Drug Monograph

Drug Name: **Cosela™ (trilaciclib) Vial**
Drug Class: **Cyclin-dependent Kinases 4 and 6 (CDK4/6) Inhibitor**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Cosela is available in a 300 mg lyophilized cake in a single-dose vial.
Manufacturer:	Distributed by: G1 Therapeutics, Inc., Durham NC 27709.
Summary of Findings:	The efficacy of Cosela was established in three, randomized, double-blind, placebo-controlled Phase 2 clinical trials in adult patients with extensive stage-small cell lung cancer (n=242) where patients were randomly assigned to either chemotherapy plus Cosela or placebo. Primary prophylactic granulocyte-colony stimulating factor (G-CSF) and erythropoiesis-stimulating agent (ESA) use was prohibited during Cycle 1 in all studies. Both were allowed during Cycle 2 onwards as clinically indicated. Therapeutic G-CSF, red blood cell (RBC), and platelet transfusions were allowed at any time as clinically indicated. To meet inclusion criteria, patients' Eastern Cooperative Oncology Group performance status had to be 0-2. Primary endpoints were: 1) Duration of severe neutropenia in Cycle 1 (days): Mean SD 2) Number (%) of patients with severe neutropenia Cosela resulted in a lower risk of developing severe neutropenia compared to placebo. In those patients who did develop severe neutropenia, the duration was shorter in those who received Cosela compared to placebo.
Status Recommendation:	☐ Clinical Edit ☐ PA Required ☐ Open Access ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

- An estimated 235,760 new cases of lung cancer will be diagnosed in 2021. Approximately 136,000 people die from lung cancer each year.
- Small cell lung cancer (SCLC) comprises approximately 14% of all lung cancers and is primarily the result of smoking.
- There are two forms of SCLC: limited-stage and extensive stage. Limited-stage SCLC (LS-SCLC) is confined to a single location in the chest and is not detectable outside the lung. Extensive-stage SCLC (ES-SCLC) is associated with bilateral lung involvement and/or metastasis outside the lungs. Chemotherapy, as opposed to radiation or surgical excision of affected tissues, is required in instances of ES-SCLC. Currently available treatment regimens indicated for ES-SCLC are rarely curative.
- Myelosuppression, or bone marrow suppression, is a common side effect observed with chemotherapy and can manifest as anemia, neutropenia, or thrombocytopenia and lead to increased risks of infection. The occurrence of any of these often leads to dose reductions, treatment delays, decreased clinical outcomes, prolonged hospital stays, and increased overall costs.
- Current mitigation strategies include the use of granulocyte colony-stimulating factors (G-CSFs), granulocyte-macrophage colony-stimulating factors (GM-CSFs), erythropoiesis-stimulating agents (ESAs) and/or blood transfusions.
- A patient's risk for development of febrile neutropenia should be evaluated prior to each chemotherapy cycle and is based on disease type, chemotherapy regimen, patient-specific factors and treatment intent. Level of risk is based on the patient's chemotherapy regimen: low (<10% risk), intermediate (10-20% risk), high (>20% risk). The National Comprehensive Cancer Network (NCCN) recommends prophylactic treatment with a G-CSF for high-risk patients and consideration based on patient-specific risk factors for those in the intermediate-risk group. ESAs are primarily utilized in cases of chemotherapy-induced anemia and are recommended by NCCN only if there is no other identifiable cause of anemia and after consideration of packed red blood cell transfusion and clinical trial enrollment, if available.
- Current NCCN guidelines provide recommendations for ES-SCLC primary therapy. Four cycles of therapy are recommended, but some patients may receive up to six cycles based on response and tolerability after 4 cycles. Below are the preferred regimens:
    - Carboplatin area under the curve (AUC) 5 day 1 plus etoposide 100 mg/m^2 days 1, 2, 3 and atezolizumab 1,200 mg day 1 – repeat every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg day 1 every 21 days
    - Carboplatin AUC 5-6 day 1 plus etoposide 80-100 mg/m^2 days 1, 2, 3 and durvalumab 1,500 mg day 1 – repeat every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days
    - Cisplatin 75-80 mg/m^2 day 1 plus etoposide 80-100 mg/m^2 days 1, 2, 3 and

durvalumab 1,500 mg day 1 – repeat every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days

- Topotecan is reserved for cases of relapse occurring 6 months or less after primary therapy.
- When utilized for SCLC, carboplatin/etoposide chemotherapeutic regimens are recognized as having an intermediate risk for febrile neutropenia (10-20%) while topotecan-containing regimens are associated with a high risk (>20%).

