SUMMARY

For more than 15 years, Neulasta[®] (pegfilgrastim) has been the preferred option for reducing the risk of CIN. Neulasta[®] is indicated to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of FN. Neulasta[®] has been shown to reduce FN hospitalizations by 93% and increase patients' odds of maintaining relative dose intensity (RDI) by 48%.^{1,2} It is also the most affordable drug of its class, priced at \$2,222 per cycle compared to biosimilars costing as much as \$3,416 per cycle.³ To ameliorate the burden of next-day administration of Neulasta[®], Amgen has developed Neulasta[®] Onpro[®], an on-body injector that allows for convenient at-home administration, and importantly, ensures that patients not only receive prophylaxis, but also receive it at the right time.

In the Draft Report, ICER has appropriately reaffirmed next-day pegfilgrastim as the current standard for preventing neutropenia. ICER has also appropriately estimated the incidental increase in bone pain directly attributable to pegfilgrastim as 5%, noting it is successfully treated primarily with OTC medications, and amended the pricing of Neulasta[®] and Neulasta[®] Onpro[®] as it is the lowest priced pegfilgrastim of its class.

To further optimize the accuracy of ICER's Report, we offer the following recommendations:

- 1. The device failure rate is over-estimated, which misaligns with current evidence and underrepresents the value of Neulasta.
 - We request that ICER amend the Neulasta[®] Onpro[®] device failure rate to <1% based on review of 30,000 devices used in the real world data that Amgen has submitted to a health authority and for presentation at scientific congresses.
- 2. The FDA CRL, after a thorough evaluation of the submission, offer ICER the opportunity to re-assess its comparative clinical benefit rating and anchor to the current information available.
 - We request that ICER adjust the rating to "Insufficient", until additional data are available.

Below we expand on these recommendations in more detail.

RECOMMENDATIONS

- 1. The device failure rate is over-estimated, which misaligns with the available evidence and underrepresents the value of Neulasta.
 - We request that ICER amend the Neulasta[®] Onpro[®] device failure rate to <1% based on review of 30,000 devices used in the real world data that Amgen has submitted to a health authority and for presentation at scientific congresses.

The Neulasta[®] Onpro[®] device offers a convenient option for the crucial next-day delivery of pegfilgrastim. The upper bound device failure rate cited in ICER's *Draft Evidence Report* (6.9% of cycles) is taken from a study with a very low sample size in which Townley *et al.*⁴ reported 4 of the 58 patients (where only 2 of the failures can be directly attributable to the Onpro[®] device) experienced a failure of the device in one cycle without providing the number of total cycles. Given that patients receive multiple cycles with a new device in each cycle, this per patient failure rate overestimates the incidence of device failure.⁵ Several other sources suggest an even lower likelihood of device failure, ranging from 0.1% to 1.92%.^{6,7,8}

Recently Amgen evaluated data from over 33K Onpro® devices used in the real world, which reaffirms the consistent reliability of the device. We recommend ICER update its comments regarding the reliability of the device as the data unequivocally demonstrate that in >98% of cases, pegfilgrastim is successfully administered. These data were submitted to ICER as 'Academic In Confidence' as they were also submitted to a health authority and accepted for presentation at an upcoming 2022 scientific conference.

- 2. The FDA CRL, after a thorough evaluation of the submission, offer ICER the opportunity to re-assess its comparative clinical benefit rating and anchor to the current information available.
 - We request that ICER adjust the rating to "Insufficient", until additional data are available.

ICER's draft report should align with the FDA's recent determination that data for plinabulin was *"not sufficiently robust to demonstrate benefit".*⁹ The insufficiency of data for plinabulin warrants a rating of "I" rather than "C++," which should be reserved for treatments with more definitive clinical advantages and complete evidence package. As ICER has indicated, key data points are not yet available for plinabulin, which, in addition to the completed trials' small sample sizes, plinabulin's trials add considerable uncertainty to the clinical and economic assessment. In the interest of safeguarding the reliability and consistency of assessments, this is an opportunity for ICER to follow its own framework with a rating that acknowledges additional evidence is needed regarding the very indication under assessment and update it when more evidence is available.

