Waiver to Allow Participation in a Food and Drug Administration Advisory Committee

DATE: March 22, 2021

TO: Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

FROM: Byron Marshall
Director, Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

Name of Advisory Committee Standing Voting Member: **Philip C. Hoffman, M.D.**

Committee: Oncologic Drugs Advisory Committee

Meeting dates: April 27-29, 2021

Description of the Particular Matters to Which the Waiver Applies:

Philip C. Hoffman, M.D., is a standing voting member and Chairperson of the Oncologic Drugs Advisory Committee (ODAC). The committee's function is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for the use in the treatment of cancer and make appropriate recommendations to the Commissioner of Food and Drugs.

On April 27th, the committee will hear updates on biologics license application (BLA) 761034/S-018, for Tecentriq (atezolizumab), submitted by Genentech, Inc., a subsidiary of Roche. Ono Pharmaceuticals and Bristol-Myers Squibb (BMS) have a global patent licensing agreement with Roche for the atezolizumab. The committee will review Tecentriq (atezolizumab) in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test. Abraxane (nab-paclitaxel) is marketed by Abraxis Bioscience, a subsidiary of Celgene; Celgene and Abraxis Bioscience are subsidiaries of BMS.

On April 28th, the committee will hear updates on BLA 125514/S-017, trade name Keytruda (pembrolizumab), submitted by Merck Sharpe & Dohme Corp., and indicated for the treatment

of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

On April 29th, the committee will hear updates on BLA 125514/S-042, trade name Keytruda (pembrolizumab), submitted by Merck Sharp & Dohme Corp. (Merck), and indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

These applications were approved under 21 CFR 601.40 (subpart E, accelerated approval regulations) with confirmatory trial(s) that have not verified clinical benefit. These updates will provide information on: (1) the status and results of confirmatory clinical studies for a given indication; and (2) any ongoing and planned trials. Confirmatory studies are post-marketing studies to verify and describe the clinical benefit of a drug after it receives accelerated approval. Based on the updates provided, the committee will have a general discussion focused on next steps for each product including whether the indications should remain on the market while additional trial(s) are conducted. These topics are particular matters involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Hoffman's employing institution, the University of Chicago, is participating in the study titled *A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab Plus Chemotherapy vs Placebo Plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (KEYNOTE 522),* sponsored by Merck. The study accrual period was between September 29, 2017 and August 21, 2018, during which two patients were enrolled and Dr. Hoffman's colleague at the University of Chicago was the institutional principal investigator. One patient at this site has finished treatment and is being followed for long-term survival. Dr. Hoffman advised that he does not have any direct experience with the trial.

The University of Chicago receives between $0 and $50,000 per year, from Merck, for this study, which is expected to run until 2025.

His employer is also participating in the study titled *A Study of Pembrolizumab (MK-3475) in Participants With Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-059/KEYNOTE-059) [NCT02335411],* sponsored by Merck. The study enrolled eight patients, and a few patients are being followed for long-term survival; the study is no longer recruiting patients. While Dr. Hoffman is listed as a Sub-Investigator, he is not involved in patient enrollment or study design, advice, or data/report review. Dr. Hoffman does not see patients with this type of cancer and has not enrolled any of his patients on the trial. The contract began on February 3, 2015, and the estimated study completion date is July 23, 2021.

The University of Chicago anticipates receiving a total of between $0 and $50,000 from Merck for its participation in this study. Dr. Hoffman does not receive salary support or personal remuneration from this funding.

Lastly, the University of Chicago is participating in the study titled *Study of Pembrolizumab (MK-3475) as First-Line Monotherapy and Combination Therapy for Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-062/KEYNOTE-062) [NCT02494583],*

sponsored by Merck. The study enrolled three patients, and the study is closed to accrual. While Dr. Hoffman is a Sub-Investigator, he is not involved in patient enrollment or study design, advice, or data/report review. Dr. Hoffman does not see patients with this type of cancer and has not enrolled any of his patients on the trial. The contract began on July 31, 2015 and the estimated study completion date is June 7, 2021.

