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

DATE: March 29, 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: **Christopher Lieu, M.D.**

Committee: Oncologic Drugs Advisory Committee

Meeting date: April 27-29, 2021

Description of the Particular Matter to Which the Waiver Applies:

Christopher Lieu, M.D., is a standing voting member of the Oncologic Drugs Advisory Committee (ODAC). ODAC'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 27, 2021, the committee will hear updates on BLA 761034/S-018, for Tecentriq (atezolizumab), submitted by Genentech, Inc., and 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.

Genentech is a subsidiary of Roche. Ono Pharmaceuticals and Bristol-Myers Squibb (BMS) have a global patent licensing agreement with Roche for atezolizumab. Abraxane (nab-paclitaxel) is marketed by Abraxis Bioscience, a subsidiary of Celgene; Celgene and Abraxis Bioscience are subsidiaries of BMS.

On April 28, 2021, the committee will hear updates on BLA 125514/S-017, trade name Keytruda (pembrolizumab), submitted by Merck Sharp & Dohme Corp., and indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for

cisplatin-containing chemotherapy; and (2) BLA 761034/S-001, trade name TECENTRIQ (atezolizumab), submitted by Genentech, Inc., and indicated for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

On April 29, 2021, the committee will hear updates on BLA 125514/S-024, trade name Keytruda (pembrolizumab), submitted by Merck Sharp & Dohme Corp., and indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy; and 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. Lieu's employing institution, the University of Colorado, is participating in a study titled *Phase 2 Study of Pembrolizumab in Combination With Binimetinib and Bevacizumab in Patients With Refractory Colorectal Cancer (NCT03475004)*, sponsored by Merck & Co. The study began in January 2018 and the estimated study completion date is April 30, 2021.

The University of Colorado to date has received between $300,000 and $350,000 for this study, and anticipates receiving between $150,000 and $200,000, from now until the study terminates. Dr. Lieu does not receive salary support or personal remuneration from this funding.

Secondly, his employer is participating in the study titled *A Phase 1b Multi-cohort Study of the Combination of Pembrolizumab (MK-3475) Plus Binimetinib Alone or the Combination of Pembrolizumab Plus Chemotherapy With or Without Binimetinib in Participants With Metastatic Colorectal Cancer (KEYNOTE-651, NCT03374254)*, sponsored by Merck Sharp & Dohme Corp. The study began in September 2017 and the estimated study completion date is August 2021.

To date the University of Colorado has received between $375,000 and $425,000 for this study, and anticipates receiving between $75,000 and $125,000, from now until the study terminates. Dr. Lieu does not receive salary support or personal remuneration from this funding.

Lastly, his employer is participating in a study titled *A Randomized Trial of FOLFOX Alone or*

Combined With Atezolizumab as Adjuvant Therapy for Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair or Microsatellite Instability (ATOMIC, Alliance A021502, NCT02912559). University of Colorado is a SWOG (Southwest Oncology Group) institution, which allows the institution to open SWOG studies as part of the National Clinical Trials Network, of the National Cancer Institute (NCI), of the National Institutes of Health. The study began in June 2016 and is expected to end in 2023. Dr. Lieu advised the study is part of a cooperative research and development agreement with Roche/Genentech. The study drug is distributed by and all funding comes from the NCI. Dr. Lieu is a site-investigator and his involvement is directly with NCI; he has no involvement with Roche/Genentech.

The University of Colorado receives between $25,000 and $75,000 per year from NCI for this study. Dr. Lieu does not receive any salary support or personal remuneration from this funding.

Basis for Granting the Waiver:

Dr. Christopher Lieu has unique qualifications and specialized expertise needed for this particular matter.

Dr. Lieu is currently an Associate Professor in the Division of Medical Oncology and Director of Colorectal Medical Oncology in the Division of Medical Oncology at the University of Colorado Anschutz Medical Campus. He is also Director of Gastrointestinal Medical Oncology and Associate Director for Clinical Research at the University of Colorado Cancer Center. Dr. Lieu earned his Doctor of Medicine from Wake Forest University School of Medicine. He then trained in internal medicine at the University of Colorado, where he also served as a Chief Medical Resident. Dr. Lieu completed his fellowship training in medical oncology at the University of Texas MD Anderson Cancer Center and served as the Chief Medical Oncology Fellow.

He is a member of several oncology organizations including American Association for Cancer Research, American Society of Clinical Oncology, Rocky Mountain Oncology Society, and Southwest Oncology Group.

Dr. Lieu's clinical interests are in gastrointestinal cancers, drug development, experimental therapeutics and translational research. In addition to serving on several university and national committees, Dr. Lieu has published approximately 40 original researched articles and abstract presentations related to his clinical and clinical research activities. He has also contributed to book chapters in eight publications related to oncology.

It is particularly important to include Dr. Lieu in the upcoming ODAC meeting given his expertise in gastrointestinal cancers and medical oncology. His background in clinical trials research, drug development, experimental therapeutics and translational research will be valuable to the discussion of the updates being discussed.

The particular matter is sensitive.

The matter 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. Christopher Lieu's expertise in this particular matter 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 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 on April 28th are Merck Sharp & Dohme'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.

Cancers that start in glandular cells are called adenocarcinomas. According to the American Cancer Society, about 90% to 95% of the stomach cancers are adenocarcinomas. A gastroesophageal junction adenocarcinoma is a cancer that begins in glandular cells located near the gastroesophageal junction. This cancer has also been referred to as esophagogastric junction adenocarcinoma. According to the National Cancer Institute, there were about 27,600 new cases of stomach cancer and about 18,440 new cases of esophageal cancer in the U.S. in 2020. The estimated number of deaths in 2020 were 11,010 for stomach cancer and 16,170 for esophageal cancer. Treatment of gastric or gastroesophageal junction adenocarcinoma depends on the stage and may include surgery, chemotherapy, targeted drug therapy, immunotherapy, and radiation therapy. These treatment options depend on the extent of the cancer. Tipiridine/trifluracil combination product and pembrolizumab are FDA-approved treatments for disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

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. Lieu 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. Christopher Lieu's expertise in this matter.

Dr. Lieu has a strong foundation in and is considered an expert in medical oncology. His experience in developing guidelines for oncology as part of the Board of the Directors for the

National Comprehensive Cancer Network (NCCN) makes him uniquely qualified to provide insight and feedback on the updates being discussed at the advisory committee meeting.

He has additionally served as an NIH reviewer of biostatistical methods and trial design. These applications require both an understanding of oncology clinical guideline development in terms of the definitions of patient populations relating to treatment eligibility as well as trial design and interpretation. His combined expertise in these topics will be invaluable.

Dr. Lieu is an expert in gastrointestinal cancers and these applications will need multiple discussants with expertise in these cancers. As an example, the treatment of HCC is complex, and involves a careful assessment of both the cancer and the underlying liver function and related abnormalities such as varices or ascites. Both gastric and hepatocellular carcinoma are also undergoing rapid changes with respect to changes in standard of care and gastrointestinal oncology expertise will be necessary to put these applications in perspective.

Accordingly, I recommend that you grant Dr. Christopher Lieu, 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
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April 6, 2021

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

Date