OTHER CONSIDERATIONS

Based on ICER's framework conditions of transparency and use of robust evidence, we recommend ICER eliminate the facility markup scenario analysis as it was developed from a non-transparent, non-public, and undefined source, and lacks face validity.

Amgen has appropriately reduced Neulasta[®] prices to remain competitive and to maximize patient access, providing savings to the healthcare system and making it the most affordable product in its class. ICER assigned a 2.5x markup for Neulasta[®] and Neulasta[®] Onpro[®] in its

granulocyte colony-stimulating factor (G-CSF) facility markup scenario analysis, however, net reimbursement rates and net acquisition costs of Neulasta and Neulasta[®] Onpro[®] have declined making Neulasta[®] the lowest priced long-acting G-CSF as evidenced by the CMS payment limit for Q1'22.^{10,11} In the period between Q3 2018 and Q2 2020 the average selling price (ASP) of Neulasta[®] fell by 16%.^{12,13}

In prior assessments, multiple manufacturers have expressed concerns about the inclusion of a markup in the model¹⁴ because not every institution negotiates markups. While we understand that payers may allow amounts for claims above ASP, these are not fixed. Within an institution, a markup differs between patients as they are based on payer-specific contracts and negotiations, complicating broad generalizations. We echo those prior comments here: Amgen does not set, control nor have any input into a facility markup. Additionally, as ICER indicates, the scenario in which the markup is applied, has little impact on the assessment of plinabulin. It is reasonable to assume that markups are not solely applied to the G-CSF class and at least some facilities would negotiate a markup for novel and/or reference therapies, including plinabulin and trilaciclib. It is unreasonable to apply fees to G-CSFs without also doing so for the interventions of interest: as infusible products, these would be significantly more expensive to administer than a subcutaneous Neulasta[®] Onpro[®] injection. Although, we appreciate ICER's interest in capturing the total cost to the healthcare system, there is no clarity nor uniform application in this input, therefore given the uncertainty introduced and the limited impact. Amgen strongly recommends the exclusion of the markup scenario analysis. If a markup fee scenario analysis must be included, a range comprising the highest and lowest markups should be applied and this range should be applied to all products including trilaciclib and plinabulin.

CONCLUSION

CIN remains a severe condition with an enormous impact, burdening patients, their caregivers, families and healthcare providers with significant health challenges. We suggest that ICER amend the failure rate of the Onpro[®] device to reflect robust, current data from 30,000 on-body injectors, align the evidence rating of plinabulin with the FDA CRL and eliminate the facility markup scenario. These adjustments will help ICER achieve a more comprehensive and accurate assessment aligned with the available evidence, core scientific principles, and the decades of value Neulasta[®] has brought to patients.

REFERENCES

¹ Vogel CL, Wojtukiewicz MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ, Wiens BL, et al. J Clin Oncol. 2005;23(6):1178-1184. <u>Link</u>

² Data on file, Amgen; [1]; 2020.

³ Data on file, Amgen; [2]; 2020.

AMGEN RESPONSE TO ICER NEUTROPENIA DRAFT EVIDENCE REPORT

⁴ Townley C, Porter C, McMullen N. Comparing grade 4 neutropenia associated with pegfilgrastim administered via the Onpro[®] device versus manual injection with a prefilled syringe. J Hematol Oncol Pharm. 2018;8(3):119-125. Link

⁵ Op. Cit. Townley *et al.* Link

⁶ Mahtani RL, Crawford J, Rifkin R, Dale D, Brookhart A, Gawade PL, et al. Abstract PS9-50: A multicenter, prospective, observational study to determine the incidence of febrile neutropenia (FN), persistence and G-CSF utilization among cancer patients at high risk for FN receiving pegfilgrastim by an on-body injector (OBI) versus other FN prophylaxis strategies: An interim analysis. SABCS20-PS9-50. 2021 Feb. Link

