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

DATE: March 22, 2022

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 Temporary Voting Member: **Gita Thanarajasingam, M.D.**

Committee: Oncologic Drugs Advisory Committee

Meeting date: April 22, 2022

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 the use in the treatment of cancer and make appropriate recommendations to the Commissioner of Food and Drugs.

On April 22, 2022, the committee will discuss supplemental new drug application (sNDA) 213176/S-002, for Ukoniq (umbralisib) tablets, and biologics license application (BLA) 761207, for ublituximab injection, both submitted by TG Therapeutics, Inc. The proposed indication (use) for these two products is in combination for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). In addition, the committee will also discuss the existing umbralisib indications in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma under 21 CFR 314.500 (subpart H, accelerated approval regulations). The matters under review by the advisory committee are particular matters involving a specific party.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Thanarajasingam is employed by Mayo Clinic. She is listed as a co-investigator on most lymphoma related studies at her institution to be able to enroll patients. 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. Her institution is participating in the following studies that potentially can be affected by the particular matters before the advisory committee:

- "A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Placebo in Subjects With Relapsed/Refractory Indolent Lymphoma (The AUGMENT Study)" (NCT01938001) sponsored by Celgene, a competing firm. The study began in April 2014 and the trial is closed to enrollment, but patients are in follow-up. Mayo Clinic receives between $0 and $50,000 per year.
- "An Open-Label, Multi-Center Phase 1 Study to Investigate the Safety and Tolerability of REGN1979, an Anti-CD20 x Anti-CD3 Bispecific Monoclonal Antibody, in Patients With CD20 B-Cell Malignancies Previously Treated With CD20-Directed Antibody Therapy" (NCT02290951) sponsored by Regeneron, a competing firm. The study began in August 2018 and is ongoing with accrual of patients anticipated to being met in 2023. Mayo Clinic receives between $350,000 and $450,000 per year.
- "A Phase II Study of Anti-PD-1 Antibody (MK-3475) in Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) and Other Low Grade B Cell Non-Hodgkin Lymphoma (NHL)" (NCT02332980) sponsored by National Cancer Institute (NCI). The study began in January 2015 and is ongoing with accrual of patients anticipated being met in 2023. Mayo Clinic receives between $100,000 and $300,000 per year.
- "A Phase 1b/2 Proof-of-Concept Study of the Combination of ACP-196 and Pembrolizumab in Subjects With Hematologic Malignancies" (NCT02362035) sponsored by Acerta, a competing firm. The study began in January 2015 and the trial is closed to enrollment, but patients are in follow-up. Mayo Clinic receives between $100,000 and $300,000 per year.
- "A Phase I, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Subjects with B-Cell Lymphoid Malignancies" (NCT02343120) sponsored by Beigene, a competing firm. The study began in September 2016 and is anticipated to close in May of 2022. Mayo Clinic receives between $100,000 and $300,000 per year.
- "A Randomized Phase 2 Study Comparing Acalabrutinib to Acalabrutinib and Obinutuzumab in the Treatment of Patients With Early-Stage Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Who Are at High Risk of Disease Progression" (NCT03516617) sponsored by Acerta and National Cancer Institute/National Institutes of Health (NCI/NIH). Acerta provides the primary funding while NCI provides minimal funding. The study began in April 2018 and accrual is anticipated being met in 2024. Mayo Clinic receives between $500,000 and $600,000 per year.
- "A Randomized Phase II Trial in Early Relapsing or Refractory Follicular Lymphoma" (NCT03269669). This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by NCI. Dr. Thanarajasingam's site never enrolled a patient on the trial and her institution is working on closing out the study. The study began in December 2017 with anticipated closure in August 2022 but the study is closed to accrual and the Mayo Clinic is working on financial close out. Mayo Clinic receives between $0 and $50,000 per year for (b) (4) costs and (b) (4) costs.

