Novel Agents to Prevent Chemotherapy-Induced Neutropenia and Other Myelosuppressive Effects

Revised Evidence Report

March 17, 2022

Prepared for

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Jeffrey Tice served as the lead author for the report and wrote the background, comparative clinical effectiveness, and potential other benefits and contextual considerations sections of the report. Avery McKenna and Belén Herce-Hagiwara led the systematic review and meta-analyses with support from Victoria Lancaster and Foluso Agboola and contributed to the associated sections in the comparative clinical effectiveness chapter. Lisa Bloudek developed the cost-effectiveness model and authored the corresponding sections in collaboration with Josh J. Carlson. Ashton Moradi developed the budget impact model, and Ashton Moradi and Melanie Whittington provided oversight of the cost-effectiveness analyses. Steven D. Pearson and Daniel A. Ollendorf provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Maggie O'Grady and Grace Sternklar for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

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For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2021/09/ICER_Neutropenia_Stakeholder_List_092221.pdf

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Table of Contents

Supplemental Materials

List of Acronyms and Abbreviations Used in this Report

1L	First line
2L	Second line
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
AIC	Academic-in-confidence
ANC	Absolute neutrophil count
ASP	Average sales price
BMI	Body mass index
CDK	Cyclin-dependent kinase
CI	Confidence interval
CIM	Chemotherapy-induced myelosuppression
CIN	Chemotherapy-induced neutropenia
CMS	Centers for Medicare & Medicaid Service
E-BC	Early-stage breast cancer
ECOG	Eastern Cooperative Oncology Group
EPA	Etoposide, carboplatin, and atezolizumab
ESA	Erythropoiesis stimulating agents
ES-SCLC	Extensive-stage small cell lung cancer
evLY	Equal value of life year
FACT-An	Functional Assessment of Cancer Therapy – Anemia
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-L	Functional Assessment of Cancer Therapy – Lung
FDA	Food and Drug Administration
FN	Febrile neutropenia
G-CSF	Granulocyte colony stimulating factor
HIDI	Health Improvement Distribution Index
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
mITT	Modified intention to treat
NR	Not reported
NSCLC	Non-small cell lung cancer
QALY	Quality-adjusted life year
RBC	Red blood cell
RDI	Relative dose intensity
RR	Risk ratio
SC	Subcutaneous
SCLC	Small cell lung cancer
SD	Standard deviation
SE	Standard error
seTE	Standard error of treatment effect
SIMBA	Selective immunomodulating microtubule-binding agent
TAC	Taxotere, Adriamycin and cyclophosphamide
TE	Treatment effect
TRAE	Treatment-related adverse event
USPSTF	United States Preventive Services Taskforce
WAC	Wholesale acquisition cost

Executive Summary

Until recently, cytotoxic chemotherapy was the primary form of chemotherapy used to treat cancer, and it remains in widespread use today. Because it targets rapidly dividing cells, one of the common side effects of cytotoxic chemotherapy is low blood cell counts (myelosuppression), including low neutrophil counts (neutropenia), low platelet counts (thrombocytopenia), and low red blood cell counts (anemia).[1] Neutropenia in particular puts patients at high risk for infection. When patients with severe neutropenia develop a fever (febrile neutropenia), they are frequently hospitalized and treated with broad spectrum antibiotics for presumed infections. In response to severe neutropenia, hematologists/oncologists may need to reduce the dose and/or frequency of chemotherapy. This can result in lower overall survival, particularly when chemotherapy is being used with the intent to cure the patient.[2,3] Guidelines recommend that granulocyte colony stimulating factor (G-CSF) be routinely used to prevent neutropenia in patients at high risk for febrile neutropenia (>20%) or when risk is intermediate (10% to 20%) and patients have additional risk factors (age >65 years, prior CIN, poor functional status, poor nutritional status).[4,5] The cost of hospitalizations for neutropenia is high. In the United States in 2012, there were over 100,000 hospitalizations for chemotherapy-associated neutropenia at a total cost of $2.7 billion.[6]

There are two new intravenous agents which may be used in place of or in conjunction with G-CSF. Trilaciclib is a cyclin-dependent kinase 4 and 6 inhibitor approved by the FDA on February 12, 2021, to decrease the incidence of myelosuppression in patients with extensive-stage small cell lung cancer (SCLC) undergoing certain chemotherapy treatments. Plinabulin, which received breakthrough designation from the FDA, is a selective immunomodulating microtubule-binding agent (SIMBA) for the prevention of CIN and possibly thrombocytopenia. On December 1, 2021, however, the FDA sent a complete response letter asking the company to perform a second trial documenting the benefits of plinabulin before approval could be considered.

There were two small, placebo-controlled Phase II trials of trilaciclib in first-line chemotherapy for extensive stage small cell lung cancer (ES-SCLC). There was a significant reduction in both severe neutropenia (relative risk (RR) 0.08; 95% confidence interval (CI): 0.03 to 0.026) and severe anemia (RR 0.50; 95% CI: 0.26 to 0.96), but no significant reduction in mortality. In a single Phase II trial of trilaciclib in second line chemotherapy for ES-SCLC there was a significant reduction in severe neutropenia, but not febrile neutropenia or death. In the pooled safety data for trilaciclib, serious adverse events were slightly more common in the trilaciclib group (29.5% vs. 25.4%) including those leading to death (4.9% vs. 2.5%) despite the reduction in serious adverse events associated with myelosuppression.[7]

There is one unpublished Phase III study of plinabulin added to G-CSF (pegfilgrastim) for the prevention of myelosuppression in women undergoing first line therapy for early breast cancer (E-BC), in comparison to pegfilgrastim alone. Presentations at conferences reported a significant reduction in severe neutropenia in the plinabulin arm (68.5% vs. 86.4%, p=0.0015), but no significant reduction in febrile neutropenia. There was also a reduction in hospitalizations (75% vs. 100%, p not reported) of unclear significance. The plinabulin group experienced fewer grade 4 adverse events (58.6% vs. 80.0%), which may reflect a reduction in adverse events due to myelosuppression. Bone pain was less common in the plinabulin group (18% vs. 33%, p: NR), but all episodes were either grade 1 or 2.

The results for trilaciclib are somewhat confusing. There is clearly a reduction in severe neutropenia, febrile neutropenia, severe anemia, serious adverse events due to myelosuppression, the need for chemotherapy dose reductions, and hospitalizations due to myelosuppression or sepsis.[7] However, these benefits did not translate into a reduction in the risk for total hospitalizations, serious adverse events, or deaths due to adverse events (all nominally higher in the trilaciclib group).[7] The HR for overall mortality in the pooled analysis was 1.0 (95% CI: 0.75 to 1.35) with approximately 50% mortality at one year and 90% mortality at two years. The total number of patients who received trilaciclib across the three trials and could be evaluated in a randomized context was only 122. Thus, we judge that there is moderate certainty that the use of trilaciclib in patients receiving chemotherapy for ES-SCLC is either comparable to or has a small net health benefit compared with standard of care (C+).

The results for plinabulin are more consistent. There was a modest reduction in the risk for severe neutropenia and there was a reduction in overall hospitalizations. There was also a reduction in bone pain. Finally, there were fewer grade 4 serious adverse events. However, several important outcomes have not yet been reported and the only trial of plinabulin added to pegfilgrastim in breast cancer has not yet been published in a peer reviewed journal. While there is no data at this point to suggest the possibility of net harm, it is possible that additional clinical data could span from no added benefit to the patient to significant added benefit. Because of these challenges, we judge that there is moderate certainty of a comparable, small, or substantial benefit (C++) for plinabulin added to pegfilgrastim versus pegfilgrastim alone.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Patients with ES-SCLC treated either with carboplatin/etoposide or topotecan		
Trilaciclib	Standard Therapy	C+
Patients with early-stage breast cancer		
Plinabulin plus pegfilgrastim	Pegfilgrastim	C++

ES-SCLC: extensive stage small cell lung cancer

In both first line and previously treated ES-SCLC, trilaciclib cost and effectiveness modeling suggests fewer severe myelosuppressive episodes and fewer deaths due to febrile neutropenia, resulting in a small incremental benefit for QALYs, evLYs, and LYs compared to no myelosuppression prophylaxis. Specifically, due to the relatively short duration of severe events, rarity of febrile neutropenia-related deaths, and limited life expectancy in the ES-SCLC population, incremental gains with trilaciclib were small (0.03 QALYs). This results in high incremental cost-effectiveness ratios for trilaciclib added to first- or second-line therapy for ES-SCLC. A societal perspective was included as a co-base because the incremental cost per QALY varied by more than 20% and/or changed by more than $200,000 relative to the health sector perspective results.

Table ES2. Incremental Cost-Effectiveness Ratios for the Base Case, Trilaciclib

Treatment	Comparator	Cost per Myelosuppressive Event Avoided	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$15,800	$871,000	$4,900,000	$844,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$37,300	$1,400,000	$1,800,000	$1,200,000
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$13,300	$735,000	$4,100,000	$712,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$32,800	$1,200,000	$1,600,000	$1,000,000

1L: first line, 2L: second line, ES-SCLC: extensive-stage small cell lung cancer, evLY: equal-value life year, FN: febrile neutropenia, QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000 or $10,000.

Cost and effectiveness modeling for plinabulin added to G-CSF compared to G-CSF alone resulted in fewer severe neutropenia episodes and fewer deaths due to febrile neutropenia. Incremental cost-effectiveness ratios were not calculated for plinabulin at this time because it is not approved by the FDA and there is no available placeholder price for the drug. However, we did estimate the prices required to achieve thresholds of $50,000 to $200,000 per QALY and per evLY gained for plinabulin (Table ES3) as well as health benefit price benchmarks from $100,000 to $150,000 per QALY and per evLY for trilaciclib (Table ES4). The base-case cost-effectiveness threshold prices ranged from a per-unit price of $1,100 to $1,600 for plinabulin, and $430 to $670 for trilaciclib. For trilaciclib, this represents a 55-71% discounted needed to align trilaciclib cost with the net health benefit realized.

Table ES3. Base-Case Per-Unit Cost-Effectiveness Threshold Pricing for Plinabulin (E-BC)

	Net Price per Unit	Unit Price to Achieve $50,000 Threshold	Unit Price to Achieve $100,000 Threshold	Unit Price to Achieve $150,000 Threshold	Unit Price to Achieve $200,000 Threshold
Health Care System Perspective					
QALYs gained	Not yet available	$630	$1,100	$1,600	$2,100
evLYs gained	Not yet available	$620	$1,100	$1,600	$2,100

evLY: equal value of life year, QALY: quality-adjusted life year

Table ES4. Base-Case Per-Unit Cost-Effectiveness Health Benefit Price Benchmarks for Trilaciclib (ES-SCLC)

	Net Price per Unit*	Unit Price to Achieve $100,000 Threshold	Unit Price to Achieve $150,000 Threshold	Additional Discounts from Net Price to Reach Threshold Prices
Health Care System Perspective				
QALYs gained	$1,491	$430	$490	67-71%
evLYs gained	$1,491	$430	$500	67-71%
Modified Societal Perspective				
QALYs gained	$1,491	$600	$660	56-60%
evLYs gained	$1,491	$610	$670	55-59%

evLY: equal value of life year, QALY: quality-adjusted life year
*Unit = 300 mg vial

The results of the one-way and probabilistic sensitivity analyses and multiple scenario analyses including using a societal perspective did not change the conclusions for trilaciclib: the results were consistently greater than $200,000 per QALY or per evLY gained. One-way sensitivity analysis was performed on the $100,000 per QALY threshold price for plinabulin. The most impactful model parameters were the proportion of patients with RDI ≤85% in each treatment arm, suggesting that assumptions around potential impact on survival is a major model driver.

The value assessment of trilaciclib should be tempered by several contextual considerations and potential other benefits. The short-term risk of death from febrile neutropenia is high. There are important impacts on caregivers who need to provide for patients who must isolate themselves while they live with severe neutropenia. Finally, the requirement to return to an infusion center for an infusion of G-CSF the day after receiving chemotherapy is a particular burden of historically underserved and low-income patients, so effective prevention of myelosuppression has the potential to reduce health inequities.

1. Background

Until recently, cytotoxic chemotherapy was the primary form of chemotherapy used to treat cancer, and it remains in widespread use today. Because it targets rapidly dividing cells, one of the common side effects of cytotoxic chemotherapy is low blood cell counts (myelosuppression), including low neutrophil counts (neutropenia), low platelet counts (thrombocytopenia), and low red blood cell counts (anemia).[1] Neutropenia in particular puts patients at high risk for infection. When patients with severe neutropenia develop a fever (febrile neutropenia), they are frequently hospitalized and treated with broad spectrum antibiotics for presumed infections. In response to severe neutropenia, hematologists/oncologists may need to reduce the dose and/or frequency of chemotherapy. This can result in lower overall survival, particularly when chemotherapy is being used with the intent to cure the patient.[2,3] In addition, the cost of hospitalizations for neutropenia is high. For example, in the United States in 2012, there were over 100,000 hospitalizations for chemotherapy-associated neutropenia at a total cost of $2.7 billion.[6]

The risk for chemotherapy-induced neutropenia (CIN) and other myelosuppressive effects varies by the type of chemotherapy used and patient characteristics.[8-10] Guidelines recommend that granulocyte colony stimulating factor (G-CSF, most commonly filgrastim or pegfilgrastim) be routinely used to prevent neutropenia in patients at high risk for febrile neutropenia (>20%) or when risk is intermediate (10% to 20%) and patients have additional risk factors (age >65 years, prior CIN, poor functional status, poor nutritional status).[4,5] During the COVID-19 pandemic, recommendations for prophylactic G-CSF were expanded to include all patients at intermediate risk for CIN, to minimize the risk for exposure to the virus in emergency rooms and hospitals.

In addition to high cost, there are several disadvantages to G-CSF. First, it must be given approximately 24 hours after the completion of a cycle of chemotherapy. This usually requires another visit to an infusion center, which is a burden for all patients, but particularly those who must travel long distances, have transportation issues, have limited incomes, or cannot easily take additional time off work. In addition, severe bone pain is a common side effect of G-CSF that greatly impacts quality of life and can lead patients to refuse subsequent G-CSF therapy.[11,12] Finally, G-CSF only improves neutrophil counts. Patients could potentially benefit from more convenient and less toxic therapies to prevent CIN and potentially other myelosuppressive effects as well.

There are two approaches to managing chemotherapy-induced anemia in patients: red blood cell transfusions and erythropoiesis stimulating agents (ESAs). Transfusion is typically recommended at a hemoglobin threshold of 7 g/dL in hospitalized patients and 8 g/dL in the setting of surgery. Patients are usually treated with blood transfusions first and only treated with ESAs if they become transfusion dependent and other causes of anemia have been ruled out.

Similarly, patients who develop chemotherapy-induced thrombocytopenia may be treated with platelet transfusions or thrombopoietin-receptor agonists. Use of these therapies is typically reserved for patients with significant bleeding and very low platelet levels.

There are two new agents which may be used in place of or in conjunction with G-CSF (Table 1.1). Trilaciclib (Cosela™, G1 Therapeutics) is a cyclin-dependent kinase 4 and 6 inhibitor approved by the FDA on February 12, 2021, to decrease the incidence of myelosuppression (neutropenia, anemia) in patients with extensive-stage small cell lung cancer (SCLC) undergoing certain chemotherapy treatments. Plinabulin, which received breakthrough designation from the FDA and is a selective immunomodulating microtubule-binding agent (SIMBA) for the prevention of CIN and possibly thrombocytopenia. On December 1, 2021, the FDA sent a complete response letter asking the company to perform a second trial documenting the benefits of plinabulin.

In addition to their impact on myelosuppression, both drugs may have direct anti-cancer effects. The focus of this review, however, is on the use of these agents to prevent or reduce myelosuppression, as these are the indications initially granted or sought for the agents of interest.

Table 1.1. Novel Agents to Prevent Chemotherapy-Induced Neutropenia

Drug	Mechanism	Dose
Trilaciclib (Cosela™)	CDK 4/6 inhibition	240 mg/m^2 IV within four hours prior to chemotherapy
Plinabulin	Selective microtubule-binding agent	40 mg IV with chemotherapy

IV: intravenous, mg: milligram

2. Patient and Caregiver Perspectives

Input from patients and patient organization has been invaluable in informing our review, though it was more challenging to glean perspectives specific to myelosuppression because the experience is tied to the other adverse effects of chemotherapy happening at the same time and the impact of the cancer diagnosis on their lives.

We heard that the bone pain that can accompany the use of G-CSF is not necessarily expected by some patients. Patients expect nausea, fatigue, and hair loss from chemotherapy, but the bone pain can come as a surprise that they are not prepared for. We heard of the importance of communicating about expected side effects, their timing, as well as preparing the patient for strategies to deal with the pain if it happens (antihistamines like loratadine [Claritin®], non-steroidal anti-inflammatory medications, and sometimes narcotics).

We also heard about the burden of coming back to clinic for the infusion of G-CSF the day after chemotherapy, including additional risk for exposure to COVID-19. The patient community really appreciates the availability of the Neulasta Onpro® device, which allows for home administration of G-CSF, but this device may occasionally fail (1.3% to 6.9% of cycles in published reports).[13] In some cases, patients can be taught to self-administer G-CSF or home nursing can be arranged. In addition, the Onpro® device is not consistently covered by the patient's insurance.

A recent patient survey highlighted that the protocols to reduce the risk of infection when a patient is neutropenic causes a sense of isolation from friends and family, and prevents them from carrying out their usual daily activities.[14] Almost 90% reported that CIN had a moderate or major impact on their lives and 30% reported that they did not feel that their oncologist understood how uncomfortable they were from CIN.[15] The isolation can be even worse for patients and caregivers during the COVID-19 pandemic.

One patient with small-cell lung cancer told us that "you cannot put a price on the benefit that trilaciclib provided to me." She described her first chemotherapy as "indescribably awful, like an out-of-body experience." After that experience, she decided that she would never get chemotherapy again. However, she had a recurrence and her oncologist told her that trilaciclib could help to protect her against the worst of the side effects. She said "I can't say enough about the difference it's made. With COSELA, I feel 100% better than I did during the first round of chemo... I'm eating, I don't look like I'm sick, and I don't feel like I have cancer." She wants us to know that it is "important that all patients who need it can get access to this drug, because the difference it can make is truly remarkable."

There are ongoing disparities in disease outcomes and clinical trial enrollment that particularly impact Black Americans. The Black Breast Cancer Alliance highlighted some of those disparities:

“The mortality rate for Black Women with breast cancer is 41% higher than White Women. Black women have a 39% higher recurrence rate than White women. Black Women under the age of 35 get breast cancer at twice the rate and die at three times the rate.” In addition, the Tigerlily Foundation highlighted the “Lack of Clinical Trial Data to Include Black Patients. For any treatment to be most effective for all populations, it is important to have equal representation.”

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence of trilaciclib and plinabulin for chemotherapy-induced neutropenia and other myelosuppressive effects are detailed in Supplement Section D1.

Scope of Review

We reviewed the clinical effectiveness of trilaciclib versus standard care, plinabulin 40 mg IV versus standard dose pegfilgrastim (6 mg IV, brand name or biosimilars) alone, and the combination of plinabulin plus pegfilgrastim to pegfilgrastim alone. We sought evidence on patient-important outcomes such as mortality, hospitalizations, chemotherapy regimen changes (delays, reduction, or discontinuation), febrile neutropenia, bone pain, red blood cell or platelet transfusions, adverse events, and health-related quality of life measures. We did not identify any subgroups of interest during the scoping period and did not identify data for any key subgroups during our review. The full scope of the review is detailed in Supplement Section D1.

Both drugs are used to reduce chemotherapy induced myelosuppression, which should improve patient's quality of life and, importantly, prevent changes to the planned chemotherapy regimen. Myelosuppression is a common reason for reducing the dose intensity of chemotherapy, which has been associated with worse cancer outcomes. The outcomes that matter to patients would be increased overall survival (no deaths due to myelosuppression and fewer deaths from cancer) as well as fewer hospitalizations. Even if mortality does not change, significant improvements in quality of life during chemotherapy would be important.

Evidence Base

Our search identified a total of 16 references for trilaciclib and plinabulin. Additionally, we received academic-in-confidence submissions for trilaciclib and plinabulin from their respective manufacturers to supplement publicly available data. The clinical evidence is summarized separately below, as each drug was studied in different populations and the interventions were not compared to each other. Detailed descriptions of the included trials can be found in Supplement Tables D5 and D15.

Trilaciclib

A total of six references on trilaciclib met our inclusion criteria. Of these, we identified one Phase II trial (Daniel 2020[16]), two Phase Ib/IIa trials (Weiss 2019[17] and Hart 2021[18]), and two pooled publications (Weiss 2021[7] and Ferrarotto 2021[19]) that studied trilaciclib in extensive-stage small cell lung cancer. We received three academic-in-confidence data submissions pertaining to these studies.[20] Additionally, we identified one Phase II trial (Tan 2019[21]) that studied trilaciclib in triple negative breast cancer. The study's results have been abstracted and summarized in the supplement tables, as they support the mechanism of action of trilaciclib (protection from chemotherapy induced myelosuppression) but are outside of the FDA indication. Details on the additional studies can be found in Supplement Section D2.

The FDA indication for trilaciclib is for patients with ES-SCLC treated with chemotherapy including platinum/etoposide (usually first line) or topotecan (usually second line). The evidence review will focus on the three studies of trilaciclib that meet the FDA indication.[16-18] Each of the trials were of good quality (see Supplement Table D4 for details). Details of the key studies are highlighted in Table 3.1 and described below. The results are summarized by chemotherapy regimen, as those containing platinum/etoposide have a lower risk for myelosuppression than those containing topotecan.

Weiss 2019[17] enrolled 122 patients with untreated extensive-stage small cell lung cancer receiving a chemotherapy regimen of carboplatin and etoposide. The study was divided into two parts. For this review, we focused on part two where patients were randomized to either trilaciclib 240 mg/m2 IV (n=39) or placebo (n=38) once daily for three days prior to chemotherapy in each cycle until completion of chemotherapy or until disease progression, withdrawal of consent or discontinuation by investigator, or other concerns, with a typical duration of four to six cycles.

Daniel 2020[16] enrolled 105 patients with untreated extensive-stage small cell lung cancer receiving a chemotherapy regimen of etoposide/carboplatin/atezolizumab (EPA). Patients were randomized to trilaciclib 240 mg/m2 IV (n=54) or placebo (n=53) once daily for three days prior to chemotherapy for up to four 21-day cycles.

Hart 2021[18] enrolled 120 patients with previously treated extensive-stage small cell lung cancer receiving a chemotherapy regimen of topotecan. We focused on part two of the trial where patients were randomized to either trilaciclib 240 mg/m2 IV (n=32) or placebo (n=29) once daily for five days prior to chemotherapy in each cycle until progression, unacceptable toxicity, or other concerns, with a mean cycle completion for the trilaciclib arm of five cycles.

Table 3.1. Overview of Key Studies[16-18]

Trials	N	Population	Primary Outcome
Weiss 2019	122	Untreated ES-SCLC	No primary outcome defined; dose finding (part 1) and safety and efficacy (part 2)
Daniel 2020	105	Untreated ES-SCLC	Duration of severe neutropenia in cycle 1 AND percentage of patients with severe neutropenia
Hart 2021	120	Previously treated ES-SCLC	Duration of severe neutropenia in cycle 1 AND percentage of patients with severe neutropenia

ES-SCLC: extensive-stage small cell lung cancer, TRAE: treatment-related adverse event

Plinabulin

A total of 10 references on plinabulin met our inclusion criteria. Of these, we identified nine references from four trials in the PROTECTIVE clinical trial program: PROTECTIVE-1 Phase II, PROTECTIVE-1 Phase III, PROTECTIVE-2 Phase II, and PROTECTIVE-2 Phase III.[22-31] We received three academic-in-confidence data submissions with additional data on the PROTECTIVE studies.[32] Additionally, we identified one reference from the Phase III DUBLIN-3 trial.[33]

The application to the FDA for plinabulin was for plinabulin added to pegfilgrastim in first line treatment for breast cancer. Only one study investigated this indication (the Phase III segment of the PROTECTIVE-2 study).[25] Details of the key study are highlighted in Table 3.2. Results of other studies of plinabulin[22] have been abstracted and summarized in the supplemental tables, as they support the mechanism of action for plinabulin (protection from chemotherapy-induced myelosuppression) and a possible anti-cancer effect (DUBLIN 3).[33] However, they will not be considered further in the main report. Details on the additional studies can be found in Supplement Section D2.

The Phase III PROTECTIVE-2 trial[25-27,30] enrolled 221 patients with stage I-III breast cancer with no prior chemotherapy. All patients received TAC chemotherapy IV on day one of each 21-day cycle and were randomized to receive either plinabulin 40 mg followed by next-day pegfilgrastim (n=111) or placebo plus next-day pegfilgrastim 6 mg (n=110) for up to four cycles.

Table 3.2. Overview of Key Studies[23,25-27]

Trial	N	Population	Primary Outcome
PROTECTIVE-2 Phase III	221	Untreated Stage 1-3 breast cancer	Patients with duration of severe neutropenia = 0 [cycle 1]

3.2. Results

Clinical Benefits

Trilaciclib

Table 3.3 below illustrates why we are considering the studies of trilaciclib in carboplatin/ etoposide-based therapy separately from the study of topotecan in the clinical section and in the modeling. The risk for severe neutropenia and febrile neutropenia is much higher in patients receiving topotecan.

Table 3.3. Severe and Febrile Neutropenia in the Placebo Groups of Studies of Trilaciclib[16-18]

Trial	Severe Neutropenia	Febrile Neutropenia
1st Line Carboplatin/Etoposide		
Weiss 2019	43%	8%
Daniel 2020	49%	6%
2nd Line Topotecan		
Hart 2021	76%	17%

Trilaciclib in 1st Line Carboplatin/Etoposide Chemotherapy for ES-SCLC

We performed meta-analyses of the key outcomes in the trials of trilaciclib in first line therapy with carboplatin/etoposide-based chemotherapy. The methods and forest plots are in the supplement (Figures D2-5), as are the detailed results from the individual studies (Supplement Table D8). The primary results are in Table 3.4 below. There was more than a 90% reduction in the risk for severe neutropenia and a 50% reduction in severe anemia. There was also about a 50% reduction in severe thrombocytopenia, but this was not statistically significant. There was no significant reduction in overall survival.

Table 3.4. Meta-analysis of Trial Results for Trilaciclib in Patients with Small Cell Lung Cancer Treated with Carboplatin/Etoposide as First Line Therapy

Outcome	Trilaciclib vs. Placebo
Severe Neutropenia (RR)	0.08 (0.03-0.26)
Severe Anemia (RR)	0.50 (0.26-0.96)
Severe Thrombocytopenia (RR)	0.44 (0.12-1.70)
Overall Survival (HR)	0.90 (0.62-1.32)

HR: hazard ratio, RR: risk ratio

Quality of life assessed by the Functional Assessment of Cancer Therapy – General (FACT-G) declined similarly for both groups (HR for time to clinically important decline 0.58 (95% CI 0.29-1.15), but there was a significantly slower decline for the trilaciclib group in the functional well-being subscale (HR 0.40, 95% CI 0.22-0.75).[16] Additional quality of life measures are summarized in the Supplement Table D14.

Trilaciclib in 2nd Line Topotecan Chemotherapy for ES-SCLC

The key results of the single trial of trilaciclib for 2nd line therapy using topotecan are summarized in Table 3.5 below. As in first line therapy, patients treated with trilaciclib had lower risks for myelosuppression, hospitalization for myelosuppression, or sepsis, but a higher risk for overall hospitalization. However, the rate of hospitalization was lower in the trilaciclib group (7.9 per 100 cycles vs. 15 per 100 cycles for placebo) suggesting that some patients in the placebo group were hospitalized multiple times. There were fewer serious infectious adverse events in the group who received trilaciclib, but more serious adverse events overall and more serious adverse events leading to death. Despite the reduction in myelosuppression, there was no trend towards a reduction in total mortality in the group treated with trilaciclib.

Table 3.5. Key Trial Results for Trilaciclib in Patients with Small Cell Lung Cancer Treated with Topotecan as Second Line Therapy

Outcome	Trilaciclib	Placebo	p-Value
Severe Neutropenia	40.6%	75.9%	0.016
Febrile Neutropenia	6.3%	17.2%	0.194
Anemia	53.1%	85.7%	NR
Thrombocytopenia	62.5%	67.9%	NR
Chemotherapy dose reductions	18.8%	31.0%	0.204
Hospitalizations for myelosuppression or sepsis	9.4%	21.4%	NR
All Hospitalizations	31.3%	25.0%	NR
Serious Infectious Adverse Events	3.1%	10.3%	NR
Serious Adverse Events	37.5%	25.0%	NR
Adverse Events Leading to Death	9.4%	3.6%	NR
Total Mortality	90.6%	85.7%	NR

NR: not reported

Quality of life assessed by FACT-G declined more slowly for the trilaciclib group (HR for time to clinically important decline 0.34 (95% CI 0.14-0.87), with a significantly slower decline for the trilaciclib group in the physical well-being subscale, but not the functional well-being subscale.[18] Additional quality of life measures are summarized in Supplement Table D14.

Plinabulin

The key results for the PROTECTIVE-2 study are summarized in Table 3.6 below. A number of the results have not been reported or are academic in confidence, reflecting the fact that the trial has not yet been published in a peer reviewed journal. There was a modest reduction in severe neutropenia with the addition of plinabulin. Furthermore, there was a potentially important reduction in all hospitalizations (75% vs. 100%) and a small reduction in the need to alter chemotherapy (2.7% vs. 6.3%), though p-values were not reported.

Table 3.6. Key Trial Results for Plinabulin added to Pegfilgrastim in Patients with Breast Cancer

Outcome	Plinabulin plus Pegfilgrastim	Pegfilgrastim	p-Value
Severe Neutropenia in first cycle of chemotherapy	68.5%	86.4%	0.0015
Febrile Neutropenia	3.6%	6.4%	0.36
Anemia	NR	NR	NR
Thrombocytopenia	NR	NR	NR
Chemotherapy impact*	2.7%	6.3%	NR
Hospitalizations for myelosuppression or sepsis	NR	NR	NR
All Hospitalizations	75%	100%	NR
Infectious Adverse Events	NR	NR	NR
Serious Adverse Events	[redacted]		NR
Grade 4 Adverse Events	58.56%	80.0%	0.0006
Adverse Events Leading to Death	[redacted]		NR
Total Mortality	NR	NR	NR

AIC: academic in confidence, NR: not reported

* Chemotherapy dose reductions and regimen changes

Harms

Many of the harms for both trilaciclib and plinabulin were summarized in the clinical benefits section above because both drugs prevent outcomes that are typically considered harms (neutropenia and associated infections, anemia, thrombocytopenia).

Trilaciclib

In the pooled safety data for trilaciclib, serious adverse events were slightly more common in the trilaciclib group (29.5% vs. 25.4%) including those leading to death (4.9% vs. 2.5%) despite the reduction in serious adverse events associated with myelosuppression.[7] It is unclear from the reported data what serious adverse events were more common in the trilaciclib group. In the list of the 17 adverse events occurring in at least 10% of patients, most were less common in the trilaciclib group. Larger trials or real-world observational studies may be needed to identify uncommon serious adverse events associated with trilaciclib.

Plinabulin

Serious adverse events, treatment related adverse events, and discontinuation due to adverse events have not been reported. The plinabulin group experienced fewer grade 4 adverse events (58.6% vs. 80.0%), which may reflect a reduction in adverse events due to myelosuppression. Bone pain was less common in the plinabulin group (18% vs. 33%, p: NR), but all episodes were either grade 1 or 2.

Subgroup Analyses and Heterogeneity

Because the available randomized trials were either small or unpublished, there was little exploration of possible heterogeneity. Older patients and those with poor functional status may experience myelosuppression more frequently or be more at risk from complications from myelosuppression, but no subgroup analyses explored whether trilaciclib or plinabulin was particularly useful in these subgroups.

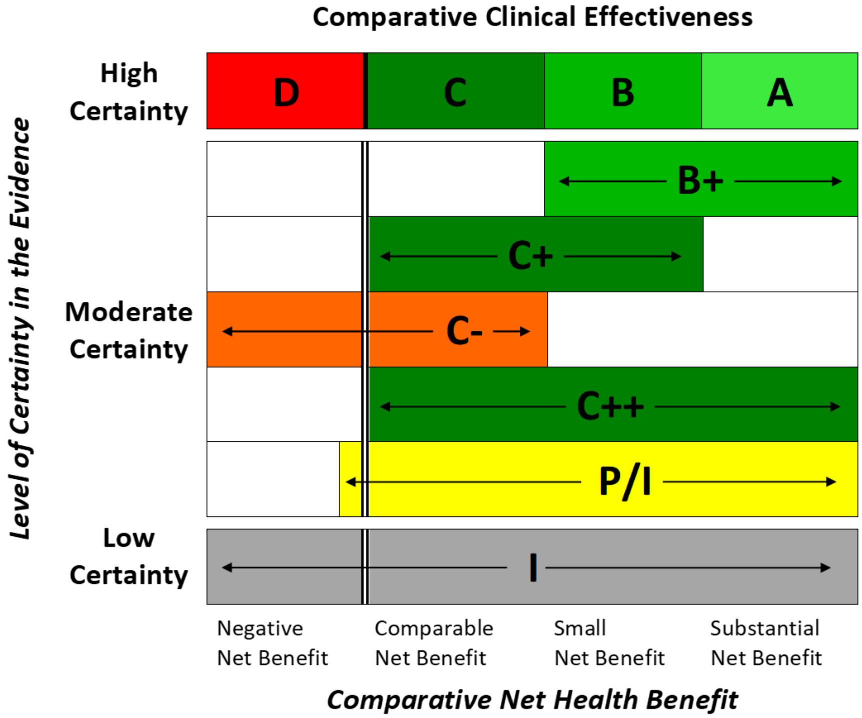
Uncertainty and Controversies

The small sample sizes of the trials of both trilaciclib and plinabulin translate into considerable uncertainties in the estimates for both the benefits and harms of the drugs. It is also unclear whether similar benefits will be seen when these drugs are used with other chemotherapy regimens that cause myelosuppression. For trilaciclib, its mechanism of action could theoretically lead to reduced chemotherapy efficacy for some cancers, so careful study is needed before expanding the indication for the drug.[34] In addition, the adverse event reporting for trilaciclib did not report non-myelosuppressive serious adverse events separately, which would help in understanding why overall serious adverse events were more common in patients receiving trilaciclib. Finally, there are ongoing studies of both therapies in both SCLC, NSCLC and breast cancer so there should be data for at least indirect comparisons of the relative efficacy of the two therapies in the future.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided in the Supplement.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

The results for trilaciclib are somewhat confusing. There is clearly a reduction in severe neutropenia, febrile neutropenia, severe anemia, serious adverse events due to myelosuppression, the need for chemotherapy dose reductions, and hospitalizations due to myelosuppression or sepsis.[7] However, these benefits did not translate into a reduction in the risk for total hospitalizations, serious adverse events, or deaths due to adverse events (all nominally higher in the trilaciclib group).[7] The HR for overall mortality in the pooled analysis was 1.0 (95% CI: 0.75 to 1.35) with approximately 50% mortality at one year and 90% mortality at two years. The total number of patients who received trilaciclib across the three trials and could be evaluated in a randomized context was only 122. Thus, we judge that there is moderate certainty that the use of trilaciclib in patients receiving chemotherapy for ES-SCLC is either comparable to or has a small net health benefit compared with standard of care (C+).

The results for plinabulin are more consistent. There was a modest reduction in the risk for severe neutropenia and there was a reduction in overall hospitalizations. There was also a reduction in bone pain. Finally, there were fewer grade 4 serious adverse events. However, several important outcomes have not yet been reported and the only trial of plinabulin added to pegfilgrastim in breast cancer has not yet been published in a peer reviewed journal. While there is no data at this point to suggest the possibility of net harm, it is possible that additional clinical data could span from no added benefit to the patient to significant added benefit. Because of these challenges, we judge that there is moderate certainty of a comparable, small, or substantial benefit (C++) for plinabulin added to pegfilgrastim versus pegfilgrastim alone.

Table 3.7. Evidence Ratings

Treatment	Comparator	Evidence Rating
Patients with ES-SCLC treated either with carboplatin/etoposide or topotecan		
Trilaciclib	Standard Therapy	C+
Patients with early-stage breast cancer		
Plinabulin plus pegfilgrastim	Pegfilgrastim	C++

ES-SCLC: extensive stage small cell lung cancer

4. Long-Term Cost Effectiveness

4.1 Methods Overview

The primary aim of this analysis is to estimate the cost effectiveness of trilaciclib for the prevention of chemotherapy-induced myelosuppressive effects and to identify a range of prices aligned with cost effectiveness for plinabulin for the prevention of chemotherapy-induced neutropenia from a United States health care sector perspective. A Markov model was developed to estimate quality-adjusted life years (QALYs) gained, equal-value of life years (evLYs) gained, total life years (LYs) gained, febrile neutropenia episodes, and total costs over a lifetime time horizon. Outcomes are reported as discounted values, using a discount rate of 3% per year.