⁷ Patel J, Rainess RA, Benfield MJ, Rogers KML, Moore DC, Larck C, et al. Retrospective analysis of clinical outcomes associated with the use of pegfilgrastim on-body injector in patients receiving chemotherapy requiring granulocyte colony-stimulating factor support. Hosp Pharm. 2021 Apr;56(2): 77-80. Link

⁸ Maahs L, Tang A, Saheli ZA, Jacob B, Polasani R, Hwang C. Real-world effectiveness of the pegfilgrastim onbody injector in preventing severe neutropenia. J Oncol Pharm Pract. 2020 Dec.

⁹ BeyondSpring. BeyondSpring Pharmaceuticals receives complete response letter from the FDA for plinabulin new drug application for prevention of chemotherapy-induced neutropenia (CIN). 2021 Dec 01; Press release. Link ¹⁰ Amgen Biosimilars. 2020 biosimilar trends report. 13 Oct 2020; 7th ed. Link

¹¹ 2022 ASP Drug Pricing Files, Centers for Medicare & Medicaid Services [Internet], CMS.gov; 2021, Link

¹² Webster J, Smith RE, Wieland D, Verniero J, Scott JA. Cost savings of biosimilar pegfilgrastim in a Medicare OCM population. J Clin Oncol; 2020 May 25;38(15): suppl19362. Link

¹³ Op. Cit. Amgen Biosimilars. Link

¹⁴ ICER. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value: Response to Public Comments on Draft Evidence Report. 15 Feb 2018. Link



February 22, 2022

To the members of the Institute for Clinical and Economic Review (ICER):

I sat across the kitchen table from Mrs. Smith, a middle-aged woman recently diagnosed with breast cancer. She slowly sipped her coffee between releasing deep, heavy sighs. Tears streamed down her face - her fear was palpable. Mrs. Smith had just received news from her Oncologist that the lifesaving chemotherapy treatment was not approved by her insurance company. Without approval of Mrs. Smith's lifesaving treatments, her life expectancy was cut short with one phone call. The worst part, Mrs. Smith was not aware that there are companies who make decisions regarding her worthiness to access to new treatments are made without input from her or the voice of other patients. Imagine Mrs. Smith is your mother/wife/sister/daughter – someone you care about.

The ICER board was established to place value on the latest and most advanced treatments for patients. The review process includes four key components for determining the value placed on a drug or treatment. This year, your board has decided to alter its own established protocols that eliminates the only accountability the board has, which is public comment. Without public comment, your process by default, is invalid and therefore, any report created without the patient voice, or public comment should also be deemed invalid.

I am a Black woman and a 17-year breast cancer survivor. I began treatment on my 40th birthday. According to the Adverse Early Childhood Experiences Study (ACEs) conducted by the Centers for Disease Control (CDC) is a study that measures the impact of potentially traumatic events that occur in childhood (0-17 years) and the likelihood of developing chronic health problems, mental illness, and substance use problems in adulthood. The study consists of 10 questions. The more questions to which a person answers, yes, the more likely that person is to have chronic health problems. I answered yes to all 10 questions. Therefore, statistically, it was of no surprise that I would develop breast cancer. What was a surprise was not only did I beat the odds of dying young, I also beat the odds of succumbing to breast cancer based on the disparate morbidity rates for Black women as compared to non-Latina white women. Racial inequities within breast cancer are not new. While breast cancer mortality rates have declined over the last few decades, sadly, Black women still carry the burden of the highest mortality rates of any racial or ethnic group.

Equitable access to quality healthcare is more important now than ever. I am disheartened that the ICER board would choose now, of all times, to alter its due process to eliminate public comment. I am inextricably clear that your role is to assign value to drugs and treatment protocols, my question is who has the authority to place value on anyone's life. The fallout of your modified process will literally displace hundreds of thousands of cancer patients and will

only create further instability to those who are impacted the most. As someone who works directly with patients and survivors daily, and as a survivor myself, I make it a priority to be aware of the challenges my fellow breast cancer survivors face. It is deeply disconcerting that one of the largest challenges is access to quality, equitable and sustainable healthcare. I see first-hand how racial inequalities in healthcare deprive Black women of the opportunity to survive and live well. It is more important now than ever to close the inequality gaps in healthcare by acknowledging that all life has value and every American can have access to lifesaving treatments. Access to more and new treatments could help close these gaps. Now is not a time to take options off the table by making them harder to access.

