NEW DRUG APPROVAL

Brand Name	Cosela™
Generic Name	trilaciclib
Drug Manufacturer	G1 Therapeutics, Inc.

New Drug Approval

FDA Approval Date: February 12, 2021

Review Designation: Priority

Type of Review: Type 1 - New Molecular Entity, New Drug Approval (NDA): 214200

Dispensing Restrictions: Specialty Primarily, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Small cell lung cancers (SCLCs) account for roughly 13% of all lung cancers and are primarily diagnosed in smokers or former smokers. They differ from other types of lung cancer in that they spread very quickly throughout the body via the blood and lymphatic system, and it is important to accurately determine the stage of SCLC before definitive therapy can begin.

- Limited-stage SCLC (LS-SCLC) is confined to a single location in the chest that is not detectable outside the lung. Patients with this type of cancer are potentially curable, although many patients have undetectable areas of cancer outside of the chest at the time of diagnosis. The median overall survival with LS-SCLC has historically been about 20 months.
- Extensive-stage SCLC (ES-SCLC) occurs when the cancer has spread to both lungs or is detectable beyond the lungs. Although many patients experience a response to treatment, available standard treatments are rarely curable with ESSCLC. Because the cancer has spread outside the chest, it can't be surgically removed or eliminated with radiation.

Lung cancer is the second most common cancer in men and women. About 229,000 patients are diagnosed with lung cancer each year in the United States (this number includes people diagnosed with both small cell lung cancer [SCLC] and non−small cell lung cancer [NSCLC]). About 13% of people diagnosed with lung cancer have SCLC, and about 136,000 people die from lung cancer each year.

Efficacy

The approval of Cosela was based on results from a pooled analysis of intent-to-treat datasets from 3 studies (NCT02499770; NCT03041311; NCT02514447) of patients with ES-SCLC. In these studies, a total of 242 patients were randomly assigned to receive standard chemotherapy plus either trilaciclib or placebo. The studies then compared the 2 groups for the proportion of patients with severe neutropenia and the duration of severe neutropenia in the first cycle of chemotherapy.

In all 3 studies, patients who received trilaciclib had a lower chance of having severe neutropenia compared to patients who received a placebo. Among those who had severe neutropenia, patients who received trilaciclib, on average, had it for a shorter time than patients who received a placebo. Studies 1 and 2 included patients who were naïve to therapy, while Study 3 examined patients who had been on previous regimens. The following table provides a summary of the study design and patient populations.

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Trilaciclib Study Design Summaries (NCT03041311; NCT02499770; NCT02514447)			
	Study 1 (G1T28-05)	**Study 2 (G1T28-02)**	**Study 3 (G1T8-03)**
Study Design	Phase 2 international, randomized, double-blind, placebo-controlled		
Pooled Study Population*	• 242 adult patients with extensive-stage small cell lung cancer (ES-SCLC) • Across the groups: ○ 97.6% (placebo) and 92.4% (treatment) were Caucasian ○ 87.8% (placebo) and 89.9% (treatment) had an ECOG performance status of 0 or 1 ○ 77.2% (placebo) and 75.6% (treatment) did not have brain metastases		
Study Population/ Therapy Status	107 adults with newly diagnosed ES-SCLC not previously treated with chemotherapy†	77 adults with newly diagnosed ES-SCLC not previously treated with chemotherapy†	61 adults with ES-SCLC previously treated with chemotherapy†
Interventions	**Trilaciclib prior to etoposide, carboplatin, and atezolizumab (E/P/A)** **Day 1:** Carboplatin (AUC 5) + 1200 mg atezolizumab **Induction phase** (Days 1–3 of each 21-day treatment cycle; up to 4 cycles): 240 mg/m^2 trilaciclib + 100 mg/m^2 etoposide or placebo **Maintenance phase:** 1200 mg atezolizumab, given every 21 days until disease progression or unacceptable toxicity Trilaciclib was not administered during the maintenance phase.	**Trilaciclib prior to etoposide and carboplatin (E/P)** • 240 mg/m^2 trilaciclib and 100 mg/m^2 etoposide (n = 39) or placebo (n = 38) on Days 1–3 of each 21-day cycle until disease progression or unacceptable toxicity	**Trilaciclib prior to topotecan** • 240 mg/m^2 trilaciclib (n = 32) or placebo (n = 29) on Days 1–5 of each 21-day cycle of topotecan (1.5 mg/m^2) until disease progression or unacceptable toxicity