- "An Open-Label, Dose Escalation and Dose Expansion Trial Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of Orally Administered CA-4948 in Patients with Relapsed or Refractory Hematologic Malignancies" (NCT03328078) sponsored by Curis, a competing firm. The study began in March 2018 and the institution anticipates accrual being met in 2023. Mayo Clinic receives between $100,000 and $300,000 per year.
- "A Phase Ia/Ib, Phase Ib Expansion Cohorts Studies of a Novel BTK Inhibitor, DTRMWXHS-12, and Combination Products DTRM-505 and DTRM-555, in Patients with Chronic Lymphocytic Leukemia or Other B-cell Lymphomas" (NCT02900716) sponsored by Zhejiang/ DTRM Biopharma, a competing firm. The study began in July 2018 and is ongoing with anticipated accrual being met in 2023. Mayo Clinic receives between $100,000 and $300,000 per year.
- "A Combined Phase 1/2 Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of TP-0903 in Patients With Previously Treated Chronic Lymphocytic Leukemia (CLL)" (NCT03572634) sponsored by Tolero, a competing firm. The study began in October 2018 and is anticipated to end in August 2022. The study is closed to accrual and the institution is working on financial closeout. Mayo clinic receives between $100,000 and $300,000 per year.
- "A Phase Ib/II, Open-Label, Multicenter, Randomized, Controlled Study Investigating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Mosunetuzumab (BTCT4465A) in Combination With CHOP or CHP-Polatuzumab Vedotin in Patients With B-Cell Non-Hodgkin Lymphoma" (NCT03677141) sponsored by Genentech, a competing firm. The study began in May 2019 and is anticipated to end August 2022 with the study closed to accrual. Mayo Clinic receives between $100,000 and $300,000 per year.
- "A Randomized Phase III Study of Ibrutinib Plus Obinutuzumab Versus Ibrutinib Plus Venetoclax and Obinutuzumab in Untreated Older Patients (>/= 70 Years of Age) With Chronic Lymphocytic Leukemia (CLL)" (NCT03737981) sponsored by Eastern Cooperative Oncology Group (ECOG)/NCI/NIH. The study began in June 2020 and accrual anticipated to be met in 2024. Mayo clinic receives between $0 and $50,000 per year.
- "An Open-label Study to Assess the Anti-Tumor Activity and Safety of REGN1979, an Anti-CD20 X Anti-CD3 Bispecific Antibody, in Patients with Relapsed or Refractory B-cell Non-Hodgkin Lymphoma" (NCT03888105) sponsored by Regeneron, a competing firm. The study opened in June 2019 and accrual anticipated to be met in 2023. Mayo clinic receives between $100,000 and $300,000 per year.
- "A Phase 1b/2 Study of TAK-981 in Combination With Rituximab in Patients With Relapsed/Refractory CD20-positive Non-Hodgkin Lymphoma" (NCT04074330) sponsored by Millennium Pharma, a competing firm. The study began in March 2020 and accrual anticipated to be met in 2023. Mayo clinic receives between $300,000 and $400,000 per year.
- "A Phase 1/2 Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of ARQ 531 in Selected Subjects with Relapsed or Refractory Hematologic Malignancies" (NCT03162536) sponsored by Arqule, a competing firm. The study began in April 2020 and accrual anticipated to be met in 2023. Mayo Clinic receives between $100,000 and $300,000 per year.