Delays in care, and access barriers on breakthrough treatments, are detrimental for the patient leading to more advanced stages of the disease and higher mortality rates. These reasons and more are why patients – and the community-based organizations who advocate on their behalf must be part of the decision-making conversations that impact access to care. I strongly urge the members of the ICER board to reconsider deciding on reviewing the new treatments for chemotherapy-induced neutropenia without providing the cancer community the opportunity to voice their concerns at a public meeting.

Thank you,

Reverend Tammie Denyse Co-Founder/President tdenyse@carriestouch.org



February 22, 2022

- Re: Novel Agents to Prevent Chemotherapy Induced Neutropenia and other Myelosuppressive Effects Draft Report; January 25, 2022
- Subject: Clinical Commentary

From: Jeffrey Crawford, MD

Over the last 30 years, I have been involved with patient care and clinical research in lung cancer¹, with a particular focus in myelosuppression. As a prior chair of the NCCN myeloid growth factor committee for many years and a member of the ASCO CSF Panel, I appreciate the detailed review that has been performed that should be quite useful to the field. Since plinabulin's approval by the FDA is pending a second trial, I will focus my comments on trilaciclib. Of note, I have served as chair of the DSMB for the small cell trials and as a consultant for G1 since trilaciclib's approval. My comments below focus on areas that I think require further attention in your review.

 Trilaciclib is unique in its ability to protect the bone marrow stem cells from chemotherapy, allowing faster recovery and better preservation of white cell, platelet and red cell lineages. This is in contrast to other strategies with growth factors where initial damage is created to stem cells from chemotherapy and surviving cells are rescued by growth factors generally in a lineage specific manner.

The clinical trial data for trilaciclib validates very nicely the reduction in neutropenia, anemia and thrombocytopenia, with the use of trilacilib compared to placebo in 3 different clinical trials in patients with small cell lung cancer. Of additional interest in the era of immuno-oncology has to do with better preservation of lymphocyte number and potential function which is a subject of ongoing research and may lead to additional benefits in studies of chemotherapy and/or immunotherapy. But for the data already available in small cell lung cancer patients, the important point is that there is a direct relationship between the mechanism of action of trilaciclib and better preservation of all cell lineages with resultant clinical benefits in less neutropenia, less febrile neutropenia, less anemia, less transfusion, and less thrombocytopenia. Collectively, this myeloprotection can be important in individual patients and impact patient outcomes.

2) While the ICER review in Section D2 nicely summarizes much of the data outlined above, I was disappointed that there was not further discussion or review of the data presented in Table D14 on Quality of Life Outcomes. As outlined in the tables, patients treated on the trilaciclib arm had significantly better patient reported outcomes utilizing well validated scales across multiple domains of physical well-being, functional wellbeing, fatigue, and anemia outcomes. To put this in graphical form, I have included Figure 3 from the Weiss 2021 paper for your review that outlines the time to deterioration in selected PRO measures. In the majority of these endpoints, quality of life was maintained for generally twice as many months or more in the trilaciclib arm compared to placebo. I am unaware of any quality of life data evaluating agents that impact myelosuppression leading to this magnitude of difference across 30 years of studies. One can argue the differences are only a matter of months, but in fact this is extremely meaningful in patients with small cell lung cancer, who unfortunately, still often survive a year or less with extensive stage disease.²

Figure 3 Time to Confirmed Deterioration in Selected PRO Measures of FACT-An. Worsening Was Defined As a Decrease From Baseline by a Clinically Meaningful Threshold for Two Consecutive Visits: ≤3 Points for Physical Wellbeing, Functional Wellbeing, and Fatigue; ≤6 Points for Anemia Trial Outcome Index Points; ≤7 Points for FACT-An Total Scores. Abbreviations: CI = confidence interval; FACT-An = Functional Assessment of Cancer Therapy-Anemia; NYR = not yet reached; PRO = patient-reported outcome; TTCD = time to confirmed deterioration.