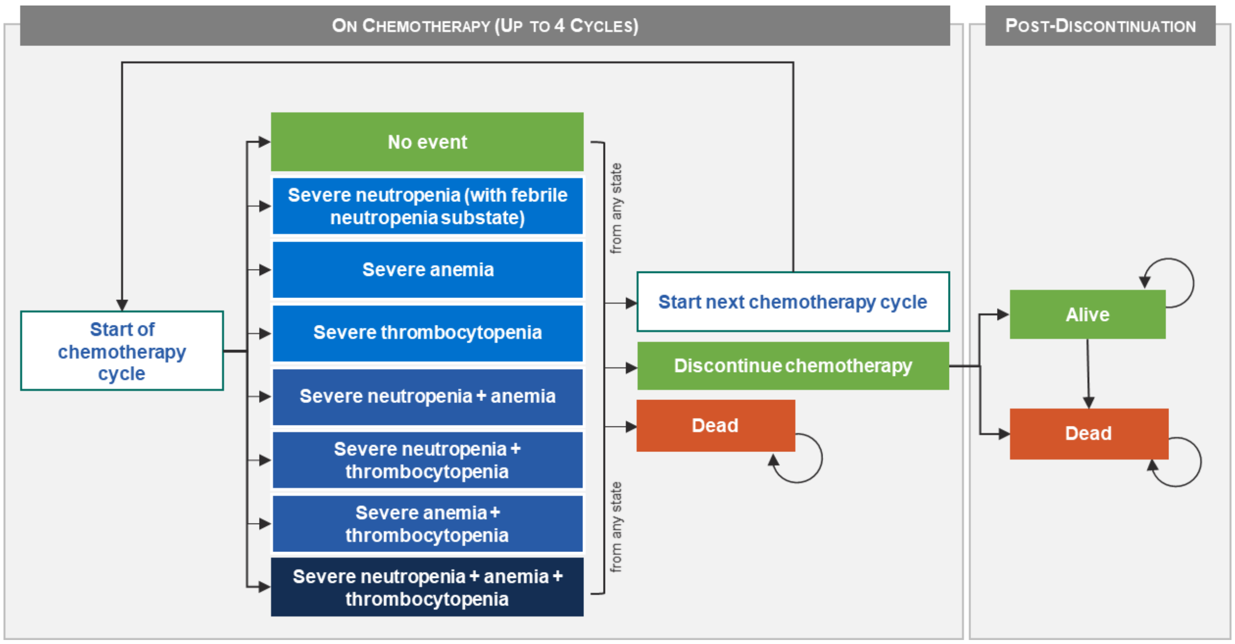
Cost effectiveness of trilaciclib was assessed for the approved indication of extensive-stage small cell lung cancer (ES-SCLC), separately in first line ES-SCLC and previously treated ES-SCLC due to differences in underlying risk of myelosuppressive effects and a different number of chemotherapy treatment cycles and dosing. Trilaciclib was compared to best supportive care (i.e., no prophylactic treatment) in both first line and previously treated ES-SCLC. For plinabulin, cost effectiveness was assessed in a population of early-stage breast cancer (E-BC) patients receiving TAC (taxotere, adriamycin and cyclophosphamide). Plinabulin + pegfilgrastim was compared to pegfilgrastim alone administered the day after chemotherapy, represented as a market basket consisting of branded and biosimilar subcutaneously injected products including the Onpro® injector device. Importantly, due to uncertainty regarding plinabulin's regulatory status and the associated lack of a price, results are presented solely in terms of threshold prices to achieve certain cost-effectiveness benchmarks (e.g., $100,000 per QALY gained).

Figure 4.1 depicts model health states and transitions. A patient cohort with age and gender that matches the clinical trial population at baseline enters the model at the start of the first chemotherapy cycle. For each cycle, patients can experience no myelosuppressive event, one event (severe neutropenia, severe anemia, severe thrombocytopenia), two concurrent events (e.g., severe neutropenia and severe anemia), or three concurrent events (severe neutropenia and severe anemia and severe thrombocytopenia). For the next model cycle, patients can start the next cycle of chemotherapy, discontinue chemotherapy, or die. After a maximum of four model cycles, all patients discontinue chemotherapy (and thus discontinue trilaciclib or plinabulin + pegfilgrastim). The model cycle length is 21 days, based on frequency of administration at (or prior to) administration of chemotherapy cycles.

Patients remain in the model until they die. All patients can transition to death from any of the alive health states, informed by the overall cancer specific survival and line of therapy. A subset of severe neutropenia cases experiences febrile neutropenia, with an associated risk of death.

Additional details on the long-term cost-effectiveness methods can be found in Supplement Section E.

Figure 4.1. Model Structure*



*Note that only severe neutropenia (and febrile neutropenia) is considered in the analysis of plinabulin.

For trilaciclib, two hypothetical cohorts were considered: first line ES-SCLC receiving carboplatin, etoposide and atezolizumab (EPA) and previously treated ES-SCLC receiving topotecan 1.5 mg/m^2. For first line ES-SCLC, the population has a baseline starting age of 65 years and 30% are female, the average across all arms in both trials.[16,17] For previously treated ES-SCLC, patients enter the model with a baseline age of 63 years and 45% are female, similar to the trial in previously treated ES-SCLC.[18] The population of focus for the economic evaluation of plinabulin is female E-BC patients being treated with TAC with a baseline age of 49 years, reflective of the PROTECTIVE-2 clinical trial.[32]

Two interventions are considered:

- Trilaciclib 240 mg/m^2 IV (Cosela™, G1 Therapeutics, Inc.)
- Plinabulin 40 mg IV (BeyondSpring Pharmaceuticals, Inc.) plus pegfilgrastim 6 mg SC

Trilaciclib has been approved for an indication that does not involve prophylactic administration of granulocyte colony-stimulating factor (G-CSF), and is compared to placebo (i.e., standard care). Plinabulin + pegfilgrastim are compared to standard dose (6 mg SC) pegfilgrastim alone. Due to differences in populations and comparators, plinabulin and trilaciclib are not compared to each other.

Several changes were made between the Draft Evidence report and this revised Evidence Report. We updated inputs based on manufacturer feedback for the proportion of patients in the 1L ES-SCLC population using G-CSF, proportion of patients hospitalized due to anemia in the 2L ES-SCLC population, modeled use of ESAs by trial arm separately from the incidence of severe anemia events and corrected the median progression-free survival in 1L ES-SCLC. Based on feedback about the limitations of the inpatient data collected from the trilaciclib trials, we added a scenario analysis which relied upon real-world data on hospitalization from Rashid 2016.[35] We revised the duration of disutility for severe myelosuppressive events to the entire 21-day cycle to align with the timeframe of the vignettes from which the health state utility values were derived and revised those model inputs to rely on Nafees 2017 rather than Nafees 2008 for the disutility of febrile neutropenia, neutropenia, and anemia (using fatigue as a proxy). To be consistent with other ICER assessments of therapies that are dosed based on body weight, and according to CMS guidance, utilization of trilaciclib at each dose was rounded up to the nearest whole vial to account for wastage. Lastly, because the incremental cost per QALY for the modified societal perspective in 1L ES-SCLC was more than 20% lower than the health care system perspective, we included the modified societal perspective as co-base case for the 1L ES-SCLC population.

4.2. Key Model Assumptions and Inputs

The occurrence of severe myelosuppressive events is based on clinical trial data, by treatment arm and cycle for trilaciclib and spread across cycles for plinabulin. The model additionally considers use of red blood cell transfusions and erythropoiesis-stimulating agents (for anemia), platelet transfusions (for thrombocytopenia), pegfilgrastim treatment for neutropenia (as opposed to prophylaxis), and bone pain.

Health state utility is based on underlying cancer type and line of therapy while on chemotherapy and off chemotherapy. Disutilities are applied for CIN and other myelosuppressive events as well as bone pain. Disutilities are applied multiplicatively for concurrent severe myelosuppressive events, while costs are additive.

Table 4.1. Key Model Assumptions

Assumption	Rationale
No direct impact on disease-related survival outside of febrile neutropenia and potential impact on survival based on relative dose intensity.	Consideration of separate anti-tumor effects is outside the scope of this evaluation. Pooled Phase II trials for trilaciclib show no impact on overall survival (HR 1.00; 95% CI: 0.75 to 1.35)[17]
Once treatment is required, patients will use pegfilgrastim for all remaining chemotherapy cycles. Initiation of pegfilgrastim is distributed equally across cycles.	Feedback obtained during scoping discussions indicated that once a patient develops severe neutropenia or severe anemia, physicians will use pegfilgrastim for prophylaxis in subsequent cycles
Next day pegfilgrastim as the standard of care for prophylaxis	Feedback obtained during scoping discussions indicated that next day is the most common schedule of administration
No serious AEs associated with trilaciclib or plinabulin are included in the model	Although the incidence of serious hematologic AEs was lower, the rate of overall serious AEs was higher in the trilaciclib arms in the pooled analysis of all three trials.[7] However, no single specific serious AE was elevated in patients taking trilaciclib enough to have an anticipated impact on cost effectiveness.

AE: adverse event

Trilaciclib in First Line ES-SCLC Inputs

For trilaciclib in first line ES-SCLC, pooled data from the two first line trials was used to inform the proportion of patients experiencing myelosuppressive events by cycle (Manufacturer Data Submission).[16,17,20] The proportion of patients who use G-CSF and ESAs was taken directly from the trials, independent of the proportion of patients experiencing severe neutropenia and severe anemia, to capture use outside of patients with grade 4 neutropenia (i.e., use in Grade 3).[16] Health state utility during chemotherapy and post-chemotherapy was taken from a real-world analysis of EQ-5D scores among Canadian SCLC patients with extensive disease to inform the chemotherapy health state and progressive disease for the post-discontinuation health state.[36] Disutility for neutropenia, febrile neutropenia, and anemia (using fatigue as a proxy) was taken from a study using a time trade-off approach to value non-small cell lung cancer toxicities.[37] Although this study also presented disutility for bleeding, not all grade 3 and 4 thrombocytopenia results in bleeding. Therefore, disutility for severe thrombocytopenia was taken from a study of UK patients with chronic lymphocytic leukemia.[38] The net cost of trilaciclib was based on ASP + 6%; as described above, utilization per dose was rounded up to the nearest whole vial to account for wastage.

Table 4.2. Key Model Inputs for First Line ES-SCLC

Parameter	Trilaciclib	No Prophylaxis	Source
Proportion experiencing myelosuppressive events by cycle	See Supplemental Information, Table E6.		Pooled data from 1L trials (Manufacturer Data Submission)[20]
Proportion of severe neutropenia which is febrile neutropenia	5.3% (95% CI 0.2%, 10.4%)	2.7% (95% CI: 1.2% to 4.2%)	Pooled data from 1L trials (Manufacturer Data Submission)[20] (95% CI calculated)
Proportion of severe febrile neutropenia which is hospitalized	100%		Assumption
Proportion of severe non-febrile neutropenia which is hospitalized	0%	4.5% (SE 0.2%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Use of G-CSF	RR 0.454 (95% CI: 0.294 to 0.701)	54.4% (95% CI: 49.2% to 59.6%)	Pooled data from 1L trials (Manufacturer Data Submission)[20] (RR calculated)
Proportion of severe anemia which is hospitalized	6.7% (95% CI: 0.2% to 13.2%)	15.6% (95% CI: 9.2% to 22.0%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
RBC transfusions per severe anemia episode	66.7% (95% CI: 54.5% to 78.9%)	62.5% (95% CI: 53.9% to 71.1%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Proportion of patients using ESAs	4.3% (95% CI: 2.2% to 6.4%)	8.9% (95% CI: 5.9% to 11.9%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Proportion of severe thrombocytopenia which is hospitalized	0%	8.3% (95% CI: 3.7% to 12.9%)	Pooled data from 1L trials (Manufacturer Data Submission) [20]
Proportion of severe thrombocytopenia episodes with platelet transfusions	33.3% (95% CI: 6.1% to 60.5%)	5.6% (95% CI: 1.8% to 9.4%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Occurrence of bone pain among users of G-CSF	5% (SE 0.3%)		Difference from placebo in the Neulasta prescribing information
Per-cycle mortality	3.7% (SE 0.2%)		Calculated based on median survival of 12.8 months in the placebo arm[16]

Parameter	Trilaciclib	No Prophylaxis	Source
Probability of mortality, hospitalized febrile neutropenia	15.7% (95% CI: 14.6% to 16.7%)		Dulisse 2013[39]
Utility on chemotherapy, no event	0.706 (95% CI: 0.670 to 0.740)		Kuehne 2021[36]
Utility post-discontinuation	0.674 (95% CI: 0.610 to 0.740)		Kuehne 2021[36]
Disutility, non-febrile neutropenia	-0.350 (SE 0.011)		Nafees 2017[37]
Disutility, febrile neutropenia	-0.470 (SE 0.008)		Nafees 2017[37]
Disutility, anemia	-0.290 (SE 0.009)		Nafees 2017[37]
Disutility, thrombocytopenia	-0.108 (95% CI: -0.097 to -0.119)		Tolley 2013[38]
Disutility, bone pain	-0.018 (SE 0.011)		Plinabulin manufacturer data submission
Drug cost of intervention (per dose)	$2,267	$0	ASP + 6%[40]
Doses per cycle	3	N/A	Daniel 2020[16]

1L: First line, ASP: average sales price, CI: confidence interval, ESA: erythropoiesis-stimulating agents, ES-SCLC: extensive-stage small cell lung cancer, G-CSF: granulocyte colony stimulating factor, RBC: red blood cell, RR: relative risk, SE: standard error

Trilaciclib in Previously Treated ES-SCLC Inputs

For trilaciclib in previously treated ES-SCLC, data was provided by the manufacturer to inform the proportion of patients experiencing myelosuppressive events by cycle based on the Hart 2020 study (Manufacturer Data Submission). The proportion of patients who use G-CSF was taken directly from the trial. Due to limited data, utility and disutility for previously treated ES-SCLC was assumed to be the same as first line ES-SCLC. The net cost of trilaciclib was based on ASP + 6%; as described above, utilization per dose was rounded up to the nearest whole vial to account for wastage.

Table 4.3. Key Model Inputs for Previously Treated ES-SCLC

Parameter	Trilaciclib	No Prophylaxis	Source
Proportion experiencing myelosuppressive events by cycle	See Supplemental Information, Table E7.		Manufacturer Data Submission Based on Hart 2020[18,20]
Proportion of severe neutropenia which is febrile neutropenia	4.9% (95% CI: 1.5% to 8.3%)	14.3% (95% CI: 9.3% to 19.3%)	Manufacturer Data Submission Based on Hart 2020[18,20]

Parameter	Trilaciclib	No Prophylaxis	Source
Proportion of severe febrile neutropenia which is hospitalized	100%		Assumption
Proportion of severe non-febrile neutropenia which is hospitalized	2.6% (SE 0.1%)	0%	Manufacturer Data Submission Based on Hart 2020[18,20]
Use of G-CSF	RR 0.76 (95% CI: 0.49 to 1.18)	65.5% (95% CI: 56.5% to 74.5%)	RR calculated based on proportions in Hart 2020[18,20]
Proportion of severe anemia which is hospitalized	0%	6.9% (95% CI: 2.2% to 11.6%)	Manufacturer Data Submission Based on Hart 2020[18,20]
RBC transfusions per severe anemia episode	80.0% (95% CI: 67.4% to 92.6%)	63.0% (95% CI: 53.7% to 72.3%)	Manufacturer Data Submission Based on Hart 2020[18,20]
Proportion of patients using ESAs	3.1% (95% CI: 0.0% to 6.2%)	20.7% (95% CI: 13.0% to 28.4%	Manufacturer Data Submission Based on Hart 2020[18,20]
Proportion of severe thrombocytopenia which is hospitalized	3.3% (95% CI: 0.0% to 6.6%)	3.2% (95% CI: 0.0% to 6.4%)	Manufacturer Data Submission Based on Hart 2020[18,20]
Proportion of severe thrombocytopenia episodes with platelet transfusions	23.3% (95% CI: 15.6% to 31.0%)	38.7% (30.0%, 47.4%)	Manufacturer Data Submission Based on Hart 2020[18,20]
Occurrence of bone pain among users of G-CSF	5% (SE 0.3%)		Difference from placebo in the Neulasta prescribing information
Per-cycle mortality	7.1% (SE 0.4%)		Calculated based on median survival of 6.5 months in the placebo arm[18]
Probability of mortality, hospitalized febrile neutropenia	15.7% (95% CI: 14.6% to 16.7%)		Dulisse 2013[39]
Utility on chemotherapy, no event	0.706 (95% CI: 0.670 to 0.740)		Kuehne 2021[36]
Utility post-discontinuation	0.674 (95% CI: 0.610 to 0.740)		Kuehne 2021[36]
Disutility, non-febrile neutropenia	-0.350 (SE 0.011)		Nafees 2017[37]
Disutility, febrile neutropenia	-0.470 (SE 0.008)		Nafees 2017[37]
Disutility, anemia	-0.290 (SE 0.009)		Nafees 2017[37]

Parameter	Trilaciclib	No Prophylaxis	Source
Disutility, thrombocytopenia	-0.108 (95% CI: -0.097 to -0.119)		Tolley 2013 [38]
Disutility, bone pain	-0.018 (SE 0.011)		Plinabulin manufacturer data submission
Drug cost of intervention (per dose)	$2,267	$0	ASP + 6%[40]
Doses per cycle	5	N/A	Hart 2020[18]

ASP: average sales price, CI: confidence interval, ESA: erythropoiesis-stimulating agents, ES-SCLC: extensive-stage small cell lung cancer, G-CSF: granulocyte colony stimulating factor, RBC: red blood cell, RR: relative risk, SE: standard error

Plinabulin in E-BC Inputs

For plinabulin in E-BC, data from the single Phase III trial was used to inform the proportion of patients experiencing at least one grade 3 or 4 neutropenia episode.[18] Data submitted by the manufacturer are academic-in-confidence until publication of the full manuscript. Utility inputs for on-treatment, post-discontinuation, febrile neutropenia, and bone pain were informed by the results of a linear regression analysis conducted using EQ-5D-5L scores collected in the PROTECTIVE-2 study of plinabulin in E-BC.[32] The EQ-5D-5L data from the trial were converted to health utility using the US health utility weights from Pickard 2019.[41] For patients alive more than five years post-chemotherapy, we attributed a utility of 0.851, the age- and gender-adjusted utility of the general population in the US.[42] The coefficient for severe non-febrile neutropenia was not statistically significant and was assumed at zero.

Table 4.4. Key Model Inputs for E-BC

Parameter	Plinabulin	No Prophylaxis	Source
Proportion experiencing severe neutropenia	[redacted]		Manufacturer Data Submission[32]
Febrile neutropenia	3.6% of all patients	6.3% of all patients	Blayney 2020[22]
Proportion of severe febrile neutropenia which is hospitalized	[redacted]		Manufacturer Data Submission[32]
Proportion of severe non-febrile neutropenia which is hospitalized	0%	0%	Assumption
Occurrence of bone pain	18% (95% CI: 14.4% to 21.7%)	30% (95% CI: 25.6% to 34.4%)	Blayney 2020[22]
Relative survival	89.2% (95% CI: 88.0% to 91.0%)		Swain 2013[43]
Probability of mortality, hospitalized febrile neutropenia	5.6% (range 4.8% to 6.3%)		Dulisse 2013[39]
Impact of RDI <85% on long-term survival (hazard ratio)	1.32 (range 1.0 to 1.8)		Lyman 2009[44]
Proportion of patients with RDI<85%	22.5% (SE 1.1%)	22.7% (SE 1.2%)	Manufacturer Data Submission[32]
Utility on chemotherapy, no event	0.9170 (95% CI: 0.825 to 1.000)		Manufacturer Data Submission[32]
Utility post-discontinuation, years 1-5	0.8588 (95% CI: 0.773 to 0.945)		Manufacturer Data Submission[32]
Utility post-discontinuation, years 5+	0.851 (SE 0.006)		Jiang 2021[42]
Disutility, non-febrile neutropenia	-0.000		Manufacturer Data Submission[32]
Disutility, febrile neutropenia	-0.1891 (SE 0.0288)		Manufacturer Data Submission[32]
Disutility, bone pain	-0.018 (SE 0.011)		Manufacturer Data Submission[32]
Doses per cycle	1	N/A	Daniel 2020[16]

ASP: average sales price, CI: confidence interval, E-BC: early breast cancer, G-CSF: granulocyte colony stimulating factor, SE: standard error

4.3. Results

Base-Case Results, Trilaciclib

Table 4.5, 4.6 and 4.7 present base-case results for trilaciclib. In both first line and previously treated ES-SCLC, trilaciclib resulted in fewer severe myelosuppressive episodes and fewer deaths due to febrile neutropenia, resulting in a small incremental benefit for QALYs, LYs, and evLYs. However, due to the relatively short duration of severe events, rarity of febrile-neutropenia related deaths, and limited life expectancy in the ES-SCLC population, incremental gains with trilaciclib were modest (0.021-0.029).

Table 4.5. Results for the Base Case for Trilaciclib Compared to No Prophylaxis in First-Line ES-SCLC

Treatment	Intervention Cost	Total Direct Cost	Indirect Cost	Severe Events*	QALYs	Life Years	evLYs
Trilaciclib	$33,900	$162,000	$1,300	0.407	1.007	1.494	1.008
No Prophylaxis	$0	$136,000	$5,200	2.023	0.977	1.498	0.977
Incremental	$33,900	$25,500	-$4,000	-1.615	0.029	0.005	0.030

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, QALYs: quality-adjusted life years
*Severe neutropenia, anemia, and thrombocytopenia. Each event counted separately in the combined health states (e.g., anemia + thrombocytopenia in a given cycle counts as two events)
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Table 4.6. Results for the Base Case for Trilaciclib Compared to No Prophylaxis in Previously Treated ES-SCLC

Treatment	Intervention Cost	Total Direct Cost	Indirect Cost	Severe Events	QALYs	Life Years	evLYs
Trilaciclib	$44,800	$65,400	$9,400	2.657	0.497	0.784	0.502
No Prophylaxis	$0	$26,500	$14,100	3.697	0.469	0.762	0.469
Incremental	$44,800	$38,800	-$4,700	-1.041	0.029	0.021	0.033

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, QALYs: quality-adjusted life years
*Severe neutropenia, anemia, and thrombocytopenia. Each event counted separately in the combined health states (e.g., anemia + thrombocytopenia in a given cycle counts as two events)
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Table 4.7. Incremental Cost-Effectiveness Ratios for the Base Case, Trilaciclib

	Comparator	Cost per Event Avoided	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$15,800	$871,000	$4,900,000	$844,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$37,300	$1,400,000	$1,800,000	$1,200,000
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$13,300	$735,000	$4,100,000	$712,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$32,800	$1,200,000	$1,600,000	$1,000,000

1L: first line, 2L: second line, ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, FN: febrile neutropenia, QALYs: quality-adjusted life years
Incremental cost-effectiveness ratios rounded to nearest $1,000 if <$1,000,000 or nearest $100,000 if >$1,000,000.

Base-Case Results, Plinabulin

Table 4.8 presents base-case results for plinabulin. Plinabulin resulted in fewer severe neutropenia episodes and fewer deaths due to febrile neutropenia. Incremental cost-effectiveness ratios were not calculated for plinabulin at this time. Similarly, treatment costs for plinabulin were not included in the base-case analysis due to lack of a placeholder price; neutropenia- and chemotherapy-related costs, however, are reported.

Table 4.8. Results for the Base Case for Plinabulin + Pegfilgrastim Compared to Pegfilgrastim Alone in E-BC

Treatment	Neutropenia and Chemo-related Cost*	Febrile Neutropenia Episodes	QALYs	Life Years	evLYs†
Plinabulin + pegfilgrastim	$74,900	0.036	16.959	19.891	16.959
Pegfilgrastim	$75,400	0.064	16.920	19.848	16.920
Incremental	-$500	-0.028	0.039	0.043	0.039

E-BC: early breast cancer, evLYs: equal-value life years, QALYs: quality-adjusted life years
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.
* Neutropenia and chemotherapy-related cost do not include plinabulin acquisition costs and therefore these findings do not represent total cost of therapy with plinabulin.
† Despite life extension with plinabulin, evLYs gained were the same as QALYs gained due to the use of a utility value for the best health state (utility post-discontinuation, years 5+) equal to that for population norms (0.851).

Threshold Analyses

The prices per 300 mg vial of trilaciclib or 40 mg vial of plinabulin required to achieve thresholds of $50,000 to $200,000 per QALY and per evLY gained are shown in Tables 4.9 and 4.10.

Table 4.9. QALY-Based Threshold Analysis Results

	Net Price per Unit*	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	$1,491	$400	$470	$540	$600
Trilaciclib, 2L+ ES-SCLC	$1,491	$250	$290	$340	$390
Plinabulin, E-BC	Not yet available	$630	$1,100	$1,600	$2,100
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	$1,491	$580	$650	$720	$780
Trilaciclib, 2L+ ES-SCLC	$1,491	$400	$450	$500	$550

*Unit = 300 mg vial of trilaciclib or one 40 mg vial of plinabulin

Table 4.10. evLY-Based Threshold Analysis Results

	Net Price per Unit	Unit Price to Achieve $50,000 per evLY Gained	Unit Price to Achieve $100,000 per evLY Gained	Unit Price to Achieve $150,000 per evLY Gained	Unit Price to Achieve $200,000 per evLY Gained
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	$1,491	$400	$470	$540	$610
Trilaciclib, 2L+ ES-SCLC	$1,491	$250	$310	$360	$416
Plinabulin, E-BC†	Not yet available	$620	$1,100	$1,600	$2,100
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	$1,491	$580	$650	$720	$780
Trilaciclib, 2L+ ES-SCLC	$1,491	$410	$460	$520	$570

*Unit = 300 mg vial of trilaciclib or one 40 mg vial of plinabulin

† Despite life extension with plinabulin, threshold prices measured in terms of QALYs gained and evLYs gained were the same due to the use of a utility value for the best health state (utility post-discontinuation, years 5+) equal to that for population norms (0.851).

Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., 95% confidence intervals) or a range of ±10% to evaluate changes in cost per additional QALY for trilaciclib and the threshold price per dose at a willingness to pay of $100,000 per QALY gained for plinabulin. For trilaciclib, results of each one-way sensitivity analysis were similar to the base case. In both first line and previously treated ES-SCLC, the most impactful model parameter was the proportion of neutropenia which is febrile neutropenia in the no prophylaxis arm. For plinabulin in E-BC, the most impactful model parameters were the proportion of patients with RDI ≤85% in each treatment arm, suggesting that assumptions around potential impact on survival is a major model driver. The next most impactful parameters were related to febrile neutropenia.

In probabilistic sensitivity analysis, no iterations resulted in an incremental cost per QALY gained or cost per evLY gained of less than $200,000 for trilaciclib compared with no prophylaxis in first line ES-SCLC or previously treated ES-SCLC. Incremental cost-effectiveness ratios, including estimates of uncertainty, were not computed in the analysis of plinabulin.

Table 4.11. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Trilaciclib vs. No Prophylaxis

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Health Care System Perspective				
Trilaciclib, 1L ES-SCLC	0%	0%	0%	0%
Trilaciclib, 2L+ ES-SCLC	0%	0%	0%	0%
Modified Societal Perspective				
Trilaciclib, 1L ES-SCLC	0%	0%	0%	0%
Trilaciclib, 2L+ ES-SCLC	0%	0%	0%	0%

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, QALYs: quality-adjusted life years

Table 4.12. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Trilaciclib vs. No Prophylaxis

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Health Care System Perspective				
Trilaciclib, 1L ES-SCLC	0%	0%	0%	0%
Trilaciclib, 2L+ ES-SCLC	0%	0%	0%	0%
Modified Societal Perspective				
Trilaciclib, 1L ES-SCLC	0%	0%	0%	0%
Trilaciclib, 2L+ ES-SCLC	0%	0%	0%	0%

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years

Additional information, including tornado plots and results of probabilistic analysis, can be found Supplement Section E4.

Scenario Analyses

Five scenarios were explored to assess the impact on model results. Additional details for scenario analyses can be found in the Supplement Section E5.

1. Modified societal perspective scenario including indirect cost of myelosuppressive events due to lost workplace productivity due to the event, transfusions, and next day return to clinic for pegfilgrastim
2. Scenario which considers additional facility mark-up on G-CSF ranging from 1.3 to 2.5 (depending on product)
3. Scenario which assumes all patients who initiate G-CSF do so in cycle 1 rather than the base-case assumption of equally spread over four cycles

4. Scenario with the cost of myelosuppressive events taken from Wong 2018 rather than the sources in the base case
5. Scenario with the probability of hospitalization per severe myelosuppressive event from Rashid 2016 rather than the clinical trials

Results of these scenarios did not impact conclusions on cost effectiveness relative to the health system case for trilaciclib in ES-SCLC.

Table 4.13. Scenario Analysis Results for Trilaciclib in ES-SCLC (Incremental Cost per QALY Gained)

	Base-Case Results	G-CSF Markup	G-CSF Initiation in Cycle 1	Costs from Wong 2018	Hospitalization from Rashid 2016
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	$871,000	$818,000	$834,000	$632,000	$883,000
Trilaciclib, 2L+ ES-SCLC	$1,400,000	$1,300,000	$1,300,000	$1,200,000	$1,300,000
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	$735,000	$682,000	$697,000	$496,000	$747,000
Trilaciclib, 2L+ ES-SCLC	$1,200,000	$1,200,000	$1,200,000	$1,000,000	$1,200,000

ES-SCLC: extensive-stage small cell lung cancer, G-CSF: granulocyte colony stimulating factor
Incremental cost-effectiveness ratios rounded to nearest $100,000.

The modified societal perspective scenario and cost of neutropenia from Wong 2018 scenarios resulted in a higher unit price to achieve the threshold of $100,000 per QALY gained for plinabulin + pegfilgrastim versus pegfilgrastim alone. As both treatment arms used pegfilgrastim starting in cycle 1, additional G-CSF markup and G-CSF initiation in cycle 1 scenarios had no impact on the threshold price for plinabulin.

Table 4.14. Scenario Analysis Results for Plinabulin in E-BC (Unit Price per Dose to Achieve $100,000 per QALY Gained)

Treatment	$100,000 per QALY Threshold Price	Modified Societal	G-CSF Markup	G-CSF Initiation in Cycle 1	Costs from Wong 2018	Hospitalization from Rashid 2016
Plinabulin, E-BC	$1,100	$1,200	No impact	No impact	$1,300	$1,200

ES-SCLC: extensive-stage small cell lung cancer, G-CSF: granulocyte colony stimulating factor

Model Validation

Model validation details can be found in Supplement Section E7.

Uncertainty and Controversies

For the analysis of trilaciclib in first line and previously treated ES-SCLC, robust data were provided by the manufacturer in order to fully populate model health states and the proportion of patients experiencing severe myelosuppressive events and health care resource use (e.g., transfusions) related to those events. However, small sample sizes for some inputs resulted in considerable uncertainty and large confidence intervals. Incremental QALY gains with trilaciclib were found to be minimal due to the relatively short duration of severe events, rarity of febrile-neutropenia related deaths, and limited life expectancy in the ES-SCLC population. Because the QALY is the denominator of the cost-effectiveness ratio, a moderate difference in the numerator (costs) can generate a very high ratio, and small changes in QALYs could change the results dramatically.

While we attempted to comprehensively capture costs associated with myelosuppressive events, inclusion of additional costs (e.g., emergency room visits) or alternative sources may have resulted in a smaller cost difference for trilaciclib versus no prophylaxis. Our analysis also excluded serious non-hematological adverse events, which were higher for trilaciclib in the pooled analysis of the three trials.[7] However, it is unclear which serious adverse events are driving this difference. Our results may underestimate full impact of avoidance of red blood cell and platelet transfusions, as adverse events associated with these treatments was not considered within the model. However, the overall impact of these adverse events is expected to be small.

Health care resource utilization per event was taken from global clinical trials, which may not be representative of real-world practice in the United States. Alternative sources such as Wong 2018 or a real-world analysis of the burden of myelosuppression generate higher estimates for the cost burden of adverse events than in our base-case analysis.[45,46] However, we did not choose these sources as our base case, as both capture all-cause costs within 12 months of starting chemotherapy in patients with ≥1 event. This differs from the model in two ways: first that all-cause costs could be driven by other events and patient characteristics irrespective of the myelosuppressive event; and second, costs would apply to a per-patient level rather than at the per-event level, which the model uses to apply costs. To explore the extent in which the full cost of myelosuppressive episodes was potentially underestimated in our model, we conducted a scenario analysis using cost data from Wong et al. Although not specific to SCLC, treatment episodes were matched in Wong et al. to reduce confounding. In this scenario, the individual cost of G-CSF, ESAs, and transfusions was removed from the model, as these costs would already be captured in the Wong costing approach. We also explored a scenario where the proportion of severe myelosuppressive events which require hospitalization were captured using claims data in patients with breast cancer. Results were similar to the base-case analysis.

For the analysis of plinabulin, the model yielded a threshold price of $1,100 per cycle to reach the willingness to pay threshold of $100,000 per QALY gained. Although febrile neutropenia-related deaths were rare, the long-life expectancy of patients with E-BC yielded a greater QALY gain than in ES-SCLC. Bone pain was included in the model but made minimal impact due to short duration of disutility. Of note, the results are extremely sensitive to assumptions around relative dose intensity (RDI) and potential impact on mortality. Our base case applied the proportion of patients with RDI <85% from the trial (22.5% for plinabulin + pegfilgrastim vs. 22.7% for pegfilgrastim alone). Due to the plinabulin study design where no dose modifications were allowed on cycle 1 and patients were allowed to stop doxorubicin for any reason after cycle 1, no significant impact on the proportion of patients with RDI <85% was demonstrated within the plinabulin clinical trial setting, despite there being some suggestion of decreased dose reduction in the plinabulin arm. In the real-world clinical setting, reducing the incidence of neutropenia may result in more patients achieving RDI ≥85%, where even a difference of 3% (e.g., 22% vs. 25%) results in a threshold price of $1,800 per cycle at the $100,000 per QALY threshold.

4.4 Summary and Comment

Using a Markov model, we compared the cost and effectiveness of trilaciclib versus no prophylaxis in ES-SCLC for the prevention of severe myelosuppressive events and generated threshold prices for plinabulin for combination plinabulin + pegfilgrastim versus pegfilgrastim alone in E-BC for the prevention of severe neutropenia (including febrile neutropenia).

We found that trilaciclib produced a small QALY gain versus no prophylaxis at a moderate added cost, resulting in estimates of $735,000 to $1,400,000 per QALY gained depending on the line of therapy and perspective taken. Plinabulin also moderately increased QALYs, driven by an avoidance of febrile neutropenia-related deaths. The calculated threshold price per dose of plinabulin was $1,100 per cycle to reach the willingness to pay threshold of $100,000 per QALY gained.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	The short-term risk of death from febrile neutropenia is high.
Magnitude of the lifetime impact on individual patients of the condition being treated	As noted in the modeling section, because severe, life-threatening myelosuppression is relatively uncommon and lasts for a short period of time, it does not have a large lifetime impact.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Minimal impact.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Caregivers often must spend significant time supporting patients during their period of isolation due to neutropenia, which impacts their work and other personal obligations.
Patients' ability to manage and sustain treatment given the complexity of regimen	None.
Health inequities	There is the potential for a reduction in health inequities associated with the burden of returning to the health care center for G-CSF the day after chemotherapy infusion, which may be reduced with these novel agents. Travel is particularly burdensome to historically underserved and low-income patients.

There is no suggestion in the epidemiology of cancer treatment-associated myelosuppressive events that there is a significant difference in prevalence of myelosuppression among key subpopulations. Therefore, we did not calculate a Health Improvement Distribution Index (HIDI).

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the per-vial cost of treatment with trilaciclib are presented in Table 6.1 (health care system perspective) and Table 6.2 (modified societal perspective) below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. Final HBPBs represent a weighted average of trilaciclib in 1L and 2L+, assuming 75.8% of use is 1L and 24.2% is 2L+ and were calculated from lowest $100,000/QALY threshold price to highest $150,000/evLY threshold price. This results in a price benchmark of $430 to $670 per vial of trilaciclib. Discounts from net trilaciclib price to achieve benchmark prices range from 55% to 71%.

HBPBs are not presented for plinabulin given considerable uncertainty around its future US FDA approval.

Table 6.1. Base-Case Per-Unit Cost-Effectiveness Health Benefit Price Benchmarks for Trilaciclib, Health Care System Perspective

	Net Price per Unit*	Unit Price to Achieve $100,000 Threshold	Unit Price to Achieve $150,000 Threshold	Additional Discounts from Net Price to Reach Threshold Prices
Trilaciclib, 1L ES-SCLC				
QALYs gained	$1,491	$470	$540	64-69%
evLYs gained	$1,491	$470	$540	64-68%
Trilaciclib, 2L+ ES-SCLC				
QALYs gained	$1,491	$290	$340	77-80%
evLYs gained	$1,491	$310	$360	76-79%
Weighted				
QALYs gained	$1,491	$430	$490	67-71%
evLYs gained	$1,491	$430	$500	67-71%

evLY: equal value of life year, QALY: quality-adjusted life year

Table 6.2. Base-Case Per-Unit Cost-Effectiveness Health Benefit Price Benchmarks for Trilaciclib, Modified Societal Perspective

	Net Price per Unit*	Unit Price to Achieve $100,000 Threshold	Unit Price to Achieve $150,000 Threshold	Additional Discounts from Net Price to Reach Threshold Prices
Trilaciclib, 1L ES-SCLC				
QALYs gained	$1,491	$650	$720	52-56%
evLYs gained	$1,491	$650	$720	52-56%
Trilaciclib, 2L+ ES-SCLC				
QALYs gained	$1,491	$450	$500	67-70%
evLYs gained	$1,491	$460	$520	65-69%
Weighted				
QALYs gained	$1,491	$600	$660	56-60%
evLYs gained	$1,491	$610	$670	55-59%

evLY: equal value of life year, QALY: quality-adjusted life year

7. Potential Budget Impact

7.1. Overview of Key Assumptions

ICER used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. The aim of this potential budgetary impact analysis is to document the number of incident patients who could be treated at select prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2021-2022, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $734 million per year for new drugs.