Endpoints	**Primary Endpoints:** • DSN in Cycle 1 (days): Mean (SD) • Number (%) of patients with severe neutropenia **Key Secondary Endpoints**: • Number of all-cause dose reductions, event rate per cycle • Number (%) of patients with RBC transfusion on/after 5 weeks • Number (%) of patients with G-CSF administration **Additional Endpoint (Study 3 Only)**: • Number (%) of patients with platelet transfusion
Efficacy Results*	**Median OS:** 10.6 months [95% CI, 9.1-11.7] vs. 10.6 months [95% CI; 7.9-12.8]) **Mean DSN:** 0 with trilaciclib and 4 days with placebo (*P* <.0001). Tumor responses were comparable between the treatment groups; 49.1% of patients who received trilaciclib prior to chemotherapy experienced a response versus 51.8% who were given placebo (*P* = .7879).
Safety Results*	• The majority of adverse reactions reported with trilaciclib were mild to moderate. • Serious adverse reactions occurred in 30% of patients receiving trilaciclib. • Treatment-emergent adverse events were experienced by 94.3% of those who received trilaciclib vs. 96.6% placebo. • Permanent discontinuation due to an AR occurred in 9% of patients who received trilaciclib. • Fatal ARs were observed in 5% of patients receiving trilaciclib. • Fewer patients needed treatment with IV antibiotics (19.5% vs. 23.5%, respectively.)

*The pooled safety and efficacy population included a total of 242 adults with extensive-stage small cell lung cancer (ES-SCLC) enrolled in 3 international randomized, double-blind, placebo-controlled Phase 2 trials (Study 1 [G1T28-05], Study 2 [G1T28-02], and Study 3 [G1T8-03]).
†For more details about each study population, refer to NCT03041311, NCT02499770, and NCT02514447.

Abbreviations: CI, confidence interval; DSN, duration of severe neutropenia; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RBC, red blood cell; SD, standard deviation; ULN, upper limit of normal.

Safety

ADVERSE EVENTS

The most common adverse reactions (≥10% of patients with ≥2% difference in incidence compared to placebo) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia.

WARNINGS & PRECAUTIONS

- **Injection-Site Reactions, Including Phlebitis and Thrombophlebitis**: Monitor for signs and symptoms of injection-site reactions, including phlebitis and thrombophlebitis during infusion. Stop infusion and permanently discontinue Cosela™ for severe or life-threatening reactions.
- **Acute Drug Hypersensitivity Reactions**: Monitor for signs and symptoms of acute drug hypersensitivity reactions, including edema (facial, eye, and tongue), urticaria, pruritus, and anaphylactic reactions. Withhold Cosela™ for moderate reactions, and permanently discontinue for severe or life-threatening reactions.
- **Interstitial Lung Disease (ILD)/Pneumonitis**: Patients treated with CDK4/6 inhibitors should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Interrupt and evaluate patients with new or worsening

symptoms suspected to be due to ILD/pneumonitis. Permanently discontinue Cosela™ in patients with recurrent symptomatic or severe/life-threatening ILD/pneumonitis.

- **Embryo-Fetal Toxicity**: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

Patients with a history of serious hypersensitivity reactions to Cosela™.

Clinical Pharmacology

MECHANISMS OF ACTION

Trilaciclib is a transient inhibitor of CDK 4 and 6. Hematopoietic stem and progenitor cells (HSPCs) in the bone marrow give rise to circulating neutrophils, RBCs, and platelets. HSPC proliferation is dependent on CDK4/6 activity.

Dose & Administration

ADULTS

240 mg/m2 as a 30-minute intravenous infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.

PEDIATRICS

None.

GERIATRICS

In the pooled efficacy dataset from Studies 1, 2, and 3, 46% of 123 patients randomized to COSELA were ≥65 years of age, and 49% of 119 patients randomized to placebo were ≥65 years of age. No overall differences in safety or effectiveness of COSELA were observed between these patients and younger patients.
Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

For injection: 300 mg of trilaciclib as a lyophilized cake in a single-dose vial.