Domain T	Events, n rilaciclib/placebo	TTCD, months Trilaciclib/placebo		H	azard ratio (95% CI)
Physical wellbeing	32/51	NYR/5.16	f		0.62 (0.40-0.97)
Functional wellbeing	31/55	7.62/3.78	<u>}</u>		0.45 (0.29-0.71)
Fatigue	39/61	7.03/2.33	<u> </u>		0.56 (0.37–0.85)
Anemia trial outcome inde	ex 33/55	7.20/3.78	├		0.54 (0.35–0.84)
FACT-An total	31/58	NYR/3.48	0.4 0.6 0.8 1	1.67 2.5	0.47 (0.30-0.73)
			Trilaciclib better	Placebo better	

3) I did not participate in the SCLC trials, due to my role on the DSMB, however, since approval of trilaciclib by the FDA in February 2021, I have had the opportunity to use this agent in my own clinical practice. My experience, though still relatively small in number, is totally consistent with the clinical trial data and the quality of life data. Thus far my patients getting trilaciclib with carboplatin, etoposide and atezolizumab have not developed febrile neutropenia. They have not required G-CSF. They have not needed transfusion and have not required ESAs, and have had significantly better preservation of

hemoglobin, compared to patients treated with my previous standard of care therapy of pegfilgrastim. I have spent the last 30 years using G-CSF to reduce the risk of neutropenia from chemotherapy, and it has been an invaluable agent in my practice. However, the added patient benefit of trilaciclib in SCLC make it not only a recognized option by NCCN, but in my opinion, the preferred option in this population. Ongoing research will determine if patient outcomes will be similarly improved with other disease and chemotherapy/immunotherapy settings.

I hope the panel will take my comments under consideration as you finalize your report. I appreciate the opportunity to provide this input.

Best regards,

Selfing Cranked MD

Jeffrey Crawford, MD George Barth Geller Professor for Research in Cancer Division of Medical Oncology Department of Medicine Lead PI of NCTN LAPS Grant Duke Cancer Institute

References

- 1) Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991 Jul 18;325(3):164-70..
- 2) Weiss J, Goldschmidt J, Andric Z, Dragnev K, Gwaltney C, Skaltsa K, Pritchett Y, Antal J, Morris S, Daniel D. 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 StudiesClin Lung Cancer. 2021 Sep;22(5):449-460.

Many countries including Canada, that provide free social medical care through their respective National Health Services, have incorporated so-called cost-effective reviews to make decisions about which drugs should be covered. **Poor decision** making and a negative review could have serious consequences for patients who might benefit from a new drug. This problem is not only restricted to European/Canadian healthcare systems, but is also playing out on stage in the United States.

The Institute for Clinical and Economic Review (ICER), a health economics organization, canceled the only public meeting for its review of two drugs for the prevention of chemotherapyinduced neutropenia. During the process of collecting data for their report, the FDA did not approve the drug that was being used as a comparator, thereby forcing the selection of another therapy, which was not substantially equivalent. The clinical performance between these two therapies was not adequately scrutinized making it difficult to conduct a reliable comparison. This approach can lead to **poor decision making, resulting in possible patient death** as a result of denying a drug that could be of significant benefit to a patient. This requires that the topic of health equity be included in the discussion.

Health equity has been widely defined as an "absence of socially unjust or unfair health disparities." To achieve health equity in the United States, one must eliminate difference in access to health services according to race, ethnicity, sex, gender identity, comorbidity, or ability. Health equity is important because health is fundamental to the human experience. It is a human right.