As the manufacturer of plinabulin has received a complete response letter delaying potential approval of the drug, and because no suitable analog is currently FDA-approved, there is not enough confidence to utilize a placeholder price for its budget impact analysis. Therefore, for estimating plinabulin budget impact, only the prices to achieve three QALY-based cost-effectiveness thresholds were considered: $150,000 per QALY ($1,600 per unit), $100,000 per QALY ($1,100 per unit), and $50,000 per QALY ($630 per unit).

Applying values from best available evidence results in estimates of approximately 60,600 incident adult E-BC patients eligible for treatment with plinabulin per year, for a total of approximately 303,000 patients over five years. All patients were assumed to remain in the cumulative patient pool over the time horizon due to high 5-year survival rates in E-BC.

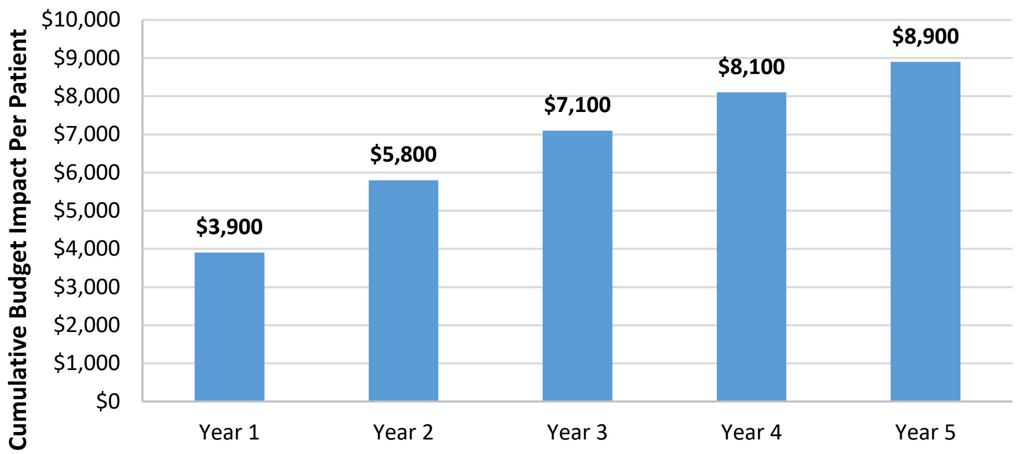
Due to trilaciclib having been approved approximately one year ago, its budgetary impact was not estimated.

7.2. Results

Figure 7.1 depicts the cumulative per-patient potential budget impact calculations for plinabulin plus pegfilgrastim as compared to pegfilgrastim alone, based on the price of plinabulin to achieve a cost-effectiveness threshold of $100,000 per QALY ($1,100 per unit of plinabulin).

All incident patients composing the eligible E-BC population could be treated without crossing the annual potential budget impact threshold of $734 million.

Figure 7.1. Plinabulin Plus Pegfilgrastim Cumulative Per-Patient Budget Impact Results Over a Five-year Time Horizon (using price to achieve a cost-effectiveness threshold of $100,000 per QALY)



References

1. Barreto JN, McCullough KB, Ice LL, Smith JA. Antineoplastic agents and the associated myelosuppressive effects: a review. *J Pharm Pract.* 2014;27(5):440-446.
2. Crawford J, Denduluri N, Patt D, et al. Relative dose intensity of first-line chemotherapy and overall survival in patients with advanced non-small-cell lung cancer. *Support Care Cancer.* 2020;28(2):925-932.
3. Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. *J Natl Compr Canc Netw.* 2009;7(1):99-108.
4. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2015;33(28):3199-3212.
5. Crawford J, Becker PS, Armitage JO, et al. Myeloid Growth Factors, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2017;15(12):1520-1541.
6. Tai E, Guy GP, Dunbar A, Richardson LC. Cost of Cancer-Related Neutropenia or Fever Hospitalizations, United States, 2012. *J Oncol Pract.* 2017;13(6):e552-e561.
7. Weiss J, Goldschmidt J, Andric Z, et al. Effects of Trilaciclib on Chemotherapy-Induced Myelosuppression and Patient-Reported Outcomes in Patients with Extensive-Stage Small Cell Lung Cancer: Pooled Results from Three Phase II Randomized, Double-Blind, Placebo-Controlled Studies. *Clin Lung Cancer.* 2021.
8. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology (Williston Park).* 2015;29(4):282-294.
9. Smith RE. Trends in Recommendations for Myelosuppressive Chemotherapy for the Treatment of Solid Tumors. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw.* 2006;4(7):649-658.
10. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. *Oncologist.* 2005;10(6):427-437.
11. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol.* 2007;25(21):3158-3167.
12. Lambertini M, Del Mastro L, Bellodi A, Pronzato P. The five "Ws" for bone pain due to the administration of granulocyte-colony stimulating factors (G-CSFs). *Crit Rev Oncol Hematol.* 2014;89(1):112-128.
13. Maahs L, Tang A, Saheli ZA, Jacob B, Polasani R, Hwang C. Real-world effectiveness of the pegfilgrastim on-body injector in preventing severe neutropenia. *J Oncol Pharm Pract.* 2022;28(1):17-23.
14. Epstein RS, Basu Roy UK, Aapro M, et al. Cancer Patients' Perspectives and Experiences of Chemotherapy-Induced Myelosuppression and Its Impact on Daily Life. *Patient Prefer Adherence.* 2021;15:453-465.
15. Epstein RS, Aapro MS, Basu Roy UK, et al. Patient Burden and Real-World Management of Chemotherapy-Induced Myelosuppression: Results from an Online Survey of Patients with Solid Tumors. *Adv Ther.* 2020;37(8):3606-3618.
16. 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;148(10):2557-2570.

17. Weiss JM, Csoszi T, Maglakelidze M, et al. Myelopreservation 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.
18. 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.* 2021;38(1):350-365.
19. Ferrarotto R, Anderson I, Medgyasszay B, et al. Trilaciclib prior to chemotherapy reduces the usage of supportive care interventions for chemotherapy-induced myelosuppression in patients with small cell lung cancer: Pooled analysis of three randomized phase 2 trials. *Cancer Med.* 2021;10(17):5748-5756.
20. G1 Therapeutics. Data on File. 2021.
21. Tan AR, Wright GS, Thummala AR, et al. Trilaciclib plus chemotherapy versus chemotherapy alone in patients with metastatic triple-negative breast cancer: a multicentre, randomised, open-label, phase 2 trial. *The Lancet Oncology.* 2019;20(11):1587-1601.
22. Blayney DW, Zhang Q, Feng J, et al. Efficacy of Plinabulin vs Pegfilgrastim for Prevention of Chemotherapy-Induced Neutropenia in Adults With Non-Small Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(11):e204429.
23. Blayney DW, Shi Y, Bondarenko I, et al. Head-to-head comparison of single agent (SA) plinabulin (Plin) versus pegfilgrastim (Peg) for the prevention of chemotherapy-induced neutropenia (CIN) in the phase 3 trial PROTECTIVE-1. *Journal of Clinical Oncology.* 2021;39(15_suppl):547-547.
24. Blayney DW, Huang L, Mohanlal R. A Randomized Phase 3 Clinical Trial of the Combination of Plinabulin (plin) + Pegfilgrastim (peg) Versus (vs) Peg Alone for Tac (docetaxel, doxorubicin, cyclophosphamide) Induced Neutropenia (cin). *Blood.* 2019;134(Supplement_1):3590-3590.
25. Blayney DW, Shi Y, Adamchuk H, et al. Clinical trial testing superiority of combination plinabulin (Plin) and pegfilgrastim (Peg) versus peg alone in breast cancer treated with high-risk febrile neutropenia risk chemotherapy (chemo): Final results of the phase 3 protective-2 in chemo-induced neutropenia (CIN) prevention. *Journal of Clinical Oncology.* 2021;39(15_suppl):533-533.
26. Shi Y, Blayney DW, Adamchuk H, et al. Chemotherapy induced profound neutropenia (PN) in patients (pt) with breast cancer (BC) after chemotherapy and plinabulin (Plin) plus pegfilgrastim (Peg) combination versus (vs) peg alone: Final phase 3 results from protective-2 (BPI-2358-106). *Journal of Clinical Oncology.* 2021;39(15_suppl):546-546.
27. Blayney DW, Shi YK, Adamchuk H, et al. Clinical trial testing superiority of combination plinabulin (Plin) and pegfilgrastim (Peg) versus peg alone in breast cancer treated with high-risk febrile neutropenia risk chemotherapy (chemo): Final results of the phase 3 PROTECTIVE-2 in chemo-induced neutropenia (CIN) prevention. ASCO OncLive; 2021.
28. Blayney DW, Ogenstad S, Shi Y, et al. Comparison of pegfilgrastim (Peg), plinabulin (Plin), and the combination for chemotherapy (Chemo) induced neutropenia (CIN) prevention: Rationale for the combination. *Journal of Clinical Oncology.* 2019;37(15_suppl):e12030-e12030.
29. Blayney DW, Bondarenko I, Shi Y, et al. The effect of increasing doses of pegfilgrastim (Peg) on thrombocytopenia (T) in breast cancer (BC) patients (pts) receiving taxotere (Doc), doxorubicin, cyclophosphamide (TAC) and plinabulin (Plin). *Annals of Oncology.* 2019;30.
30. Blayney DW, Lelorier Y, Mitchell D, Huang L, Mohanlal R. Combination plinabulin+pegfilgrastim (Plin+Peg) had better toxicity management and health related quality-of-life (HrQoL) compared to Peg alone in early-stage breast cancer (BC) patients (pts) treated with taxotere, doxorubicin and cyclophosphamide (TAC). San Antonio Breast Cancer Symposium (SABCS); 2021.

31. Blayney DW, Mohanlal R, Adamchuk H, et al. Efficacy of Plinabulin vs Pegfilgrastim for Prevention of Docetaxel-Induced Neutropenia in Patients With Solid Tumors: A Randomized Clinical Trial. *JAMA Netw Open.* 2022;5(1):e2145446.
32. BeyondSpring Pharmaceuticals Inc. Data on File. 2021.
33. Han B, Shi Y, Feinstein T, et al. LBA48 DUBLIN-3 (BPI-2358-103): A global phase (Ph) III trial with the plinabulin/docetaxel (Plin/Doc) combination vs. Doc in 2nd/3rd Line NSCLC patients (pts) with EGFR-wild type (wt) progressing on a prior platinum-based regimen. *Annals of Oncology.* 2021;32:S1326.
34. Roberts PJ, Kumarasamy V, Witkiewicz AK, Knudsen ES. Chemotherapy and CDK4/6 Inhibitors: Unexpected Bedfellows. *Mol Cancer Ther.* 2020;19(8):1575-1588.
35. Rashid N, Koh HA, Baca HC, Lin KJ, Malecha SE, Masaquel A. Economic burden related to chemotherapy-related adverse events in patients with metastatic breast cancer in an integrated health care system. *Breast Cancer (Dove Med Press).* 2016;8:173-181.
36. Kuehne N, Hueniken K, Xu M, et al. Longitudinal Assessment of Health Utility Scores, Symptoms and Toxicities in Patients with Small Cell Lung Cancer Using Real World Data. *Clin Lung Cancer.* 2021.
37. Nafees B, Lloyd AJ, Dewilde S, Rajan N, Lorenzo M. Health state utilities in non-small cell lung cancer: An international study. *Asia Pac J Clin Oncol.* 2017;13(5):e195-e203.
38. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ.* 2013;14(5):749-759.
39. Dulisse B, Li X, Gayle JA, et al. A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia. *J Med Econ.* 2013;16(6):720-735.
40. CMS. ASP Drug Pricing Files October 2021 Update. https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2021-asp-drug-pricing-files. Published 2021. Accessed October 29, 2021.
41. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value Health.* 2019;22(8):931-941.
42. Jiang R, Janssen MFB, Pickard AS. US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples. *Qual Life Res.* 2021;30(3):803-816.
43. Swain SM, Tang G, Geyer CE, Jr., et al. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *J Clin Oncol.* 2013;31(26):3197-3204.
44. Lyman GH, Lalla A, Barron RL, Dubois RW. Cost-effectiveness of pegfilgrastim versus filgrastim primary prophylaxis in women with early-stage breast cancer receiving chemotherapy in the United States. *Clin Ther.* 2009;31(5):1092-1104.
45. Goldschmidt J MA, Shi P, Huang H, Chioda M. Real-world burden of myelosuppression among patients with extensive-stage small cell lung cancer treated in the community oncology setting. Paper presented at: AMCP NEXUS; October 18-21, 2021; Denver, CO.
46. Wong W, Yim YM, Kim A, et al. Assessment of costs associated with adverse events in patients with cancer. *PLoS One.* 2018;13(4):e0196007.
47. American Academy of Allergy Asthma & Immunology. Neutropenia Defined. https://www.aaaai.org/Tools-for-the-Public/Allergy,-Asthma-Immunology-Glossary/Neutropenia-Defined#:~:text=Neutropenia%20is%20defined%20as%20an,microliter%20(500%2FmicroL). Published 2021. Accessed.

48. National Comprehensive Cancer Network. Anemia and Neutropenia - Low Red and White Blood Cell Counts (Version 2021). https://www.nccn.org/patients/guidelines/content/PDF/anemia-patient-guideline.pdf. Published 2021. Accessed.
49. Madeddu C, Gramignano G, Astara G, et al. Pathogenesis and Treatment Options of Cancer Related Anemia: Perspective for a Targeted Mechanism-Based Approach. *Front Physiol.* 2018;9:1294.
50. Arnold MD, Cuker A. Diagnostic approach to the adult with unexplained thrombocytopenia. In: UpToDate, ed. *UpToDate.* UpToDate; 2021.
51. American Society of Clinical Oncology. *Ten Things Physicians and Patients Should Question.* 2019.
52. American Society of Breast Surgeons. *Five Things Physicians and Patients Should Question.* 2021.
53. National Comprehensive Cancer Network (NCCN). Hematopoietic Growth Factors (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Published 2021. Accessed.
54. National Institute for Health and Care Excellence (NICE). Neutropenic sepsis: prevention and management in people with cancer [Clinical guideline CG151]. 2012.
55. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
56. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current. Published 2020. Accessed.
57. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine.* 2009;6(7):e1000097.
58. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. Published 2008. Accessed.
59. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
60. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. https://icer-review.org/methodology/icers-methods/icer-evidence-ratingmatrix/. . Published 2020. Updated January 31, 2020. Accessed.
61. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
62. CMS. Centers for Medicare and Medicaid Services (CMS) Healthcare Common Procedure Coding System (HCPCS) Application Summaries and Coding Decisions Second Quarter 2021 Coding Cycle for Drug and Biological Products. https://www.cms.gov/files/document/2021-hcpcs-application-summary-quarter-2-2021-drugs-and-biologics-updated-08062021.pdf. Published 2021. Accessed.
63. Rolston KV, Frisbee-Hume SE, Patel S, Manzullo EF, Benjamin RS. Oral moxifloxacin for outpatient treatment of low-risk, febrile neutropenic patients. *Support Care Cancer.* 2010;18(1):89-94.
64. HMD. Human Mortality Database. https://www.mortality.org/. Accessed October 27, 2021.
65. SEER. Recent Trends in SEER Relative Survival Rates, 2004-2018. https://seer.cancer.gov/explorer/application.html?site=55&data_type=4&graph_type=2&compareBy=stage&chk_stage_104=104&relative_survival_interval=5&sex=3&race=1&age_range=1&advopt_precision=1&advopt_show_ci=on&advopt_display=2#graphArea. Published 2021. Accessed October 27, 2021.

66. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes.* 2008;6:84.
67. Kirshner JJ, Heckler CE, Janelsins MC, et al. Prevention of pegfilgrastim-induced bone pain: a phase III double-blind placebo-controlled randomized clinical trial of the university of rochester cancer center clinical community oncology program research base. *J Clin Oncol.* 2012;30(16):1974-1979.
68. Amgen I. Data on File. 2021.
69. CMS. Billing and Coding: Neulasta® (pegfilgrastim) Onpro® Kit (On-body Injector). https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=54682. Published 2015. Updated October 10, 2019. Accessed October 29, 2021.
70. CMS. Medicare Physician Fee Schedule. https://www.cms.gov/medicare/physician-fee-schedule/search. Published 2021. Updated 07/01/2021. Accessed October 29, 2021.
71. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst.* 2011;103(2):117-128.
72. Weycker D, Li X, Edelsberg J, et al. Risk and Consequences of Chemotherapy-Induced Febrile Neutropenia in Patients With Metastatic Solid Tumors. *J Oncol Pract.* 2015;11(1):47-54.
73. Weycker D, Hatfield M, Grossman A, et al. Risk and consequences of chemotherapy-induced thrombocytopenia in US clinical practice. *BMC Cancer.* 2019;19(1):151.
74. Toner RW, Pizzi L, Leas B, Ballas SK, Quigley A, Goldfarb NI. Costs to hospitals of acquiring and processing blood in the US: a survey of hospital-based blood banks and transfusion services. *Appl Health Econ Health Policy.* 2011;9(1):29-37.
75. Barnett CL, Mladsi D, Vredenburg M, Aggarwal K. Cost estimate of platelet transfusion in the United States for patients with chronic liver disease and associated thrombocytopenia undergoing elective procedures. *J Med Econ.* 2018;21(8):827-834.
76. Stephens JM, Li X, Reiner M, Tzivelekis S. Annual patient and caregiver burden of oncology clinic visits for granulocyte-colony stimulating factor therapy in the US. *J Med Econ.* 2016;19(5):537-547.
77. BLS. Table B-3. Average hourly and weekly earnings of all employees on private nonfarm payrolls by industry sector, seasonally adjusted. https://www.bls.gov/news.release/empsit.t19.htm. Published 2021. Accessed October 29, 2021.
78. Calhoun EA, Chang CH, Welshman EE, Fishman DA, Lurain JR, Bennett CL. Evaluating the total costs of chemotherapy-induced toxicity: results from a pilot study with ovarian cancer patients. *Oncologist.* 2001;6(5):441-445.
79. MSKCC. About Your Blood Transfusion. https://www.mskcc.org/cancer-care/patient-education/about-blood-transfusion. Published 2021. Accessed October 29, 2021.
80. Abraham I, Onyekwere U, Deniz B, et al. Trilaciclib and the economic value of multilineage myeloprotection from chemotherapy-induced myelosuppression among patients with extensive-stage small cell lung cancer treated with first-line chemotherapy. *J Med Econ.* 2021:1-37.
81. Lin S, Luo S, Gu D, et al. First-Line Durvalumab in Addition to Etoposide and Platinum for Extensive-Stage Small Cell Lung Cancer: A U.S.-Based Cost-Effectiveness Analysis. *Oncologist.* 2021;26(11):e2013-e2020.
82. Liu Q, Luo X, Yi L, Zeng X, Tan C. First-Line Chemo-Immunotherapy for Extensive-Stage Small-Cell Lung Cancer: A United States-Based Cost-Effectiveness Analysis. *Front Oncol.* 2021;11:699781.
83. Zhang L, Hang Y, Liu M, Li N, Cai H. First-Line Durvalumab Plus Platinum-Etoposide Versus Platinum-Etoposide for Extensive-Stage Small-Cell Lung Cancer: A Cost-Effectiveness Analysis. *Front Oncol.* 2020;10:602185.

84. Zhu Y, Hu H, Ding D, et al. First-line pembrolizumab plus chemotherapy for extensive-stage small-cell lung cancer: a United States-based cost-effectiveness analysis. *Cost Eff Resour Alloc.* 2021;19(1):77.
85. Zhou K, Zhou J, Huang J, et al. Cost-effectiveness analysis of atezolizumab plus chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer. *Lung Cancer.* 2019;130:1-4.
86. Ding D, Hu H, Li S, et al. Cost-Effectiveness Analysis of Durvalumab Plus Chemotherapy in the First-Line Treatment of Extensive-Stage Small Cell Lung Cancer. *J Natl Compr Canc Netw.* 2021.
87. Fust K, Li X, Maschio M, et al. Cost-Effectiveness Analysis of Prophylaxis Treatment Strategies to Reduce the Incidence of Febrile Neutropenia in Patients with Early-Stage Breast Cancer or Non-Hodgkin Lymphoma. *Pharmacoeconomics.* 2017;35(4):425-438.
88. Yu JL, Chan K, Kurin M, et al. Clinical Outcomes and Cost-effectiveness of Primary Prophylaxis of Febrile Neutropenia During Adjuvant Docetaxel and Cyclophosphamide Chemotherapy for Breast Cancer. *Breast J.* 2015;21(6):658-664.
89. Li E, Mezzio DJ, Campbell D, Campbell K, Lyman GH. Primary Prophylaxis With Biosimilar Filgrastim for Patients at Intermediate Risk for Febrile Neutropenia: A Cost-Effectiveness Analysis. *JCO Oncol Pract.* 2021;17(8):e1235-e1245.
90. US Census Bureau. 2017 National Population Projections Datasets. 2017.
91. US Census Bureau. Census QuickFacts. 2020.
92. American Cancer Society. *Cancer Facts & Figures.* 2021.
93. American Society of Clinical Oncology. Breast Cancer: Statistics. https://www.cancer.net/cancer-types/breast-cancer/statistics. Published 2021. Accessed.
94. Li S, Liu J, Guo H, et al. Trends in the use of primary prophylactic colony-stimulating factors and neutropenia-related hospitalization in elderly cancer patients receiving myelosuppressive chemotherapy in the USA: 1995-2015. *Support Care Cancer.* 2020;28(6):2637-2649.
95. Gawade PL, Li S, Henry D, et al. Patterns of granulocyte colony-stimulating factor prophylaxis in patients with cancer receiving myelosuppressive chemotherapy. *Support Care Cancer.* 2020;28(9):4413-4424.
96. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-4.pdf. Published 2020. Accessed.
97. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value Health.* 2018;21(3):258-265.

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Chemotherapy-Induced Neutropenia (CIN): Low white blood cell count as a result of cytotoxic chemotherapy.[1]

Chemotherapy-Induced Myelosuppression (CIM): A reduction in bone marrow activity (reduced red blood cell, white blood cell, and platelet counts) as a result of cytotoxic chemotherapy.[1]

Severe Neutropenia: Defined as having an absolute neutrophil count (ANC) of less than 0.5×10^9 cells per liter of blood. In the clinical trials, severe neutropenia is equivalent to grade 4 neutropenia.[22,47]

Febrile Neutropenia (FN): An occurrence of a fever of 100.4°F (38°C) while a patient has neutropenia. Risk of developing FN depends on a patient's type of cancer, chemotherapy, comorbidities and defined as low, intermediate, or high[48]:

- **Low**: Less than a 10 percent chance of developing FN. Prophylaxis is not needed.
- **Intermediate**: 10-20 percent chance of developing FN. Treatment with granulocyte colony-stimulating factors (G-CSFs) may be needed to stimulate development of white blood cells called granulocytes.
- **High**: Greater than a 20 percent chance of developing FN and requires treatment with G-CSFs before a first chemotherapy cycle.

Anemia: Defined as a lower-than-normal hemoglobin level (i.e., ≥12 g/dL in women, and ≥13 g/dL in men. Severe anemia is defined as a hemoglobin level of 6.5 to 8 g/dL.[49]

Thrombocytopenia: Defined as a lower-than-normal platelet count (i.e., below 150,000/µl for adults). Severe thrombocytopenia is generally defined as a platelet count of <50,000/µl.[50]

Health Improvement Distribution Index (HIDI): Defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health.

A2. Potential Cost-Saving Measures in CIN and other Myelosuppressive Effects

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for CIN and other myelosuppressive effects (e.g., reduction in hospitalizations), as these services are captured in the economic model. Rather, we are seeking services used in the current management of CIN and other myelosuppressive effects beyond the potential offsets that arise from a new intervention.

During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with CIN and other myelosuppressive effects that could be reduced, eliminated, or made more efficient. No suggestions were received. We identified examples from the American Society of Clinical Oncology Choosing Wisely Recommendations and the American Society of Breast Surgeons.

American Society of Clinical Oncology Choosing Wisely Recommendations[51]:

- Don't use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20 percent risk for this complication.
- Don't perform PET, CT, and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.
- Don't perform PET, CT, and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.
- Don't perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.
- Don't use combination chemotherapy (multiple drugs) instead of chemotherapy with one drug when treating an individual for metastatic breast cancer unless the patient needs a rapid response to relieve tumor-related symptoms.

American Society of Breast Surgeons Recommendations[52]:

- Do not routinely order breast MRI in new breast cancer patients.
- Do not routinely excise all lymph nodes beneath the arm in patients having lumpectomy for breast cancer.
- Do not routinely order specialized tumor gene testing in all new breast cancer patients.
- Do not routinely re-operate on patients with invasive cancer if the cancer is close to the edge of the excised lumpectomy tissue.

- Do not routinely perform a double mastectomy in patients who have a single breast with cancer.

B. Patient Perspectives: Supplemental Information

B1. Methods

During ICER's scoping, public comment, and early report development periods, we received public comment submissions from five stakeholders (one patient advocacy group and four manufacturers) and participated in conversations with 15 key informants (two patients, two patient advocacy groups, six clinical experts, one industry analyst, and four manufacturers). The feedback received from written input and scoping conversations helped us to discuss the impact on patients described in Chapter 2 of the Report.

C. Clinical Guidelines

The sections below summarize the current guidelines for the primary prevention of neutropenia in patients receiving cytotoxic chemotherapy.

American Society for Clinical Oncology (ASCO)[4]

The most recent update to the ASCO guideline on the use of WBC growth factors was published in 2015. The guideline's recommendations for the use of G-CSF in the first cycle of chemotherapy is based on the absolute risk for febrile neutropenia. Primary prophylaxis is recommended for patients who have a 20% or higher risk for febrile neutropenia based on the cancer being treated, the chemotherapy regimen, and patient characteristics (for example: age> 65 years, advanced disease, prior chemotherapy or radiation therapy, or pre-existing neutropenia). The guideline makes no recommendations about the use of either trilaciclib or plinabulin.

National Comprehensive Cancer Network (NCCN)[53]

The most recent NCCN guideline on hematopoietic growth factors was updated on December 22, 2021. The recommendations are similar to those of ASCO. Primary prophylaxis with G-CSF is recommended for patients whose risk for febrile neutropenia is high (>20%) based on the cancer being treated, the chemotherapy regimen, and patient characteristics (for example: age> 65 years, advanced disease, prior chemotherapy or radiation therapy, or pre-existing neutropenia). Primary prophylaxis should be considered for patients at intermediate risk (10-20%) based on patient risk factors. If a patient has no risk factors, G-CSF is not recommended. If they have or more risk factors (> 65 years, prior chemotherapy or radiation therapy, pre-existing neutropenia, etc.) then prophylactic G-CSF should be considered.

The NCCN guidelines highlight specific cancer and chemotherapy regimens that fall into specific risk categories. For instance, patients with breast cancer treated with TAC are at high risk for febrile neutropenia. Patients with small cell lung cancer treated with carboplatin / etoposide are at intermediate risk and those treated with topotecan are at high risk.

Prophylactic growth factors are not generally recommended for chemotherapy induced anemia. However, trilaciclib may be considered prior to platinum/etoposide or topotecan containing regimens for ES-SCLC to decrease the risk for myelosuppression including anemia.

The guideline makes no recommendations about the use of plinabulin.

National Institute for Health and Care Excellent (NICE)[54]

The most recent NICE guideline is "Neutropenic sepsis: prevention and management in people with cancer (CG151)." It was published in 2012 but confirmed as up to date in 2021. The only guidance on the prevention of neutropenia is as follows: "Do not routinely offer G-CSF for the prevention of neutropenic sepsis in adults receiving chemotherapy unless they are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity." The guideline makes no recommendations about the use of either trilaciclib or plinabulin.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review was adults ≥18 years of age with ECOG performance status of zero to two at intermediate or high risk for CIN.

Interventions

The full list of interventions is as follows:

- Trilaciclib (Cosela™)
- Plinabulin 40 mg IV
- Plinabulin 40 mg IV plus pegfilgrastim 6 mg SC

Comparators

We compared plinabulin to standard dose (6 mg IV) pegfilgrastim (brand name or biosimilars) alone and the combination of plinabulin plus pegfilgrastim to pegfilgrastim alone. Pegfilgrastim is administered the day after chemotherapy. Trilaciclib has been approved for an indication that does not involve prophylactic administration of G-CSF, and so was compared to placebo (i.e., standard care).

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Mortality
    - Hospitalizations (incidence and duration)
    - Delayed or reduced dose chemotherapy
    - Chemotherapy discontinuation
    - Febrile neutropenia (incidence and duration)
    - Sepsis (incidence)
    - Bone pain

    - Red blood cell transfusions
    - Platelet transfusions
    - Quality of life (fatigue, physical function, cognitive function, depression, anxiety, social isolation, etc.)
- Other Outcomes
    - Incidence of severe neutropenia
    - Duration of severe neutropenia
    - Mean absolute neutrophil count (ANC)
    - Mean ANC nadir
    - Use of G-CSF
    - Use of erythropoiesis stimulating agents (ESA)
    - Adverse events including
        - Significant adverse events
        - Infections
        - Antibiotic use
        - Thrombocytopenia/platelet count
        - Anemia/red blood cell count

Timing

Evidence on intervention effectiveness and harms was derived from studies of at least one month's duration.

Settings

All relevant settings were considered, including both inpatient and outpatient.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size were included. Comparative observational studies were also included.

Table D1. PRISMA 2009 Checklist

		Checklist Items
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policymakers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for chemotherapy-induced neutropenia and other myelosuppressive effects followed established best research methods.[55,56] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[57] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table D1.

We searched MEDLINE and EMBASE for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/).

Table D2. Search Strategy of Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to Present

1	(Trilaciclib OR Cosela OR GZ38-1 OR GZ381 OR G1-T28 OR G1 T28).ti,ab
2	(Plinabulin OR NPI-2358 OR NPI2358 OR NPI 2358 OR BPI-2358 OR BPI2358 OR BPI 2358).ti,ab
3	1 OR 2
4	(animals not (humans and animals)).sh.
5	(addresses or autobiography or bibliography or biography or clinical trial, Phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
6	3 NOT (4 OR 5)

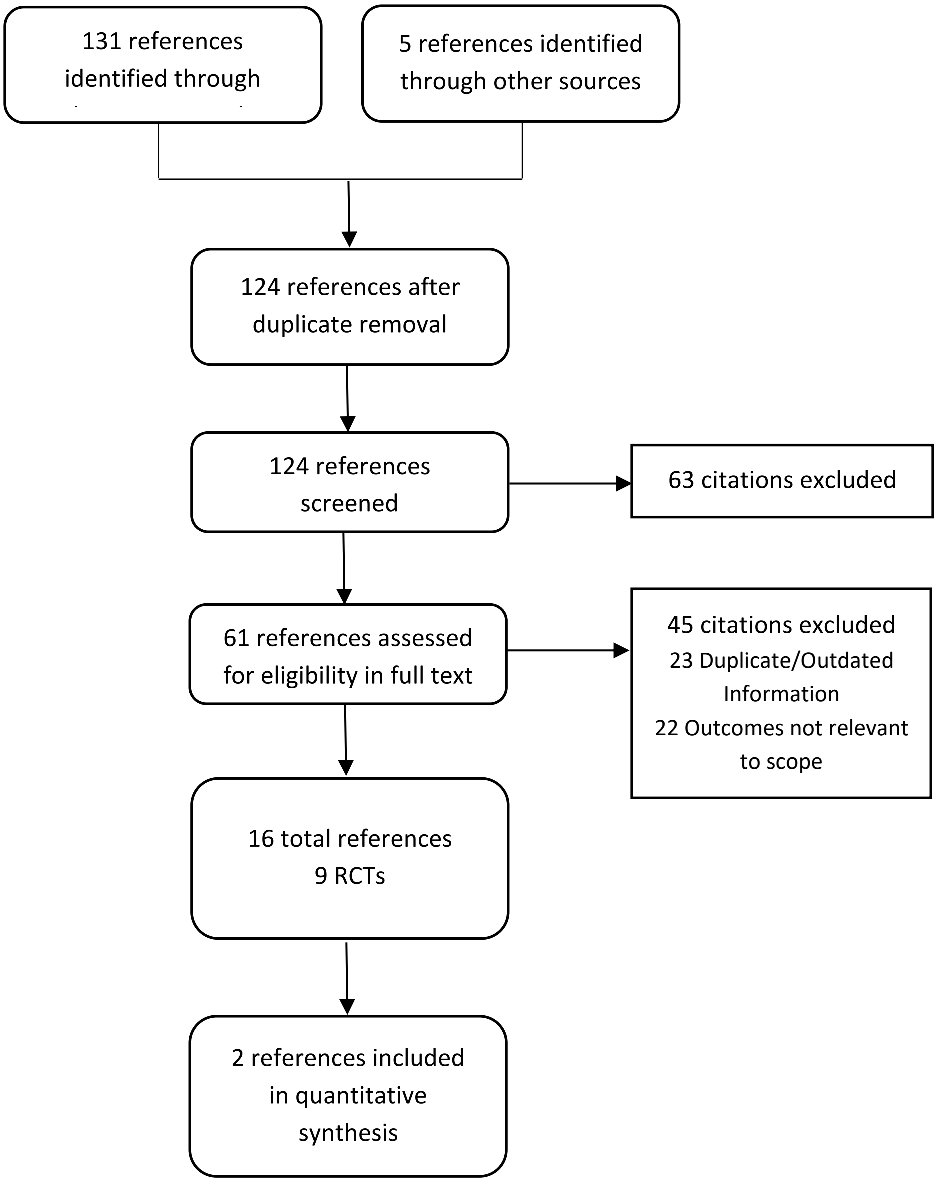
Search ran on September 27, 2021

Table D3. Search Strategy of Embase

1	(‘Trilaciclib’ OR ‘Cosela’ OR ‘GZ38-1’ OR ‘GZ381’ OR ‘G1-T28’ OR ‘G1 T28’):ti,ab
2	(‘Plinabulin’ OR ‘NPI-2358’ OR ‘NPI2358’ OR ‘NPI 2358’ OR ‘BPI-2358’ OR ‘BPI2358’ OR ‘BPI 2358’):ti,ab
3	#1 OR #2
4	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
5	'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/it OR 'questionnaire'/it OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it
6	#3 NOT (#4 OR #5)
7	#6 AND [medline]/lim
8	#6 NOT #7

Search ran on September 27, 2021

Figure D1. PRISMA Flow Chart Showing Results of Literature Search for Trilaciclib and Plinabulin



Study Selection

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to trilaciclib. These included the manufacturer's submission to the agency and internal FDA review documents. All literature that did not undergo a formal peer review process is described separately.

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor"[58] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[59,60]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for trilaciclib and plinabulin using clinicaltrials.gov.

Search terms included “plinabulin,” “trilaciclib,” and “neutropenia.” We selected studies which would have met our inclusion criteria and for which no findings have been published. We provided qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized qualitatively and quantitatively in the body of the report. Key differences between studies (study design, patient characteristics, interventions, outcomes, study quality) were explored in the text of the report. The feasibility of conducting a quantitative synthesis was evaluated by looking at the enrolled patient population, study design, and analytic methods across various outcomes of interest in two trilaciclib trials enrolling first-line extensive-stage small cell lung cancer patients.

In an exploratory analysis, the two trilaciclib trials[16,17] were included in a fixed-effects pairwise meta-analyses of key primary and secondary endpoints (incidence of severe neutropenia, severe anemia, severe thrombocytopenia, and overall survival). The analyses were conducted in R. Risk ratios and respective 95%CIs for severe neutropenia, anemia, and thrombocytopenia were calculated using the Mantel-Haenszel method. A hazard ratio was calculated for overall survival. Heterogeneity was assessed using Cochran's Q test and the I^2 statistic. We applied a continuity correction of 0.5 for zero values.

D2. Supplemental Results

Evidence Base

An overview of the key trials is highlighted in Section 3.1 of the main report. The remaining trials for trilaciclib and plinabulin included in the review are described below.

Trilaciclib

Weiss 2021[7] and Ferrarotto 2021[19] are two publications that pooled data from three trials studying extensive-stage small cell lung cancer (Daniel 2020, Weiss 2019, Hart 2021). Two trials (Daniel 2020 and Weiss 2019) enrolled untreated ES-SCLC patients and one trial (Hart 2021) enrolled previously treated ES-SCLC patients. Each trial used a different background chemotherapy regimen. Primary endpoints included duration of severe neutropenia in cycle 1 and occurrence of severe neutropenia during the overall treatment period. Details on the study design for each trial are outlined in Supplement Table D5.

Tan 2019[21] enrolled 102 patients with metastatic triple negative breast cancer receiving a gemcitabine and carboplatin chemotherapy regimen. Patients were randomized to receive either gemcitabine/carboplatin chemotherapy on days 1 and 8 in 21-day cycles (n=34), trilaciclib IV prior to chemotherapy on days 1 and 8 in 21-day cycles (n=33), or trilaciclib on days 1, 2, 8, and 9 and chemotherapy on days 2 and 9 in 21-day cycles (n=35).

Plinabulin

In the pivotal Phase III PROTECTIVE-1 trial[31], 105 patients with either locally advanced or metastatic non-small cell lung cancer, advanced or metastatic breast cancer, or hormone refractory metastatic prostate cancer receiving docetaxel were enrolled. Patients were randomized to receive either docetaxel on day one followed by plinabulin 40 mg (n=52) thirty minutes after or docetaxel on day one followed by pegfilgrastim 6 mg (n=53) 24 hours later for up to four 21-day cycles.