The University of Chicago to date has received between $150,000 and $200,000 for this study, and anticipates receiving between $0 and $50,000, from now until the study terminates. Dr. Hoffman does not receive salary support or personal remuneration from this funding.

Basis for Granting the Waiver:

Dr. Philip C. Hoffman has unique qualifications and specialized expertise needed for these particular matters.

Dr. Hoffman received his medical degree from Thomas Jefferson University and completed a fellowship in Hematology/Oncology at the University of Chicago. He is currently a Professor of Medicine, Section of Hematology/Oncology at the University Chicago.

Dr. Hoffman is an expert in cancers of the lung, breast and esophagus. His academic interests lie mainly with malignancies of the chest. He has participated in clinical trials in lung and esophageal cancer, with particular emphasis on patients with advanced disease. He has conducted a series of studies of combined chemotherapy plus radiation therapy for locally advanced lung cancer, as well as chemotherapy drug trials for patients with lung cancer that has spread to other body sites. For many years, he has also had an active interest in management of breast cancer, both early stage and later stage, and has participated in a number of clinical trials in that disease.

The author of more than 80 medical journal articles, Dr. Hoffman's research interests include small cell and non-small cell lung cancer and breast cancer. He is also the author of book chapters ranging from cancer emergencies to breast cancer.

In addition to serving on several University and national committees, Dr. Hoffman is a reviewer for several medical journals, including the Journal of Clinical Oncology, the Lancet and JAMA.

It is particularly important to include Dr. Hoffman in the upcoming ODAC meeting, given his vast experiences and research in hematology and oncology with specific expertise in treating cancers of the lung, breast and esophagus. His background in clinical trials research and treating patients with all stages of these cancers will be valuable to the meeting discussions.

Multiple medical oncologists including breast, genitourinary, gastrointestinal, and hepatocellular carcinoma experts were invited to attend this meeting to allow for a diverse panel of experts to provide a balanced assessment of the acceptability of the known and anticipated risks associated with the proposed treatment settings. To conduct the meetings without multiple experts would render the advice from the meeting difficult to interpret; the clearance of multiple cancer experts

is imperative. Dr. Hoffman has been a standing member of the Committee since 2017 and Chairperson since 2019. His diverse collection of previous experiences with advisory meetings and as a standing member and Chairperson of the ODAC will be invaluable to a robust and productive discussion of the meeting topics.

The particular matters are sensitive.

The matters coming before the committee will garner public interest as it relates to the regulatory pathway of accelerated approval which was promulgated in 1992. This pathway has been used extensively in oncology approvals to bring new therapies to patients in an expedited fashion.

Dr. Philip C. Hoffman's expertise in these particular matters is necessary in the interest of public health.

Breast cancer is the second leading cause of cancer-related death in women in the United States each year after lung cancer and it is the most common cancer among women worldwide. Triple-negative breast cancer (TNBC) is a term that has historically been applied to cancers that lack the three most significant therapeutic markers for clinical management of breast cancer patients: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC accounts for 15-20% of all breast cancers but it is more aggressive and has a poorer prognosis compared to other types of breast cancers. TNBC is more commonly diagnosed in younger, premenopausal women and among Black and Hispanic women. Presence of a BRCA-1 mutation (breast cancer susceptibility gene) is another risk factor associated with the diagnosis of TNBC. Approximately 50-70% of women with a BRCA1 mutation will develop breast cancer by 70-80 years.

Because TNBC lacks estrogen, progesterone and HER2 protein receptors, treatment options for this cancer are limited. TNBC is typically treated with a combination of surgery, radiation therapy, and chemotherapy (the main systemic option). In recent years, targeted therapies such as PARP (poly ADP ribose polymerase) inhibitors and/or immunotherapy medicine in combination with chemotherapy have been shown to have positive results for patients with metastatic disease. There is currently one other FDA-approved first-line therapy, which was also approved under the accelerated-approval process, for the treatment of unresectable locally advanced or metastatic TNBC. The product at issue for the April 27th meeting is Genentech's immunotherapeutic agent, Tecentriq (atezolizumab) indicated in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test.

