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

DATE: October 12, 2023

TO: Rachel Bressler
Acting 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 Meeting Temporary Member: **Gita Thanarajasingam, M.D.**

Committee: Oncologic Drugs Advisory Committee

Meeting date: November 16, 2023

Description of the Particular Matter to Which the Waiver Applies:

Gita Thanarajasingam, M.D., is a temporary voting member 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 use in the treatment of cancer and make appropriate recommendations to the Commissioner of Food and Drugs.

On November 16, 2023, the committee will receive updates on the accelerated approval program in oncology and two new drug applications (NDAs) approved under 21 CFR 314.500 (subpart H, accelerated approval regulations) that have not met their agreed-upon milestones for completion of confirmatory trial(s). Confirmatory trials are post-marketing studies to verify and describe the clinical benefit of a drug after it receives accelerated approval. These updates will provide information on the status of all accelerated approvals granted in oncology, including products with delayed confirmatory trials, and the status of confirmatory trials for the specific NDAs to be discussed, including any ongoing and planned trials. The two products to be discussed are: (1) Folotyn (pralatrexate), NDA 022468 submitted by Acrotech Biopharma Inc, indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL), and (2) Beleodaq (belinostat), NDA 206256 submitted by Acrotech Biopharma Inc, indicated for the treatment of patients with relapsed or refractory PTCL. Based on the updates provided, the committee will have a general discussion about delayed confirmatory trials as well as a focused discussion on next steps for the two products, Folotyn (pralatrexate) and Beleodaq (belinostat), approved for PTCL. The overall goal will be the continued optimization of the accelerated approval process with a focus on decreasing the amount of time to

verify (or fail to verify) clinical benefit while continuing to provide early availability of promising oncology products. The topic of the meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interest(s):

Dr. Thanarajasingam is employed by Mayo Clinic. She is listed as a co-investigator on most lymphoma related studies at her institution. She receives no salary support or personal remuneration for her role as co-investigator. The funding per year for the studies varies dependent on patient accrual and projected study completion date. Her institution is participating in the following studies that potentially can be affected by the particular matters before the advisory committee:

- "Phase I Trial of Systemic Administration of Vesicular Stomatitis Virus Genetically Engineered to Express Sodium Ion Symporter (NIS) and Human Interferon, in Patients With Relapsed or Refractory Multiple Myeloma, Acute Myeloid Leukemia, and T-Cell Neoplasms" [MC1684] (NCT03017820) sponsored by the National Institutes of Health. The study has been ongoing since January 2017. Mayo Clinic receives between $500,000 and $700,000 per year.
- "Phase 2 Single-Arm, Open-Label Study of Nivolumab in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma" [MC1681] (NCT03075553) sponsored by Effector. The study has been ongoing since February 2017. Mayo Clinic receives between $0 and $50,000 per year.
- "A Phase 1 Study of SGN-TGT in Subjects With Advanced Malignancies" (SGNTGT-001) [NCT04254107] sponsored by Seattle Genetics, a competing firm. The study has been ongoing since July 2020. Mayo Clinic receives between $100,000 and $300,000 per year.
- "A First-in-Human, Open Label, Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Clinical Activity of HH2853, an EZH1/2 Inhibitor, in Patients With Relapsed/Refractory Non-Hodgkin's Lymphomas or Advanced Solid Tumors" (HH2853-G101) [NCT04390737] sponsored by Shanghai Hai He. The study has been ongoing since September 2020. Mayo Clinic receives between $50,000 and $100,000 per year.
- "A Phase 1/2, Multicenter, Open-label Study to Assess Safety, Pharmacokinetics, and Preliminary Efficacy of CC-220, Alone and in Combination with an Anti-CD20 Monoclonal Antibody in Subjects With Relapsed or Refractory Lymphomas" (CC-220-NHL-011) [NCT04464798] sponsored by Celgene, a competing firm. The study has been ongoing since January 2021. Mayo Clinic receives between $0 and $50,000 per year.
- "Single-Arm, Phase 2 Study of Valemetostat Tosylate Monotherapy in Subjects with Relapsed/Refractory Peripheral T-Cell Lymphoma (VALENTINE-PTCL01)" (DS3201-A-U202) [NCT04703192] sponsored by Daiichi Sankyo, a competing firm. The study has been ongoing since October 2021. Mayo Clinic receives between $0 and $50,000 per year.
- "Phase 1/2 Study of 9-ING-41, a Glycogen Synthase Kinase-3 Beta (GSK-3β) Inhibitor, as a Single Agent and Combined With Chemotherapy, in Patients With Refractory Hematologic Malignancies or Solid Tumors" (Actuate 1801) [NCT03678883] sponsored by Actuate Therapeutics. The study has been ongoing since March 2019. Mayo Clinic receives between $300,000 and $500,000 per year.
- "A Phase Ia/b Trial to Evaluate the Safety and Tolerability of CG-806 in Patients With CLL/SLL or Non-Hodgkin's Lymphomas" (APTO-CG-806-01) [NCT03893682] sponsored by Aptose. The study has been ongoing since November 2019. Mayo Clinic receives between $0 and $50,000 per year.
- (b) (4)

