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Date of Request: September 18, 2020
NCCN Guidelines Panel: Hematopoietic Growth Factors
Subject: Submission Request - Hematopoietic Growth Factors

Dear NCCN Hematopoietic Growth Factors Panel:

On behalf of G1 Therapeutics, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Hematopoietic Growth Factors to review the enclosed data for inclusion of trilaciclib, currently an investigational drug, as a preferred option for the prevention of chemotherapy-induced myelosuppression from SCLC treatment regimens containing platinum + etoposide +/- checkpoint inhibitor; or a regimen containing topotecan. This request is based on the results of three randomized, double-blind, placebo-controlled clinical studies demonstrating multilineage myelopreservation of patients with SCLC undergoing frontline or subsequent systemic therapy [1-3].

Specific Changes Requested: We respectfully request trilaciclib to be included as a preferred option in the footnotes on the following pages in the current HGF guidelines: **MGF-1** (Prior to First Chemotherapy Cycle), **MGF-3** (Prior to Second and Subsequent Chemotherapy Cycles) and **MGFA, 1&2/5** (Under Small Cell Lung Cancer regimens) and as a new pathway in **ANEM-1** as preferred option for the prevention of chemotherapy induced myelosuppression from regimens containing platinum + etoposide +/- checkpoint inhibition; or a regimen containing topotecan.

FDA Priority Review of the Trilaciclib NDA: Trilaciclib was granted Breakthrough Therapy Designation for the mitigation of clinically significant chemotherapy-induced myelosuppression in adult patients with small cell lung cancer. A New Drug Application (NDA) has been accepted for Priority Review by the FDA and assigned a Prescription Drug User Fee Act (PDUFA), or target action date of February 15, 2021.

Rationale: Trilaciclib can provide protection against both neutropenia and anemia in SCLC patients receiving regimens containing platinum + etoposide +/- checkpoint inhibitor; or a topotecan-containing regimen. As highlighted below, trilaciclib was associated with significantly lower duration of severe neutropenia, occurrence of severe neutropenia, occurrence of febrile neutropenia, G-CSF use, ESA use, red blood cell (RBC) transfusions, and grade 3/4 decreased hemoglobin across three randomized, double-blind, placebo-controlled clinical trials of adult patients with SCLC. [1-3] Overall, trilaciclib provides a safe and effective myelopreservation option for SCLC patients receiving regimens containing platinum + etoposide +/- checkpoint inhibitor; 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) [1] in patients receiving carboplatin, etoposide and atezolizumab for newly diagnosed ES-SCLC, Study 2 (G1T28-02) [2] in patients receiving etoposide/carboplatin for newly diagnosed ES-SCLC, and Study 3 (G1T28-03) [3] 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. Pooled data from all three studies were evaluated to provide more precise estimates of trilaciclib treatment effects for low frequency RBC-related events and to assess consistency of treatment effect by trilaciclib across relevant subgroups [4].

Myelopreservation 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** [2]: carboplatin/ etoposide	**Study 3** [3]**:** Topotecan	**Pooled analysis of all three studies** [4]
	Trilaciclib (240 mg/m^2) vs. Placebo			
Number of patients (N)	54 vs. 53	38 vs. 37	32 vs. 29	123 vs. 119
Mean duration of severe G4 neutropenia in cycle 1 (days)	0 vs. 4 (P<0.0001)	0 vs. 3 (P<0.001)	2 vs. 8 (P<0.0001)	0 vs. 4 (P<0.0001)
% patients with severe G4neutropenia	2 vs. 49 (P<0.0001)	5 vs. 43 (P<0.0001)	41 vs. 76 (P=0.016)	11 vs. 53 (P<0.0001)
% patients with febrile neutropenia TEAE	2 vs. 6	3 vs. 8	6 vs. 17	3 vs. 9 (P=0.089)
% patients with G-CSF administration	30 vs. 47	11 vs. 65	50 vs. 66	29 vs. 56 (P<0.0001)
% patients with ESA administration	6 vs. 11	3 vs. 5	3 vs. 31	3 vs. 12 (P=0.025)
% patients with RBC transfusions on/after week 5	13 vs. 21	5 vs. 24	31 vs. 41	15 vs. 26 (P=0.025)
% patients with Grade 3/4 anemia	19 vs 28	11 vs. 19	39 vs. 63	20 vs. 32 (P=0.028)

Anti-tumor efficacy results, including overall response rate, progression-free survival, and overall survival, were comparable between SCLC patients receiving trilaciclib or placebo across the three clinical trials. [4]

Safety

In the pooled safety analysis of Studies 1, 2 & 3 (Trilaciclib n= 122; placebo n=118), serious treatment emergent adverse events (TEAEs) occurred in 30% and 25% of patients, respectively. The most common non-hematological Treatment Emergent Adverse Events (TEAE) (≥ 20 % of patients) in the trilaciclib or placebo groups include nausea (34% vs 33%), fatigue (34% vs 27%) and alopecia (13% vs. 25%). Fatal TEAEs occurred in 5% in the trilaciclib group and 3% in the placebo group [4].

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

1. Daniel D, Kuchava V, Bondarenko I et al. Trilaciclib Decreases Myelosuppresion in Extensive-Stage Small Cell Lung Cancer (ES-SCLC) Patients Receiving First-Line Chemotherapy Plus Atezolizumab [Poster Presentation]. European Society of Medical Oncology (ESMO). October, 2019; Barcelona, Spain.
2. 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.
3. Hart LL, Andric ZG, Hussein MA et al. Effect of Trilaciclib, a CDK4/6 Inhibitor, on Myelosuppresion in Patients with Previously Treated Extensive-Stage Small Cell Lung Cancer [Oral Presentation]. Presented at: American Society of Clinical Oncology (ASCO). June 2019; Chicago, US
4. Weiss J, Goldschmidt J, Andric Z et al. Myelopreservation and Reduced Use of Supportive Care with Trilaciclib in Patients with Small Cell Lung Cancer [Poster Presentation]. Presented at: American Society of Clinical Oncology (ASCO). May 2020.

We greatly appreciate the Panel's through consideration of the data for trilaciclib.

Sincere regards,

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