after treatment.

Bacillus Calmette-Guerin (**BCG**) is a standard treatment for HR NMIBC. BCG is an immunotherapy, which is a treatment that helps the immune system fight cancer. However, it may not work to treat HR NMIBC in some people. Researchers want to know if giving **pembrolizumab**, another type of immunotherapy, with BCG works to treat HR NMIBC.

The goal of this study is to learn if more people who receive pembrolizumab with BCG have no signs of cancer in their body and live longer without the cancer growing, spreading, or coming back compared to people who receive BCG alone.

Who will take part in this study?

About 1,405 people with HR NMIBC will be in this study. They will be ages 18 years and older, and:

- Have HR NMIBC that came back, did not respond, or got worse after BCG treatment
- Have never been treated with BCG or had a response to BCG treatment lasting over 2 years
- Have not received certain treatments for cancer

How is this study designed?

People will be assigned to one of these treatment groups based on if they have previously been treated

- **Group A**: People who have been treated with BCG before will receive either:
  - **Pembrolizumab** every 3 weeks for about 2 years with **BCG** for about 3 years
  - **BCG alone** for about 3 years
- **Group B:** People who have not been previously treated with BCG will receive either:
  - **Pembrolizumab** every 6 weeks for about a year with **BCG** for 4 months
  - **Pembrolizumab** every 6 weeks for about a year with **BCG** for about 1 and a half years
  - **BCG alone** for about 1 and a half years

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 tumor, blood, and urine samples, have imaging tests and physical examinations, and answer sets of questions about their health and their ability to perform daily tasks.

People may be in this study for up to 8 years.

What treatments are being given?

People will be assigned by chance to receive one or both treatments:

- **BCG**, given directly into the bladder using a tube (intravesical therapy) for up to 3 years.
  - First it will be given once a week for 6 weeks (**induction therapy**)
  - Then, it will be given once a week for 3 weeks every 3 to 6 months (**maintenance therapy**)
- **Pembrolizumab**, given every 3 or 6 weeks through a needle into a vein as an intravenous infusion for up to 2 years.

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

Main goals	How they will be measured
To compare how cancer responds in people who receive pembrolizumab with BCG to people who receive BCG alone	During the study, researchers will measure: • **Complete Response Rate (CRR)** for people who begin study treatment for early-stage cancer that is in the bladder cells only (**carcinoma in situ**). CRR is the number of people in Group A who no longer have signs of cancer • **Event-free survival (EFS)** is the length of time people in Group B live without cancer growing, spreading, coming back, or death from any cause
Other goals	**How they will be measured**
To learn how long cancer responds in people who receive pembrolizumab with BCG compared to BCG alone	The length of time from when people start the study until: • Either the cancer comes back, or spreads, or death from any cause (**recurrence-free survival or RFS**) • Death from any cause (**overall survival or OS**) • Death from bladder cancer (**disease specific survival or DSS**) • They have surgery to remove the entire bladder (**cystectomy**) • **12-month EFS Rate**: the number of people in Group A with EFS at 12 months • **24-month EFS Rate**: the number of people in Group B with EFS at 24 months • **EFS** for people in Group A only
To learn how cancer responds in people who have **carcinoma in situ** and receive pembrolizumab with BCG compared to BCG alone	Researchers will measure responses throughout the study: • **Duration of Response** (**DOR**): the length of time from when cancer first responds to treatment until cancer grows, spreads, or death from any cause • **12-month DOR Rate**: the number of people with a CR who have no signs of cancer for at least 12 months • **CRR** for people in Group B only
To learn how long it takes for a person's **health-related quality of life** (**HRQoL**) to change	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 the length of time from the start of treatment until people's HRQoL improves or worsens.

To learn about the safety of pembrolizumab with BCG and how well people tolerate it	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

What are the possible benefits and risks?

People in this study may or may not have their cancer stop growing 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.