The Phase II PROTECTIVE-1 trial[22] enrolled 55 patients with non-small cell lung cancer who have failed platinum-based therapy. All patients received docetaxel and were randomized to either plinabulin 5 mg/m^2, plinabulin 10 mg/m^2, plinabulin 20 mg/m^2, or pegfilgrastim 6 mg. Docetaxel was received on day one and either pegfilgrastim on day two or plinabulin after docetaxel on day one. Patients were treated every three weeks for four cycles.

The Phase II PROTECTIVE-2 trial[24,28,29] enrolled 115 women with stage I-III breast cancer with no prior chemotherapy. All patients received TAC chemotherapy and were randomized to 1 of 7 arms: plinabulin 10 mg/m^2, plinabulin 20 mg/m^2, plinabulin 30 mg/m^2, pegfilgrastim 6 mg, pegfilgrastim

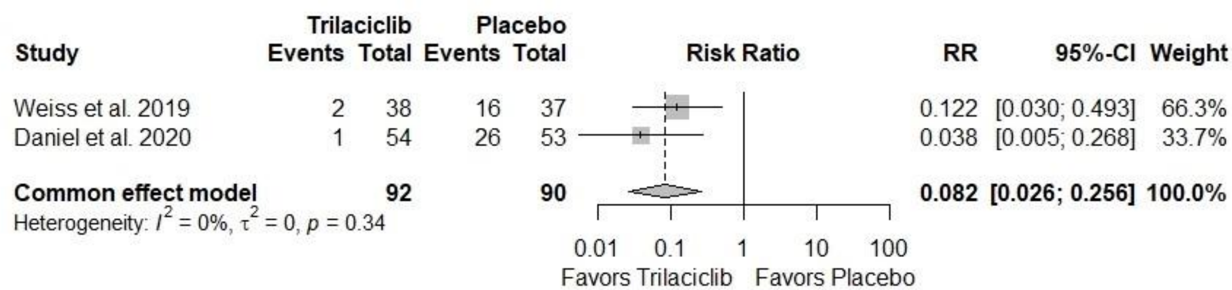
1.5 mg and plinabulin 20 mg/m^2, pegfilgrastim 3 mg and plinabulin 20 mg/m^2, and pegfilgrastim 6mg and plinabulin 20 mg/m^2.

The Phase III DUBLIN-3 trial[33] enrolled 559 patients with advanced non-small cell lung cancer receiving second or third line systemic therapy. Patients were randomized to either docetaxel or docetaxel plus plinabulin 30 mg/m^2. The primary outcome of the trial was overall survival and explored other anti-tumor efficacy endpoints. For this review, we focused on data related to neutropenia or other myelosuppressive effects.

Clinical Benefits

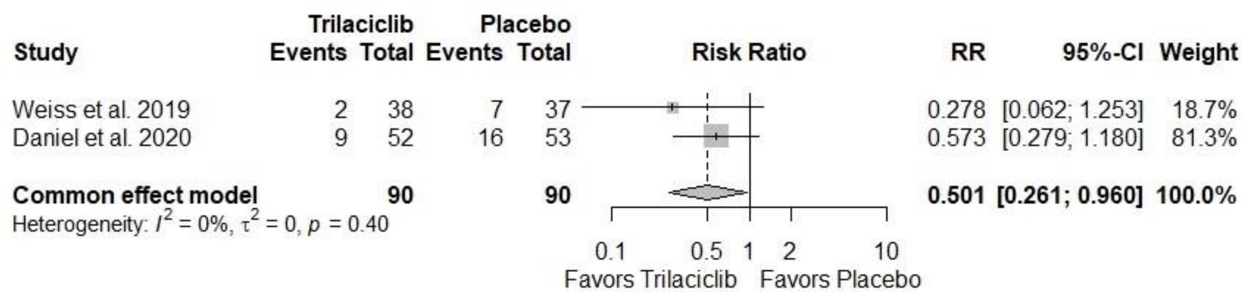
We conducted meta-analyses on key outcomes of the trilaciclib trials in first line therapy with carboplatin/etoposide-based chemotherapy. These outcomes include severe neutropenia, severe anemia, severe thrombocytopenia, and overall survival. The results are outlined in forest plots in Figures D2-5 below.

Figure D2. Meta-Analysis of Severe Neutropenia



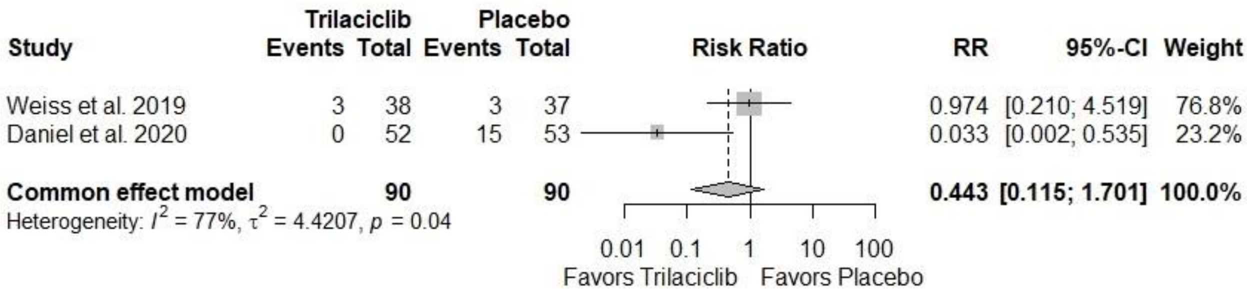
95%-CI: 95 percent confidence interval, RR: risk ratio

Figure D3. Meta-Analysis of Severe Anemia



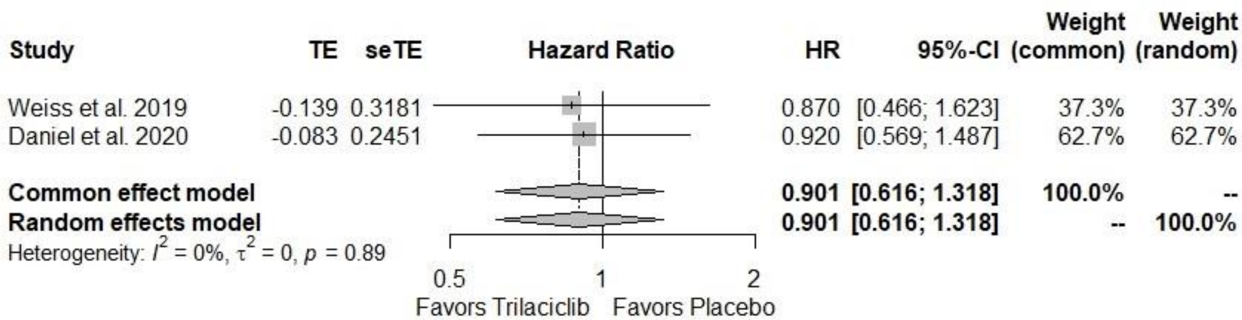
95%-CI: 95 percent confidence interval, RR: risk ratio

Figure D4. Meta-Analysis of Severe Thrombocytopenia



95%-CI: 95 percent confidence interval, RR: risk ratio

Figure D5. Meta-Analysis of Overall Survival



95%-CI: 95 percent confidence interval, HR: hazard ratio, seTE: standard error of treatment estimate, TE: estimate of treatment effect

D3. Evidence Tables

Table D4. Study Quality – Trilaciclib[16-18,21] and Plinabulin[22,31]

Intervention	Trilaciclib				Plinabulin	
Trial	**Weiss 2019**	**Daniel 2020**	**Hart 2021**	**Tan 2019**	**PROTECTIVE-1 Phase II Blayney 2020**	**PROTECTIVE-1 Phase III Blayney 2022**
USPSTF Rating						
Comparable Groups	Yes	Yes	Yes	Yes	Yes	Yes
Non-differential Follow-Up	Yes	Yes	Yes	Yes	Yes	Yes
Patient/Investigator Blinding	Yes	Yes	Yes	No	No	Yes
Clear Definition of Intervention	Yes	Yes	Yes	Yes	Yes	Yes
Clear Definition of Outcomes	Yes	Yes	Yes	Yes	Yes	Yes
Selective Outcome Reporting	No	No	No	No	No	No
Measurements Valid	Yes	Yes	Yes	Yes	Yes	Yes
Intent-to-treat Analysis	mITT	ITT	ITT	ITT	ITT	ITT
Approach to Missing Data	NA	NA	NA	NA	NA	NA*
USPSTF Overall Rating	Good	Good	Good	Good	Good	Good

ITT: intention-to-treat, mITT: modified intention-to-treat, NA: not applicable, USPSTF: United States Preventive Services Taskforce

* Missing data was not imputed for primary and key secondary endpoints but used for sensitivity analyses (e.g., missing pain score data was imputed using last observation carried forward, worst observation carried forward, and baseline observation carried forward methods.

Table D5. Study Design – Trilaciclib

Trial	Study Design & Population	Arms & Dosing	Inclusion & Exclusion Criteria	Key Outcomes [Timepoint]
G1T28-02 **Phase Ib/IIa** NCT02499770 Weiss 2019 Annals of Oncology[17]	Phase Ib/IIa (Part 2: DB RCT) Adults with untreated ES-SCLC N = 122	PART 1* 1. Car/Eto + Trilaciclib 200 or 240 mg/m^2 PART 2 1. Car/Eto + Placebo 2. Car/Eto + Trilaciclib 240 mg/m^2 Trilaciclib administered by IV	**Inclusions** - Adults ≥ 18 years with diagnosis of SCLC - ECOG 0-2 - >1 target lesion that is unirradiated **Exclusions** - Prior chemo for ES SCLC - Symptomatic brain metastases requiring immediate treatment - Uncontrolled ischemic heart disease/symptomatic congestive heart	**Primary** No primary outcome defined; dose finding (part 1) and safety and efficacy (part 2) **Secondary** Part 2 [Treatment Period] - Severe neutropenia - Febrile neutropenia - G-CSF and RBC transfusions

Trial	Study Design & Population	Arms & Dosing	Inclusion & Exclusion Criteria	Key Outcomes [Timepoint]
		once daily before chemotherapy.	failure - History stroke/cerebrovascular accident <6 months prior to study	
G1T28-05 **Phase II** NCT03041311 Daniel 2020 International Journal of Cancer[16]	Phase II DB, PC, RCT Adults with untreated ES-SCLC N = 105	Induction 1. Eto/Car/Ate + Placebo 2. Eto/Car/Ate + Trilaciclib 240mg/m^2 Trilaciclib administered by IV once daily for three days prior to chemotherapy for a maximum of four 21-day cycles	**Inclusions** - Adults ≥ 18 years with diagnosis of ES-SCLC - ECOG 0-2 - ≥1 target lesion that is unirradiated and measurable by RECIST v1.1 **Exclusions** - Limited-stage SCLC - Prior chemo for limited- or ES-SCLC - Prior immunotherapies including CD137, anti-PD-1, anti-PD-L1, CTLA4 - Symptomatic brain metastases requiring immediate treatment - Uncontrolled ischemic heart disease/symptomatic congestive heart failure - History stroke/cerebrovascular accident <6 months prior to study	**Primary** - Duration of severe neutropenia in cycle 1 and percentage of patients with severe neutropenia **Secondary** [36 months] - Overall survival - Progression-free survival - Patients with objective response
G1T28-03 **Phase Ib/IIa** NCT02514447 Hart 2021 Advances in Therapy[18]	Phase Ib/IIa (Part 2: DB RCT) Adults with previously treated ES-SCLC N = 120	PART 1* 1. Topotecan + Trilaciclib PART 2 1. 2:1 Topotecan + Placebo 2. 1:2 Topotecan + Trilaciclib Trilaciclib administered before Topotecan on days 1-5 of each 21-day cycle.	**Inclusions** - Adults ≥ 18 years with diagnosis of SCLC - Disease progression during/after prior first/second-line chemotherapy - ECOG 0-2 - ≥1 target lesion that is unirradiated **Exclusions** - History of topotecan treatment for SCLC - Symptomatic brain metastases requiring immediate treatment - Uncontrolled ischemic heart disease/symptomatic congestive heart failure	**Primary** - Duration of severe neutropenia in cycle 1 and percentage of patients with severe neutropenia **Secondary** - Pharmacokinetics [Cycle 1] - Progression free survival & overall survival [24 months]

Trial	Study Design & Population	Arms & Dosing	Inclusion & Exclusion Criteria	Key Outcomes [Timepoint]
			- History stroke/cerebrovascular accident <6 months prior to study	
Pooled Analysis G1T28-02, 03, 05 Weiss 2021 Clinical Lung Cancer,[7] Ferrarotto 2021 Cancer Medicine[19]	Retrospective pooled analysis of three Phase II DB, PC, RCT N = 242	See individual trials for Arms & Dosing Regimen	See individual trials for Inclusion & Exclusion Criteria	See individual trials for Key Outcomes And Timepoints
G1T28-04 **Phase II** NCT02978716 Tan 2019 Lancet Oncology[21]	Phase II OL, MC, RCT Adults with HR-negative, HER2-negative TNBC breast cancer N = 102	1. Gem/Car 2. Gem/Car + Trilaciclib 240mg/m^2 3. Trilaciclib 240mg/m^2 prior to Gem/Car + Trilaciclib Arm 2: Trilaciclib by IV with chemotherapy on day 1, 8 of a 21-day cycle Arm 3: Trilaciclib alone on days 1, 8, and with chemo-therapy on days 2, 9 of a 21-day cycle	**Inclusions** - Adults ≥18 years with HR-negative, HER2-negative (locally or recurrent or metastatic TNBC) breast cancer - Available TNBC diagnostic tumor tissue - ECOG 0-1 - Adequate organ function - Life expectancy greater than three months **Exclusions** - >2 prior chemo regimens for locally recurrent or metastatic TNBC - CNS metastases or leptomeningeal disease requiring treatment with radiation or steroids - Investigational drug within 30 days of first dose	**Primary** - Treatment related adverse events [18 months] **Secondary** **-** Progression free survival [27 months] - Overall survival [36 months] - Hematologic parameters [18 months]

Ate: atezolizumab, Car: carboplatin, DB: double-blind, ECOG: Eastern Cooperative Oncology Group, ES-SCLC: extensive-stage small cell lung cancer, Eto: etoposide, G-CSF: granulocyte colony-stimulating factor, Gem: gemcitabine, HR-negative: hormone receptor negative, IV: intravenous, MC: multi-center, mg/m^2: milligrams per meter squared, N: total number, OL: open-label, PC: placebo-controlled, RBC: red blood cell, RCT: randomized controlled trial, SCLC: small-cell lung cancer, TNBC: triple-negative breast cancer

* Part 1 results not of interest

Table D6. Baseline Characteristics I – Trilaciclib Phase II Small Cell Lung Cancer Trials[16-18]

Trial		G1T28-02 Phase II Weiss 2019		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021	
Chemotherapy Regimen		**Carboplatin/Etoposide**		**Etoposide/Carboplatin/Atezolizumab**		**Topotecan**	
Arm		**Placebo**	**Trilaciclib 240 mg/m^2**	**Placebo**	**Trilaciclib 240 mg/m^2**	**Placebo**	**Trilaciclib 240 mg/m^2**
N		38	39	53	54	29	32
Age, years	**Mean (SD)**	65 (9.5)	65 (8.4)	NR	NR	NR	NR
	Median (Range)	66 (39, 86)	64 (49, 82)	64 (46, 83)	65 (45, 81)	64 (47, 82)	62 (47, 77)
Sex, n (%)	**Male**	27 (71.1)	27 (69.2)	34 (64.2)	41 (75.9)	12 (41.4)	22 (68.8)
	Female	11 (28.9)	12 (30.8)	19 (35.8)	13 (24.1)	17 (58.6)	10 (31.3)
Race, n (%)	**White**	NR	NR	51 (96.2)	53 (98.1)	NR	NR
	Black	NR	NR	1 (1.9)	0 (0)	NR	NR
	Asian	NR	NR	NR	NR	NR	NR
	Other	NR	NR	1 (1.9)	1 (1.9)	NR	NR
ECOG Status	**0** **1**	35 (92.1)	35 (89.7)	46 (86.8)	45 (85.2)	27 (93.1)	29 (90.6)
	2	3 (7.9)	4 (10.3)	7 (13.2)	8 (14.8)	2 (6.9)	3 (9.4)
Any Prior Radiation Therapy	**Mean (SD)**	4 (10.5)	3 (7.7)	NR	NR	NR	NR
Treatment Line, n (%)	**Second**	NR	NR	NR	NR	24 (82.8)	26 (81.2)
	Third	NR	NR	NR	NR	5 (17.2)	6 (18.8)
Brain Metastases, n (%)		8 (21.1)	5 (12.8)	15 (28.3)	15 (27.8)	5 (17.2)	8 (25.0)
Baseline characteristics not reported: Body mass index (BMI), number of prior lines of therapy, neutrophil count, pre-dose blood pressure							

%: percent, ECOG: Eastern Cooperative Oncology Group, mg/m^2: milligrams per meter squared, N: total number, n: number, NR: not reported, SD: standard deviation

Table D7. Baseline Characteristics II – Trilaciclib Additional Trials[7,19,21]

Trial		Pooled Analysis: G1T28-02, 03, 05 Weiss 2021		G1T28-04 Phase II Tan 2019		
Cancer Population		Small Cell Lung Cancer		Triple Negative Breast Cancer		
Chemotherapy Regimen		Varies by trial		Gemcitabine/Carboplatin		
Arm		Placebo	Trilaciclib 240 mg/m^2	Chemotherapy	Trilaciclib 240 mg/m^2 + Chemotherapy	Trilaciclib/ Trilaciclib 240 mg/m^2+ Chemotherapy
N		119	123	34	33	35
Age, years	Mean (SD)	NR	NR	NR	NR	NR
	Median (Range)	64 (39, 86)	64 (45, 82)	55 (43, 64)	55 (47, 66)	58 (49, 65)
Sex, n (%)	Male	73 (61.3)	89 (72.4)	0	1 (3.1)	0
	Female	46 (38.7)	34 (27.6)	34 (100)	32 (96.9)	35 (100)
Race, n (%)	White	110 (92.4)	120 (97.6)	28 (82)	22 (67)	28 (80)
	Black	NR	NR	5 (15)	7 (21)	2 (6)
	Asian	NR	NR	0	2 (6)	4 (11)
	Other	9 (7.6)	3 (2.4)	1 (3)	2 (6)	1 (3)
ECOG Status	0	107 (89.9)	108 (87.8)	15 (44)	17 (52)	21 (60)
	1			19 (56)	16 (48)	14 (40)
	2	12 (10.1)	15 (12.2)	0	0	0
Brain Metastases, n (%)		28 (23.5)	27 (22.0)	NR	NR	NR
Baseline characteristics not reported: Body mass index (BMI), any prior radiation therapy, number of prior lines of therapy, second or third treatment line, neutrophil count, pre-dose blood pressure						

ECOG: Eastern Cooperative Oncology Group, mg/m^2: milligrams per meter squared, N: total number, n: number, NR: not reported, SD: standard deviation

Table D8. Key Efficacy I – Trilaciclib Phase II Small Cell Lung Cancer Trials[16-18,20]

Trial		G1T28-02 Phase II Weiss 2019		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021	
Chemotherapy Regimen		**Carboplatin/Etoposide**		**Etoposide/Carboplatin/Atezolizumab**		**Topotecan**	
Arm		**Placebo**	**Trilaciclib 240 mg/m²**	**Placebo**	**Trilaciclib 240 mg/m²**	**Placebo**	**Trilaciclib 240 mg/m²**
N		37	38	53	54	29	32
Grade 3/4 Neutropenia	Timepoint	**Overall Treatment Period**					
	Incidence, n (%); p-value	NR	NR	*25 (47.2)*	*10 (19.2)*	*24/28 (85.7)*	*22 (68.8)*
Severe Neutropenia	Timepoint	**Cycle 1**					
	Incidence, n (%); p-value	13 (35.1)	1 (2.6); 0.0003	[redacted]			
	Mean Duration days (SD); p-value	3 (3.9)	0 (0.5); 0.0003	4.0 (4.7)	0 (1.0); <0.0001	7 (6.2)	2 (3.9); <0.0001
	Timepoint	**Overall Treatment Period**					
	Incidence, n (%); p-value	16 (43)	2 (5); 0.0001	26 (49.1)	1 (1.9); <0.0001	22 (75.9)	13 (40.6); 0.016
	Mean Duration days (SD); p-value	NR	NR	[redacted]			
Febrile Neutropenia	Timepoint	**Overall Treatment Period**					
	Overall, n (%); p-value	3 (8.1)	1 (2.6); 0.28	3 (5.7)	1 (1.9); 0.3105	5 (17.2)	2 (6.3); 0.1941
	Grade 3, n (%)	NR	NR	NR	NR	2 (7.1)	0 (0)
	Grade 4, n (%)	NR	NR	NR	NR	3 (10.7)	2 (6.3)
Hospitalizations	Timepoint	**Overall Treatment Period**					
	All Cause, n (%)	NR	NR	14 (26.4)	12 (23.1)	7/28 (25.0)	10 (31.3)
	All Cause, event rate (per 100 cycles)	NR	NR	12.5	10.77	15.04	7.89
	Due to CIM or Sepsis n (%); p-value	NR	NR	6 (11.3)	2 (3.8); 0.1287	6/28 (21.4)	3 (9.4); NR
	Due to CIM or Sepsis, event rate (per 100 cycles)	NR	NR	5.50	1.03	9.73	1.97
	Due to Neutropenia, n (%)	NR	NR	NR	NR	5/28 (17.9)	2 (6.3)
	Due to Neutropenia, event rate (per 100 cycles)	NR	NR	NR	NR	6.19	1.32
	Due to Anemia, n (%)	NR	NR	NR	NR	2/28 (7.1)	0 (0)

Trial		G1T28-02 Phase II Weiss 2019		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021	
Chemotherapy Regimen		**Carboplatin/Etoposide**		**Etoposide/Carboplatin/Atezolizumab**		**Topotecan**	
Arm		**Placebo**	**Trilaciclib 240 mg/m^2**	**Placebo**	**Trilaciclib 240 mg/m^2**	**Placebo**	**Trilaciclib 240 mg/m^2**
	Due to Anemia, event rate (per 100 cycles)	NR	NR	NR	NR	1.77	0
	Due to Thrombo-cytopenia, n (%)	NR	NR	NR	NR	1/28 (3.6)	1 (3.1)
	Due to Thrombocytopenia, event rate (per 100 cycles)	NR	NR	NR	NR	0.88	0.66
Chemotherapy	Timepoint	**Overall Treatment Period**					
	Dose Reductions n (%); p-value	13 (35.1)	3 (7.9); 0.0033	Eto: 14 (26.4) Car: 13 (24.5)	Eto: 3 (5.8) Car: 1 (1.9)	9 (31.0)	6 (18.8); 0.2040
	Regimen Change, n (%)	NR	NR	31 (58.5)	18 (34.6)	17 (60.7)	21 (65.6)
Transfusions	Timepoint	**On/after week 5**					
	RBC, n (%); p-value	9 (24.3)	2 (5.3); 0.034	11 (20.8)	7 (13.0); 0.13	12 (41.4)	10 (31.3); 0.3222
	Timepoint	**Overall Treatment Period**					
	Platelet, n (%); p-value	0 (0)	2 (5.3); 0.15	2 (3.8)	1 (1.9); 0.55	9 (31.0)	8 (25.0); 0.3222
Anti-Cancer Efficacy	Timepoint	**Max four years**		**36 months**		**24 months**	
Objective Response Rate	**% (95%CI)**	56.8 (NR)	66.7 (NR)	63.5 (49.0, 76.4)	56.0 (41.3, 70.0)	n (%): 6 (23.1)	n (%): 5 (16.7)
Duration of Objective Response	**Median months (95%CI)**	5.4 (NR)	5.7 (NR)	4.3 (3.4, 4.7)	5.6 (4.4, 7.0)	4.9 (2.1, NE)	6.8 (2.8, NE)
Progression Free-Survival	**Median months (95%CI)**	5.0 (4.4, 6.8)	6.2 (4.7, 8.3)	5.4 (4.3, 5.7)	5.9 (4.2, 7.1)	4.2	4.2
	HR (95%CI); p-value	0.70 (0.51, 0.98)*; 0.1695		0.83 (0.55, 1.24); 0.3079		0.88 (0.61, 1.27)*; 0.5886	
Overall Survival	**Median months (95%CI)**	10.6 (7.7, 15.2)	10.9 (9.1, 16.4)	12.8 (7.9, 15.5)	12.0 (9.6, 16.2)	6.5	6.2
	HR (95%CI); p-value	0.87 (0.61, 1.24)*; 0.6107		0.92 (0.57, 1.49); 0.8228		1.38 (0.95, 2.01)*; 0.3377	
Efficacy outcomes not reported: Mean duration of grade 3/4 and febrile neutropenia, profound neutropenia, chemotherapy discontinuation							

Trial	G1T28-02 Phase II Weiss 2019		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021	
Chemotherapy Regimen	**Carboplatin/Etoposide**		**Etoposide/Carboplatin/Atezolizumab**		**Topotecan**	
Arm	**Placebo**	**Trilaciclib 240 mg/m^2**	**Placebo**	**Trilaciclib 240 mg/m^2**	**Placebo**	**Trilaciclib 240 mg/m^2**

95%CI: 95 percent confidence interval, AIC: academic in confidence, Car: carboplatin, CIM: chemotherapy-induced myelosuppression, Eto: etoposide, HR: hazard ratio, mg/m^2: milligrams per meter squared, n: number, N: total number, NE: not explored, NR: not reported, RBC: red blood cell, SD: standard deviation

* 80% confidence interval

Note: Italicized data is digitized or ICER-calculated

Table D9. Key Efficacy II – Trilaciclib Additional Trials[7,19,21]

Trial		Pooled Analysis: G1T28-02, 03, 05 Weiss 2021		G1T28-04 Phase II Tan 2019		
Cancer Population		**Small Cell Lung Cancer**		**Triple Negative Breast Cancer**		
Chemotherapy Regimen		**Varies by trial**		**Gemcitabine/Carboplatin**		
Arm		**Placebo**	**Trilaciclib 240 mg/m^2**	**Chemotherapy**	**Trilaciclib 240 mg/m^2 + Chemotherapy**	**Trilaciclib/Trilaciclib + Chemotherapy**
N		119	123	34	33	35
Grade 3/4 Neutropenia	Timepoint	**Overall Treatment Period**				
	Incidence, n (%); p-value	81 (68.6)	39 (32.0)	NR	NR	NR
Severe Neutropenia	Timepoint	**Cycle 1**				
	Incidence, n (%); p-value	NR	NR	9 (26)	12 (36)	8 (23); 0.70
	Mean Duration days (SD); p-value	4 (5.1)	0 (1.8); <0.0001	0.8 (2.4)	1.5 (3.5)	1.0 (2.6); 0.70
	Timepoint	**Overall Treatment Period**				
	Incidence, n (%); p-value	63 (52.9)	14 (11.4); <0.001	NR	NR	NR
	Mean Duration days (SD); p-value	NR	NR	NR	NR	NR
Febrile Neutropenia	Timepoint	**Overall Treatment Period**				
	Overall, n (%); p-value	*11* (9.2)	*4* (3.3); 0.089	1/30 (3)	1/30 (3)	0
	Grade 3, n (%)	6 (5.0)	1 (0.8)	1/30 (3)	1/30 (3)	0
	Grade 4, n (%)	5 (4.2)	3 (2.5)	0	0	0
Hospitalizations	Timepoint	**Overall Treatment Period**				
	All Cause, n (%)	30 (25.4)	30 (24.6)	NR	NR	NR
	Due to CIM or Sepsis	16 (13.6)	5 (4.1)	NR	NR	NR

Trial		Pooled Analysis: G1T28-02, 03, 05 Weiss 2021		G1T28-04 Phase II Tan 2019		
Cancer Population		**Small Cell Lung Cancer**		**Triple Negative Breast Cancer**		
Chemotherapy Regimen		**Varies by trial**		**Gemcitabine/Carboplatin**		
Arm		**Placebo**	**Trilaciclib 240 mg/m^2**	**Chemotherapy**	**Trilaciclib 240 mg/m^2 + Chemotherapy**	**Trilaciclib/Trilaciclib + Chemotherapy**
	n (%)					
Chemotherapy Regimen	Timepoint	**Overall Treatment Period**				
	Dose Reduction, n (%)	36 (30.3)	11 (8.9)	Car: 10 (33) Gem: 13 (43)	Car: 13 (39) Gem: 20 (61)	Car: 15 (43) Gem: 17 (49)
Transfusions	Timepoint	**Cycle 1**		**Overall Treatment Period**		
	Red Blood Cell, n (%)	*10* (8.4)	*9* (7.3)	15 (44.1)	13 (39.4)	10 (28.6)
	Timepoint	**On/after week 5**				
	Platelet, n (%); p-value	*31* (26.1)	*18* (14.6); 0.025	12 (35.3)	11 (33.3)	8 (22.9); 0.075
	Timepoint	**Overall Treatment Period**				
	Platelet, n (%); p-value	*11* (9.2)	*10* (8.1); 0.96	4 (12)	3 (9)	6 (17); 0.98
Anti-Cancer Efficacy	Timepoint	**Pooled (24 months - 4 years)**		**Overall Treatment Period**		
Objective Response Rate	**% (95%CI); p-value**	n/N (%): 59/114 (51.8)	n/N (%): 56/114 (49.1); 0.7879	33 (15.6, 55.3)	50 (31.3, 68.7)	37 (19.9, 56.1)
Duration of Objective Response	**Median months (95% CI)**	4.6 (4.1, 5.0)	5.7 (4.7, 7.0)	NR	NR	NR
Progression-Free Survival	**Median months (95% CI)**	5.0 (4.4, 5.5)	5.3 (4.6, 6.1)	5.7 (3.4, 9.2)	9.4 (6.1, 13.0)	7.3 (6.2, 12.9)
	HR (95% CI); p-value	0.8 (0.61, 1.06); 0.1404		REF	0.60 (0.30, 1.18); 0.13	0.59 (0.30, 1.16); 0.12
Overall Survival	**Median months (95% CI)**	10.6 (7.9, 12.8)	10.6 (9.1, 11.7)	12.6 (6.3, 15.6)	20.1 (10.2, not reached)	17.8 (12.9, not reached)
	HR (95% CI); p-value	1.00 (0.75, 1.35); 0.8136		REF	0.33 (0.15, 0.74); 0.028	0.34 (0.16, 0.70); 0.0023
Efficacy outcomes not reported: Duration of grade 3/4 and febrile neutropenia, profound neutropenia, all cause hospitalizations (cycle 1), hospitalizations due to neutropenia, anemia, thrombocytopenia; chemotherapy regimen change or discontinuation						

95% CI: 95 percent confidence interval, Car: carboplatin, CIM: chemotherapy-induced myelosuppression, Eto: etoposide, Gem: gemcitabine, HR: hazard ratio, mg/m^2: milligrams per meter squared, n: number, N: total number, NE: not explored, NR: not reported, REF: reference, SD: standard deviation

Note: Italicized data is digitized or ICER-calculated

Table D10. Secondary Efficacy I – Trilaciclib Phase II Small Cell Lung Cancer Trials[16-18]

Trial	G1T28-02 Phase II Weiss 2019		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021	
Chemotherapy Regimen	**Carboplatin/Etoposide**		**Carboplatin/Etoposide/ Atezolizumab**		**Topotecan**	
Arm	**Placebo**	**Trilaciclib 240 mg/m²**	**Placebo**	**Trilaciclib 240 mg/m²**	**Placebo**	**Trilaciclib 240 mg/m²**
N	37	38	53	54	29	32
Timepoint	**Overall Treatment Period**					
G-CSF administration, n (%); p-value	24 (65)	4 (11); <0.0001	25 (47.2)	16 (29.6); 0.069	19 (65.5)	16 (50.0); 0.2544
ESA administration, n (%); p-value	2 (5)	1 (3); NS	6 (11.3)	3 (5.6); 0.33	6 (20.7)	1(3.1); 0.0359
Timepoint	**Cycle 1**					
ANC Nadir, Mean ; p-value	0.82; NR	1.899; <0.0001	NR	NR	0.284; NR	1.244; NR
Efficacy outcomes not reported: Change from baseline in red blood cells or platelets, absolute neutrophil count						

ANC: absolute neutrophil count, ESA: erythropoiesis-stimulating agent, G-CSF: granulocyte colony-stimulating factor, mg/m²: milligrams per meter squared, n: number, N: total number, NR: not reported, NS: not significant, SD: standard deviation

Table D11. Secondary Efficacy II – Trilaciclib Additional Trials[7,19,21]

Trial	Pooled Analysis G1T28-02, 03, 05 Weiss 2021		G1T28-04 Phase II Tan 2019		
Cancer Population	**Small Cell Lung Cancer**		**Triple Negative Breast Cancer**		
Chemotherapy Regimen	**Varies by trial**		**Gemcitabine/Carboplatin**		
Arm	**Placebo**	**Trilaciclib 240 mg/m²**	**Chemotherapy**	**Trilaciclib 240 mg/m² + Chemotherapy**	**Trilaciclib/Trilaciclib 240 mg/m² + Chemotherapy**
N	119	123	34	33	35
Timepoint	**Overall Treatment Period**				
G-CSF administration, n (%); p-value	*67* (56.3)	*35* (28.5); <0.0001	16 (47)	21 (64)	14 (40); 0.14
ESA administration, n (%); p-value	*14* (11.8)	*4* (3.3); 0.025	NR	NR	NR
Efficacy outcomes not reported: Change from baseline in red blood cells or platelets, absolute neutrophil count (ANC), ANC nadir					

ESA: erythropoiesis-stimulating agent, G-CSF: granulocyte colony-stimulating factor, mg/m²: milligrams per meter squared, n: number, N: total number, NR: not reported

Note: Italicized data is digitized or ICER-calculated

Table D12. Safety Outcomes I – Trilaciclib Phase II Small Cell Lung Cancer Trials[16-18,20]

Trial		G1T28-02 Phase II Weiss 2019		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021	
Chemotherapy Regimen		**Carboplatin/Etoposide**		**Carboplatin/Etoposide/Atezolizumab**		**Topotecan**	
Arm		**Placebo**	**Trilaciclib 240 mg/m²**	**Placebo**	**Trilaciclib 240 mg/m²**	**Placebo**	**Trilaciclib 240 mg/m²**
Timepoint		**End of Treatment (max 12 months)**		**Up to 24 months**		**Week 24**	
N		37	38	53	54	28	32
Adverse Events, n (%)	**Overall**	35 (94.6)	34 (89.5)	52 (98.1)	49 (94.2)	27 (96.4)	32 (100)
	Grade 3	31 (84)	18 (47)	15 (28.3)	23 (44.2)	27 (96.4)	28 (87.5)
	Grade 4			26 (49.1)	6 (11.5)	21 (75.0)	18 (56.3)
Serious Adverse Events, n (%)	**Overall**	9 (24.3)	11 (28.9)	25 (47.2)	17 (32.7)	7 (25.0)	12 (37.5)
	Infection	NR	NR	7 (13.2)	3 (5.6)	3 (10.3)	1 (3.1)
	Pulmonary Infection	NR	NR	5 (9.4)	2 (3.7)	1 (3.4)	1 (3.1)
Treatment-related AEs, n (%)	**Overall**	NR	NR	NA	15 (27.8)	12 (42.9)	8 (25.0)
	Serious	NR	0 (0)	NA	1 (1.9)	6 (21.4)	5 (15.6)
Discontinuation, n (%)	**Overall**	NR	NR	5 (9.4)	11 (21.2)	28 (100)	31 (96.9)
	AE-related	NR	NR	2 (3.8)	4 (7.7)	1 (3.1)	7 (25.0)
	Tx-related	NR	NR	NR	NR	0 (0)	0 (0)
Death, n (%)	**Overall**	NR	NR	34 (64.2)	33 (61.1)	24 (85.7)	29 (90.6)
	AE-related	NR	NR	4 (7.5)	2 (3.7)	1 (3.6)	3 (9.4)
	Tx-related	NR	NR	0 (0)	0 (0)	0 (0)	0 (0)
Anemia, n (%)	**Mean Duration,** days	NR	NR	[redacted]			
	Overall	15 (40.5)	10 (26.3)	33 (62.3)	19 (36.5)	24 (85.7)	17 (53.1)
	Grade 3	7 (18.9)	2 (5.3)	15 (28.3)	9 (17.3)	17 (60.7)	9 (28.1)
	Grade 4	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)
Thrombocytopenia, n (%)	**Mean Duration,** days	NR	NR	[redacted]			
	Overall	10 (27.0)	10 (26.3)	23 (43.4)	7 (13.5)	19 (67.9)	20 (62.5)
	Grade 3	3 (8.1)	3 (7.9)	8 (15.1)	0 (0)	5 (17.9)	8 (25.0)
	Grade 4			7 (13.2)	0 (0)	11 (39.3)	9 (28.1)
Use of Antibiotics, n (%)		NR	NR	12 (22.6)	10 (18.5)	8 (27.6)	7 (21.9); 0.6483

Trial	G1T28-02 Phase II Weiss 2019		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021	
Chemotherapy Regimen	**Carboplatin/Etoposide**		**Carboplatin/Etoposide/Atezolizumab**		**Topotecan**	
Arm	**Placebo**	**Trilaciclib 240 mg/m^2**	**Placebo**	**Trilaciclib 240 mg/m^2**	**Placebo**	**Trilaciclib 240 mg/m^2**
Safety outcomes not reported: Bone pain and infection						