Dosage Form [3]

Cosela is available in a 300 mg lyophilized cake in a single-dose vial.

Manufacturer [3]

Distributed by: G1 Therapeutics, Inc., Durham NC 27709.

Indication(s) [3]

Cosela is approved 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.

Clinical Efficacy [3,4,5,6,7,8] (mechanism of action/pharmacology, comparative efficacy)

Cosela is a small-molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Self-renewing hematopoietic stem and progenitor cells (HSPCs) are present in bone marrow and are responsible for the differentiation of all blood cell types (i.e., red and white blood cells and platelets). HSPCs are dependent upon CDK4/6 activity for proliferation. Chemotherapy causes dose-limiting damage to normal proliferating cells, including HSPCs, which leads to long-term hematopoietic "exhaustion" and resultant hematopoietic cell apoptosis. Many human cancers are resistant to CDK4/6 inhibition which allows for the co-administration of a CDK4/6 inhibitor along with the cytotoxic chemotherapeutic regimen to augment the therapeutic window by protecting normal HSPCs without minimizing the response to chemotherapy. In short, Cosela protects the hematopoietic stem cells from chemotherapy-induced bone marrow exhaustion.

Pharmacokinetics:

Absorption	Volume of distribution: 1130 L
Metabolism	Extensive
Excretion	Fecal (79%); Renal (14%)
Half-life	14 hours

- Three, randomized, double-blind, placebo-controlled Phase 2 clinical trials in adult patients with ES-SCLC (n=242) where patients were randomly assigned to either chemotherapy plus Cosela or placebo
- Primary prophylactic granulocyte-colony stimulating factor (G-CSF) and erythropoiesis-stimulating agent (ESA) use was prohibited during Cycle 1 in all studies. Both were allowed during Cycle 2 onwards as clinically indicated. Therapeutic G-CSF, red blood cell (RBC), and platelet transfusions were allowed at any time as clinically indicated.
- Primary endpoints: 1) Duration of severe neutropenia in Cycle 1 (days): Mean SD; 2) Number (%) of patients with severe neutropenia

- Cosela resulted in a lower risk of developing severe neutropenia compared to placebo. In those patients who did develop severe neutropenia, the duration was shorter in those who received Cosela compared to placebo.

Clinical Trials Experience

<table>
<tr><td>STUDY 1 DESIGN</td><td>Randomized, double-blind, placebo-controlled Phase 2 clinical trial (N=107) (NCT03041311)</td></tr>
<tr><td>INCLUSION CRITERIA</td><td>• Male or female subjects aged ≥18 years
• Confirmed diagnosis of SCLC
• At least 1 target lesion that is measurable by Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1
• Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
• Adequate organ function</td></tr>
<tr><td>EXCLUSION CRITERIA</td><td>• Prior chemotherapy for ES-SCLC
• Prior immunotherapies including but not limited to CD137, anti-PD-L1, and CTLA4
• Presence of systematic brain metastases requiring immediate treatment with radiation therapy or steroids
• History of pulmonary fibrosis, organizing pneumonia or pneumonitis on screening chest CT
• Active, known, suspected autoimmune disease requiring systemic treatment in the past 2 years
• Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure
• Known history of stroke or cerebrovascular accident within 6 months prior to enrollment
• Other uncontrolled serious chronic disease or conditions that in the investigator's opinion could affect compliance or follow-up in the protocol
• Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to enrollment
• Receipt of any investigational medication within 4 weeks prior to enrollment
• Administration of attenuated vaccine within 4 weeks before enrollment
• Systemic treatment with corticosteroids or other immunosuppressive medications within 14 days of study drug administration</td></tr>
<tr><td>TREATMENT REGIMEN</td><td>Randomized (1:1) to Cosela or placebo administered prior to treatment with etoposide, carboplatin, and atezolizumab (E/P/A) for patients with newly diagnosed ES-SCLC not previously treated with chemotherapy.</td></tr>
<tr><td>RESULTS</td><td>• Primary endpoints:
1. Duration of severe neutropenia in Cycle 1 (days): Mean SD;
2. Number (%) of patients with severe neutropenia
<table>
<tr><th>Endpoint</th><th>Cosela 240mg/m² (n=54)</th><th>Placebo (n=53)</th><th>Treatment Effect (Mean Difference or Adjusted Relative Risk) (95% CI)</th><th>Adjusted 1-sided p-value</th></tr>
<tr><td colspan="5">Primary Endpoints</td></tr>
<tr><td>DSN in Cycle 1 (days): mean (SD)</td><td>0 (1.0)</td><td>4 (4.7)</td><td>-3.6
(-4.9, -2.3)</td><td><0.0001</td></tr>
<tr><td>Number (%) of patients with severe neutropenia</td><td>1 (1.9%)</td><td>26 (49.1%)</td><td>0.038
(0.008, 0.195)</td><td><0.0001</td></tr>
<tr><td colspan="5">Key Secondary Endpoints</td></tr>
<tr><td>Number of all-cause dose reductions, event rate per cycle</td><td>0.021</td><td>0.085</td><td>0.242
(0.079, 0.742)</td><td>0.0195</td></tr>
<tr><td>Number (%) of patients with RBC transfusion on/after 5 weeks</td><td>7 (13.0%)</td><td>11 (20.8%)</td><td>0.642
(0.294, 1.404)</td><td>-</td></tr>
<tr><td>Number (%) of patients with G-CSF administration</td><td>16 (29.6%)</td><td>25 (47.2%)</td><td>0.646
(0.403, 1.034)</td><td>-</td></tr>
</table>
Abbreviations: CI = confidence interval; DSN = duration of severe neutropenia; SD = standard deviation</td></tr>
</table>

SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN	Randomized, double-blind, placebo-controlled Phase 2 clinical trial (N=77) (NCT02499770)
INCLUSION CRITERIA	• Male or female subjects aged ≥18 years • Confirmed diagnosis of SCLC • At least 1 target lesion that is measurable by RECIST, Version 1.1 • ECOG performance status of 0-2 • Adequate organ function
EXCLUSION CRITERIA	• Prior chemotherapy for extensive-stage SCLC • Presence of symptomatic brain metastases requiring immediate treatment with radiation therapy or steroids. • Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure • Known history of stroke or cerebrovascular accident within 6 months prior to enrollment • Other uncontrolled serious chronic disease or conditions that in the investigator's opinion could affect compliance or follow-up in the protocol • Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to enrollment or previous radiotherapy to the target lesion sites (the sites that are to be followed for determination of a response) • Receipt of any investigational medication within 4 weeks prior to enrollment
TREATMENT REGIMEN	Randomized (1:1) to Cosela or placebo administered prior to treatment with etoposide and carboplatin (E/P) for patients newly diagnosed ES-SCLC not previously treated with chemotherapy.
RESULTS	• Primary endpoints: 1. Duration of severe neutropenia in Cycle 1 (days): Mean SD; 2. Number (%) of patients with severe neutropenia
SAFETY	Discussed in the Adverse Effects section below.

Endpoint	Cosela 240 mg/m² (n=39)	Placebo (n=38)
DSN in Cycle 1 (days): mean (SD)	0 (0.5)	3 (3.9)
Number (%) of patients with severe neutropenia	2 (5.1%)	16 (42.1%)
Number of all-cause dose reductions, event rate per cycle	0.022	0.084
Number (%) of patients with RBC transfusion on/after 5 weeks	2 (5.1%)	9 (23.7%)
Number (%) of patients with G-CSF administration	4 (10.3%)	24 (63.2%)

STUDY 3 DESIGN	Randomized, double-blind, placebo-controlled Phase 2 clinical trial (N=61) (NCT02514447)
INCLUSION CRITERIA	• Male or female subjects aged ≥18 years • Unequivocally confirmed diagnosis of SCLC by histology or cytology, preferably including the presence of neuroendocrine features by immunohistochemistry • Progression during or after prior first- or second-line chemotherapy and eligible to receive topotecan therapy • At least 1 target lesion that is measurable by RECIST, Version 1.1 • ECOG performance status of 0 - 2 • Adequate organ function
EXCLUSION CRITERIA	• Presence of symptomatic brain metastases requiring immediate treatment with radiation therapy or steroids. • Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure

<table>
<tr><td></td><td>

Known history of stroke or cerebrovascular accident within 6 months prior to enrollment
Other uncontrolled serious chronic disease or conditions that in the investigator's opinion could affect compliance or follow-up in the protocol
Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to enrollment or previous radiotherapy to the target lesion sites (the sites that are to be followed for determination of a response)
Receipt of any investigational medication within 2 weeks prior to enrollment
History of topotecan treatment for SCLC

</td></tr>
<tr><td>TREATMENT REGIMEN</td><td>Randomized to receive Cosela or placebo administered prior to topotecan in patients with ES-SCLC previously treated with chemotherapy. Topotecan (1.5 mg/m^2) and Cosela (240 mg/m^2) or placebo were administered on Days 1-5 of a 21-days cycle.</td></tr>
<tr><td>RESULTS</td><td>

Primary endpoints:

Duration of severe neutropenia in Cycle 1 (days): Mean SD;
Number (%) of patients with severe neutropenia