The value of one's life and health equity are protected by a variety of tools in the United States, including civil rights legislation and constitutional jurisprudence, which addresses many aspects of the rights of citizens. The14th Amendment of the United States Constitution is one such tool which addresses many aspects of citizenship and the rights of citizens. A commonly discussed phrase in the 14th Amendment, "equal protection of the laws", is incorporated prominently in a wide variety of landmark cases including Brown v. Board of Education (racial discrimination) and Roe v. Wade (reproductive rights), which places a high value on life and protects our inalienable right of good health.

From a health equity perspective, the United States is different than other countries (e.g., Canada, UK and some countries in South America and the far east) and the decision making tools and processes which are used in these countries cannot be deployed in the U.S. Furthermore, groups that lack transparency in their approach should not be allowed to affect health equity in a society because they are indirectly opposed to the fundamental principles of our constitution and "equal protection of the laws" afforded to us by the 14th Amendment. Tools such as QALY (quality-adjusted life year), if not monitored closely, will interfere with achieving a more just society and decrease the quality of human life for all.

Institutions, such as ICER, are generating reports that include questionable comparison data. These reports are being more frequently used by insurers to exclude coverage or justify restrictive policies including prior authorization, step therapy and specialty tier placement. ICER's plan to cancel an opportunity to speak out about the experience of living with chemotherapy-induced neutropenia or the value they see in new treatment options will be detrimental not only to the type of treatments available to an individual but also the quality of life of those patients. Health equity

and the rights of individuals negatively affected by chemotherapy-induced neutropenia must be part of the conversation prior to finalizing drug coverage policies.

Respectfully,

•

Keith Crawford

February 21, 2022

Steven D. Pearson, MD, MSc

President, Institute for Clinical and Economic Review

Two Liberty Square, 9th Floor, Boston, MA 02109

Re: ICER's Assessment of Treatments for Chemotherapy-Induced Neutropenia and Other Myelosuppressive Effects

Dear Dr. Pearson,

Florida Cancer Specialists (FCS) is one of the largest community oncology practices in the US, with nearly 100 sites of service, approximately 450 providers and greater than 70,000 new patient visits yearly.

We ran a RWD analysis at FCS to understand the burden of chemotherapy-induced myelosuppression (CIM) in patients with extensive-stage small-cell lung cancer (ES-SCLC). In our RWD study, with 1239 patients, grade 3 or greater neutropenia was 42.7%, grade 3 or greater anemia was 32.7%, grade 3 or greater thrombocytopenia was 36.1%. 858 (69.5%) patients had grade \geq 3 AEs in \geq 1 lineage; 419 (33.9%) patients had grade \geq 3 AEs in \geq 2 lineages;191 (15.5%) patients had grade \geq 3 AEs in all 3 lineages.

The availability and efficacy of Trilaciclib have been important tools in mitigating CIM and its consequences (neutropenic fever, hospitalizations, use of GCSF, ER visits) in community oncology practice. GCSF has common toxicities including significant bone pain, asthenia, and the potential need for multiple visits to the office. As our physicians prescribe and gain experience with Trilaciclib, we have noted excellent tolerability and efficacy (data collection ongoing). It is my opinion that Trilaciclib represents a significant advancement in the science of supportive care in oncology practice.

We strongly endorse its continued use, development and hopefully label expansion to other cancer types and other indications.

Sincerely,

Lucio N Gordan, MD Chief Medical Officer for Therapeutics & Analytics Past President Florida Cancer Specialists and Research Institute



February 22, 2022

Steven D. Pearson, MD, MSc President, Institute for Clinical and Economic Review Two Liberty Square, 9th Floor, Boston, MA 02109

Re: ICER's Assessment of Treatments for Chemotherapy-Induced Neutropenia and Other Myelosuppressive Effects

Dear Dr. Pearson,

G1 Therapeutics (G1) appreciates the opportunity to provide comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on the assessment for novel agents to prevent chemotherapy-induced neutropenia (CIN) and other myelosuppressive effects. G1's suggestions for updates to ICER's evidence report are organized below.