AE: adverse event, AIC: academic in confidence, max: maximum, mg/m^2: milligrams per meter squared, n: number, N: total number, NA: not applicable, NR: not reported, Tx: treatment

Table D13. Safety Outcomes II – Trilaciclib Additional Trials[7,21]

Trial		Pooled Analysis G1T28-02, 03, 05 Weiss 2021		G1T28-04 Phase II Tan 2019		
Chemotherapy Regimen		**Varies by trial**		**Gemcitabine/Carboplatin**		
Arm		**Placebo**	**Trilaciclib 240 mg/m^2**	**Chemotherapy**	**Trilaciclib 240 mg/m^2 + Chemotherapy**	**Trilaciclib/ Trilaciclib 240 mg/m^2 + Chemotherapy**
Timepoint		**Pooled (18-24 months)**		**Up to 18 months**		
N		118	122	34	33	35
Adverse Events, n (%)	**Overall**	114 (96.6)	115 (94.3)	30 (100)	33 (100)	34 (97)
	Grade 3	98 (83.1)	73 (59.8)	*27 (90)*	*29 (88)*	*29 (83)*
	Grade 4	62 (52.5)	30 (24.6)			
Serious Adverse Events, n (%)	**Overall**	30 (25.4)	36 (29.5)	10 (33)	11 (33)	4 (11)
	Infection	*12* (10.1)	*8* (6.5)	NR	NR	NR
Treatment-related AEs, n (%)	**Overall**	49 (41.5)	45 (36.9)	NR	NR	NR
	Serious	1 (0.8)	2 (1.6)	NR	NR	NR
Discontinuation, n (%)	**Overall**	NR	NR	29 (85)	31 (94)	35 (100)
	AE-related	13 (11.0)	11 (9.0)	10 (33)	14 (42)	11 (31)
Death, n (%)	**Overall**	NR	NR	20 (59)	11 (33)	14 (40)
	AE-related	3 (2.5)	6 (4.9)	1 (3)	0	0
	Tx-related	0	0	NR	NR	NR
Bone Pain, n (%)	**Overall**	NR	NR	4 (13.3)	2 (6.1)	2 (5.7)
	Grade 1	NR	NR	4 (13.3)	2 (6.1)	2 (5.7)
	Grade 2	NR	NR			
Anemia, n (%)	**Overall**	71 (60.2)	46 (37.7)	22 (73)	17 (52)	15 (43)
	Grade 3	39 (33.1)	20 (16.4)	14 (47)	8 (24)	11 (31)
	Grade 4	1 (0.8)	0 (0.0)	0	0	0
Thrombocytopenia, n (%)	**Overall**	50 (42.4)	37 (30.3)	18 (60)	18 (55)	22 (63)
	Grade 3	18 (15.3)	12 (9.8)	8 (27)	3 (9)	9 (26)
	Grade 4	21 (17.8)	10 (8.2)	7 (23)	6 (18)	6 (17)
Use of Antibiotics, n (%)		*28/119* (23.5)	*24/123* (19.5)	NR	NR	NR
Safety outcomes not reported: Serious adverse events due to pulmonary infection, treatment-related discontinuation, mean duration of anemia and thrombocytopenia, infection						

AE: adverse event, mg/m^2: milligrams per meter squared, n: number, N: total number, NR: not reported, Tx: treatment

Note: Italicized data is digitized or ICER-calculated

Table D14. Quality of Life Outcomes – Trilaciclib Trials[7,16,18]

Trial		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021		Pooled Analysis G1T28-02, 03, 05 Weiss 2021	
Chemotherapy Regimen		Carboplatin/Etoposide/ Atezolizumab		Topotecan		Varies by trial	
Arm		Placebo	Trilaciclib 240 mg/m^2	Placebo	Trilaciclib 240 mg/m^2	Placebo	Trilaciclib 240 mg/m^2
Functional Assessment of Cancer Therapy – General (FACT-G)							
FACT-G	Events, n	22	13	13	7	NR	NR
	Median TDD, months	NYR	NYR	2.86	NYR	NR	NR
	Hazard ratio (95% CI)	0.58 (0.29, 1.15)		0.34 (0.14, 0.87)		NR	
PWB	Events, n	22	17	16	7	51	32
	Median TDD, months	NYR	NYR	1.64	NYR	5.16	NYR
	Hazard ratio (95% CI)	0.82 (0.44, 1.56)		0.25 (0.10, 0.62)		0.62 (0.40, 0.97)	
FWB	Events, n	30	15	13	10	55	31
	Median TDD, months	3.53	8.57	2.23	8.84	3.78	7.62
	Hazard ratio (95% CI)	0.40 (0.22, 0.75)		0.43 (0.18, 1.03)		0.45 (0.29, 0.71)	
EWB	Events, n	15	15	8	8	NR	NR
	Median TDD, months	NYR	NYR	NYR	NYR	NR	NR
	Hazard ratio (95% CI)	1.09 (0.53, 2.25)		0.75 (0.28, 2.02)		NR	
SWB	Events, n	18	19	8	6	NR	NR
	Median TDD, months	NYR	NYR	NYR	6.7	NR	NR
	Hazard ratio (95% CI)	1.02 (0.53, 1.95)		0.50 (0.16, 1.57)		NR	
Functional Assessment of Cancer Therapy – Lung (FACT-L)							
FACT-L	Events, n	23	17	16	12	NR	NR
	Median TDD, months	7.16	NYR	2.1	4.4	NR	NR
	Hazard ratio (95% CI)	0.70 (0.38, 1.32)		0.45 (0.21, 1.09)		NR	
LCS	Events, n	13	13	11	4	NR	NR
	Median TDD, months	NYR	NYR	10.02	NYR	NR	NR
	Hazard ratio (95% CI)	1.08 (0.50, 2.33)		0.29 (0.09, 0.92)		NR	
L-TOI	Events, n	24	11	14	10	NR	NR
	Median TDD, months	7.95	NYR	2.1	NYR	NR	NR
	Hazard ratio (95% CI)	0.42 (0.21, 0.87)		0.48 (0.21, 1.09)		NR	
Functional Assessment of Cancer Therapy – Anemia (FACT-An)							
FACT-An	Events, n	28	16	16	14	58	31

Trial		G1T28-05 Phase II Daniel 2020		G1T28-03 Phase II Hart 2021		Pooled Analysis G1T28-02, 03, 05 Weiss 2021	
Chemotherapy Regimen		**Carboplatin/Etoposide/ Atezolizumab**		**Topotecan**		**Varies by trial**	
Arm		**Placebo**	**Trilaciclib 240 mg/m²**	**Placebo**	**Trilaciclib 240 mg/m²**	**Placebo**	**Trilaciclib 240 mg/m²**
	Median TDD, months	4.17	NYR	1.02	3.75	3.48	NYR
	Hazard ratio (95% CI)	0.52 (0.28, 0.96)		0.53 (0.25, 1.12)		0.47 (0.30, 0.73)	
Fatigue	Events, n	28	20	17	14	61	39
	Median TDD, months	2.6	7.2	0.95	3.09	2.33	7.03
	Hazard ratio (95% CI)	0.66 (0.37, 1.18)		0.46 (0.22, 0.96)		0.56 (0.37, 0.85)	
Anemia TOI	Events, n	27	19	17	13	55	33
	Median TDD, months	3.84	3.84	1.02	3.09	3.78	7.2
	Hazard ratio (95% CI)	0.65 (0.36, 1.18)		0.44 (0.21, 0.94)		0.54 (0.35, 0.84)	
Quality of life outcomes not reported for G1T28-02 (Weiss 2019) and G1T28-04 (Tan 2019) trials							

95% CI: 95 percent confidence interval, EWB: emotional well-being, FWB: functional well-being, LCS: Lung Cancer Subscale, mg/m²: milligrams per meter squared, n: number, NR: not reported, NYR: not yet reached, PWB: physical well-being, SWB: social well-being, TDD: time to deterioration, TOI: trial outcome index

Table D15. Study Design – Plinabulin

Trial	Study Design & Population	Arms & Dosing	Inclusion & Exclusion Criteria	Key Outcomes [Timepoint]
PROTECTIVE-2 Phase III[25-27,30] NCT03294577	Phase III MC, DB RCT Adult women with breast cancer N = 221	1. TAC + Plinabulin 40 mg + Pegfilgrastim 6 mg 2. TAC + Placebo + Pegfilgrastim 6 mg	**Inclusions** - Adult women ≥ 18 years - ECOG 0-1 - Biopsy-proven stage I, II, III breast cancer with no prior chemo - Candidates for ≥4 cycles of TAC chemo **Exclusions** - History of ML, MDS, or concomitant SCD - Use of CYP3A4, CYP2D6, or P-glycoprotein inhibitors and inducers 14 days prior	**Primary** **-** Patients with Days of Severe Neutropenia = 0 [Cycle 1] **Secondary** - Mean DSN - Mean ANC nadir - Grade 3/4 neutropenia - Bone pain [Cycle 1]
PROTECTIVE-1 Phase III[31] NCT03102606	Phase III MC, DB, RCT Adults with NSCLC, breast cancer, or prostate cancer N = 105	1. Doc + Plinabulin 40 mg 2. Doc + Pegfilgrastim 6 mg	**Inclusions** - Adults ≥ 18 years - NSCLC failing platinum-based therapy, breast cancer failing <5 prior lines of chemo, or HRPC - ECOG 0-1 **Exclusions** - History of myelogenous leukemia (ML), myelodysplastic syndrome (MDS), or concomitant sickle cell disease (SCD) - Chemo within four weeks prior to first dose - Current use of strong CYP3A4 inhibitors	**Primary** - Days of Severe Neutropenia (DSN) [Cycle 1] **Secondary** - Bone pain - Platelet count - Thrombocytopenia - Antibiotic use [Cycle 1]
PROTECTIVE-2 Phase II[24,28,29] NCT04227990	Phase II OL, MC, RCT Adult women with breast cancer N = 115	1. TAC + Pegfilgrastim 6 mg 2. TAC + Plinabulin 10 mg/m^2 3. TAC + Plinabulin 20 mg/m^2 4. TAC + Plinabulin 30 mg/m^2 5. TAC + Plinabulin 20 mg/m^2 + Pegfilgrastim 1.5 mg 6. TAC + Plinabulin 20 mg/m^2 + Pegfilgrastim 3 mg 7. TAC + Plinabulin 20 mg/m^2 + Pegfilgrastim 6 mg	**Inclusions** - Adult women ≥ 18 years - Biopsy-proven stage I, II, III breast cancer with no prior chemo - Candidates for ≥4 cycles of TAC chemo - ECOG 0-1 **Exclusions** - History of ML, MDS, or concomitant SCD - Use of CYP3A4, CYP2D6, or P-	**Primary** - Days of Severe Neutropenia [Cycle 1] **Secondary** - Grade 4 neutropenia - Bone pain score [Cycle 1]

Trial	Study Design & Population	Arms & Dosing	Inclusion & Exclusion Criteria	Key Outcomes [Timepoint]
			glycoprotein inhibitors and inducers 14 days prior	
PROTECTIVE-1 Phase II[22] NCT04345900	Phase II MC, OL, RCT Adults with NSCLC N = 55	1. Doc + Plinabulin 5 mg/m^2 2. Doc + Plinabulin 10 mg/m^2 3. Doc + Plinabulin 20 mg/m^2 4. Doc + Pegfilgrastim 6 mg	**Inclusions** - Adults ≥ 18 years - NSCLC failing platinum-based therapy - ECOG 0-1 **Exclusions** - History of ML, MDS, or SCD - Chemo within four weeks prior to first dose - Current use of strong CYP3A4 inhibitors	**Primary** - Days of Severe Neutropenia [Cycle 1] **Secondary** **-** Peak plasma concentration - Neutropenia curve [Cycle 1]
DUBLIN-3[33] NCT02504489	Phase III MC, Blinded RCT Adults with previously treated advanced NSCLC N = 559	1. Doc 2. Doc + Plinabulin 30 mg/m^2	**Inclusions** - Adults ≥18 years - Confirmed non-squamous/squamous NSCLC - Disease progression during/after treatment - ECOG ≤2 - Active brain metastasis - ≥1 measurable lung lesion of ≥10mm **Exclusions** - Chemo, immunotherapy, biological, targeted, radiation therapy, or investigational agent within three weeks prior to study drug - Significant cardiac history - Prior treatment with docetaxel	**Primary** Overall Survival [2 years] **Secondary** - Severe neutropenia [Cycle 1] - Overall response rate - Progression-free survival - Overall survival - Duration of response [2 years]

ANC: absolute neutrophil count, DB: double-blind, Doc: docetaxel, DSN: days of severe neutropenia, ECOG: Eastern Cooperative Oncology Group, HRPC: hormone refractory prostate cancer, MC: multicenter, MDS: myelodysplastic syndrome, mg: milligram, mg/m^2: milligram per meter squared, ML: myelogenous leukemia, mm: millimeter, NSCLC: non-small cell lung cancer, OL: open label, RCT: randomized controlled trial, SCD: sickle cell disease, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide

Table D16. Baseline Characteristics I – Plinabulin Phase III Trials[23,25-27,31,32]

Trial		PROTECTIVE-2 Phase III		PROTECTIVE-1 Phase III	
Cancer Population		**Breast Cancer**		**Breast Cancer, NSCLC, HRPC**	
Chemotherapy Regimen		**TAC**		**Docetaxel**	
Arm		**Pegfilgrastim + Placebo**	**Pegfilgrastim + Plinabulin 40 mg**	**Pegfilgrastim**	**Plinabulin 40 mg**
N		110	111	53	52
Age, years	**Mean (SD)**	50.0 ([redacted])	48.5 ([redacted])	58.9 (10.85)	57.0 (10.79)
	Median (Range)	[redacted]	[redacted]	60 (36, 81)	58.5 (31, 81)
Sex, n (%)	**Male**	0	0	21 (39.6)	19 (36.5)
	Female	110 (100)	111 (100)	32 (60.4)	33 (63.5)
Race, n (%)	**White**	[redacted]	[redacted]	NR	NR
	Black	NR	NR	NR	NR
	Asian	[redacted]	[redacted]	NR	NR
	Other	[redacted]	[redacted]	NR	NR
BMI, kg/m²	**Mean (SD)**	[redacted]	[redacted]	NR	NR
ECOG Status	**0**	[redacted]	[redacted]	53 (100)	52 (100)
	1	[redacted]	[redacted]		
	2	0	0	0	0
Any Prior Radiation Therapy	**Mean (SD)**	[redacted]	[redacted]	49 (92.5)	51 (98.1)
Baseline characteristics not reported: Number of prior lines of therapy, second- or third-line treatment, brain metastases, neutrophil count, pre-dose blood pressure					

%: percent, HRPC: hormone refractory prostate cancer, kg/m^2: kilograms per meter squared, mg: milligram, n: number, NR: not reported, NSCLC: non-small cell lung cancer, SD: standard deviation, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide

Table D17. Baseline Characteristics II – Plinabulin Phase II and Anti-Cancer Trials[22]

Trial		PROTECTIVE-1 Phase II			
Cancer Population		**Non-Small Cell Lung Cancer (NSCLC)**			
Chemotherapy Regimen		**Docetaxel**			
Arm		**Pegfilgrastim**	**Plinabulin 20 mg/m²**	**Plinabulin 10 mg/m²**	**Plinabulin 5 mg/m²**
N		13	14	14	14
Age, years	**Mean (SD)**	59.5 (8.08)	63.0 (10.44)	58.6 (11.72)	64.1 (10.33)
Sex, n (%)	**Male**	10 (76.92)	10 (71.43)	9 (64.29)	9 (64.29)
	Female	3 (23.08)	4 (28.57)	5 (35.71)	5 (35.71)
Race, n (%)	**White**	10 (76.92)	10 (71.43)	11 (78.57)	11 (78.57)
	Black	0 (0)	0 (0)	0 (0)	0 (0)
	Asian	3 (23.08)	4 (28.57)	3 (21.43)	3 (21.43)
	Other	0 (0)	0 (0)	0 (0)	0 (0)
BMI, kg/m²	**Mean (SD)**	22.9 (3.33)	26.5 (5.64)	23.9 (3.49)	25.2 (4.79)
ECOG Status	**0** **1**	13 (100)	14 (100)	14 (100)	14 (100)
	2	0	0	0	0
Any Prior Radiation Therapy	**Mean (SD)**	NR	NR	NR	NR
Number of Prior Lines of Therapy	**Mean (SD)**	2.5 (1.05)	2.0 (1.11)	2.9 (2.07)	1.7 (0.73)
Neutrophil Count, GI/L, Mean (SD)	**Screening**	5.9 (1.93)	5.4 (2.08)	6.6 (2.48)	5.3 (2.58)
	Pre-Dose	9.8 (3.46)	8.1 (3.94)	8.9 (3.03)	7.5 (2.34)
Pre-Dose Blood Pressure, mmHG, Mean (SD)	**Systolic**	122.2 (9.28)	122.9 (11.56)	125.5 (7.26)	124.5 (12.34)
	Diastolic	77.8 (6.77)	76.6 (5.26)	78.0 (4.40)	75.8 (7.55)
Baseline characteristics not reported: Median age, second- or third-line treatment, brain metastases. No baseline characteristics for the DUBLIN-3 or PROTECTIVE-2 Phase II trials.					

%: percent, BMI: body mass index, ECOG: Eastern Cooperative Oncology Group, GI/L: gill to liters, kg/m²: kilograms per meter squared, mmHG: millimeters of mercury, mg: milligram, mg/m²: milligrams per meter squared, n: number, N: total number, NR: not reported, NSCLC: non-small cell lung cancer, SD: standard deviation, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide

Table D18. Key Efficacy I – Plinabulin Phase III Trials[23,25-27,31,32]

Trial		PROTECTIVE-2 Phase III		PROTECTIVE-1 Phase III	
Chemotherapy Regimen		TAC		Docetaxel	
Arm		Pegfilgrastim + Placebo	Pegfilgrastim + Plinabulin 40 mg	Pegfilgrastim	Plinabulin 40 mg
N		110	111	53	52
Grade 3/4 Neutropenia	Timepoint	**Cycle 1**			
	Incidence, n (%); p-value	[redacted]		NR	NR
Severe Neutropenia	Timepoint	**Cycle 1**			
	Incidence, n (%); p-value	*95 (86.4)*	*76 (68.5);* 0.0015	*6 (11.3)*	*4 (7.7)*
	Mean Duration, days (SD); p-value	1.51 (NR)	1.24 (NR); 0.0324	0.25 (95%CI: 0.21, 0.29)	0.77 (95%CI: 0.68, 0.86)
	Timepoint	**Overall Treatment Period**			
	Incidence, n (%); p-value	[redacted]		NR	NR
Profound Neutropenia	Timepoint	**Cycle 1**			
	Incidence, n (%); p-value	*51* (46.4)	*24* (21.6); 0.0001	NR	NR
	Mean Duration days (SD); p-value	0.63	0.34; 0.0004	NR	NR
Febrile Neutropenia	Timepoint	**Overall Treatment Period**			
	Overall, n (%); p-value	7 (6.36)	4 (3.60); 0.36	1 (1.89)	0 (0)
	Grade 3, n (%)	3 (2.7)	3 (2.7)	NR	NR
	Grade 4, n (%)	4 (3.6)	1 (0.9)	NR	NR
	Mean Duration, days (SD); p-value	2.28 (NR)	1.25 (NR)	NR	NR
All Cause Hospitalizations	Timepoint	**Overall Treatment Period**			
	Incidence, n (%); p-value	*110* (100)	*83* (75)	5 (9.4)	7 (13.5)
	Mean duration, days	7.14	3.75	NR	NR
Chemotherapy	Timepoint	**Overall Treatment Period**			
	Dose Reductions, n (%)	*7* (6.3)	*3* (2.7)	to < 85%: 2 (3.8)	to <85%: 3 (5.8)
	Regimen Change, n (%)			3 (5.66)	2 (3.85)
	Discontinuation, n (%)	NR	NR	14 (26.4)	7 (13.5)

Efficacy outcomes not reported: Duration of grade 3/4 neutropenia (cycle 1) and severe neutropenia (overall treatment period), hospitalizations due to CIM, sepsis, neutropenia, anemia, thrombocytopenia, red blood cell transfusions, platelet transfusions, anti-tumor efficacy

CIM: chemotherapy-induced myelosuppression, mg: milligrams, n: number, N: total number, NR: not reported, SD: standard deviation

Note: Italicized data is digitized or ICER-calculated

* Not reported numerically. Plinabulin described in text as meeting non-inferiority criteria: the upper limit of the 95% confidence interval for the difference between plinabulin and pegfilgrastim is <0.65 days.

Table D19. Key Efficacy II – Plinabulin Phase II and Anti-Cancer Trials[22,24,28,29,33]

Trial		PROTECTIVE-2 Phase II		PROTECTIVE-1 Phase II		DUBLIN-3 Phase III	
Chemotherapy Regimen		**TAC**		**Docetaxel**		**Docetaxel**	
Arm		**Pegfilgrastim + Placebo**	**Pegfilgrastim + Plinabulin 20 mg/m²**	**Pegfilgrastim**	**Plinabulin 20 mg/m²**	**Placebo**	**Plinabulin 30 mg/m²**
N		21	16	13	14	281	278
Grade 3/4 Neutropenia	Timepoint	**Cycle 1**					
	Incidence, n (%); p-value	*17* (81)	*8* (50); <0.05	NR	NR (NR); 0.460	NR	NR
	Mean Duration days (SD); p-value	1.4 (1)	0.9 (1.1); NS	NR	NR	NR	NR
Severe Neutropenia	Timepoint	**Cycle 1**					
	Incidence, n (%); p-value	*12* (57)	*6* (38); NS	NR	NR	*78* (27.8)	*15* (5.3); <0.001
	Mean Duration days (SD); p-value	NR	NR	0.15 (0.38)	0.36 (0.93); 0.755	NR	NR
Febrile Neutropenia	Timepoint	**Cycle 1**				**Overall Treatment Period**	
	Incidence, n (%)	1 (4.8)	1 (6.3)	NR	NR	NR	NR
All Cause Hospitalization	Timepoint	**Cycle 1**					
	Incidence, n (%)	NR	NR	1 (7.7)	2 (14.3)	NR	NR
Anti-Cancer Efficacy	Timepoint	**Up to Two Years post Study Initiation**					
Objective Response Rate	**% (95% CI); p-value**	NR	NR	NR	NR	6.8 (NR)	12.2 (NR); 0.0275
Progression-Free Survival	**Median months (95% CI)**	NR	NR	NR	NR	3.0 (NR)	3.6 (NR)
	HR (95% CI); p-value	NR	NR	NR	NR	0.76 (0.63, 0.93); 0.008	
Overall Survival	**Median months (95% CI)**	NR	NR	NR	NR	9.4	10.5
	HR (95% CI); p-value	NR	NR	NR	NR	0.82 (0.68, 0.99); 0.0399	

Efficacy outcomes not reported: Severe neutropenia (overall treatment period), profound neutropenia, grade 3/4 febrile neutropenia, duration of febrile neutropenia, hospitalizations (overall treatment period), hospitalizations due to CIM, sepsis, neutropenia, anemia, or thrombocytopenia; chemotherapy dose reductions, regimen changes, or discontinuation; red blood cell or platelet transfusions, duration of objective response

95% CI: 95 percent confidence interval, AIC: academic in confidence, CIM: chemotherapy-induced myelosuppression, mg/m^2: milligrams per meter squared, n: number, N: total number, NR: not reported, NS: not significant, SD: standard deviation
Note: Italicized data is digitized or ICER-calculated

Table D20. Secondary Efficacy I – Plinabulin Phase III Trials[23,25-27,31,32]

Trial		PROTECTIVE-2 Phase III		PROTECTIVE-1 Phase III	
Chemotherapy Regimen		**TAC**		**Docetaxel**	
Arm		**Pegfilgrastim + Placebo**	**Pegfilgrastim + Plinabulin 40 mg**	**Pegfilgrastim**	**Plinabulin 40 mg**
N		110	111	53	52
Percent Change from Baseline in Platelets	Timepoint	**Day 15**			
	Mean (SD); p-value	NR	NR	10 (19)	-62 (23); <0.001
ANC Nadir	Timepoint	**Cycle 1**			
	Mean (SD); p-value	0.31 (NR)	0.54 (NR); 0.0002	NR	NR
Efficacy outcomes not reported: G-CSF and ESA administration, change from baseline in red blood cells					

ANC: absolute neutrophil count, mg: milligrams, N: total number, NR: not reported, SD: standard deviation, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide

Table D21. Secondary Efficacy II – Plinabulin Phase II and Anti-Cancer Trials[22,24,28,29,33]

Trial		PROTECTIVE-2 Phase II		PROTECTIVE-1 Phase II	
Chemotherapy Regimen		**TAC**		**Docetaxel**	
Arm		**Pegfilgrastim + Placebo**	**Pegfilgrastim + Plinabulin 20 mg/m²**	**Pegfilgrastim**	**Plinabulin 20 mg/m²**
N		21	16	13	14
Platelet Count	Timepoint	**Day 15**			
	Mean (SD); p-value	NR	NR	*-10.5 (7.8)*	*1.5 (5.9)*; 0.290
Absolute Neutrophil Count	Timepoint	**Day 15**			
	Mean (SD); p-value	1.15 (SE: 0.39)	6.05 (SE: 0.60)	*11.9 (1.38)*	*4.62 (0.31);* NR
ANC Nadir	Timepoint	**Cycle 1**			
	Mean (SD); p-value	0.77 (0.90)	1.15 (0.94); NS	NR	NR
Efficacy outcomes not reported: G-CSF and ESA administration, change from baseline in red blood cells. Not reported for the DUBLIN-3 trial.					

ANC: absolute neutrophil count, mg/m²: milligrams per meter squared, N: total number, NR: not reported, NS: not significant, SD: standard deviation, SE: standard error, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide

Note: Italicized data is digitized

Table D22. Safety Outcomes I – Plinabulin Phase III Trials[23,25-27,31,32]

Trial		PROTECTIVE-2 Phase III		PROTECTIVE-1 Phase III	
Chemotherapy Regimen		**TAC**		**Docetaxel**	
Arm		**Pegfilgrastim + Placebo**	**Pegfilgrastim + Plinabulin 40 mg**	**Pegfilgrastim**	**Plinabulin 40 mg**
N		110	111	53	52
Timepoint		**End of Treatment Period**		**Day 15**	
Adverse Events, n (%)	**Overall**	*106* (96.36)	*108* (97.30)	49 (92.5)	51 (98.1)
	Grade 3	*7* (6.36)	*20* (18.02)	NR *(24.5)*	NR *(32.7)*
	Grade 4	*88* (80.0)	*65* (58.56)	NR *(17.0)*	NR *(32.7)*
Serious Adverse Events, n (%)	**Overall**	[redacted]		6 (11.3)	8 (15.4)
Treatment-related AEs, n (%)	**Overall**	NR	NR	44 (83.0)	50 (96.2)
Discontinuation, n (%)	**Overall**	[redacted]		14 (26.4)	7 (13.5)
	AE-related			1 (4.8)	1 (4.8)
Death, n (%)	**Overall**	NR	NR	3 (5.7)	3 (5.8)
	AE-related	[redacted]		1 (1.9)	2 (3.8)

Trial		PROTECTIVE-2 Phase III		PROTECTIVE-1 Phase III	
Chemotherapy Regimen		**TAC**		**Docetaxel**	
Arm		**Pegfilgrastim + Placebo**	**Pegfilgrastim + Plinabulin 40 mg**	**Pegfilgrastim**	**Plinabulin 40 mg**
	Treatment-related	NR	NR	0 (0)	0 (0)
Bone Pain, n (%)	**Overall**	*33* (30.0)	*20* (18.02)	NR* **LS Mean difference: -0.67, p=0.0099**	
	Grade 1	*20* (18.18)	*9* (8.11)		
	Grade 2	*13* (11.82)	*11* (9.91)		
Thrombocytopenia, n (%)	**Mean duration, days**	NR	NR	NR	NR
	Overall	NR	NR	19 (35.8)	10 (19.2); p = 0.06
	Grade 3	NR	NR	NR	NR
	Grade 4	NR	NR	NR	NR
Infection, n (%)		NR	NR	*8* (15.1)	*4* (7.69)
Use of Antibiotics, n (%)		NR	NR	*7* (13.2)	*8* (15.4)
Safety outcomes not reported: Serious AEs due to infections, serious treatment-related AEs, treatment-related discontinuation, anemia					

AE: adverse event, AIC: academic in confidence, mg: milligram, n: number, N: total number, NR: not reported, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide

Note: Italicized data is ICER-calculated or digitized

* Data for individual arms not reported

Table D23. Safety Outcomes II – Plinabulin Phase II Trials[22,24,28,29]

Trial		PROTECTIVE-2 Phase II		PROTECTIVE-1 Phase II	
Chemotherapy Regimen		TAC		Docetaxel	
Arm		Pegfilgrastim + Placebo	Pegfilgrastim + Plinabulin 20 mg/m²	Pegfilgrastim	Plinabulin 20 mg/m²
Timepoint		End of Treatment Period			
N		21	16	13	14
Serious Adverse Events, n (%)	Overall	NR	NR	2 (15.4)	2 (14.3)
Discontinuation, n (%)	Overall	NR	NR	2 (15.4)	5 (35.7)
	Treatment-related	NR	NR	0 (0)	1 (7.1)
Death, n (%)	Overall	NR	NR	1 (7.7)	1 (7.1)
	Treatment-related	NR	NR	0 (0)	0 (0)
Bone Pain, n (%)	Overall	*20* (95)	*1* (6)	NR	1 (7.1)
Anemia, n (%)	Overall	NR	NR	1 (7.7)	2 (14.3)
	Grade 3	NR	NR	0	0
	Grade 4	NR	NR		
Thrombocytopenia, n (%)	Overall	NR	15 (93.8)	1 (7.7)	0 (0)
	Grade 3	NR	3 (18.8)	NR	NR
	Grade 4	NR	NR	NR	NR
Infection, n (%)	Treatment-related	NR	NR	2 (15.4)	2 (14.3)
Safety outcomes not reported: Overall adverse events, serious AEs due to infection, treatment-related AEs, discontinuation or death due to adverse events, grade 1-2 bone pain, mean duration of anemia and thrombocytopenia, use of antibiotics, overall infections					

%: percent, AE: adverse event, AIC: academic in confidence, mg: milligram, mg/m^2: milligrams per meter squared, n: number, N: total number, NR: not reported, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide

Note: Italicized data is ICER-calculated

Table D24. Quality of Life Outcomes II – Plinabulin Phase III Trials[30-32]

Trial		Timepoint	PROTECTIVE-2 Phase III		PROTECTIVE-1 Phase III	
Chemotherapy Regimen			TAC		Docetaxel	
Arm			Pegfilgrastim + Placebo	Pegfilgrastim + Plinabulin 40 mg	Pegfilgrastim	Plinabulin 40 mg
N			106	109	53	52
EQ5D02-EQ VAS Score	LS Mean (SE)	Across all timepoints	NR	NR	79.1 (1.01)	78.5 (1.00)
	Mean (95%CI)				–	-0.5 (-3.4, 2.3)
	p-value				–	0.7117
Health Utility	LS Mean (SE)	Across all timepoints			0.812 (0.0094)	0.816 (0.0093)
	Mean (95%CI)				–	0.004 (-0.022, 0.030)
	p-value				–	0.7637
EQ-5D-5L Health Utilities*	Mean	Cycle 1, Day -1	0.93	0.93	NR	NR
		Cycle 2, Day -1	0.91	0.95		
		Cycle 3, Day -1	0.89	0.93		
		Cycle 4, Day -1	0.87	0.92		
	p-value	Overall	–	0.0245		
Physical Well Being (FACT G)		[redacted]				

95%CI: 95 percent confidence interval, AIC: academic in confidence, EQ5D02-EQ VAS: EuroQol-5 dimension-EuroQol-visual analogue scales, EQ-5D-5L: EuroQol-5 dimension 5-level, FACT G: Functional Assessment of Cancer Therapy-General, LS mean: least squares mean, mg: milligram, n: number, N: total number, NR: not reported, SE: standard error, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide

* Measured on the day before TAC dosing

Table D25. Quality of Life Outcomes I – Plinabulin Phase II Trial[22]

Trial		Timepoint	PROTECTIVE-1 Phase II	
Chemotherapy Regimen			Docetaxel	
Arm			Pegfilgrastim	Plinabulin 20 mg/m^2
Global Health Status*	Mean (SE)	Cycle 1, Day 1	*64.3 (5.6)*	*66.6 (4.5)*
		Cycle 2, Day 1	*57.1 (3.9)*	*67.4 (6.2)*
		Cycle 3, Day 1	*54.4 (4.1)*	*66.5 (2.6)*
		Cycle 4, Day 1	*45.5 (5.6)*	*62.3 (3.8)*
		End of Treatment	*51.0 (5.9)*	*61.9 (3.0)*

Trial		Timepoint	PROTECTIVE-1 Phase II	
Chemotherapy Regimen			Docetaxel	
Arm			**Pegfilgrastim**	**Plinabulin 20 mg/m²**
Fatigue†	**Mean (SE)**	Cycle 1, Day 1	*28.8 (5.7)*	*28.4 (5.1)*
		Cycle 2, Day 1	*29.7 (5.1)*	*21.6 (3.3)*
		Cycle 3, Day 1	*29.9 (2.1)*	*25.9 (3.0)*
		Cycle 4, Day 1	*33.9 (2.0)*	*28.2 (4.4)*
		End of Treatment	*36.9 (6.1)*	*30.8 (3.3)*
Pain†	**Mean (SE)**	Cycle 1, Day 1	*18.8 (4.7)*	*14.3 (5.8)*
		Cycle 2, Day 1	*18.7 (5.2)*	*5.5 (2.3)*
		Cycle 3, Day 1	*19.5 (6.1)*	*7.5 (3.4)*
		Cycle 4, Day 1	*16.0 (5.2)*	*15.4 (4.1)*
		End of Treatment	*22.2 (8.9)*	*19.8 (6.5)*
Insomnia†	**Mean (SE)**	Cycle 1, Day 1	*17.6 (8.1)*	*14.2 (6.1)*
		Cycle 2, Day 1	*20.3 (8.1)*	*8.1 (4.4)*
		Cycle 3, Day 1	*11.8 (5.4)*	*9.1 (4.8)*
		Cycle 4, Day 1	*9.1 (4.4)*	*11.8 (5.1)*
		End of Treatment	*23.9 (7.9)*	*20.3 (5.4)*
Bone Pain	**Worst within prior 24 hours, mean change % (95% CI)**	Cycle 1, Day 2	*-9.7 (-50.4, 31.8)*	*-25.1 (-50.4, 0)*
		Cycle 1, Day 5	*114.3 (18.2, 214.5)*	*-74.5 (NR)*
		Cycle 2, Day 1	*58.0 (-0.88, 115.8)*	*-44.24 (-39.1, -49.4)*
	Average within prior 24 hours, mean change % (95% CI)	Cycle 1, Day 2	*-16.6 (-33.7, 0)*	*-28.7 (-56.9, 0)*
		Cycle 1, Day 5	*33.4 (0, 66.2)*	*-50.1 (NR)*
		Cycle 2, Day 1	NR	*-25.09 (-0.16, -50.01)*

%: percent, 95% CI: 95 percent confidence interval, mg/m²: milligram per meter squared, NR: not reported, SE: standard error

Bone pain evaluated with the Brief Pain Inventory Short Form questionnaire; Health-related quality of life evaluated by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and EuroQoL Group, collected before docetaxel infusion on day one of each cycle

Note: Italicized data is digitized

* Higher score indicates better quality of life

† Lower score indicates better quality of life

D4. Ongoing Studies

Table D26. Ongoing Studies

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Key Outcomes	Status
Trilaciclib					
PRESERVE 1: Trilaciclib, a CDK 4/6 Inhibitor, in Patients Receiving FOLFOXIRI/Bevacizumab for Metastatic Colorectal Cancer (mCRC) **Phase III** [NCT04607668]	Phase III DB RCT Estimated N: 296	1. Trilaciclib + FOLFOXIRI/bevacizumab 2. Placebo + FOLFOXIRI/bevacizumab	***Inclusion*** - Adults with proficient mismatch repair/microsatellite stable (pMMR/MSS), histologically or cytologically confirmed **adenocarcinoma of the colon or rectum** - Unresectable and measurable or evaluable disease - ECOG performance status of 0-1 ***Exclusion*** - Prior systemic therapy for mCRC - Any radiotherapy, chemotherapy, immunotherapy, biologic, investigational, or hormonal therapy for cancer treatment within three weeks of first dose - Prior allogeneic or autologous hematopoietic stem cell or bone marrow transplantation	***Primary Outcome*** Myelopreservation [24 weeks, up to 12 cycles] ***Secondary Outcomes*** - Quality of Life - Anti-tumor efficacy	Recruiting Initiation: Oct 2020 Primary Completion: Nov 2022
PRESERVE 2: Trilaciclib, a CDK 4/6 Inhibitor, in Patients Receiving Gemcitabine and	Phase III DB RCT	**Cohort 1:** first line therapy regardless of PD-L1 status who are PDL-1 inhibitor therapy naïve	***Inclusion*** - Adults with evaluable **locally advanced unresectable or**	***Primary Outcome*** - Overall survival up to 39 months in cohort 1 and up to	Recruiting Initiation: April 2021

