Company: G1 Therapeutics
Address: 700 Park Offices Drive, Suite 200, Research Triangle Park, NC 27709
Phone: 1 (917) 678-5884
E-mail: mchioda@g1therapeutics.com
Date of Request: February 12, 2021
NCCN Guidelines Panel: Small Cell Lung Cancer (SCLC)
Subject: Submission Request - SCLC

Dear NCCN SCLC Panel:

On behalf of G1 Therapeutics, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Small Cell Lung Cancer (SCLC) to review the enclosed data for inclusion of trilaciclib (COSELA™) as a preferred option to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC). This request is in accordance with the FDA approved label and it is based on the results of three randomized, double-blind, placebo-controlled clinical studies demonstrating reduced myelosuppression of patients with ES-SCLC undergoing frontline or subsequent systemic therapy [1-4].

Specific Changes Requested: We respectfully request for trilaciclib to be included as a preferred option to decrease incidence of chemotherapy-induced myelosuppression in regimens containing platinum + etoposide +/- checkpoint inhibition; or a topotecan-containing regimen on the following pages in the current SCLC guidelines: **SCL-D** (Principles of Supportive Care), **SCL-E1** (Principles of Systemic Therapy, Primary Therapy for Extensive Stage SCLC), and **SCL-E2** (Principles of Systemic Therapy, SCLC Subsequent Systemic Therapy) and relevant discussion sections.

FDA Approval: Trilaciclib is a kinase inhibitor indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC). [1].

Rationale: Trilaciclib can help provide protection against myelosuppression in ES-SCLC patients receiving regimens containing platinum + etoposide +/- checkpoint inhibition; or a topotecan-containing regimen. As highlighted below, trilaciclib was associated with reduced myelosuppression endpoints across three randomized, double-blind, placebo-controlled clinical trials of adult patients with ES-SCLC [1-4]. Overall, trilaciclib provides an effective myeloprotective option for ES-SCLC patients receiving regimens containing platinum + etoposide +/- checkpoint inhibition; or a topotecan-containing regimen.

Summary of Evidence:

Trilaciclib was investigated in three randomized, double-blind, placebo-controlled clinical trials of adult patients with SCLC; Study 1 (G1T28-05) [2] in patients receiving carboplatin, etoposide and atezolizumab for newly diagnosed ES-SCLC, Study 2 (G1T28-02) [3] in patients receiving etoposide/carboplatin for newly diagnosed ES-SCLC, and Study 3 (G1T28-03) [4] in patients receiving topotecan for previously treated ES-SCLC. In these studies, prophylactic G-CSF or ESA use was not allowed in cycle 1 and was allowed beyond cycle 1; therapeutic G-CSF was allowed in cycle 1. Transfusions were allowed throughout the studies. The primary endpoints were the duration and occurrence of severe neutropenia in Study 1 and 3. Study 2 was a proof-of-concept study and did not have specified primary endpoints.

Myeloprotective Efficacy Results In Patients Treated With Trilaciclib Or Placebo Prior To Chemotherapy (Intent-To-Treat Analysis)

	Study 1 [1]**:** carboplatin, etoposide and atezolizumab	**Study 2** [3]**:** carboplatin/ etoposide	**Study 3** [4]**:** Topotecan
	Trilaciclib vs. Placebo		
Number of patients (N)	54 vs. 53	39 vs. 38	32 vs. 29
Mean duration of severe G4 neutropenia in cycle 1 (days)	0 vs. 4 (P<0.0001)	0 vs. 3	2 vs. 7
% patients with severe G4 neutropenia	2 vs. 49 (P<0.0001)	5 vs. 42	41 vs. 76
% patients with G-CSF administration	30 vs. 47	10 vs. 65	50 vs. 66
% patients with ESA administration	6 vs. 11	3 vs. 5	3 vs. 21
% patients with RBC transfusions on/after week 5	13 vs. 21	5 vs. 24	31 vs. 41
% patients with Grade 3/4 anemia	19 vs 28	10 vs. 18	38 vs. 59

Safety

Trilaciclib is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib. Warnings and precautions include injection-site reactions (phlebitis and thrombophlebitis), acute drug hypersensitivity reactions, interstitial lung disease/pneumonitis, and embryofetal toxicity. In the pooled safety analysis of Studies 1, 2 & 3 (n= 122), serious adverse reactions (ARs) occurred in 30% of patients. The most common ≥ Grade 3 AR (≥5%) in patients receiving trilaciclib occurring at the same or higher incidence than in patients receiving placebo was hypophosphatemia. Fatal ARs were observed in 5% in the trilaciclib group (pneumonia: 2%, respiratory failure: 2%, acute respiratory failure: <1%, hemoptysis: <1%, cerebrovascular accident: <1%). The most common ARs (≥ 10% of patients with ≥2% difference in incidence compared to placebo) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia. [1].

The following resources are included in support of the requested changes:

1. COSELA™ (trilaciclib) Prescribing Information. G1 Therapeutics, Research Triangle Park, NC. 2021
2. Daniel D, Kuchava V, Bondarenko I et al. Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: A multicentre, randomised, double-blind, placebo-controlled Phase II trial. Int J. Cancer. 2020;1-14. . doi: 10.1002/ijc.33453.
3. Weiss JM, Csoszi T, Maglakelidze M et al. Myelosuppresion with the CDK4/6 inhibitor Trilaciclib in Patients with Small-Cell Lung Cancer Receiving First-Line Chemotherapy: a Phase Ib/ Randomized Phase II Trial. Ann Oncol. 2019 ;30(10):1613-1621.
4. Hart LL, Ferrarotto R, Andric ZG et al. Myelopreservation with Trilaciclib in patients receiving topotecan for small cell lung cancer: Results from a randomized, double-blind, placebo-controlled phase II study. Adv Ther. 2020.. doi:10.1007/s12325-020-01538-0.

We greatly appreciate the Panel's through consideration of the data for trilaciclib (COSELA™).

Sincere regards,

Marc Chioda, PharmD
Vice President Medical Affairs | G1 Therapeutics, Inc.
Cell 917-678-5884 | mchioda@g1therapeutics.com