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This study is still in development. Mayo Clinic is projected to receive between (b) (4) per year.

Basis for Granting the Waiver:

Dr. Gita Thanarajasingam has unique qualifications and specialized expertise needed for this particular matter.

Dr. Gita Thanarajasingam is Associate Professor of Medicine at Mayo Clinic College of Medicine and Science and Consultant, Division of Hematology in the Department of Internal Medicine at Mayo Clinic. She is a lymphoma clinician and health outcomes researcher at Mayo Clinic and serves as a co-Investigator on most lymphoma protocols to be able to enroll patients.

Dr. Thanarajasingam earned a Bachelor of Science in Research Intensive: Molecular, Cellular, & Developmental Biology from Yale University. She earned her medical degree from Mayo Medical School, Mayo Clinic College of Medicine, and completed her Internal Medicine Residency at Brigham and Women's Hospital, Harvard Medical School. She further completed a Hematology/Oncology Fellowship Program and an Advanced Hematology Fellowship - Lymphoma with Mayo Clinic, Rochester, Minnesota. She is board certified in Internal Medicine, Hematology and Medical Oncology.

Dr. Thanarajasingam's research interests are in Hodgkin's and non-Hodgkin's lymphoma, adverse event analysis in cancer clinical trials, patient-oriented outcomes research as well as therapeutic and cancer control clinical trials. While she is a lymphoma clinician, she also focuses on translational health outcomes research to improve patients' experience of cancer treatment. As part of her fellowship, she developed a novel, longitudinal statistical approach to evaluating the toxicity of cancer therapy called Toxicity over Time (ToxT). She expanded this work to also include patient-reported toxicity data. Dr. Thanarajasingam is a recognized leader in advocating for a more compressive approach to analysis of adverse events. In 2018, she led an international *Lancet Haematology* Commission to generate awareness and action around the world.

Dr. Thanarajasingam is uniquely qualified by having the specialized knowledge and research experiences in blood disorders, hematologic malignancies, and lymphoma. Dr. Thanarajasingam's expertise in hematologic malignancies will be helpful in understanding the issues around safety and efficacy of pralatrexate and belinostat, the continued availability under accelerated approval, and the need to verify clinical benefit. Further, the information being discussed relates to the conduct of confirmatory trials in patients with peripheral T-cell lymphoma. Dr. Thanarajasingam possesses the expertise to provide context to the information being discussed, which will allow her to provide valuable insight and understanding to the issues brought to the Committee. Hematologists, such as Dr. Thanarajasingam, with knowledge of the PTCL treatment landscape and the safety and efficacy of treatments administered to these patients is needed to provide context to the data and information presented to the Committee. Finally, Dr. Thanarajasingam's professional expertise in clinical trial conduct and research in patients with hematologic malignancies combined with her experiences

with treating these patients will be invaluable to a robust and productive discussion on the issue coming before the Committee.