Carboplatin for Metastatic Triple-Negative Breast Cancer (TNBC) **Phase III** NCT04799249	Estimated N: 250	**Cohort 2:** PD-L1 positive patients receiving second-line therapy following prior PD-L1 inhibitor therapy in locally advanced unresectable/metastatic setting **Arms in cohorts:** 1. Trilaciclib (240 mg/m^2) + gemcitabine (1000mg/m^2) + carboplatin (AUC2) 2. Placebo + gemcitabine + carboplatin Trilaciclib IV administered over 30 min prior to chemo on day 1 and 8 of each 21-day cycle	**metastatic triple negative breast cancer** - Documentation of triple-negative - Cohort 1: prior systemic therapies – no prior systemic therapy in locally advanced unresectable/metastatic setting, Prior PD-1 inhibitor treatment is not permitted in any saying, time between completion of last treatment with curative intent and first metastatic recurrence must be greater than six months - Cohort 2: prior systemic therapies – documentation of PD-L1 positive status, treated with PD-1 inhibitor for minimum duration of four months in locally advanced unresectable/metastatic settings - Radiation therapy for metastatic disease is permitted - ECOG score 0-1 ***Exclusion*** - Prior treatment with gemcitabine in any setting - Prior treatment with carboplatin in locally advanced unresectable/metastatic setting - Presence of CNS metastases or leptomeningeal disease requiring immediate treatment	28 months in cohort 2 ***Secondary Outcomes*** *[up to 14 months]* - QoL: chemotherapy-induced fatigue - Myeloprotective effects - Progression free survival	Expected Data: July-Dec 2023

			- Receipt of any cytotoxic chemo within 14 days prior to first dose - Known hypersensitivity to carboplatin or other platinum-containing compounds, or mannitol - Prior hematopoietic stem cell or bone marrow transplantation		
PRESERVE 3: Trilaciclib, a CDK 4/6 Inhibitor, in Patients With Advanced/Metastatic Bladder Cancer Receiving Chemotherapy Then Avelumab Phase II **NCT04887831**	Phase II OL RCT Estimated N: 90	1. Platinum-based chemotherapy followed by avelumab maintenance therapy 2. Trilaciclib + Platinum-based chemotherapy followed by avelumab maintenance therapy	***Inclusion*** - Adults with histologically document, **locally advanced (T4b, any N; or any T, N2-3) or metastatic urothelial carcinoma (M1, Stage IV)** - Measurable disease -ECOG performance status of 0-2 ***Exclusion*** - Prior treatment with IL-2, IFN-α, or an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or CD137 agonist, or cytotoxic T-lymphocyte associated protein 4 antibody - Malignancies other than urothelial carcinoma within three years prior to randomization - Presence of CNS metastases/leptomeningeal disease requiring immediate treatment	***Primary Outcome*** Progression-free survival [until documented disease progression or death] ***Secondary Outcomes*** - Anti-tumor effects - Myeloprotective effects	Recruiting **Primary Completion:** March 2023 **Study Completion:** May 2024

PRESERVE 4: Trilaciclib, a CDK 4/6 Inhibitor, in Patients Receiving Docetaxel for Metastatic Non-Small Cell Lung Cancer (NSCLC) **Phase II** **NCT04863248**	Phase II, DB, MC RCT Estimated N: 146	1. Trilaciclib* + docetaxel 2. Placebo + docetaxel Trilaciclib IV / Placebo administered prior to docetaxel on day 1 of each 21-day cycle * no dose reported	***Inclusion*** - Adults with histologically or cytologically confirmed **metastatic non-small cell lung cancer (squamous or non-squamous)** with no known actionable driver mutations - Must have received max of 1 line of platinum containing chemo, max of 1 line of locally approved/authorized PD-1/PD-L1 mAb - Measurable or non-measurable disease per RECIST v1.1 - ECOG Score 0-2 - Formalin-fixed paraffin-embedded tumor specimen with associated pathology report documenting NSCLC ***Exclusion*** - Prior explanation with docetaxel - Contraindication to admin. of docetaxel - Mixed NSCLC/SCLC or lung tumors - Any chemo, immunotherapy, biologic, investigational or hormonal therapy for cancer treatment within three weeks prior to first dose - Presence of CNS metastases needing immediate treatment	***Primary Outcome*** Overall Survival ***Secondary Outcomes*** - Progression-free survival - Anti-tumor endpoints - Neutrophil, RBC, and platelet lineage - Effect of chemo - Hospitalizations - TEAEs	Recruiting **Initiation:** April 2021 **Expected Data:** Jan – Jun 2023

			- Prior allogenic or autologous hematopoietic stem cell or bone marrow transplantation		
Evaluation of Trilaciclib in Chinese Patients With Extensive-stage Small Cell Lung Cancer (ES-SCLC) for Chemotherapy-induced Myelosuppression, Antitumor Effects of Combination Regimens, and Safety in a Real-world Study NCT05071703	Phase IV OL Real-world Study Estimated N: 30	1. Trilaciclib	***Inclusion*** - Adults with **extensive stage small-cell lung cancer** - Patients suitable for trilaciclib combined with platinum/etoposide or Trilaciclib combined with topotecan treatment ***Exclusion*** - Currently participating in other interventional clinical studies - Received systemic chemotherapy other than regiments recommended during trilaciclib treatment	***Primary Outcome*** Incidence of severe neutropenia [up to six months] ***Secondary Outcomes*** - Incidence of GR3-4 hematologic toxicity, IV or oral antibiotic administration, G-CSF use, RBC transfusions, ESA or TPO administration - Changes of absolute neutrophil and platelet count - All cause chemotherapy drugs reduction - Significant hematologic AE	Recruiting **Primary Completion:** Oct 2021 **Study Completion:** March 2023
Trilaciclib in Patients Receiving Sacituzumab Govitecan-hziy for Triple Negative Breast Cancer NCT05113966	OL Single-Arm Trial Estimated N: 45	1. Trilaciclib + Sacituzumab Govitecan-hziy	***Inclusion*** - Adults with **unresectable locally advanced or metastatic triple-negative breast cancer** - Documentation of histologically or cytologically confirmed ER-negative, PR-negative, and HER2-negative tumor - Documented disease progression during or after two	***Primary Outcome*** Progression-free survival [up to 24 months] ***Secondary Outcomes*** - Objective response rate - Clinical benefit rate	Recruiting **Primary Completion:** June 2023 **Study Completion:** July 2024

			lines of systemic chemotherapy treatment - ECOG performance status of 0-1 ***Exclusion*** - Prior treatment with trilaciclib, sacituzumab govitecan-hziy, irinotecan, trop-2 antibody drug conjugate, or any therapy with topoisomerase-1 payload - Known brain metastases - Malignancies other than TNBC within three years prior to enrollment - Current use of immunosuppressive medication	- Overall survival -Neutrophil/RBC/ Platelet-related myeloprotective effects - Safety and tolerability	
Trilaciclib, a CDK4/6 Inhibitor, in Patients With Early-Stage Triple Negative Breast Cancer **NCT05112536**	Phase II OL Single-Arm Study Estimated N: 30	1. Trilaciclib + chemotherapy: trilaciclib lead-in followed by trilaciclib + anthracycline/cyclophosphamide, then trilaciclib + taxane chemotherapy	***Inclusion*** - Documented diagnosis of **estrogen receptor (ER)-negative and progesterone receptor (PR)-negative tumor** - ECOG performance status of 0-1 - Primary tumor ≥ 2 cm with any nodal status ***Exclusion*** - Prior systemic therapies or radiation for current breast cancer - Invasive malignancy ≤ 3 years to study	***Primary Outcome*** Immune-based mechanism of action [up to eight days] ***Secondary Outcomes*** - pathologic complete response -TEAEs - Pharmacokinetics	Recruiting **Primary Completion:** August 2022 **Study Completion:** February 2023

			- History of breast cancer including ipsilateral ductal carcinoma in situ (DCIS) treated with radiotherapy at any time		
Phase 3 Study Evaluating Efficacy, Safety and Pharmacokinetics of Trilaciclib In Extensive-Stage Small Cell Lung Cancer Patients Receiving Carboplatin Combined With Etoposide or Topotecan NCT04902885	Phase III DB, PC, Multi-center RCT Estimated N: 92	1. Trilaciclib + carboplatin + etoposide 2. Placebo + carboplatin + etoposide 3. Trilaciclib + topotecan 4. Placebo + topotecan Part 1: safety run-in of 12 patients stratified by treatment line Part 2: Randomized DB, PC efficacy study of 80 patients stratified by first and second/third line, ECOG score, and brain metastases	***Inclusion*** - Adults with histology or cytology diagnosed **extensive-stage small cell lung cancer** - Patients who plan to receive carboplatin combine with etoposide: naïve with systemic treatment - Patients who plan to receive topotecan: previously received 1-2 lines chemotherapy or combined immunotherapy except for topotecan - ECOG performance status of 0-2 ***Exclusion*** - Symptomatic brain metastases that require local radiotherapy or hormone therapy - Other history of malignant cancer - Uncontrolled ischemic heart disease or congestive heart failure with clinical significance - Received radiotherapy within two weeks of enrollment	***Primary Outcomes*** - Peak plasma concentration [cycle 1] - Time to reach peak concentration [cycle 1] - Incidence of AEs, SAEs, and AEs leading to discontinuation [up to 30 days after last dose] - Duration of severe neutropenia [cycle 1] ***Secondary Outcomes*** - Incidence of SN - Incidence of RBC transfusion, G-CSF treatment, GR3-4 hematological toxicity, ESA treatment - Composite endpoint: important hematologic AEs	Recruiting **Primary Completion:** October 2021 **Study Completion:** March 2023
Plinabulin					

A Phase 3, Randomized Study to Evaluate Plinabulin vs. Pegfilgrastim in the Prevention of Severe Neutropenia in Breast Cancer Patients Receiving Myelosuppressive Chemotherapy With Docetaxel, Doxorubicin, and Cyclophosphamide (TAC) (PROTECTIVE-2) BeyondSpring Pharmaceuticals Inc. NCT03294577	RCT, MC, DB N: 221	1. TAC + Pegfilgrastim + Plinabulin 40 mg 2. TAC + Pegfilgrastim + Placebo TAC administered before plinabulin on day 1 and peg administered on day 2	***Inclusion*** - Adult women with **biopsy-proven stage I, II, III breast cancer with no prior chemotherapy** - ECOG 0-1 - Candidates for ≥4 cycles of chemotherapy with TAC (docetaxel, doxorubicin, cyclophosphamide) ***Exclusion*** - History of myelogenous leukemia, myelodysplastic syndrome, or concomitant sickle cell disease - Use of CYP3A4, CYP2D6, or P-glycoprotein inhibitors and inducers 14 days prior	***Primary Outcome*** Percentage of patients with Duration of Severe Neutropenia =0 [cycle 1] ***Secondary Outcomes*** - Mean DSN assessment - Mean ANC nadir - Percentage of patients with grade 3, 4 neutropenia - Avg. change in bone pain - Rate of composite risks - Mean DSN assessment within 15 days	Interim Results ***Primary Completion***: September 2020 ***Study Completion***: September 2025
A Phase I/II Study of Nivolumab, Ipilimumab and Plinabulin in Patients With Recurrent Small Cell Lung Cancer: Big Ten Cancer Research Consortium. BTCRC-LUN17-127 Jyoti Malhotra NCT03575793	Open Label Phase I/II study: Dose escalation part (Phase I) and single-arm part (Phase II) Estimated N: 35	1. Phase I: Nivolumab + Ipilimumab + Plinabulin (escalating from 13.5 to 20 to 30 mg/m^2) 2. Phase II: Nivolumab + Ipilimumab + Plinabulin (MTD from Phase I)	***Inclusion*** - Adults with **confirmed extensive-stage SCLC** - Progression after ≥1 platinum-based chemotherapy or platinum resistance - Phase II: prior treatment with one life of PD-1/PD-L 1 therapy - ECOG status 0-1 ***Exclusion*** - Active interstitial lung disease or pneumonitis or history of either requiring steroid treatment; history of ileus or	***Primary Outcome*** Phase I: Maximum Tolerated Dose [9 months] Phase II: Progression free survival [36 months] ***Secondary Outcomes*** - Adverse events - Objective response - Overall Survival	Recruiting ***Primary Completion***: September 2021 ***Study Completion***: September 2022

			other significant gastrointestinal disorder - Received CTLA-4 targeted therapy	[36 months]	
Randomized Blinded Phase III Assessment of Second or Third-Line Chemotherapy With Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients With Advanced Non-Small Cell Lung Cancer and With at Least One Measurable Lung Lesion (DUBLIN-3) BeyondSpring Pharmaceuticals Inc. NCT02504489	Randomized, Blinded, Phase III Estimated N: 559	1. Docetaxel 2. Docetaxel + Plinabulin	***Inclusion*** - Adults with histopathologically or cytologically confirmed **non-squamous or squamous NSCLC** - ECOG performance status ≤ 2 - Disease progression during or after treatment with one or two treatment regimens (see clinicaltrials.gov for more details) ***Exclusion*** - Administration of chemo, immunotherapy, biological, targeted, or radiation therapy or investigational agent within three weeks prior to study drug - Significant cardiac history - Prior treatment with docetaxel - Prior transient ischemic attack or cerebrovascular accident within past year	***Primary Outcome*** Overall survival [2 years] ***Secondary Outcomes*** - ORR - PFS -Severe Neutropenia - Month 24 OS Rate - Duration of response - Quality of Life	Active, not recruiting **Primary Completion:** March 2021 **Study Completion:** Dec 2021
An Open-label, Single-Center, Phase 1b/2 Study to Evaluate the Safety of Plinabulin in Combination With Radiation/ Immunotherapy in Patients With Select	OL, Single-Center, Phase Ib/2 Estimated N: 12	1. Arm A: radiation therapy, plinabulin, immunotherapy 2. Arm B: radiation therapy, immunotherapy	***Inclusion*** - Adults with one of seven histologically or cytologically confirmed malignant neoplasms, progressed on previous anti-PD-1/PD-L1 mAb treatment +/- chemotherapy or anti-CTLA4 requiring further	***Primary Outcome*** Incidence of AEs [up to 30 days after last dose] and objective tumor response rate [up to four years]	Recruiting **Study Completion:** June 2025

Advanced Malignancies After Progression on PD-1 or PD-L1 Targeted Antibodies MD Anderson Cancer Center NCT04902040			treatment: **NSCLC, SCLC, renal, bladder, merkle cell, MSI-H cancers, and melanoma** - At least one lesion is amenable to radiation - At least one additional non-contiguous lesion that has not been irradiated amenable to radiographic eval ***Exclusion*** - Evidence of complete or partial bowel obstruction - Subjects with primary CNS tumor or tumor involvement - Allergic to any anti-PD/PD-L1 monoclonal antibody - Prior exposure to plinabulin - Diagnosis or recurrence of invasive cancer other than present cancer within three years	***Secondary Outcomes*** - Disease control rate - Progression-free survival - Overall Survival	
A Phase I Study of Nivolumab in Combination With Escalating Doses of Plinabulin in Patients With Metastatic Non-Small Cell Lung Cancer (NSCLC) Lyudmila Bazhenova, MD NCT02812667	OL Phase I Estimated N: 38	1. Nivolumab + Plinabulin	***Inclusion*** - Adults with histologically or cytologically confirmed **metastatic NSCLC** whose disease progressed during/after treatment with at least one platinum-containing chemotherapy regimen - At least one prior systemic therapy for metastatic disease - ECOG Performance Status ≤ 1 - Prior chemotherapy must have been completed at least four weeks or five half-lives	***Primary Outcome*** Maximum tolerated dose and frequency and severity of TRAEs [2 years] ***Secondary Outcomes*** - Objective response rate - Disease control rate - Progression free survival	Recruiting **Primary Completion Date:** Dec 2021 **Study Completion Date:** Dec 2022

			before study drug administration ***Exclusion*** - History of grade 3 or above hypersensitivity reactions to other monoclonal antibodies - Subjects with history of cardiovascular illness - Uncontrolled hypertension - Symptomatic or untreated brain metastases - Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody	- Overall survival	
Study of Plinabulin and Pegfilgrastim With Multiple Myeloma Undergoing an Autologous Hematopoietic Stem Cell Transplant (AHCT) **NCT05130827**	OL Pilot Trial Estimated N: 15	1. Plinabulin	***Inclusion*** - Adults with histologic confirmation of **multiple myeloma in patients undergoing autologous HCT** with melphalan 140 or 200 mg/m^2 - Have at least 3 x 10^6 CD34+ autologous stem cells/kg to be infused - Karnofsky performance greater than or equal to 60 within two weeks prior to enrollment ***Exclusion*** - Other malignancy within past two years - Clinically significant infection - Received an investigational drug or used invasive investigational medical device	***Primary Outcome*** Average duration of absolute neutropenia [1 year] ***Secondary Outcomes*** - incidence of toxicities	Not yet recruiting **Study Completion Date:** Nov 2023

			within 14 days or five half-lives before enrollment - Hospitalization for infection or major surgery within 14 days of enrollment		

AE: adverse event, ANC: absolute neutrophil count, CNS: central nervous system, DB: double-blind, DSN: duration of severe neutropenia, ECOG: Eastern Cooperative Oncology Group, ESA: erythropoiesis-stimulating agent, G-CSF: granulocyte colony-stimulating factor, HCT: hematocrit, IV: intravenous, MC: multi-center, mCRC: metastatic colorectal cancer, mg: milligram, Mg/m^2: milligram per meter squared, MSI-H: microsatellite instability-high, MTD: maximum tolerable dose, n: number, N: total number, NSCLC: non-small cell lung cancer, OS: overall survival, QoL: quality of life, RBC: red blood cell, RCT: randomized controlled trial, SAE: serious adverse event, SCLC: small-cell lung cancer, TAC: chemotherapy regimen of docetaxel, doxorubicin hydrochloride, and cyclophosphamide, TEAE: treatment-emergent adverse event, TPO: thyroid peroxidase, TRAE: treatment-related averse event

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

D5. Previous Systematic Reviews and Technology Assessments

We identified one health technology assessment on plinabulin awaiting development by NICE. No other ongoing assessment were identified.

NICE Technology Assessments

Plinabulin with docetaxel for previously treated advanced non-small-cell lung cancer [ID3895]

NICE has indicated that they are awaiting development of a clinical and cost-effectiveness review of plinabulin in advanced non-small-cell lung cancer. As of December 2021, there is no expected publication date posted.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from [...] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	
	Unpaid caregiver-time costs	NA	X	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	

Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.61

Target Population

For trilaciclib, two hypothetical cohorts were considered: first line ES-SCLC receiving carboplatin, etoposide and atezolizumab (EPA) and previously treated ES-SCLC receiving topotecan 1.5 mg/m^2. The population of focus for the economic evaluation of plinabulin is E-BC patients being treated with docetaxel, doxorubicin, and cyclophosphamide (TAC).

Table E2. Baseline Population Characteristics, First Line ES-SCLC

	Total	Trilaciclib (N=39)	Placebo (N=38)	Trilaciclib (N=54)	Placebo (N=53)
Mean age	65	65	65	65 (median)	64 (median)
Female, %	30%	30.8%	28.9%	24.1%	35.8%
BSA	1.90 (SD 0.20)*	1.89 (SD 0.223)	1.91 (SD 0.210)	[redacted]	
Source	Average	Weiss 2019[17]	Weiss 2019[17]	Daniel 2020[16]	Daniel 2020[16]

BSA: body surface area, ES-SCLC: extensive-stage small cell lung cancer, N: number, SD: standard deviation

*Based on Weiss 2019

Table E3. Baseline Population Characteristics, Previously Treated ES-SCLC

	Total	Trilaciclib (N=32)	Placebo (N=29)
Age (Median)	63	62	64
Female, %	45%	31.3%	58.6%
BSA	Calculated	[redacted]	
Source	Average	Hart 2021	Hart 2021

BSA: body surface area, ES-SCLC: extensive-stage small cell lung cancer, N: number

*Assumed same as first line

Table E4. Baseline Population Characteristics, E-BC

	Total (N=221)	Plinabulin + Pegfilgrastim (N=111)	Pegfilgrastim (N=110)
Mean age (years)	49.2	48.5	50.0
Female	100%	100%	100%
Mean BSA (m^2)	1.713	1.692	1.734
Source	PROTECTIVE-2 manufacturer data submission	PROTECTIVE-2 manufacturer data submission	PROTECTIVE-2 manufacturer data submission

BSA: body surface area, E-BC: early breast cancer, N: number

Treatment Strategies

Two interventions are considered:

- Trilaciclib 240 mg/m^2 IV (Cosela™, G1 Therapeutics, Inc.)
- Plinabulin 40 mg IV (BeyondSpring, Inc.) plus pegfilgrastim 6 mg SC

Trilaciclib has been approved for an indication that does not involve prophylactic administration of granulocyte colony-stimulating factor (G-CSF), and so is compared to placebo (i.e., standard care/no prophylaxis). Plinabulin + pegfilgrastim is compared to standard dose (6 mg SC) pegfilgrastim (brand name or biosimilars) alone. Pegfilgrastim for prophylaxis is administered the day after chemotherapy. Due to differences in populations and comparators, plinabulin and trilaciclib are not compared to each other.

Pegfilgrastim was represented by a market basket of commercially available branded and biosimilar products and the Onpro® injector device.

- Pegfilgrastim (Neulasta®, Amgen Inc.)
- Pegfilgrastim (Neulasta® Onpro®, Amgen Inc.)
- Pegfilgrastim-apgf (Nyvepria™, Pfizer Inc.)
- Pegfilgrastim-bmez (Ziextenzo®, Sandoz)
- Pegfilgrastim-cbqv (Udenyca®, Coherus BioSciences)
- Pegfilgrastim-jmdb (Fulphila®, Viatris Inc.)

E2. Model Inputs and Assumptions

Key model inputs and assumptions are listed in the main text in Section 4.2. Additional assumptions are listed below.

Table E5. Additional Model Assumptions

Assumption	Rationale
Equal cost of myelosuppressive events across cancer types and lines of therapy	Simplifying assumption
Equal utility assumed for first line ES-SCLC and previously treated ES-SCLC	Due to limited data separating by line of therapy, assumed equal baseline utility and disutility
Long-term utility in E-BC based on population norms	Some sources provide a utility estimate for long-term post discontinuation among E-BC survivors which is higher than the assumed population average, but this does not take into consideration utility decline with age. In lieu of this adjustment and to align with evLY calculations, the population average was assumed.
No modeling of anemia or thrombocytopenia in the E-BC population	Lack of data from the PROTECTIVE-2 trial and no anticipated treatment benefit for plinabulin
Cost of trilaciclib rounded up to the nearest whole vial	Account for wastage; this strategy is supported by Centers for Medicare and Medicaid Services for reimbursement of trilaciclib.[62]

E-BC: early breast cancer, ES-SCLC: extensive-stage small cell lung cancer

Model Inputs

Clinical Inputs

Clinical Probabilities/Response to Treatment

For trilaciclib in first line ES-SCLC, pooled data from the two first line trials was used to inform the proportion of patients experiencing myelosuppressive events by cycle (Manufacturer Data Submission).[16,17] The proportion of patients who use G-CSF and ESAs was taken directly from the trials, independent of the proportion of patients experiencing severe myelosuppressive events. Health state utility during chemotherapy and post-chemotherapy was taken from a real-world analysis of EQ-5D scores among Canadian SCLC patients with extensive disease at encounter for the chemotherapy health state and progressive disease for the post-discontinuation health state.[36] Disutility for neutropenia, febrile neutropenia, and anemia (using fatigue as a proxy) was taken from a study using a time trade-off approach to value non-small cell lung cancer toxicities.[37] Although this study also presented disutility for bleeding, not all Grade 3 and 4 thrombocytopenia results in bleeding. Therefore, disutility for severe thrombocytopenia was taken from a study of UK patients with chronic lymphocytic leukemia.

Table E6. Clinical Inputs for First Line ES-SCLC

Parameter	Trilaciclib	No Prophylaxis	Source
Severe neutropenia, cycle 1	5.6%	41.1%	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Severe neutropenia, cycle 2	3.5%	27.9%	
Severe neutropenia, cycle 3	5.0%	22.9%	
Severe neutropenia, cycle 4	6.8%	16.3%	
Severe anemia, cycle 1	1.1%	1.1%	
Severe anemia, cycle 2	1.2%	5.8%	
Severe anemia, cycle 3	3.8%	8.4%	
Severe anemia, cycle 4	5.5%	10.0%	
Severe thrombocytopenia, cycle 1	0.0%	0.0%	
Severe thrombocytopenia, cycle 2	0.0%	4.7%	
Severe thrombocytopenia, cycle 3	0.0%	6.0%	
Severe thrombocytopenia, cycle 4	0.0%	7.5%	
Severe neutropenia and anemia, cycle 1	0.0%	0.0%	
Severe neutropenia and anemia, cycle 2	1.2%	1.2%	
Severe neutropenia and anemia, cycle 3	1.3%	2.4%	
Severe neutropenia and anemia, cycle 4	0.0%	1.3%	
Severe neutropenia and thrombocytopenia, cycle 1	0.0%	8.9%	
Severe neutropenia and thrombocytopenia, cycle 2	0.0%	0.0%	
Severe neutropenia and thrombocytopenia, cycle 3	0.0%	3.6%	
Severe neutropenia and thrombocytopenia, cycle 4	0.0%	3.8%	
Severe anemia and thrombocytopenia, cycle 1	1.1%	0.0%	
Severe anemia and thrombocytopenia, cycle 2	1.2%	1.2%	
Severe anemia and thrombocytopenia, cycle 3	0.0%	2.4%	
Severe anemia and thrombocytopenia, cycle 4	1.4%	1.3%	
Severe neutropenia, anemia and thrombocytopenia, cycle 1	0.0%	1.1%	
Severe neutropenia, anemia and thrombocytopenia, cycle 2	0.0%	1.2%	
Severe neutropenia, anemia and thrombocytopenia, cycle 3	0.0%	1.2%	

Parameter	Trilaciclib	No Prophylaxis	Source
Severe neutropenia, anemia and thrombocytopenia, cycle 4	0.0%	0.0%	
Proportion of severe neutropenia which is febrile neutropenia	5.3% (95% CI 0.2%, 10.4%)	2.7% (95% CI: 1.2% to 4.2%)	Pooled data from 1L trials (Manufacturer Data Submission)[20] (95% CI calculated)
Duration of neutropenia and febrile neutropenia disutility	21 days		Aligns with health state disutilities[37]
Proportion of severe febrile neutropenia which is hospitalized	100%	100%	Assumption
Proportion of severe non-febrile neutropenia which is hospitalized	0%	4.5% (SE 0.2%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Use of G-CSF	RR 0.454 (95% CI: 0.294 to 0.701)	54.4% (95% CI: 49.2% to 59.6%)	Pooled data from 1L trials (Manufacturer Data Submission)[20] (RR calculated)
Proportion of severe anemia which is hospitalized	6.7% (95%CI: 0.2% to 13.2%)	15.6% (95%CI: 9.2% to 22.0%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Duration of severe anemia disutility	21 days		Aligns with health state disutilities[37]
RBC transfusions per severe anemia episode	66.7% (95%CI: 54.5% to 78.9%)	62.5% (95%CI: 53.9% to 71.1%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
RBC units per transfusion	1.70 (SE 0.1)	1.85 (SE 0.1)	(Manufacturer Data Submission)[20]
Proportion of patients using ESAs	4.3% (95% CI: 2.2% to 6.4%)	8.9% (95% CI: 5.9% to 11.9%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Proportion of severe thrombocytopenia which is hospitalized	0%	8.3% (95%CI: 3.7% to 12.9%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Duration of thrombocytopenia disutility	21 days		Aligns with health state disutilities[37]

Parameter	Trilaciclib	No Prophylaxis	Source
Proportion of severe thrombocytopenia episodes with platelet transfusions	33.3% (95%CI: 6.1% to 60.5%)	5.6% (95%CI: 1.8% to 9.4%)	Pooled data from 1L trials (Manufacturer Data Submission)[20]
Platelet units per transfusion	1.0 (SE 0.1)	1.5 (SE 0.1)	(Manufacturer Data Submission)[20]
Occurrence of bone pain attributable to G-CSF	5% (SE 0.3%)		Difference from placebo in the Neulasta prescribing information
Completion of 1 chemotherapy cycle	100.0%	100.0%	Exponential drop off between 100% at one cycle and proportion of patients completing four cycles Daniel 2020[16]
Completion of 2 chemotherapy cycles	94.0%	97.1%	
Completion of 3 chemotherapy cycles	90.4%	94.8%	
Completion of 4 chemotherapy cycles	84.6%	90.6%	
Median progression-free survival	5.4 months		Represented by the placebo arm Daniel 2020[16]

CI: confidence interval, ESA: erythropoiesis-stimulating agents, ES-SCLC: extensive-stage small cell lung cancer, G-CSF: granulocyte colony stimulating factor, RBC: red blood cell, RR: relative risk, SD: standard deviation

For trilaciclib in previously treated ES-SCLC, data was provided by the manufacturer to inform the proportion of patients experiencing myelosuppressive events by cycle based on the Hart 2020 study (Manufacturer Data Submission). The proportion of patients who use G-CSF and ESAs was taken directly from the trial. Due to limited data, utility and disutility for previously treated ES-SCLC was assumed to be the same as first line ES-SCLC.

Table E7. Clinical Inputs for Previously Treated ES-SCLC

Parameter	Trilaciclib	No Prophylaxis	Source
Severe neutropenia, cycle 1	34.4%	28.6%	(Manufacturer Data Submission Based on Hart 2020)[20]
Severe neutropenia, cycle 2	15.4%	36.4%	
Severe neutropenia, cycle 3	11.8%	25.0%	
Severe neutropenia, cycle 4	14.3%	25.0%	
Severe anemia, cycle 1	0.0%	10.7%	
Severe anemia, cycle 2	3.8%	4.5%	
Severe anemia, cycle 3	5.9%	12.5%	
Severe anemia, cycle 4	0.0%	8.3%	
Severe thrombocytopenia, cycle 1	9.4%	3.6%	

Parameter	Trilaciclib	No Prophylaxis	Source
Severe thrombocytopenia, cycle 2	15.4%	9.1%	
Severe thrombocytopenia, cycle 3	0.0%	18.8%	
Severe thrombocytopenia, cycle 4	7.1%	0.0%	
Severe neutropenia and anemia, cycle 1	0.0%	3.6%	
Severe neutropenia and anemia, cycle 2	3.8%	4.5%	
Severe neutropenia and anemia, cycle 3	0.0%	6.3%	
Severe neutropenia and anemia, cycle 4	7.1%	0.0%	
Severe neutropenia and thrombocytopenia, cycle 1	28.1%	28.6%	
Severe neutropenia and thrombocytopenia, cycle 2	11.5%	4.5%	
Severe neutropenia and thrombocytopenia, cycle 3	11.8%	6.3%	
Severe neutropenia and thrombocytopenia, cycle 4	0.0%	8.3%	
Severe anemia and thrombocytopenia, cycle 1	0.0%	0.0%	
Severe anemia and thrombocytopenia, cycle 2	3.8%	4.5%	
Severe anemia and thrombocytopenia, cycle 3	0.0%	0.0%	
Severe anemia and thrombocytopenia, cycle 4	7.1%	0.0%	
Severe neutropenia, anemia and thrombocytopenia, cycle 1	6.3%	21.4%	
Severe neutropenia, anemia and thrombocytopenia, cycle 2	0.0%	9.1%	
Severe neutropenia, anemia and thrombocytopenia, cycle 3	17.6%	6.3%	
Severe neutropenia, anemia and thrombocytopenia, cycle 4	0.0%	25.0%	

Parameter	Trilaciclib	No Prophylaxis	Source
Proportion of severe neutropenia which is febrile neutropenia	4.9% (95% CI: 1.5% to 8.3%)	14.3% (95% CI: 9.3% to 19.3%)	Manufacturer Data Submission Based on Hart 2020[18,20]
Duration of neutropenia and febrile neutropenia disutility	21 days		Aligns with health state disutilities[37]
Proportion of severe febrile neutropenia which is hospitalized	100%	100%	Assumption
Proportion of severe non-febrile neutropenia which is hospitalized	2.6% (SE 0.1%)	0%	Manufacturer Data Submission Based on Hart 2020[18,20]
Use of G-CSF	RR 0.763 (95% CI: 0.494 to 1.180)	65.5% (95% CI: 56.5% to 74.5%)	RR calculated based on proportions in Hart 2020[18,20]
Proportion of severe anemia which is hospitalized	0%	6.9% (95% CI: 2.2% to 11.6%)	Manufacturer Data Submission Based on Hart 2020[18,20]
Duration of severe anemia disutility	21 days		Aligns with health state disutilities[37]
RBC transfusions per severe anemia episode	80.0% (95% CI: 67.4% to 92.6%)	63.0% (95% CI: 53.7% to 72.3%)	Manufacturer Data Submission Based on Hart 2020[18,20]
RBC units per transfusion	1.75 (SE 0.1)	2.24 (SE 0.1)	Manufacturer Data Submission Based on Hart 2020[18,20]
Proportion of patients using ESAs	3.1% (95% CI: 0.0% to 6.2%)	20.7% (95% CI: 13.0% to 28.4%	Manufacturer Data Submission Based on Hart 2020[18,20]
Proportion of severe thrombocytopenia which is hospitalized	3.3% (95% CI: 0.0% to 6.6%)	3.2% (95% CI: 0.0% to 6.4%)	Manufacturer Data Submission Based on Hart 2020[18,20]
Duration of thrombocytopenia disutility	21 days		Aligns with health state disutilities[37]
Proportion of severe thrombocytopenia episodes with platelet transfusions	23.3% (95% CI: 15.6% to 31.0%)	38.7% (30.0%, 47.4%)	Manufacturer Data Submission Based on Hart 2020[18,20]
Platelet units per transfusion	8.0 (SE 0.4)	2.2 (SE 0.1)	Manufacturer Data Submission Based on Hart 2020[18,20]
Occurrence of bone pain attributable to G-CSF	5% (SE 0.3)		Difference from placebo in the Neulasta prescribing information

Parameter	Trilaciclib	No Prophylaxis	Source
Completion of 1 chemotherapy cycle	100.0%	100.0%	Mean (SD) of 5 (4.4) cycles in the trilaciclib arm and 4 (3.4) in the placebo arm. Proportions assuming a normal distribution, but capping at four cycles to reflect contemporary treatment practice based on manufacturer feedback [18,20]
Completion of 2 chemotherapy cycles	75.2%	72.2%	
Completion of 3 chemotherapy cycles	67.5%	61.6%	
Completion of 4 chemotherapy cycles	59.0%	50.0%	

CI: confidence interval, ESA: erythropoiesis-stimulating agents, ES-SCLC: extensive-stage small cell lung cancer, G-CSF: granulocyte colony stimulating factor, RBC: red blood cell, RR: relative risk, SD: standard deviation

For plinabulin in E-BC, data from the single Phase III trial was used to inform the proportion of patients experiencing at least one grade 3 or 4 neutropenia episode.[18] Data submitted by the manufacturer are academic in confidence until publication of the full manuscript.

Table E8. Clinical Inputs for E-BC

Parameter	Plinabulin + Pegfilgrastim	Pegfilgrastim	Source
Proportion experiencing severe neutropenia	[redacted]		Manufacturer Data Submission[32]
Febrile neutropenia	3.6% of all patients	6.3% of all patients	Blayney 2020[22]
Duration of non-febrile neutropenia disutility	21 days		Assumed for the duration of 1 cycle
Duration of febrile neutropenia disutility	21 days		Assumed for the duration of 1 cycle
Proportion of severe febrile neutropenia which is hospitalized	[redacted]		Manufacturer Data Submission[32]
Proportion of severe non-febrile neutropenia which is hospitalized	0%	0%	Assumption
Occurrence of bone pain	18% (95% CI: 14.4% to 21.7%)	30% (95%CI: 25.6% to 34.4%)	Blayney 2020[22]

CI: confidence interval, E-BC: early breast cancer

Mortality

Overall mortality is based on mortality rates in each cancer type and line of therapy. In addition, a risk of mortality is applied for febrile neutropenia events.

For first line ES-SCLC, survival data is available from both trials with a maximum follow-up of 26 months. Although the overall survival data are not yet mature, our base case applies an exponential survival curve to the median overall survival of 12.8 months in the placebo arm from NCT03041311.[16] In both trials, trilaciclib had no statistically significant impact on overall survival (HR 0.87; 95% CI: 0.61 to 1.24 in Weiss 2019 and HR 0.92 [0.57 to 1.49] in Daniel 2020).[16,17]

Table E9. Mortality Inputs for First Line ES-SCLC

Parameter	Value	Source
Overall survival	Exponential curve applied median survival data for the placebo arm	Daniel 2020[16]
Probability of mortality during febrile neutropenia event (inpatient)	15.7% (95% CI 14.6%, 16.7%)	Dulisse 2013[39]
Probability of mortality during febrile neutropenia event (outpatient)	0% (range 0% to 0%)	Assumption based on Rolston 2010[63]

CI: confidence interval, ES-SCLC: extensive-stage small cell lung cancer

For previously treated ES-SCLC, complete survival data is available, with no patients surviving beyond 16 months in either treatment arm. Our base case applies an exponential survival curve to the median overall survival of six and a half months. In this study, the HR for OS for trilaciclib relative to placebo was 1.36 (95% CI: 0.96 to 2.01), indicating no direct treatment benefit.[18] Survival numerically favored placebo, potentially influenced by a baseline imbalance of prognostic factors.

