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

Revised Background and Scope

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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 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.[4]

The risk for chemotherapy-induced neutropenia (CIN) and other myelosuppressive effects varies by the type of chemotherapy used and patient characteristics.[5-7] Guidelines recommend that granulocyte colony stimulating factor (G-CSF, most commonly filgrastim or pegfilgrastim) be routinely used to decrease neutropenia in patients at high risk for CIN (>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).[8,9] 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 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, 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.[10,11] Finally, G-CSF only improves neutrophil counts. Patients could potentially benefit from more convenient and less toxic therapies to prevent CIN and potentially other cell lines 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 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 has received breakthrough designation from the FDA and is currently under review (anticipated FDA decision November 30, 2021), is a selective immunomodulating microtubule-binding agent (SIMBA) for the prevention of CIN and possibly thrombocytopenia. In addition to their impact on myelosuppression, both drugs may have direct anti-cancer effects.

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 4 hours prior to chemotherapy
Plinabulin	Selective microtubule-binding agent	40 mg IV with chemotherapy

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, including patients, patient organizations, clinicians, researchers, and the manufacturers of the therapies under review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

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 Onpro® device, which allows for home administration of G-CSF, but this device may fail with some frequency. In some cases, patients can be taught to self-administer G-CSF or home nursing can be arranged.

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.[12] 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.[13]

We received several comments highlighting the differences in the populations studied, which makes indirect comparisons between the novel agents of interest methodologically unsound. We have clarified in the scope that given the lack of comparable populations, we do not plan to do perform a network meta-analysis in this review.

In response to comments, we have added several additional outcomes such as chemotherapy discontinuation, platelet transfusions, use of G-CSF, use of ESAs, and we gave examples of the domains of quality of life that are relevant to this review.

We also heard that we should include the anti-cancer effects of plinabulin. We will summarize the data for context, but the study was for a different cancer type using different dosing, so will have only peripheral impact on the assessments in the report.

Finally, we received helpful suggestions about the structure of the cost-effectiveness modeling which have been incorporated and will be described in detail in the forthcoming model analysis plan.

Report Aim

This project will evaluate the health and economic outcomes of trilaciclib and plinabulin for chemotherapy-induced neutropenia. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. However, our initial review of available data and study populations suggests that formal, quantitative indirect comparisons of the interventions of interest will not be feasible. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults ≥18 years of age with ECOG performance status of 0 to 2 at intermediate or high risk for CIN.

Interventions

The full list of interventions is as follows:

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

Comparators

Data permitting, we intend to compare 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 will be 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 will be derived from studies of at least one month's duration.

Settings

All relevant settings will be considered, including both inpatient and outpatient.

Potential Other Benefits and Contextual Considerations

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 would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen. For example, avoiding a second trip to an infusion center for pegfilgrastim infusion one day after chemotherapy.
Health inequities
Other (as relevant): For example, both drugs have potential anti-cancer effects that are not captured in the model; the novel mechanism of action of both drugs.

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions. We heard that the potential incremental societal value from greater health equity and fairness from plinabulin may be difficult to fully capture in structured cost-effectiveness analysis and should be noted here. In addition, because the risk of missing G-CSF administrations is expected to disproportionately impact patients with sub-optimal access to healthcare services, plinabulin may play a role in reducing inequities in cancer care

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of the treatments of interest relative to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of prevention of CIN, with expansion of this conceptual framework to consider impact on other myelosuppressive

events such as anemia and thrombocytopenia.[14-23] The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. Costs and outcomes will be discounted at 3%. We anticipate that the modeled patient populations and comparators will align with the available data from clinical trials for plinabulin in early-stage breast cancer and trilaciclib in extensive-stage small cell lung cancer.