- "A Phase I, Multicenter, Open-Label, Dose Escalation Study of a Novel Bruton's Tyrosine Kinase Inhibitor, ICP-022, in Patients With Relapsed/Refractory B-Cell Malignancies" (NCT04014205) sponsored by InnoCare Pharma, a competing firm. The study began in February 2020 and accrual anticipated to be met in 2023. Mayo Clinic receives between $300,000 and $400,000 per year.
- "A Multi-Center, Open Label Phase 1/2 Study of CYT-0851, an Oral RAD51 Inhibitor, in Patients With Relapsed/Refractory B-Cell Malignancies and Advanced Solid Tumors" (NCT03997968) sponsored by Cyteir, a competing firm. The study began in July 2020 and accrual anticipated to be met in 2023. 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" (NCT04390737) sponsored by Shangai HaiHe, a competing firm. The study began in October 2020 and accrual anticipated to be met in 2023. Mayo Clinic receives between $50,000 and $100,000 per year.
- "A Phase Ib Trial of Low-Dose Selinexor (KPT-330) in Combination With Choline Salicylate (CS) for the Treatment of Patients With Residual/Relapsed/Refractory Non-Hodgkin Lymphoma (NHL)" (NCT04640779) sponsored by Karyopharm, a competing firm. The study began in November 2020 and accrual anticipated to be met in 2023. Mayo Clinic receives between $100,000 and $300,000 per year.
- "Open-label, Multi-center, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients With B-cell Malignancies" (NCT04170283) sponsored by Beigene, a competing firm. The study began in November 2020 and is closed to accrual, however long term follow up as an extension of NCT02343120 is ongoing. 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 (mAb) in Subjects With Relapsed or Refractory Lymphomas" (NCT04464798) sponsored by Celgene, a competing firm. The study began in February 2021 and accrual anticipated to be met in 2023. Mayo Clinic receives between $50,000 and $100,000 per year.
- "A Phase 1/2 Study of Oral LOXO-305 in Patients With Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL)" (NCT03740529) sponsored by LOXO Oncology, a competing firm. The study began in May 2021 and accrual anticipated to be met in 2025. Mayo Clinic receives between $100,000 and $300,000 per year.
- "A Phase 3B Randomized Study of Lenalidomide (CC-5013) Plus Rituximab Maintenance Therapy Followed by Lenalidomide Single-Agent Maintenance Versus Rituximab in Subjects With Relapsed/Refractory Follicular, Marginal Zone, or Mantle Cell Lymphoma (The MAGNIFY Study)" (NCT01996865), sponsored by Celgene, a competing firm. The study began in May 2017 and anticipated to end in 2024. The study is closed to accrual but patients are on long-term follow up. Mayo Clinic receives between $0 and $50,000 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" (NCT03893682), sponsored by Aptose, a

competing firm. The study began in January 2019 and anticipated to end in 2023. Mayo Clinic receives between $50,000 and $100,000 per year.

- "A Phase 1 Study of Oral LOXO-338, a Selective BCL-2 Inhibitor, in Patients With Advanced Hematologic Malignancies" (NCT05024045), sponsored by LOXO Oncology, a competing firm. The study began in December 2021 and anticipated to end in 2024. Mayo Clinic receives between $100,000 and $300,000 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 Assistant Professor of Medicine, Mayo Clinic College of Medicine and Sciences and Consultant, Division of Hematology, Department of Internal Medicine, Mayo Clinic. She is a lymphoma clinician and health outcomes researcher at Mayo Clinic and serves as a Co-Investigator on most lymphoma protocols so that she may enroll her 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.

Her research interests are in Hodgkin and non-Hodgkin 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 translation 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.

The committee will discuss umbralisib (Ukoniq) and ublituximab in combination for the treatment of adult patients with CLL or SLL. In addition, the committee will discuss the existing umbralisib indications for relapsed or refractory follicular lymphoma and marginal zone lymphoma. Her expertise in assessing safety and analysis of safety in hematologic malignancies and her expertise non-Hodgkin lymphoma are very important to assess the overall safety and efficacy of the products for discussion. Dr. Thanarajasingam's knowledge of the treatment landscape and safety and efficacy of hematologic malignancies is needed to provide a meaningful discussion at the meeting.

The particular matter is sensitive.

The FDA Division responsible for review of umbralisib and ublituximab does expect the matter coming before the committee to 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 Division seeks ODAC input on the risk-benefit of the combination in the proposed indication and how the current information impacts the existing indications under accelerated approval.