Table E10. Mortality Inputs for Previously Treated ES-SCLC

Parameter	Value	Source
Overall survival	Exponential curve fit to published Kaplan-Meier data for the placebo arm	Hart 2021[18]
Probability of mortality during febrile neutropenia event (inpatient)	15.7% (95% CI: 14.6% to 16.7%)	Dulisse 2013[39]
Probability of mortality during febrile neutropenia event (outpatient)	0% (range 0% to 0%)	Assumption

CI: confidence interval, ES-SCLC: extensive-stage small cell lung cancer

For E-BC, the five-year relative survival is 89.2% (95% CI: 88% to 91%).[43] We applied this relative survival to age-specific population mortality for women in the United States.[64] A constant relative survival was assumed for the duration of the modeled time horizon. A HR for survival based on relative dose intensity of 1.32 is applied to the proportion of patients with RDI <85%.[44] Due to the plinabulin study design where no dose modifications were allowed on cycle 1 and patients were allowed to stop doxorubicin for any reason after cycle one, the proportion of patients with RDI <85% was similar across treatment arms (22.5% with RDI <85% vs. 22.7% with RDI <85% for plinabulin + pegfilgrastim vs. pegfilgrastim, respectfully).

Table E11. Mortality Inputs for E-BC

Parameter	Value	Source
Overall survival	5-Year relative survival applied to age and gender-specific US mortality	SEER[65], Mortality database[64]
Proportion of patients with RDI <85%	22.5% for plinabulin + pegfilgrastim 22.7% for pegfilgrastim alone	Manufacturer Data Submission[32]
Impact of RDI <85% on long-term survival (hazard ratio)	1.32 (range 1.0 to 1.8)	Lyman 2009[44]
Probability of mortality during febrile neutropenia event (inpatient)	5.6% (range 4.8% to 6.3%)	Dulisse 2013[39]
Probability of mortality during febrile neutropenia event (outpatient)	0% (range 0% to 0%)	Rolston 2010[63]

RDI: relative dose intensity

Utilities

For ES-SCLC, health state utility during chemotherapy and post-chemotherapy was taken from a real-world analysis of EQ-5D scores among Canadian SCLC patients with extensive disease at encounter for the chemotherapy health state and progressive disease for the post-discontinuation health state.[36] These data are recently published (2021) and have not yet been used in published models. Disutility for neutropenia, febrile neutropenia, and anemia (using fatigue as a proxy) was taken from Nafees 2017, a revision from the draft report which relied on Nafees 2008. This change in disutility in the revised report was driven by stakeholder feedback that Nafees 2017 reflected a more recent study with larger sample size.[37,66] Disutility for severe thrombocytopenia was taken from a study of UK patients with chronic lymphocytic leukemia which has been used in prior published models in a variety of cancers. Due to limited data, the same utility values were used for first line ES-SCLC and previously treated ES-SCLC.

Table E12. Utility Values for ES-SCLC Health States

Parameter	Value	Source
Utility on chemotherapy, no event	0.706 (95% CI: 0.670 to 0.740)	Kuehne 2021[36]
Utility post-discontinuation	0.674 (95% CI: 0.610 to 0.740)	Kuehne 2021[36]
Disutility, non-febrile neutropenia	-0.350 (SE 0.011)	Nafees 2017[37]
Disutility, febrile neutropenia	-0.470 (SE 0.008)	Nafees 2017[37]
Disutility, anemia	-0.290 (SE 0.009)	Nafees 2017[37]
Disutility, thrombocytopenia	-0.108 (95% CI: -0.097 to -0.119)	Tolley 2013[38]

CI: confidence interval, ES-SCLC: extensive-stage small cell lung cancer, SE: standard error

Utility inputs for on-treatment, post-discontinuation, febrile neutropenia, and bone pain were informed by the results of a linear regression analysis conducted using EQ-5D-5L scores collected in the PROTECTIVE-2 study of plinabulin in E-BC.[32] The EQ-5D-5L data from the trial were converted to health utility using the US health utility weights from Pickard 2019.[41] The coefficient for severe non-febrile neutropenia was not statistically significant and was assumed at zero.

Table E13. Utility Values for E-BC Health States

Parameter	Value	Source
Utility on chemotherapy, no event	0.9170	Manufacturer Data Submission[32]
Utility post-discontinuation, years 1-5	0.8588	Manufacturer Data Submission[32]
Utility post-discontinuation, years 5+	0.851 (SE 0.006)	Jiang 2021[42]
Disutility, non-febrile neutropenia	-0.000	Manufacturer Data Submission[32]
Disutility, febrile neutropenia	-0.1891 (SE 0.0288)	Manufacturer Data Submission[32]

E-BC: early breast cancer, SE: standard error

Adverse Events

Specific AEs related to chemotherapy outside of severe myelosuppressive events are not included in the model. Although the incidence of serious hematologic AEs was lower, the rate of overall serious AEs was higher in the trilaciclib arms in the pooled analysis of all three trials.[7] However, no single specific serious AE was elevated in patients taking trilaciclib enough to have an anticipated impact on cost effectiveness. AE rates were also lower for trilaciclib compared with placebo in NCT03041311 and NCT02499770.[7,16] For plinabulin, published data for specific serious AEs related to plinabulin are not yet available, but aggregate rates of grade 3/4 AEs were lower in the plinabulin + pegfilgrastim arm compared with the pegfilgrastim arm.[22]

Bone pain was included as an AE associated with use of pegfilgrastim. Over the course of the PROTECTIVE-2 trial, bone pain was experienced by 18% of patients on plinabulin + pegfilgrastim and 30% of patients on pegfilgrastim alone.[22] All bone pain experienced was grade 1 or 2. This proportion is applied in the model as the proportion of patients who experience bone pain at any given time while still on treatment. The occurrence of bone pain is not available directly from the trilaciclib trials. The occurrence of bone pain among patients initiating pegfilgrastim in ES-SCLC is assumed to equal the difference between placebo and pegfilgrastim in the Neulasta prescribing information (5%). Disutility from bone pain is taken from a manufacturer-submitted regression analysis of clinical trial data from PROTECTIVE-2. Disutility is applied for a duration of seven days. This assumption comes from a study of patients experiencing bone pain where pain was still present, but declining at day seven.[67]

Table E14. Adverse Events

Adverse Events	Rate: Plinabulin + Pegfilgrastim	Rate: Pegfilgrastim	Cost	Disutility
Bone pain, ES-SCLC	N/A	5%	$0	-0.018 (SE 0.011)
Bone pain, E-BC	30%	18%	$0	-0.018 (SE 0.011)

E-BC: early breast cancer, ES-SCLC: extensive-stage small cell lung cancer, SE: standard error

Economic Inputs

Drug Acquisition Costs

With the exception of ESAs, all drugs considered in the model are costed based on CMS average sales price (ASP) + a 6% markup, reflecting current reimbursement practice.[40] The cost of pegfilgrastim is informed by a market basket of commercially available branded and biosimilar products and the Neulasta® Onpro® injector device.[68] Use of trilaciclib was rounded up to the nearest whole vial to account for wastage.

Table E15. Drug Cost Inputs

Drug	ASP + 6% per mg	mg Per Dose	Doses Per Cycle	Net Price per Cycle
Trilaciclib, 1L ES-SCLC	$4.971	600*	3	$8,948
Trilaciclib, 2L+ ES-SCLC	$4.971	600*	5	$14,900
Plinabulin (E-BC)	Not applicable	40	1	Not applicable
Neulasta®	-	6	1	$2,222
Neulasta® Onpro®	-	6	1	$2,222
Pegfilgrastim-apgf	-	6	1	$3,416†
Pegfilgrastim-bmez	-	6	1	$2,945†
Pegfilgrastim-cbqv	-	6	1	$2,669†
Pegfilgrastim-jmdb	-	6	1	$2,534†

ASP: average sales price, E-BC: early breast cancer, ES-SCLC: extensive-stage small cell lung cancer, mg: milligram
*Rounded up to 600 (two 300 mg vials) to account for wastage.
†ASP + 6% of the Neulasta ASP

Table E16. Drug Costs for ESAs

Drug	WAC	Discount	Net Price per Cycle
Darbepoetin alfa (SC) 500 mcg	$3,870.00	64.4%	$1,378*
Epoetin alfa (SC) (Epogen) 10000 u/1 ml	$165.80	58.5%	$619†
Epoetin alfa (SC) (Procrit) 10000 u/1 ml (6)	$1,603.50	61.2%	$933†
Epoetin alfa-epbx (SC) 10000 u/1 ml (10)	$1,103.00	40.8%	$587†

ESA: erythropoiesis-stimulating agent, SC: subcutaneous, WAC: wholesale acquisition cost
*Every three weeks
†10,000 units three times weekly

Table E17. Drug Costs for Chemotherapy[40]

Drug	mg Per Dose	Doses per Cycle	ASP + 6% per Dose	Net Price per Cycle
Docetaxel 75 mg/m^2	128	1	$61	$61
Doxorubicin 50 mg/m^2	86	1	$2,013	$2,013
Cyclophosphamide 500 mg/m^2	857	1	$250	$250
Etoposide 100 mg/m^2	190	3	$15	$45
Carboplatin AUC 5	Assume 750	1	$40	$40
Atezolizumab 1200 mg	1200	1	$9,570	$9,570
Topotecan 1.5 mg/m^2	2.85	5	$22	$109

ASP: average sales price, mg: milligram

Administration and Monitoring Costs

As patients are already undergoing IV administration for chemotherapy, each additional IV administration for trilaciclib or plinabulin incurred an additional cost of $32.10 based on the CMS physician fee schedule CPT code 96365. Each next-day subcutaneous administration of pegfilgrastim has a cost of $14.31 based on the CMS physician fee schedule CPT code 96372 and a return office visit cost of $131.20 (CPT 99214). Additional administration costs for the Onpro® injector device are reimbursable for outpatient physicians but covered under a bundled payment for outpatient hospital administration and not separately reimbursable.[69] The base-case analysis assumes an additional administration cost for the Onpro® injector device.

Table E18. Administration Costs

Cost per Administration	CPT	Amount	Source
IV administration (chemotherapy)	96413	$148.30	CMS[70]
IV administration (additional infusion)	96367	$32.10	CMS[40]
SC administration (non-chemotherapy)	96372	$14.31	CMS[70]
Neulasta® Onpro® administration	96372 96377	$14.31 $20.24	CMS[70]
Next day follow-up visit	99214	$131.20	CMS[70]

CMS: Centers for Medicare and Medicaid Services, CPT: Current Procedural Terminology, IV: intravenous, SC: subcutaneous

Monitoring Costs

No specific monitoring costs are included outside of those captured within the cost of severe myelosuppressive events.

Health Care Utilization Costs

Future related health care costs were applied after discontinuation of chemotherapy by a per-cycle cost of subsequent treatment. Annual costs of continuing care for patients <65 years of age for lung cancer and breast cancer were inflated to 2021 USD and converted to a per-cycle cost.[71] Costs were applied as a weighted average of males and females based on baseline patient demographics used in the model to generate estimates for post-discontinuation cost of first line ES-SCLC ($9,483 per year), previously-treated ES-SCLC ($9,582 per year), and E-BC ($2,700 per year).

Cost of severe myelosuppressive events outside of ESAs, pegfilgrastim, and transfusions are based on whether the event is managed in an ambulatory care setting or results in hospitalization. All values were inflated to 2021. Cost of febrile and non-febrile neutropenia were taken from a 2011 MarketScan analysis in the metastatic lung cancer population.[72]

The cost of severe anemia is taken from an analysis of a cohort of metastatic breast cancer patients newly initiating treatment within an integrated health care system between 2007 and 2011. The cost of non-hospitalized severe anemia was calculated by taking the total cost of care for outpatient + emergency department-managed anemia and dividing by the number of events. The cost of hospitalized severe anemia was calculated by taking the total cost of care for inpatient-managed anemia and dividing by the number of events. Both potentially include ESAs and transfusions, thus may overestimate the true cost of managing severe anemia as the cost of ESAs and transfusions are captured independently within the model.[35]

The cost of severe thrombocytopenia is taken from a claims analysis of patients with solid tumors and non-Hodgkin's lymphoma with evidence of chemotherapy-induced thrombocytopenia between 2010 and 2016.[73] Both outpatient and inpatient estimates include transfusions, and thus may overestimate the true cost of managing severe thrombocytopenia, as the cost of transfusions are captured independently within the model.

The cost of a red blood cell transfusion consisted of the cost of blood transfusion services (CPT 36430, $37.69) and a cost of $578 per unit.[70,74] This cost was based on a mean amount charged to the patient ($343.63 ± $135) in 2007 dollars, inflated to 2021 USD.

The cost of platelet transfusion consisted of blood transfusion services (CPT 36430, $37.69) and a cost of $655 per unit.[70,75] This cost per unit was based on mean cost per apheresis-derived unit in 2017 dollars ($592), inflated to 2021 USD.

Table E19. Myelosuppressive Event Health Care Utilization Cost Inputs

Parameter	Input (SE)	Source
Drug cost of G-CSF per cycle	$2,433 ($124)	Weighted average of available G-CSF products (ASP + 6%)[40]
Drug cost of ESAs per cycle	$879 ($45)	Weighted average net price of available ESA products (WAC minus Discount)
Severe non-febrile neutropenia, inpatient	$19,606 ($1,000)	Assumed to be the same as febrile neutropenia
Severe non-febrile neutropenia, outpatient	$1,461 ($75)	Weycker 2015[72]
Severe febrile neutropenia, inpatient	$19,606 ($1,000)	Weycker 2015[72]
Severe febrile neutropenia, outpatient	$1,461 ($75)	Weycker 2015[72]
Severe anemia, inpatient	$13,552 ($691)	Rashid 2016[35]
Severe anemia, outpatient	$419 ($21)	Rashid 2016[35]
Severe thrombocytopenia, inpatient	$40,567 ($2,070)	Weycker 2019[73]
Severe thrombocytopenia, outpatient	$1,286 ($66)	Weycker 2019[73]
RBC transfusion	$37.69 ($2)	CMS Physician Fee Schedule[70]
RBC cost per unit	$578 ($29)	Toner 2011[74]
Platelet transfusion	$37.69 ($2)	CMS Physician Fee Schedule[70]
Platelet cost per unit	$655 ($33)	Barnett 2018[75]

ASP: average sales price, CMS: Centers for Medicare & Medicaid Services, ESA: erythropoiesis-stimulating agents, G-CSF: granulocyte colony stimulating factor, RBC: red blood cell, SE: standard error, WAC: wholesale acquisition cost.

Adverse Event Costs

No adverse event costs are considered in the model.

Productivity Costs

A modified societal perspective including indirect costs is included as a scenario analysis. Inputs for this scenario for are presented in Table E20. Assumptions are intended to represent an average and may overestimate indirect costs by assuming each patient is employed or underestimate direct costs by failing to capture the full time required on behalf of the patient or caregiver (e.g., having to take the full day off of work to attend an appointment). Indirect cost of febrile neutropenia, severe anemia, and severe thrombocytopenia have been inflated to 2021 USD using the Personal Consumption Expenditures price index.

Table E20. Modified Societal Perspective Scenario Analysis Inputs

Parameter	Value	Source/Notes
Next day return to clinic for prophylactic pegfilgrastim (patient)	Calculated as 1.72 hours x average hourly wage of $30.85	Stephens 2016, BLS 2021[76,77]
Next day return to clinic for prophylactic pegfilgrastim (caregiver)	Calculated as 2/3 of patients requiring a caregiver x 1.72 hours x average hourly wage of $30.85	Stephens 2016, BLS 2021[76,77]
Severe neutropenia	$5,482	Assumed equal to severe anemia
Febrile neutropenia	$6,201*	Represented by a cohort of ovarian cancer patients; inflated to 2021 USD[78]
Severe anemia	$5,482*	Represented by a cohort of ovarian cancer patients; inflated to 2021 USD[78]
Severe thrombocytopenia	$6,926*	Represented by a cohort of ovarian cancer patients; inflated to 2021 USD[78]
Red blood cell transfusion	Calculated as 4 hours per unit of red blood cells administered x average hourly wage of $30.85	BLS 2021, MSKCC 2021[77,79]
Platelet transfusion	Calculated as 1 hour per unit of platelets administered x average hourly wage of $30.85	BLS 2021, MSKCC 2021[77,79]

*Inflated to 2021 using most recent annual estimate from the Personal Consumption Expenditures – Health Care

E3. Results

Description of evLYs Gained Calculations

The cost per equal value of life years (evLYs) gained considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive evLYs gained.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[41,42]

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLY gained).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arms.

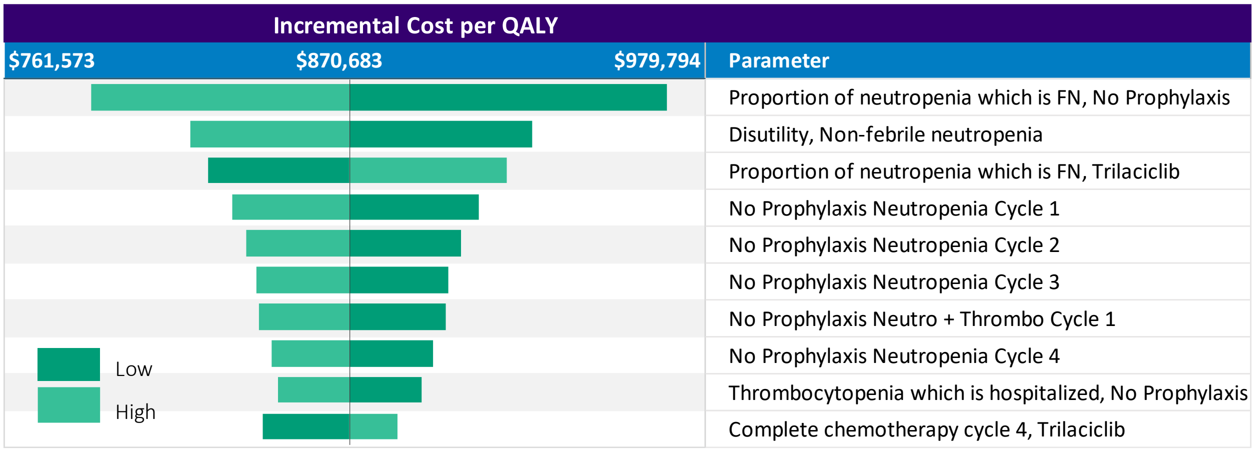
E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., 95% confidence intervals) or a range of ±10% to evaluate changes in cost per additional QALY for trilaciclib and the threshold price per dose at a willingness to pay of $100,000 per QALY gained for plinabulin.

Trilaciclib in First Line ES-SCLC

The top 10 most impactful parameters on the incremental cost per QALY for trilaciclib compared to no prophylaxis in first-line ES-SCLC are presented in Figure E1 and Table E22 for the health care system perspective and Figure E2 and Table E23 for the modified societal perspective. The most impactful model parameter was the proportion of neutropenia which is febrile neutropenia in the no prophylaxis arm, followed by the disutility of non-febrile severe neutropenia. The proportion of neutropenia which is febrile neutropenia in the trilaciclib arm, occurrence of severe neutropenia in the no prophylaxis arm, proportion of thrombocytopenia which is hospitalized, and proportion of patients completing all 4 chemotherapy cycles were among the top 10 most impactful parameters.

Figure E1. Tornado Diagram for Trilaciclib Compared to No Prophylaxis in First-Line ES-SCLC, Health Care System Perspective



ES-SCLC: extensive-stage small cell lung cancer, FN: febrile neutropenia, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years.

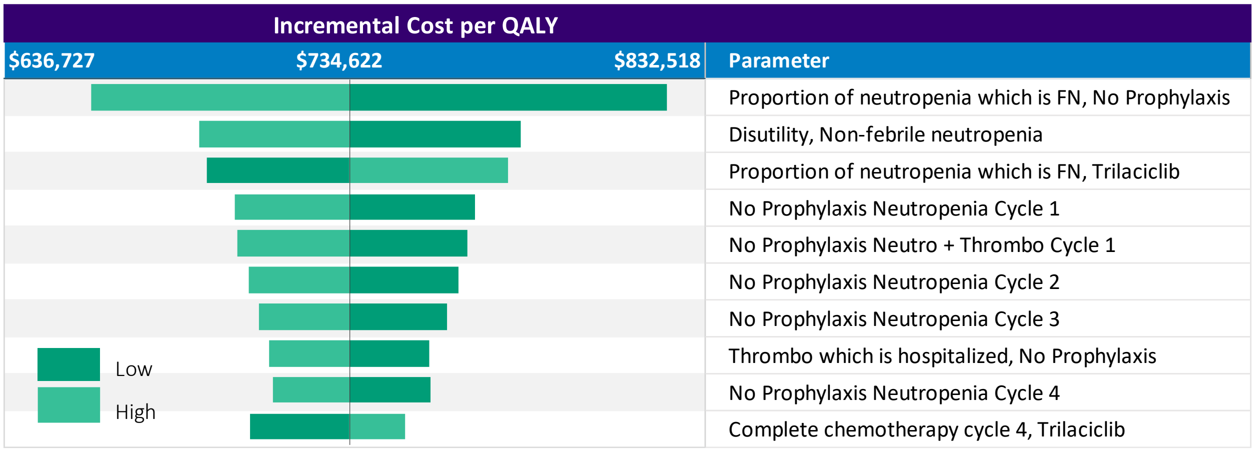
Table E21. Tornado Diagram Inputs and Results for Trilaciclib Compared to No Prophylaxis in First-Line ES-SCLC, Health Care System Perspective

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Proportion of neutropenia which is febrile neutropenia, no prophylaxis	$780,000	$980,000	1.2%	4.2%
Disutility of non-febrile severe neutropenia	$816,000	$933,000	-0.385	-0.315
Proportion of neutropenia which is febrile neutropenia, trilaciclib	$822,000	$925,000	0.2%	10.4%
No prophylaxis, neutropenia in cycle 1	$830,000	$915,000	35.9%	46.3%
No prophylaxis, neutropenia in cycle 2	$835,000	$909,000	23.2%	32.6%
No prophylaxis, neutropenia in cycle 3	$839,000	$905,000	18.5%	27.3%
No prophylaxis, neutropenia and thrombocytopenia in cycle 1	$840,000	$904,000	5.9%	11.9%
No prophylaxis, neutropenia in cycle 4	$844,000	$899,000	12.4%	20.2%
Proportion of thrombocytopenia which is hospitalized, no prophylaxis	$846,000	$895,000	3.7%	12.9%
Complete chemotherapy cycle 4, trilaciclib	$841,000	$887,000	76.1%	93.1%

ICER: incremental cost-effectiveness ratio, ES-SCLC: extensive-stage small cell lung cancer

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Figure E2. Tornado Diagram for Trilaciclib Compared to No Prophylaxis in First-Line ES-SCLC, Modified Societal Perspective



ES-SCLC: extensive-stage small cell lung cancer, FN: febrile neutropenia, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years.

Table E22. Tornado Diagram Inputs and Results for Trilaciclib Compared to No Prophylaxis in First-Line ES-SCLC, Modified Societal Perspective

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Proportion of neutropenia which is febrile neutropenia, no prophylaxis	$655,000	$833,000	1.2%	4.2%
Disutility of non-febrile severe neutropenia	$688,000	$788,000	-0.385	-0.315
Proportion of neutropenia which is febrile neutropenia, trilaciclib	$690,000	$784,000	0.2%	10.4%
No prophylaxis, neutropenia in cycle 1	$699,000	$773,000	35.9%	46.3%
No prophylaxis, neutropenia + thrombocytopenia in cycle 1	$700,000	$771,000	5.9%	11.9%
No prophylaxis, neutropenia in cycle 2	$704,000	$768,000	23.2%	32.6%
No Prophylaxis, neutropenia in cycle 3	$707,000	$764,000	18.5%	27.3%
Proportion of thrombocytopenia which is hospitalized, no prophylaxis	$710,000	$759,000	3.7%	12.9%
No prophylaxis, neutropenia in cycle 4	$711,000	$760,000	12.4%	20.2%

ICER: incremental cost-effectiveness ratio, ES-SCLC: extensive-stage small cell lung cancer

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

In probabilistic sensitivity analysis, no iterations resulted in an incremental cost per QALY of less than $200,000.

Table E23. Results of Probabilistic Sensitivity Analysis for Trilaciclib Compared to No Prophylaxis in First-Line ES-SCLC

	Trilaciclib		No Prophylaxis		Incremental	
	Mean	**95% Credible Range**	**Mean**	**95% Credible Range**	**Mean**	**95% Credible Range**
Health Care System Perspective						
Total Costs	$162,000	($151,000, $174,000)	$136,000	($125,000, $148,000)	$25,700	($22,100, $29,400)
Total QALYs	1.008	(0.890, 1.142)	0.979	(0.862, 1.110)	0.029	(0.025, 0.033)
ICER	-	-	-	-	$894,000	($725,000, $1,100,000)
Modified Societal Perspective						
Total Costs	$163,000	($152,000, $175,000)	$142,000	($130,000, $153,000)	$22,000	($17,800, $26,600)
Total QALYs	1.007	(0.877, 1.133)	0.978	(0.849, 1.103)	0.029	(0.025, 0.033)
ICER	-	-	-	-	$769,000	($601,000, $985,000)

QALY: quality-adjusted life years
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000. Incremental cost-effectiveness ratios rounded to the nearest $100,000.

Figure E3 and E4 presents cost-effectiveness clouds from the probabilistic sensitivity analysis. All iterations resulted in greater QALYs at greater cost for trilaciclib compared with no prophylaxis.

Figure E3. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Trilaciclib Compared to No Prophylaxis in First-Line ES-SCLC, Health Care System Perspective

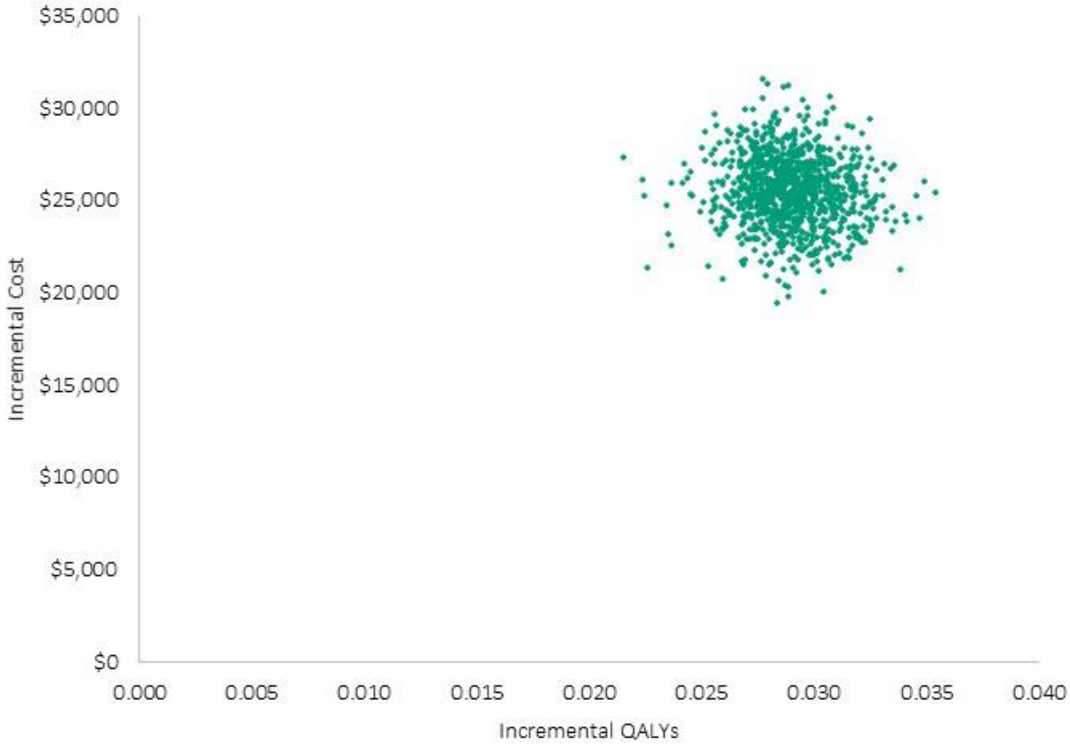
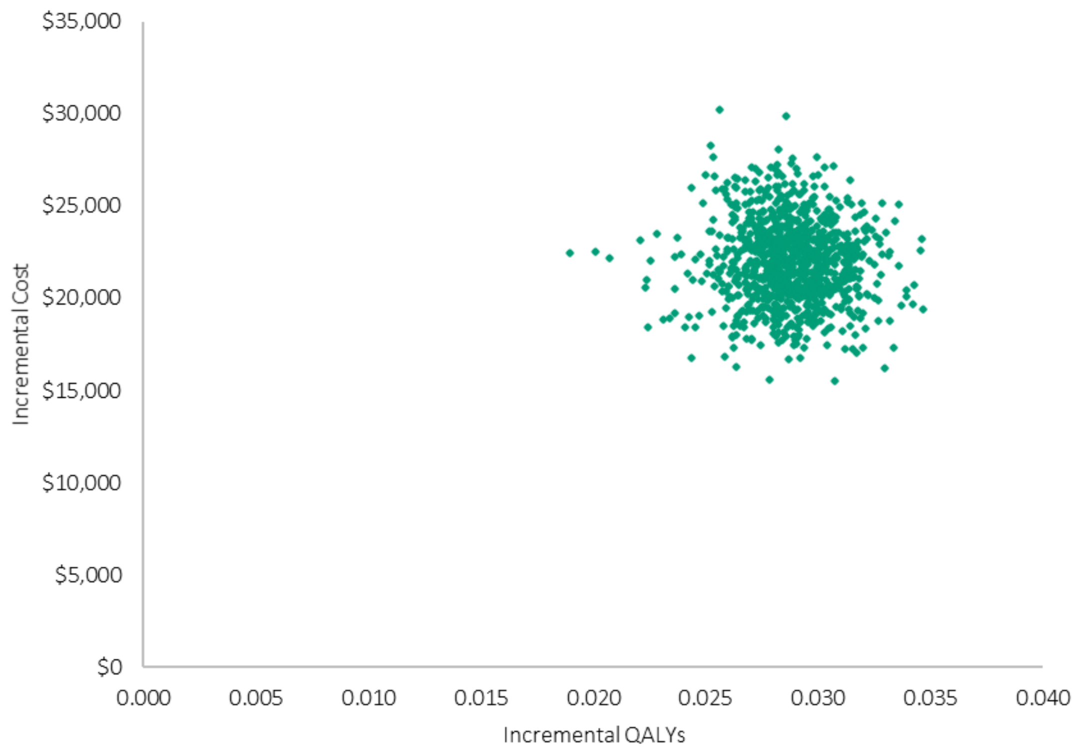


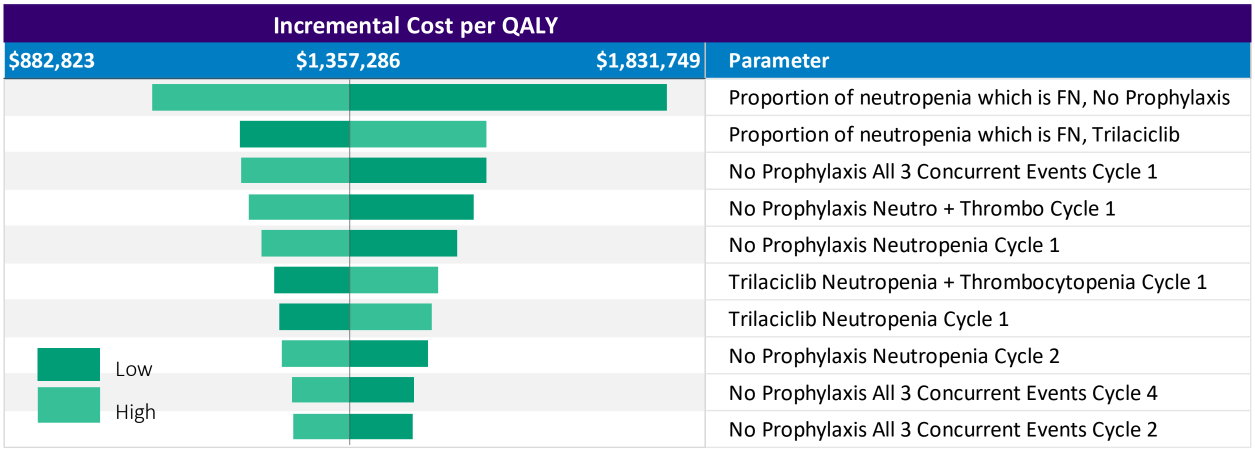
Figure E4. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Trilaciclib Compared to No Prophylaxis in First-Line ES-SCLC, Modified Societal Perspective



Trilaciclib in Previously Treated ES-SCLC

The top 10 most impactful parameters on the cost per QALY for trilaciclib compared to no prophylaxis in previously treated ES-SCLC are presented in Figure E5 and Table E24 for the health care system perspective and Figure E6 and Table E25 for the modified societal perspective. The most impactful model parameters were the proportion of severe neutropenia cases which were febrile neutropenia in each arm. The next most impactful parameters were the proportion of patients with myelosuppressive events in cycle 1, followed by other rates of severe myelosuppressive events.

Figure E5. Tornado Diagram for Trilaciclib Compared to No Prophylaxis in Previously Treated ES-SCLC, Health Care System Perspective



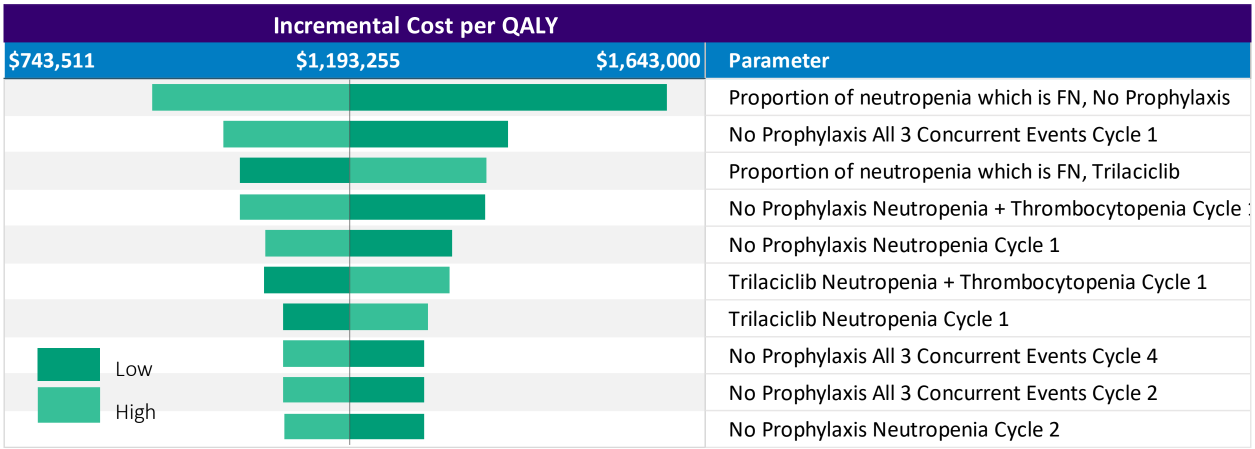
ES-SCLC: extensive-stage small cell lung cancer, FN: febrile neutropenia, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years.

Table E24. Tornado Diagram Inputs and Results for Trilaciclib Compared to No Prophylaxis in Previously Treated ES-SCLC, Health Care System Perspective

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Proportion of neutropenia which is febrile neutropenia, no prophylaxis	$1,100,000	$1,800,000	9.3%	19.3%
Proportion of neutropenia which is febrile neutropenia, trilaciclib	$1,200,000	$1,600,000	1.5%	8.3%
No prophylaxis all 3 concurrent events in cycle 1	$1,200,000	$1,600,000	13.6%	29.2%
No prophylaxis neutro + thrombo in cycle 1	$1,200,000	$1,500,000	20.1%	37.1%
No Prophylaxis, neutropenia in cycle 1	$1,200,000	$1,500,000	20.1%	37.1%
Trilaciclib, neutropenia + thrombocytopenia in cycle 1	$1,200,000	$1,500,000	20.2%	36.0%
Trilaciclib, neutropenia in Cycle 1	$1,300,000	$1,500,000	26.0%	42.8%
No prophylaxis, neutropenia in cycle 2	$1,300,000	$1,500,000	27.3%	45.5%
No prophylaxis, all 3 concurrent events in cycle 4	$1,300,000	$1,500,000	16.8%	33.2%
No prophylaxis, all 3 concurrent events in cycle 2	$1,300,000	$1,500,000	3.7%	14.5%

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Figure E6. Tornado Diagram for Trilaciclib Compared to No Prophylaxis in Previously Treated ES-SCLC, Modified Societal Perspective



ES-SCLC: extensive-stage small cell lung cancer, FN: febrile neutropenia, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years.

Table E25. Tornado Diagram Inputs and Results for Trilaciclib Compared to No Prophylaxis in Previously Treated ES-SCLC, Health Care System Perspective

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Proportion of neutropenia which is febrile neutropenia, no prophylaxis	$913,000	$1,600,000	9.3%	19.3%
No prophylaxis, all 3 concurrent events in cycle 1	$1,000,000	$1,400,000	13.6%	29.2%
Proportion of neutropenia which is FN, trilaciclib	$1,000,000	$1,400,000	1.5%	8.3%
No prophylaxis, neutropenia + thrombocytopenia in cycle 1	$1,000,000	$1,400,000	20.1%	37.1%
No prophylaxis, neutropenia in cycle 1	$1,100,000	$1,300,000	20.1%	37.1%
Trilaciclib, neutropenia + thrombocytopenia in cycle 1	$1,100,000	$1,300,000	20.2%	36.0%
Trilaciclib, neutropenia in cycle 1	$1,100,000	$1,300,000	26.0%	42.8%
No prophylaxis, all 3 concurrent events in cycle 4	$1,100,000	$1,300,000	16.8%	33.2%
No prophylaxis, all 3 concurrent events in cycle 2	$1,100,000	$1,300,000	3.7%	14.5%
No prophylaxis, neutropenia in cycle 2	$1,100,000	$1,300,000	27.3%	45.5%

ES-SCLC: extensive-stage small cell lung cancer, ICER: incremental cost-effectiveness ratio

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

In probabilistic sensitivity analysis, no iterations resulted in an incremental cost per QALY of less than $200,000.