The particular matter is sensitive.

The particular matter is considered to be sensitive, as the FDA Division responsible for review of these products expects the meeting is likely to receive significant public interest, (non-trade) press interest, significant congressional interest, and may be considered highly controversial. 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. The advisory committee meeting will discuss Folotyn (pralatrexate) and Beleodaq (belinostat) that received accelerated approval and are delayed in fulfilling their post-marketing requirements, and whether clinical benefit has been demonstrated.

Dr. Gita Thanarajasingam's expertise in this particular matter is necessary in the interest of public health.

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoproliferative disorders arising from mature T-cells, accounting for about 10% of non-Hodgkin lymphoma (NHL). PTCL-not otherwise specified (PTCL-NOS; 26%) is the most common subtype, followed by angioimmunoblastic T-cell lymphoma (AITL; 19%), anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive (7%), ALCL, ALK-negative (6%), and enteropathy-associated T-cell lymphoma (EATL; <5%). In the 2017 WHO classification, nodal PTCL with T-follicular helper (TFH) phenotype (PTCL, TFH) and follicular T-cell lymphoma (FTCL) are also included as provisional entities of TFH origin (which were previously classified as PTCL-NOS).

Most PTCLs are considered aggressive types of NHL. In general, PTCL is associated with a poor prognosis, with a 5-year survival rate of approximately 30% to 40%. PTCLs are often curable with systemic therapy, though effective treatment options are more limited, particularly in the relapsed or refractory setting. Treatment options for relapsed or refractory PTCL include the following: combination chemotherapy, antibody conjugates (brentuximab vedotin for CD30-positive patients), histone deacetylase inhibitors (romidepsin, belinostat), dihydrofolate reductase inhibitors (pralatrexate), anti-CD52 monoclonal antibodies (alemtuzumab which is only available through a restricted distribution program), or stem cell transplant.

Folotyn (pralatrexate) and Beleodaq (belinostat) are currently FDA-approved therapies under 21 CFR 314.500 (subpart H, accelerated approval regulations) for the treatment of patients with relapsed or refractory PTCL.

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

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Gita Thanarajasingam's *expertise in this matter.*

The Committee will discuss the accelerated approval program in oncology and the two products, Folotyn (pralatrexate) and Beleodaq (belinostat), which are approved for the treatment of patients with relapsed or refractory PTCL under 21 CFR 314.500 (subpart H, accelerated approval regulations) that have not met their agreed-upon milestones for completion of confirmatory trial(s). A productive discussion will depend upon having strong expertise in the area of hematology, which Dr. Thanarajasingam possesses. Her expertise in non-Hodgkin lymphomas and knowledge of the treatment landscape are very important for assessing the overall safety and efficacy of the products for discussion.

Dr. Thanarajasingam has served as a temporary voting member at multiple meetings of the ODAC since 2016. Her diverse collection of previous experiences with advisory meetings in combination with a strong foundation in Hematology Oncology will ensure an expansive level of expertise and objectivity required to provide expert advice and recommendations to the Agency. Dr. Thanarajasingam's professional expertise in clinical trial conduct and her research and experiences with treating patients with hematologic malignancies will be invaluable to a robust and productive discussion on the issue coming before the committee.

Accordingly, I recommend that you grant Dr. Gita Thanarajasingam, a temporary member of the Oncologic Drugs Advisory Committee, a waiver from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

__X__ 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.

Rachel S. Bressler -S Digitally signed by Rachel S. Bressler -S Date: 2023.10.27 19:16:16 -04'00'

Rachel Bressler
Acting Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

October 27, 2023
Date