According to the American Cancer Society (ACS) bladder cancer is the fourth most common cancer in men. The ACS estimates that in 2021 in the United States there will be about 83,730 new cases of bladder cancer (about 64,280 in men and 19,450 in women) and about 17,200 deaths from bladder cancer (about 12,260 in men and 4,940 in women). Urothelial carcinoma (UCC), also known as transitional cell carcinoma (TCC), accounts for about 90% of all bladder cancers. It also accounts for 10% to 15% of kidney cancers diagnosed in adults. Bladder cancer

begins when healthy cells in the bladder lining—most commonly urothelial cells—change and grow out of control, forming tumors. Cancer that develops in the renal pelvis and ureters is also considered a type of urothelial cancer and is often called upper tract urothelial cancer. Bladder cancer is considered metastatic when it spreads to other parts of the body. There are no methods to permanently cure metastatic urothelial cancer (mUCC) for most people. The goals of treatment are to slow the spread of cancer, delay its growth, shrink the tumor, and extend life for as long as possible. Platinum-based (cisplatin or carboplatin) combination chemotherapy has been the standard of care in the first-line treatment of mUCC. The FDA has approved 5 immune checkpoint inhibitors, pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab for the treatment of people with metastatic disease whose disease is not shrunk or stabilized by platinum-based chemotherapy. The FDA has also approved targeted therapy drugs, erdafitinib and enfortumab vedotin-ejfv to treat patients with locally advanced or metastatic urothelial carcinoma that has previously progressed on platinum-based chemotherapy. The products at issue are Merck's Keytruda (pembrolizumab) and Genentech's Tecentriq (atezolizumab) for the first-line treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

Hepatocellular carcinoma or HCC starts in the liver and is one of the most prevalent cancers in the world. HCC accounts for about 85%-90% of all primary liver cancers. The number of people who develop HCC in the U.S. has risen in the last four decades. There are approximately six new cases of HCC per every 100,000 people in the general population of the U.S. Most patients with HCC have an underlying liver disease such as infection with hepatitis B or C virus, or non-alcoholic fatty liver disease. Treatment for HCC is either surgical (liver resection or transplantation), nonsurgical (ablation or embolization), or systemic treatments. Systemic treatment includes molecularly targeted therapy and immunotherapy with immune checkpoint inhibitors. Atezolizumab in combination with bevacizumab, sorafenib, or lenvatinib are FDA-approved for first-line therapy for HCC. Regorafenib, ramucirumab, nivolumab, ipilimumab (in combination with nivolumab), cabozantinib and pembrolizumab are approved second-line treatments for HCC.

In the interest of public health, it is important that the Agency has available the unique expertise that Dr. Hoffman will provide for the discussion of the particular matters before the committee.

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Philip C. Hoffman's expertise in these matters.

It is particularly important to include Dr. Hoffman in the upcoming ODAC meeting, given his vast experiences and research in hematology and oncology. Dr. Hoffman has a strong foundation in and is considered an expert in medical oncology. He has been a standing member of the Committee since 2017 and Chairperson since 2019. Dr. Hoffman's professional experiences combined with his diverse collection of previous experiences with advisory meetings and as a standing member and Chairperson of the ODAC will be invaluable to a robust and productive discussion on the applications coming before the committee.

Accordingly, I recommend that you grant Dr. Philip C. Hoffman, the Chair and a voting member of the Oncologic Drugs Advisory Committee, a waiver from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

_✓_ The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Regular Government Employee's or Special Government Employee's Ability to Act:

_____ Non-voting

_____ Other (specify):

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_____ Denied – The individual may not participate.

Russell Fortney -S Digitally signed by Russell Fortney -S Date: 2021.04.02 08:10:58 -04'00'

April 2, 2021

Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

Date