Table E26. Results of Probabilistic Sensitivity Analysis for Trilaciclib Compared to No Prophylaxis in Previously Treated ES-SCLC

	Trilaciclib		No Prophylaxis		Incremental	
	Mean	95% Credible Range	Mean	95% Credible Range	Mean	95% Credible Range
Health Care System Perspective						
Total Costs	$65,200	($60,500, $70,500)	$26,500	($24,200, $29,200)	$38,700	($33,900, $44,200)
Total QALYs	0.500	(0.441, 0.569)	0.471	(0.411, 0.539)	0.030	(0.020, 0.040)
ICER	-	-	-	-	$1,400,000	($911,000, $2,000,000)
Modified Societal Perspective						
Total Costs	$74,300	($68,900, $81,000)	$40,000	($36,300, $44,000)	$34,000	($28,300, $40,200)
Total QALYs	0.500	(0.437, 0.567)	0.470	(0.410, 0.534)	0.030	(0.020, 0.040)
ICER	-	-	-	-	$1,200,000	($746,000, $1,900,000)

ES-SCLC: extensive-stage small cell lung cancer, ICER: incremental cost-effectiveness ratio, QALYs: quality-adjusted life years

Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000. Incremental cost-effectiveness ratios rounded to the nearest $100,000.

Figures E7 and E8 present cost-effectiveness clouds from the probabilistic sensitivity analysis. All iterations resulted in greater QALYs at greater cost for trilaciclib compared with no prophylaxis.

Figure E7. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Trilaciclib Compared to No Prophylaxis in Previously Treated ES-SCLC, Health Care System Perspective

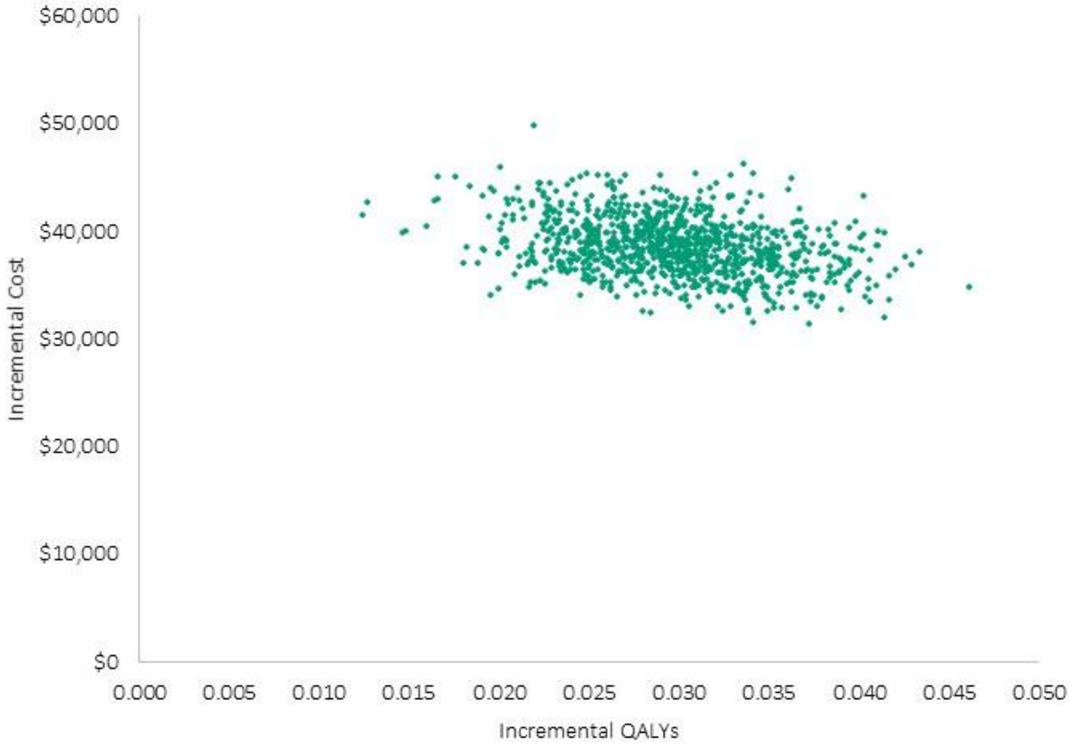
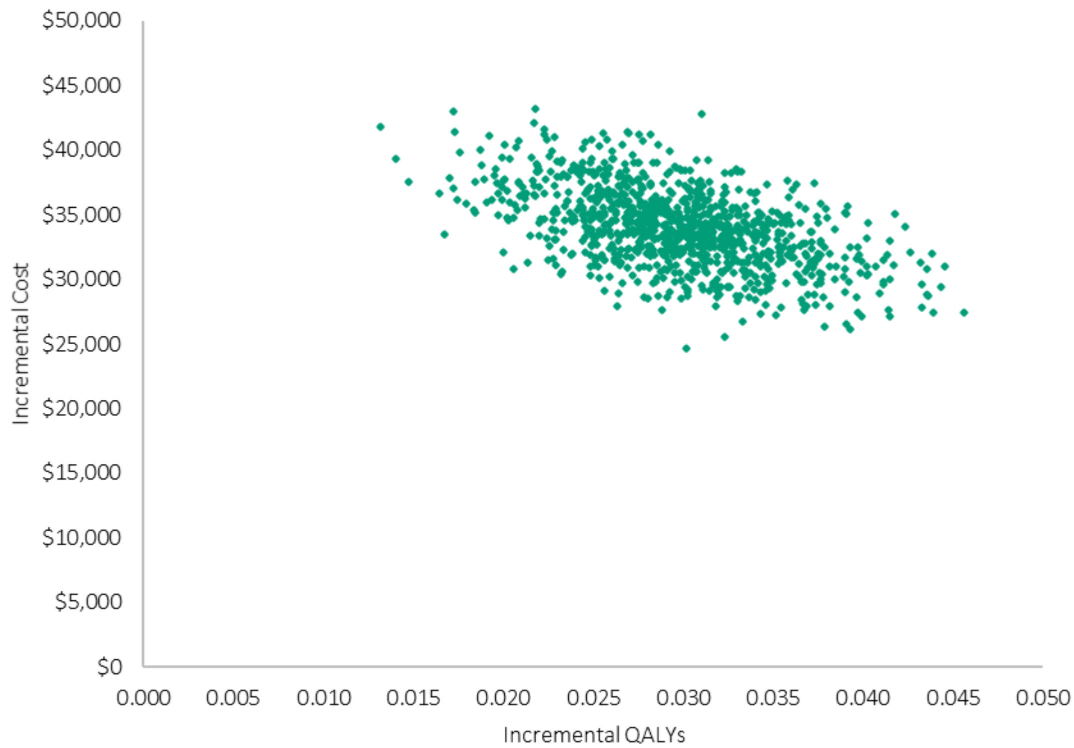


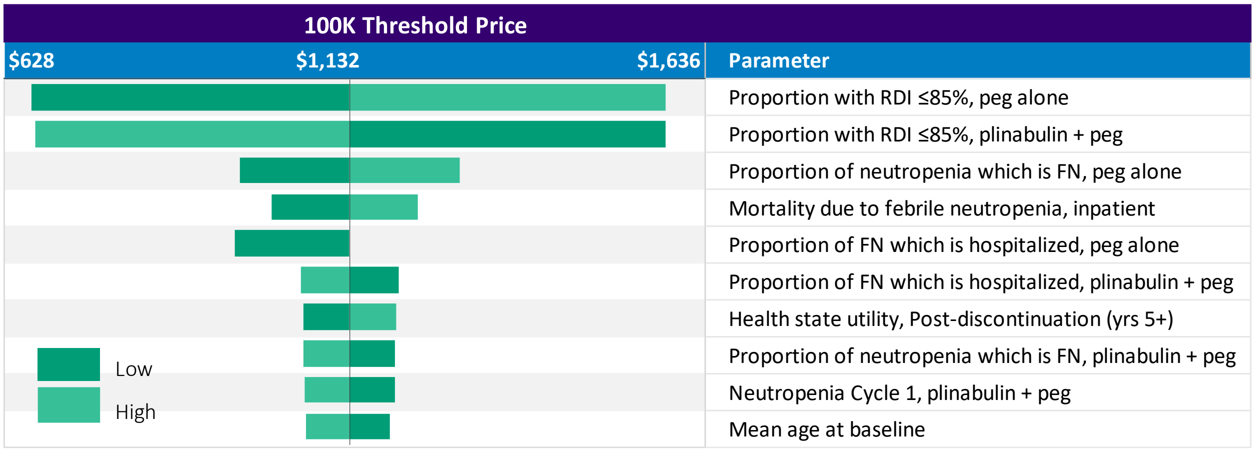
Figure E8. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Trilaciclib Compared to No Prophylaxis in Previously Treated ES-SCLC, Modified Societal Perspective



Plinabulin in E-BC

The top 10 most impactful parameters on the $100,000 per QALY threshold price per dose for plinabulin + pegfilgrastim compared with pegfilgrastim alone in E-BC are presented in Figure E9 and Table E28. The most impactful model parameters were the proportion of patients with RDI ≤85% in each treatment arm, suggesting that assumptions around potential impact on survival is a major model driver. The next most impactful parameters were related to febrile neutropenia: occurrence, mortality, and hospitalization rates, followed by long-term utility and mean age at baseline (parameters which would impact the number of QALYs gained from avoidance of febrile-neutropenia-related deaths). Lastly, the proportion of patients who completed chemotherapy cycle 4 (thus were at risk of events) was among the top 10 most impactful model parameters.

Figure E9. Tornado Diagram for Plinabulin + Pegfilgrastim Compared to Pegfilgrastim Alone in E-BC



E-BC: early breast cancer, FN: febrile neutropenia, peg: pegfilgrastim, RDI: relative dose intensity.

Table E27. Tornado Diagram Inputs and Results for Plinabulin + Pegfilgrastim Compared to Pegfilgrastim in E-BC

	Lower $100,000/QALY Threshold Price	Upper $100,000/QALY Threshold Price	Lower Input*	Upper Input*
Proportion with RDI ≤85%, pegfilgrastim alone	$630	$1,600	20.4%	25.0%
Proportion with RDI ≤85%, plinabulin + pegfilgrastim	$630	$1,600	20.3%	24.8%
Proportion of neutropenia which is febrile neutropenia, pegfilgrastim alone	$960	$1,300	[redacted]	
Mortality due to febrile neutropenia, inpatient	$1,000	$1,200	4.8%	6.3%
Proportion of febrile neutropenia which is hospitalized, pegfilgrastim alone	$950	$1,100	[redacted]	
Proportion of febrile neutropenia which is hospitalized, plinabulin + pegfilgrastim	$1,100	$1,200		
Health state utility, post-discontinuation (yrs 5+)	$1,100	$1,200	0.766	0.936
Proportion of neutropenia which is febrile neutropenia, plinabulin + pegfilgrastim	$1,100	$1,200	[redacted]	
Neutropenia in cycle 1, plinabulin + pegfilgrastim	$1,100	$1,200	75.5%	83.1%
Mean age at baseline	$1,100	$1,200	44.1	53.9

QALY: quality-adjusted life year

*Note lower input may reflect either upper or lower $100,000 per QALY threshold price value depending on the direction that the input has on the threshold price output.

Probabilistic sensitivity analysis was conducted to generate credible ranges around total costs and QALYs for each arm, as well as incremental costs and QALYs. Incremental cost-effectiveness ratios were not computed in the analysis of plinabulin.

Table E28. Results of Probabilistic Sensitivity Analysis for Plinabulin + Pegfilgrastim Compared to Pegfilgrastim in E-BC

	Plinabulin + Pegfilgrastim		Pegfilgrastim		Incremental	
	Mean	**95% Credible Range**	**Mean**	**95% Credible Range**	**Mean**	**95% Credible Range**
Neutropenia and Chemotherapy Costs*	$74,900	($69,600, $80,200)	$75,400	($70,100, $80,600)	-$460	(-$630, -$300)
Total QALYs	16.967	(16.511, 17.336)	16.928	(16.467, 17.293)	0.039	(0.011, 0.068)

E-BC: early breast cancer, QALYs: quality-adjusted life years
Costs rounded to the nearest $1,000.
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000.
* Neutropenia and chemotherapy-related cost do not include plinabulin acquisition costs and therefore these findings do not represent total cost of therapy with plinabulin.

E5. Scenario Analyses

Modified Societal Perspective

Inclusion of the indirect cost of lost productivity reduced the total incremental cost of trilaciclib relative to no prophylaxis and resulted in a lower incremental cost per QALY but did not differ in conclusions relative to the base case for both first line ES-SCLC and previously treated ES-SCLC Because the incremental cost per QALY varied by more than 20% and/or resulted in a difference of more than $200,000 per QALY gained for the modified societal perspective relative to base case, the societal perspective was included as co-base case for ES-SCLC.

Greater cost offsets in this scenario from the inclusion of indirect costs (Table E29) yielded similar threshold prices for plinabulin to achieve various willingness to pay thresholds relative to the health system case (Table E30).

Table E29. Results for Plinabulin in E-BC from the Modified Societal Perspective Scenario Analysis

Treatment	Neutropenia and Chemotherapy Cost	FN Events	Life Years	QALYs*	evLYs†
Plinabulin + pegfilgrastim	$75,400	0.036	19.891	16.959	16.959
Pegfilgrastim	$76,100	0.064	19.848	16.920	16.920
Incremental	-$700	-0.028	0.043	0.039	0.039

E-BC: early breast cancer, evLYs: equal-value life years, FN: febrile neutropenia, QALYs: quality-adjusted life years
Costs rounded to the nearest $1,000; incremental results may not match calculated results due to rounding
* Neutropenia and chemotherapy-related cost do not include plinabulin acquisition costs and therefore these findings do not represent total cost of therapy with plinabulin.
† Despite life extension with plinabulin, evLYs gained were the same as QALYs gained due to the use of a utility value for the best health state (utility post-discontinuation, years 5+) equal to that for population norms (0.851).

Table E30. QALY-Based Threshold Analysis Results for Plinabulin from the Modified Societal Scenario Analysis

	Price per Dose to Achieve $50,000 per QALY Gained	Price per Dose to Achieve $100,000 per QALY Gained	Price per Dose to Achieve $150,000 per QALY Gained	Price per Dose to Achieve $200,000 per QALY Gained
Base case	$630	$1,100	$1,600	$2,100
Modified societal	$680	$1,200	$1,700	$2,200

QALY: quality-adjusted life year

Additional Markup on G-CSF

It was noted during the analysis that the ASP for branded Neulasta is lower than the pegfilgrastim biosimilars and that facility markup on products may be substantial. Average markup on pegfilgrastim products was provided by OncoHealth. A scenario analysis was conducted in which this facility markup applied to ASP + 6%. Because both arms of plinabulin contain pegfilgrastim, this scenario has little impact on the analysis of plinabulin.

Table E31. Additional G-CSF Markup Scenario Analysis Inputs

Pegfilgrastim Product	Value	Source/Notes
Neulasta®	2.5x	OncoHealth Correspondence, November 2021
Neulasta® Onpro®	2.5x	
Pegfilgrastim-apgf	1.5x	
Pegfilgrastim-bmez	1.3x	
Pegfilgrastim-cbqv	1.6x	
Pegfilgrastim-jmdb	1.5x	

Inclusion of a higher markup on G-CSF reduced the total incremental cost of trilaciclib relative to no prophylaxis due to greater cost-offsets from a reduction in use of G-CSF with equal health outcomes in first line ES-SCLC (Table E32) and previously treated ES-SCLC (Table E33).

Table E32. Results for Trilaciclib in First Line ES-SCLC from the Additional G-CSF Markup Scenario Analysis

Treatment	Drug Cost	Total Direct Cost	Indirect Costs	Events	Life Years	QALYs	evLYs
Trilaciclib	$32,900	$163,100	$1,300	0.407	1.494	1.007	1.008
No Prophylaxis	$0	$139,200	$5,200	2.023	1.489	0.977	0.977
Incremental	$32,900	$23,900	-$4,000	-1.615	0.005	0.029	0.030

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years

Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Table E33. Results for Trilaciclib in Previously Treated ES-SCLC from the Additional G-CSF Markup Scenario Analysis

Treatment	Drug Cost	Total Direct Cost	Indirect Costs	Events	Life Years	QALYs	evLYs
Trilaciclib	$44,800	$68,000	$9,400	2.657	0.784	0.497	0.502
No Prophylaxis	$0	$30,000	$14,100	3.697	0.763	0.469	0.469
Incremental	$32,300	$38,000	-$4,700	-1.041	0.021	0.029	0.033

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years

Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Lower incremental costs in this scenario yielded a lower incremental cost per QALY for trilaciclib compared with no prophylaxis, but did not differ in conclusions relative to the base case (Table E34).

Table E34. Incremental Cost-Effectiveness Ratios for Trilaciclib from the Additional G-CSF Markup Scenario Analysis

	Comparator	Cost per Event Avoided	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$14,800	$818,000	$4,600,000	$793,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$36,500	$1,300,000	$1,800,000	$1,200,000
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$12,300	$682,000	$3,800,000	$661,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$32,000	$1,200,000	$1,600,000	$1,000,000

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years
Incremental cost-effectiveness ratios rounded to nearest $1,000 if <$1,000,000 or nearest $10,000 if >$1,000,000.

For plinabulin in E-BC, both treatment arms receive pegfilgrastim, thus this scenario had minimal impact on model results.

G-CSF Initiation in Cycle 1

The base-case analysis assumes that among ES-SCLC patients who initiate G-CSF, initiation is spread equally across cycles. A scenario analysis was conducted in which all patients who initiated G-CSF do so in cycle 1, thus incurring the cost of G-CSF over all four cycles. Because both arms of plinabulin contain pegfilgrastim started in cycle 1, this scenario has no impact on the analysis of plinabulin in E-BC.

Assuming all patients initiate G-CSF in cycle 1 reduced the total incremental cost of trilaciclib relative to no prophylaxis due to greater cost-offsets from a reduction in use of G-CSF with equal health outcomes in first line ES-SCLC (Table E35) and previously treated ES-SCLC (Table E36). However, differences from the base case were not detectable due to rounding.

Table E35. Results for Trilaciclib in First Line ES-SCLC from the G-CSF Initiation in Cycle 1 Scenario Analysis

Treatment	Drug Cost	Total Direct Cost	Indirect Cost	Events	Life Years	QALYs	evLYs
Trilaciclib	$32,900	$162,700	$1,300	0.407	1.494	1.007	1.008
No Prophylaxis	$0	$138,300	$5,200	2.023	1.489	0.977	0.977
Incremental	$32,900	$24,400	-$4,000	-0.1.615	0.005	0.029	0.030

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years

Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Table E36. Results for Trilaciclib in Previously Treated ES-SCLC from the G-CSF Initiation in Cycle 1 Scenario Analysis

Treatment	Drug Cost	Total Direct Cost	Indirect Cost	Events	Life Years	QALYs	evLYs
Trilaciclib	$44,800	$67,200	$9,400	2.657	0.784	0.497	0.502
No Prophylaxis	$0	$28,900	$14,100	3.697	0.762	0.469	0.469
Incremental	$44,800	$38,300	-$4,700	-1.041	0.021	0.029	0.033

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years

Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Lower incremental costs in this scenario yielded a lower incremental cost per QALY for trilaciclib compared with no prophylaxis, but did not differ in conclusions relative to the base case (Table E37).

Table E37. Incremental Cost-Effectiveness Ratios for Trilaciclib from the G-CSF Initiation in Cycle 1 Scenario Analysis

	Comparator	Cost per Event Avoided	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$15,100	$834,000	$4,700,000	$808,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$36,800	$1,300,000	$1,800,000	$1,200,000
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$12,600	$697,000	$3,900,000	$676,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$32,300	$1,200,000	$1,600,000	$1,000,000

ES-SCLC: extensive-stage small cell lung cancer, evLY: equal-value life year, G-CSF: granulocyte colony stimulating factor, QALYs: quality-adjusted life years

Incremental cost-effectiveness ratios rounded to nearest $1,000 if <$1,000,000 or nearest $10,000 if >$1,000,000.

Cost of Severe Myelosuppressive Events from Wong 2018[46]

The base-case analysis uses a microcosting approach to assign cost per severe myelosuppressive event episode. While we attempted to comprehensively capture costs, some costs (e.g., emergency room visits) were not explicitly accounted for. To explore the extent in which the full cost of myelosuppressive episodes was potentially underestimated in our model, we conducted a scenario analysis using cost data from Wong et al., a commonly-cited source for cost of AEs in oncology.[46] In this scenario, the individual cost of G-CSF, ESAs, and transfusions was removed from the model, as these costs would be captured in the macrocosting.

Table E38. Event Cost from Wong 2018 Scenario Analysis Inputs

Parameter	Value	Source/Notes
Severe non-febrile neutropenia, inpatient	$19,400	Wong 2018 inflated to 2021 USD[46]
Severe non-febrile neutropenia, outpatient	$6,008	
Severe febrile neutropenia, inpatient	$19,400	
Severe febrile neutropenia, outpatient	$6,008	
Severe anemia, inpatient	$22,877	
Severe anemia, outpatient	$4,915	
Severe thrombocytopenia, inpatient	$25,630	
Severe thrombocytopenia, outpatient	$7,142	

Inclusion of cost of myelosuppressive events from Wong et al. reduced the total incremental cost of trilaciclib relative to no prophylaxis due to greater cost-offsets from a reduction in myelosuppressive episodes with equal health outcomes in first line ES-SCLC (Table E39) and previously treated ES-SCLC (Table E40).

Table E39. Results for Trilaciclib in First Line ES-SCLC from Wong 2018 Scenario Analysis

Treatment	Drug Cost	Total Direct Cost	Indirect Cost	Events	Life Years	QALYs	evLYs
Trilaciclib	$32,900	$163,700	$1,300	0.407	1.494	1.007	1.008
No Prophylaxis	$0	$145,200	$5,200	2.023	1.489	0.977	0.977
Incremental	$32,900	$18,500	-$4,000	-1.615	0.005	0.029	0.030

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, QALYs: quality-adjusted life years
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Table E40. Results for Trilaciclib in Previously Treated ES-SCLC from Wong 2018 Scenario Analysis

Treatment	Drug Cost	Total Cost	Indirect Cost	Events	Life Years	QALYs	evLYs
Trilaciclib	$44,800	$77,600	$9,400	2.657	0.784	0.497	0.502
No Prophylaxis	$0	$43,000	$14,100	3.697	0.762	0.469	0.469
Incremental	$32,300	$35,000	-$4,700	-1.041	0.021	0.029	0.033

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, QALYs: quality-adjusted life years
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Lower incremental costs in this scenario yielded a lower incremental cost per QALY for trilaciclib compared with no prophylaxis, but did not differ in conclusions relative to the base case (Table E41).

Table E41. Incremental Cost-Effectiveness Ratios for Trilaciclib from Wong 2018 Scenario Analysis

	Comparator	Cost per Event Avoided	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$11,400	$632,000	$3,600,000	$613,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$33,000	$1,200,000	$1,600,000	$1,100,000
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$9,000	$496,000	$2,800,000	$481,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$28,600	$1,000,000	$1,400,000	$911,000

ES-SCLC: extensive-stage small cell lung cancer, evLY: equal-value life year, QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000 if <$1,000,000 or nearest $10,000 if >$1,000,000.

Inclusion of cost of myelosuppressive events from Wong et al. resulted in similar cost outcomes relative to the base case with equal health outcomes in E-BC (Table E42).

Table E42. Results for Plinabulin in E-BC from Wong 2018 Scenario Analysis

Treatment	Neutropenia and Chemotherapy Cost	FN Events	Life Years	QALYs	evLYs
Plinabulin + pegfilgrastim	$78,400	0.036	19.891	16.959	16.959
Pegfilgrastim alone	$79,400	0.064	19.848	16.920	16.920
Incremental	-$1,000	-0.028	0.043	0.039	0.039

E-BC: early breast cancer, evLYs: equal-value life years, FN: febrile neutropenia, QALYs: quality-adjusted life years

Greater cost-offsets in this scenario yielded higher threshold prices for plinabulin to achieve various willingness to pay thresholds relative to the base case (Table E43).

Table E43. QALY-Based Threshold Analysis Results for Plinabulin from Wong 2018 Scenario Analysis

	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Base case	$630	$1,100	$1,600	$2,100
Wong 2018 scenario	$770	$1,300	$1,800	$2,300

QALY: quality-adjusted life year

Probability of Hospitalization Due to Severe Myelosuppressive Events from Rashid 2016[35]

The base-case analysis uses data from the trilaciclib and plinabulin clinical trials to assign a probability of hospitalization per severe myelosuppressive event, by treatment arm. As a scenario analysis, we instead derived the probability of hospitalization from an analysis of claims data of a cohort of metastatic breast cancer patients initiating 1L treatment in order to be more reflective of real-world practice.[35] Cost of myelosuppressive events in the model for health states where more than one myelosuppressive event is present are additive. Therefore, the estimates for single episodes were used to derive probabilities rather than multiple episodes. In this study, 16 of 203 episodes of care for neutropenia resulted in hospitalization, (7.9%), 46 of 947 episodes of care for anemia resulted in a hospitalization (4.9%), and 7 of 108 episodes of thrombocytopenia resulted in hospitalization (6.5%). These probabilities were applied to both intervention and comparator arms for ES-SCLC and E-BC. Assumptions for hospitalization of febrile neutropenia remained the same as the base case.

The scenario with hospitalization rates from Rashid et al. resulted in similar costs with equal health outcomes in first line ES-SCLC (Table E44) and previously treated ES-SCLC (Table E45).

Table E44. Results for Trilaciclib in First Line ES-SCLC from Rashid 2016 Scenario Analysis

Treatment	Drug Cost	Total Direct Cost	Indirect Cost	Events	Life Years	QALYs	evLYs
Trilaciclib	$32,900	$162,100	$1,300	0.407	1.494	1.007	1.008
No Prophylaxis	$0	$136,300	$5,200	2.023	1.489	0.977	0.977
Incremental	$32,900	$25,800	-$4,000	-1.615	0.005	0.029	0.030

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, QALYs: quality-adjusted life years
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Table E45. Results for Trilaciclib in Previously Treated ES-SCLC from Rashid 2016 Scenario Analysis

Treatment	Drug Cost	Total Direct Cost	Indirect Cost	Events	Life Years	QALYs	evLYs
Trilaciclib	$44,800	$68,000	$9,400	2.657	0.784	0.497	0.502
No Prophylaxis	$0	$29,900	$14,100	3.697	0.762	0.469	0.469
Incremental	$32,300	$38,100	-$4,700	-1.041	0.021	0.029	0.033

ES-SCLC: extensive-stage small cell lung cancer, evLYs: equal-value life years, QALYs: quality-adjusted life years
Costs rounded to nearest $100 if <$100,000 or nearest $1,000 if >$100,000; incremental results may differ from calculated results from the table due to rounding.

Results did not differ in conclusions relative to the base case (Table E46).

Table E46. Incremental Cost-Effectiveness Ratios for Trilaciclib from Rashid 2016 Scenario Analysis

	Comparator	Cost per Event Avoided	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Health Care System Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$16,000	$883,000	$5,000,000	$856,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$36,600	$1,300,000	$1,800,000	$1,200,000
Modified Societal Perspective					
Trilaciclib, 1L ES-SCLC	No Prophylaxis	$13,500	$747,000	$4,200,000	$724,000
Trilaciclib, 2L+ ES-SCLC	No Prophylaxis	$32,100	$1,200,000	$1,600,000	$1,000,000

ES-SCLC: extensive-stage small cell lung cancer, evLY: equal-value life year, QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000 if <$1,000,000 or nearest $10,000 if >$1,000,000.

Probability of hospitalization per non-febrile neutropenia event from Rashid et al. resulted in similar cost outcomes relative to the base case with equal health outcomes in E-BC (Table E47).

Table E47. Results for Plinabulin in E-BC from Rashid 2016 Scenario Analysis

Treatment	Neutropenia and Chemotherapy Cost	FN Events	Life Years	QALYs	evLYs
Plinabulin + pegfilgrastim	$76,000	0.036	19.891	16.959	16.959
Pegfilgrastim alone	$76,600	0.064	19.848	16.920	16.920
Incremental	-$650	-0.028	0.043	0.039	0.039

E-BC: early breast cancer, evLYs: equal-value life years, FN: febrile neutropenia, QALYs: quality-adjusted life years
incremental results may differ from calculated results from the table due to rounding.

Greater cost-offsets in this scenario yielded higher threshold prices for plinabulin to achieve various willingness to pay thresholds relative to the base case (Table E48).

Table E48. QALY-Based Threshold Analysis Results for Plinabulin from Rashid 2016 Scenario Analysis

	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Base case	$630	$1,100	$1,600	$2,100
Rashid 2016 scenario	$670	$1,200	$1,700	$2,200

QALY: quality-adjusted life year

E6. Heterogeneity and Subgroups

Other than distinguishing between first- and subsequent-line ES-SCLC, no subgroup analyses were conducted.

E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings as well as a comparison of the number of outcomes experienced over four cycles generated by the model against the clinical trial publications. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

One manufacturer-sponsored published model assessed the cost effectiveness of trilaciclib in first line ES-SCLC based on the Daniel 2020 study.[80] This model was similar in structure to ours but generated a lower QALY gain compared to no prophylaxis (0.005 in Abraham 2021 vs. 0.029 in our model). This difference is primarily driven by the use of utility values from the literature applied to severe myelosuppressive events in our model versus utility by treatment arm derived directly from the clinical trial in Abraham 2021. This suggests that our model may overestimate the QALY gains with trilaciclib in 1L ES-SCLC Greater incremental QALYs in our model can also potentially be attributable to the longer time horizon used to capture LYs and QALYs gained from avoiding febrile-neutropenia related deaths. Using lower estimates for disutility for myelosuppressive events such as those from Nafees 2008[66], excluding febrile-neutropenia mortality or shortening the time horizon in our model resulted in a nearly identical QALY gain as the Abraham 2021 model (0.006). Both models found that administration of trilaciclib prior to chemotherapy was associated with fewer myelosuppressive events compared with administration of chemotherapy alone, with some differences, potentially due to Abraham 2021 relying on data from Daniel 2020 and our model using pooled data from both first line studies (Daniel 2020 and Weiss 2019).

Table E49. Comparison of Myelosuppressive Event Outcomes

	Trilaciclib vs. no Prophylaxis (Difference)	
	Abraham 2021	**ICER 2022**
Neutropenia	0.3 vs. 1.5 (-1.2)	0.2 vs. 1.23 (-1.0)
Febrile neutropenia	0.02 vs. 0.1 (-0.1)	0.01 vs. 0.03 (-0.02)
Anemia	0.3 vs. 0.5 (-0.2)	0.16 vs. 0.36 (-0.2)
Thrombocytopenia	0.03 vs. 0.7 (-0.6)	0.03 vs. 0.40 (-0.37)

The result of this model differ substantially from ours in terms of cost outcomes, where Abraham 2021 found trilaciclib to be cost saving versus ours which found that trilaciclib had higher total costs compared with no prophylaxis. One difference is that the Abraham 2021 study used the WAC price without consideration of discounts for the price of pegfilgrastim ($5,733), approximately twice as high as the ASP + 6% price. However, the cost of treated AEs was the major driver. Costs were based on Wong 2018, a scenario analysis included in this evaluation which yielded similar results to the base case.

Although not explicitly stated, the cost per event assumptions used in the Abraham 2021 model assume that all Grade 3/4 events considered within the model are hospitalized events, with an assumed cost of $21,089 per neutropenia episode, $22,563 per febrile neutropenia episode, $24,868 per anemia episode, and $27,860 per thrombocytopenia episode. Our model differs from this assumption in that our model assumes that the majority of events (other than febrile neutropenia) are managed on an outpatient basis. This is supported by outcomes in the Daniel 2020 trial which show few hospitalizations relative to the number of severe events. In this trial, 11.3% of patients in the placebo arm were hospitalized due to myelosuppressive events versus 3.8% in the trilaciclib arm. This equates to an absolute difference of 7.5%, or the cost savings of 0.075 hospitalizations averted (~$1,875 assuming ~$25,000 per hospitalization). In Abraham 2021, essentially the cost of 2.1 hospitalizations are averted if each myelosuppressive event was assigned cost of a hospitalization (~$52,500 assuming ~$25,000 per hospitalization). Moreover, the cost of AE management for these four AEs in the no prophylaxis arm is estimated at $64,139 over 12 weeks, a cost burden which is substantially higher than estimated in prior models of etoposide + platinum in first line ES-SCLC (for example, etoposide-platinum cost of AEs was $978 in another published cost-effectiveness model).[81,82] The estimated cost of managing these four adverse events in Abraham 2021 exceeds the total cost of the etoposide-platinum arm including AEs in all other recently-published models of first line etoposide-platinum in ES-SCLC ($11,874[83]; $17,067[84]; $24,582[82]; $30,558[85] except one that also assumed a very high cost of AEs ($73,038).[86]

The majority of prior analyses have found primary prophylaxis to be a cost-effective intervention. However, LYs, QALYs, and evLYs gained from avoidance of febrile neutropenia-related deaths is highly dependent on the life expectancy of patients and few models have focused on a metastatic cancer population. One published study evaluated the cost effectiveness of primary prophylaxis with pegfilgrastim in patients with advanced ovarian cancer treated with docetaxel or topotecan.

These patients had a median life-expectancy of six to 13 months, similar to that of previously treated and first line ES-SCLC, respectively.[87] Results of the analysis in advanced ovarian cancer yielded an incremental cost per QALY gained for pegfilgrastim primary prophylaxis versus secondary prophylaxis of $7,900 ($9,179 2021 USD). The difference in findings between this analysis and our analysis in ES-SCLC can primarily be attributed to the differences in inputs (e.g., baseline febrile neutropenia episodes [~0.40 in advanced ovarian cancer vs. 0.03-0.25 in ES-SCLC] and cost of prophylaxis) rather than structural differences or assumptions. If we adapt our model to generate a similar number of febrile neutropenia episodes in the no prophylaxis arm as the model by Fust et al., the cost per QALY for trilaciclib falls below the $150,000 per QALY threshold for first line ES-SCLC.

No published economic models were identified for plinabulin. Prior models of the cost effectiveness of primary prophylaxis in E-BC for the prevention of neutropenia have found prophylaxis to be cost effective or generate greater QALYs at lower cost compared to no prophylaxis. Our model takes a similar approach to these models in regard to structure, assumptions, and inputs, except that plinabulin is applied in addition to ongoing prophylaxis with pegfilgrastim. Prior models compare pegfilgrastim primary prophylaxis to secondary prophylaxis or no prophylaxis. As a result, the number of febrile neutropenia episodes in our comparator arm (pegfilgrastim only in the PROTECTIVE-2 study) is much lower than that in the comparator arm of prior economic evaluations, and thus fewer febrile neutropenia events are avoided. In general, our model is consistent with prior models in that prophylaxis is likely to be cost effective if a survival benefit is assumed based on impact on RDI[3,88,89] but not cost-effective based on QALYs alone without any impact on survival outside of febrile neutropenia-related deaths.[88] Due to trial design, we were unable to assess impact of plinabulin on RDI at the time of analysis.

F. Potential Budget Impact: Supplemental Information

Methods

This potential budget impact analysis includes the estimated number of individuals in the US who would be eligible for treatment with plinabulin in the E-BC population. To estimate the size of the potential candidate populations for plinabulin treatment, we used inputs for the projected total US population size from 2021 to 2025 (~339 million)[90], proportion female (50.8%)[91], E-BC incidence (~163 per 100,000 adult females per year)[92,93] proportion of patients utilizing chemotherapy (66.7%)[94], proportion of chemotherapy patients on regimens with high risk for neutropenia (48.1%)[94], proportion of chemotherapy patients on regimens with intermediate risk for neutropenia (16.5%)[95], and a real world neutropenia prophylaxis rate in patients on an intermediate risk chemotherapy regimen risk (18.7%).[95] Applying these values results in estimates of 60,600 incident patients in the US per year. For the purposes of this analysis, we assumed that one cohort of incident patients would initiate treatment in each of the five years, for a total of 303,000 patients over five years. All patients were assumed to remain in the cumulative patient pool over the time horizon due to high 5-year survival rates in E-BC.

The intervention under examination in the budget impact analysis was plinabulin added to pegfilgrastim therapy, while the comparator was pegfilgrastim alone. Market shares were not included within the model, as all eligible E-BC patients were assumed to switch from pegfilgrastim to plinabulin added to pegfilgrastim.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[96,97] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent five-year period for which data were available, and the contribution of spending on retail and facility-based drugs to total health care spending over the most recent five-year period for which data were available.

Results

Table F1 illustrates the per-patient budget impact calculations on an average annual basis for the plinabulin prices to reach $150,000, $100,000, and $50,000 per QALY ($1,600 per unit, $1,100 per unit, and $630 per unit, respectively) for plinabulin plus pegfilgrastim compared to pegfilgrastim alone.

Table F1. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Plinabulin Plus Pegfilgrastim vs. Pegfilgrastim Alone

	Average Annual Per-Patient Budget Impact					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**5-Year Average**
$150,000 per QALY	$5,800	$2,900	$1,900	$1,500	$1,200	$2,660
$100,000 per QALY	$3,900	$1,900	$1,300	$1,000	$800	$1,780
$50,000 per QALY	$1,900	$900	$600	$500	$400	$860

QALY: quality-adjusted life year