A Markov model will be developed with likely health states based on initial chemotherapy, severe neutropenia requiring hospitalization and/or initiation of G-CSF, anemia requiring hospitalization and/or initiation of erythropoietin stimulating agents (ESAs) and/or red blood cell transfusion, thrombocytopenia requiring hospitalization and/or platelet transfusion, experiencing two of these severe myelosuppressive events, experiencing all of these myelosuppressive events, post-initial chemotherapy, and death. A subset of severe neutropenia cases will experience febrile neutropenia, with an associated risk of death. Severe myelosuppressive events may result in dose delay, dose reduction, or discontinuation of chemotherapy and a resulting impact on survival. A cohort of patients will transition between states during predetermined cycles of 21 days (coinciding with chemotherapy regimen cycles) over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost effectiveness will be estimated for shorter time horizons (e.g., five years). Our analysis will focus on the approved labeled indication for trilaciclib and anticipated labeled indication for plinabulin. Plinabulin + pegfilgrastim will be compared to pegfilgrastim alone administered the day after chemotherapy, represented as a market basket consisting of branded and biosimilar products and the Onpro® wearable kit. Trilaciclib will be compared to best supportive care (i.e., no prophylactic treatment).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using the proportion of patients experiencing severe myelosuppressive episodes (neutropenia, including febrile neutropenia, anemia, and thrombocytopenia) for interventions and comparators from the individual clinical trials. Data permitting, we will also consider treatment effectiveness in terms of avoiding dose delays and dose reductions (and improvement in survival related to avoiding dose reductions), red blood cell transfusions, platelet transfusions, use of G-CSF, bone pain, and other serious myelosuppressive events. Although both plinabulin and trilaciclib have reported potential anti-cancer effects, it is not anticipated that the available evidence at the time of this review will be sufficient to model this as a direct treatment benefit in the populations of interest.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of febrile neutropenia events avoided, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYGs). Quality of life weights will be applied to each health state, including quality of life decrements for serious myelosuppressive episodes. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and cost of treating serious myelosuppressive episodes (e.g., hospitalization, G-CSF, ESAs). In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments and individual in-trial comparators. Results will be expressed in terms of the incremental cost per QALY gained, cost per evLYG, cost per life year gained, and cost per febrile neutropenia event avoided.

In separate analyses, we will explore the potential health care system budgetary impact of these treatments over a five-year time horizon, utilizing published or otherwise publicly available information on the potential populations eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

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 additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by plinabulin or trilaciclib, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of chemotherapy-induced neutropenia beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

Examples might include these from the American Society of Clinical Oncology Choosing Wisely Recommendations[24]:

- 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.

And these from the American Society of Breast Surgeons[25]:

- Don’t routinely order breast MRI in new breast cancer patients.

- Don’t routinely excise all lymph nodes beneath the arm in patients having lumpectomy for breast cancer

- Don’t routinely order specialized tumor gene testing in all new breast cancer patients.

- Don’t routinely re-operate on patients with invasive cancer if the cancer is close to the edge of the excised lumpectomy tissue.

- Don’t routinely perform a double mastectomy in patients who have a single breast with cancer.

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. 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.
5. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology (Williston Park).* 2015;29(4):282-294.
6. 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.
7. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. *Oncologist.* 2005;10(6):427-437.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. Liu Z, Doan QV, Malin J, Leonard R. The economic value of primary prophylaxis using pegfilgrastim compared with filgrastim in patients with breast cancer in the UK. *Appl Health Econ Health Policy.* 2009;7(3):193-205.

17. Hill G, Barron R, Fust K, et al. Primary vs secondary prophylaxis with pegfilgrastim for the reduction of febrile neutropenia risk in patients receiving chemotherapy for non-Hodgkin's lymphoma: cost-effectiveness analyses. *J Med Econ.* 2014;17(1):32-42.
18. Lee EK, Wong WW, Trudeau ME, Chan KK. Cost-effectiveness of prophylactic granulocyte colony-stimulating factor for febrile neutropenia in breast cancer patients receiving FEC-D. *Breast Cancer Res Treat.* 2015;150(1):169-180.
19. Ramsey SD, Liu Z, Boer R, et al. Cost-effectiveness of primary versus secondary prophylaxis with pegfilgrastim in women with early-stage breast cancer receiving chemotherapy. *Value Health.* 2009;12(2):217-225.
20. Aarts MJ, Grutters JP, Peters FP, et al. Cost effectiveness of primary pegfilgrastim prophylaxis in patients with breast cancer at risk of febrile neutropenia. *J Clin Oncol.* 2013;31(34):4283-4289.
21. Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer in the United Kingdom. *Value Health.* 2011;14(4):465-474.
22. Silber JH, Fridman M, Shpilsky A, et al. Modeling the cost-effectiveness of granulocyte colony-stimulating factor use in early-stage breast cancer. *J Clin Oncol.* 1998;16(7):2435-2444.
23. Bojke L, Sculpher M, Stephens R, Qian W, Thatcher N, Girling D. Cost effectiveness of increasing the dose intensity of chemotherapy with granulocyte colony-stimulating factor in small-cell lung cancer: based on data from the Medical Research Council LU19 trial. *Pharmacoeconomics.* 2006;24(5):443-452.
24. American Society of Clinical Oncology. *Ten Things Physicians and Patients Should Question.* 2019.
25. American Society of Breast Surgeons. *Five Things Physicians and Patients Should Question.* 2021.