<table>
<tr><th>Endpoint</th><th>Cosela 240 mg/m^2 (n=32)</th><th>Placebo (n=29)</th></tr>
<tr><td colspan="3">Primary Endpoints</td></tr>
<tr><td>DSN in Cycle 1 (days): mean (SD)</td><td>2 (3.9)</td><td>7 (6.2)</td></tr>
<tr><td>Number (%) of patients with severe neutropenia</td><td>13 (40.6%)</td><td>22 (75.9%)</td></tr>
<tr><td colspan="3">Key Secondary Endpoints</td></tr>
<tr><td>Number of all-cause dose reductions, event rate per cycle</td><td>0.051</td><td>0.116</td></tr>
<tr><td>Number (%) of patients with RBC transfusion on/after 5 weeks</td><td>10 (31.3%)</td><td>12 (41.4%)</td></tr>
<tr><td>Number (%) of patients with G-CSF administration</td><td>16 (50.0%)</td><td>19 (65.5%)</td></tr>
<tr><td>Number (%) of patients with platelet transfusion</td><td>8 (25.0%)</td><td>9 (31.0%)</td></tr>
</table>
</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
</table>

Contraindications [3,4]

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

Warnings and Precautions [3,4]

- 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 hypersensitivity reactions, including edema (facial, eye and tongue), urticarial, 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.

Adverse Effects [3,4]

Most common, ≥ 5%	Cosela (N=122) %	Placebo (N=118) %
Fatigue	34	27
Hypocalcemia	24	21
Hypokalemia	22	18
Hypophosphatemia	21	16
Aspartate aminotransferase increased	17	14
Headache	13	9
Pneumonia	10	8
Rash	9	6
Infusion-related reaction	8	2
Edema peripheral	7	4
Abdominal pain upper	7	3
Thrombosis	7	2
Hyperglycemia	6	3

Drug Interactions [3,4]

- Certain OCT2, MATE1, and MATE-2K substrates: Co-administration of Cosela may increase the concentration or the net accumulation of OCT2, MATE1, and MATE-2K substrates in the kidney (e.g., dofetilide, dalfampridine, and cisplatin).

Dosage and Administration [3,4]

- The recommended dose of Cosela is 240 mg/m^2 as a 30-minute IV infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/cycle
Trilaciclib	Cosela®	G1 Therapeutics	240 mg/m^2 IV each day of chemotherapy	$34,008-$56,680
Granulocyte-Colony Stimulating Factors				
Pegfilgrastim	Fulphila®	Mylan BmbH	Varies based on agent	$3,500-6,000
Tbo-filgrastim	Granix®	Teva		
Sargromostim	Leukine®	Sanofi-Aventis		
Pegfilgrastim	Neulasta® Onpro®	Amgen, Inc.		
Pegfilgrastim	Neulasta® Syringe	Amgen, Inc.		
Filgrastim	Neupogen®	Amgen, Inc.		
Filgrastim	Nivestym™	Pfizer Labs		
Pegfilgrastim	Nyvepria™	Pfizer Labs		
Pegfilgrastim	Udenyca®	Coherus BioSci.		
Filgrastim	Zarxio®	Sandoz, Inc.		
Pegfilgrastim	Ziextenzo™	Sandoz, Inc.		
Erythropoiesis Stimulating Agents				
Darbepoetin	Aranesp®	Amgen, Inc.	Varies based on agent	$450-1,000
Epoetin Alfa	Epogen®	Amgen, Inc.		
Methoxy PEG-Epoetin Beta	Mircera®	Vifor, Inc. Janssen Products		
Epoetin Alfa	Procrit®	Pfizer Labs		
Epoetin Alfa	Retacrit®			

** Wholesale Acquisition Cost

Conclusion

Cosela is the first CDK4/6 inhibitor approved 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. In short, Cosela protects the hematopoietic stem cells from chemotherapy-induced bone marrow exhaustion. The previous CDK4/6 inhibitors are indicated for the treatment of breast cancer, which is why Cosela is more closely related therapeutically to the granulocyte-colony stimulating factors and the erythropoiesis stimulating agents. The efficacy of Cosela was established in three randomized, double-blind, placebo-controlled Phase 2 clinical trials with a total of 242 patients with ES-SCLC. Cosela resulted in a lower risk of developing severe neutropenia compared to placebo. In those patients who did develop severe neutropenia, the duration was shorter in those who received Cosela compared to placebo. The most common adverse events were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia. The cost of Cosela is anywhere from 10 to 30 times greater than the alternative therapies used to protect patients from myelosuppression caused by chemotherapy.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

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