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

Non-Hodgkin lymphoma (NHL) is one of the most common cancers in the United States, accounting for about 4% of all cancers. The American Cancer Society's estimates for Non-Hodgkin Lymphoma in 2022 are about 80,470 people (both adults and children) will be diagnosed with NHL and about 20,250 people will die from this cancer. There are an estimated 672,980 people living with or in remission from non-Hodgkin lymphoma. Indolent lymphomas are slow-moving and tend to grow more slowly and have fewer signs and symptoms when first diagnosed. Slow-growing or indolent subtypes represent about 40 percent of all NHL cases. Indolent NHL subtypes include but are not limited to Follicular lymphoma (FL), which is the most common subtype of indolent NHL, followed by Marginal Zone Lymphoma (MZL) and Chronic Lymphocytic Leukemia or Small-Cell Lymphocytic Lymphoma (CLL/SLL).

Chronic lymphocytic leukemia or small lymphocytic lymphoma is an indolent malignancy characterized by increased production of mature but dysfunctional B lymphocytes. CLL comprises 25 to 30% of total leukemias in the United States. According to the American Cancer Society, in 2021 there were an estimated 21,250 new CLL cases and about 4,320 deaths from CLL. Patients with CLL or SLL are not cured with conventional therapy, and most will relapse eventually.

There are many current first-line treatment options for CLL or SLL. Active treatment is started if the patient begins to develop disease-related symptoms or there are signs that the disease is progressing based on testing during follow-up visits. The choice of treatment depends on the stage of the disease, the patient's symptoms, the age and overall health of the patient, and the benefits versus side effects of treatment. The treatment landscape has also expanded with the development of targeted agents, in addition to the traditional chemotherapy agents. For relapsed or refractory disease, treatment may incorporate one or more of the following targeted agents, often administered as combinations: Bruton tyrosine kinase inhibitors, phosphoinositide 3'-kinase (PI3K) inhibitors, BCL2 inhibitors and anti-CD-20 monoclonal antibodies.

For lymphoma, about 1 out of 5 lymphomas in the United States (U.S.) is a follicular lymphoma. FL is the second common form of NHL in the U.S. with an estimated incidence of six new cases/ 100,000 persons/year. The vast majority of patients treated for FL will have an initial response to therapy with 40 to 80 percent demonstrating a complete response, depending on the initial regimen used. However, conventional therapy for FL is not curative and most of these patients will ultimately develop progressive disease. In addition, less than 10 percent of patients treated

with initial chemoimmunotherapy will not respond to treatment (i.e., refractory disease). Marginal zone lymphomas account for about 5% to 10% of lymphomas. MZL is the second most common indolent non-Hodgkin's lymphoma which accounts for approximately eight percent of all NHL cases. Although conventional first-line treatment options are proved beneficial, many the patients become resistant to or experience a relapse following treatment.

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 coming 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 information being discussed relates to safety and efficacy outcomes in patients with hematologic malignancies, diseases of the blood, bone marrow, and/or immune system, which can have unique safety and efficacy considerations given the underlying disease and the treatments administered to these patients. Multiple PI3K inhibitors have been approved for the treatment of patients with hematologic malignancies. Hematologists with knowledge of the treatment landscape and the safety and efficacy of treatments administered to these patients are needed to provide context to the data and information presented at the ODAC. Multiple hematologist/oncologists were invited but either declined due to schedule conflicts or had financial interests creating more significant conflicts. Dr. Thanarajasingam possesses the expertise to provide context to the safety and efficacy data being discussed, which will allow her to provide valuable insight and understanding to the issues brought to the committee. Her expertise in hematologic malignancies will be helpful in understanding the assessment of benefit and risk, and the overall clinical trial design concepts being discussed in order to provide informative insight.

Accordingly, I recommend that you grant Dr. Gita Thanarajasingam, a temporary 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 interests involved.

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

_____ Non-voting

_____ Other (specify):

_____

_____

_____ Denied – The individual may not participate.

Russell Fortney -S Digitally signed by Russell Fortney -S Date: 2022.04.05 10:00:35 -04'00'

April 5, 2022

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

Date