1. The characterization of the safety profile associated with trilaciclib is inaccurately represented in the report. The focus should be on appropriate and clinically relevant metrics. G1 offers additional data to help clarify the substantial benefit of trilaciclib.

In the draft report, ICER appropriately acknowledges that treatment with trilaciclib is associated with reductions in risks of developing severe neutropenia (92% reduction), severe anemia (50%), and severe thrombocytopenia (56%) in Table 3.4. However, ICER noted confusion related to all-cause hospitalization and adverse event (AE) rates associated with trilaciclib. Specifically, ICER noted that "these benefits did not translate into a reduction in the risk for total hospitalizations, serious AEs (SAEs) or deaths due to AEs (all nominally higher in the trilaciclib group)" on page ES1 and ES2 of the draft report.

- These metrics (i.e., total hospitalization, SAE, death due to AEs) are not appropriate for the main evaluation of trilaciclib, as they do not reflect excess events attributable to trilaciclib. Trilaciclib is indicated to reduce chemotherapy-induced myelosuppression (CIM) and thus should only be expected to impact CIM/sepsis-related hospitalizations. Trilaciclib should not be expected to reduce all-cause hospitalizations such as those attributable to advanced disease status of small cell lung cancer or comorbidities, e.g., those associated with chronic smoking, a known risk factor for small cell lung cancer.
- The SAE data referenced in the draft report are from a pooled analysis of 3 trials with different chemotherapy backbones in different lines of therapy.¹ Results from each individual trial (Appendix Table 1) showed that the observed difference between the trilaciclib and placebo groups in the % of patients with SAE is primarily from one study (2L, G1T28-03).² In this study, prognostic factors for survival were not balanced between the trilaciclib arm had 4-5 prognostic factors, and fewer patients in that arm had 0-1 prognostic factors, when compared with the placebo arm (Appendix Table 2**Error! Reference source not found.**). This imbalance is likely unfavorable to trilaciclib for both survival and AEs, as the trilaciclib patients were notably more frail.
- Although the proportion of patients who experienced all-cause hospitalizations may be similar or nominally higher in the trilaciclib group, the incidence of hospitalizations per cycle was lower. The numbers of total and CIM-related hospitalizations per 100 cycles of treatment were consistently lower across individual trilaciclib studies and pooled analyses.¹⁻⁴ Patients receiving placebo experienced more *recurring* hospitalizations than those receiving trilaciclib. This event-level metric is more accurate and clinically far more relevant (Appendix Table 3) than the patient-level metric.
- ICER notes that AE-related mortality was not lower in the trilaciclib group across the three studies. However, the difference is primarily noted in the G1T28-03 study (Appendix Table 4),² and the prognostic



factors for survival were not balanced between the two arms in this study as mentioned above. None of these deaths were deemed attributable to trilaciclib by investigators^{2, 3} (details submitted to ICER in confidence). Furthermore, the limited life expectancy of the ES-SCLC population, the high severity of disease, the use of highly toxic chemotherapy, and the relatively low numbers of events make it less appropriate to use this measure to evaluate trilaciclib.

- 2. The clinical evidence rating for trilaciclib should be changed to A, due to the high certainty of the evidence and substantial benefit.
 - The current clinical evidence rating does not adequately capture the value or clinical benefit of trilaciclib. G1 has offered additional data and clarity on relevant metrics for assessment of benefit in point 1 above.
 - ES-SCLC is a highly fatal disease associated with significant morbidity and limited life expectancy.
 - There is no other available treatment that broadly mitigates multilineage myelosuppressive effects and their corresponding impact on patient wellbeing before chemotherapy damage occurs.
 - Trilaciclib was granted breakthrough therapy designation for ES-SCLC in August 2019 by the US FDA, received priority review status in August 2020, and was approved by the FDA in February 2021, based on three Phase II randomized clinical trials.⁵⁻⁷ The accelerated approval timeline underscores the unmet need for patients with ES-SCLC.
 - Following approval, trilaciclib was included in two National Comprehensive Cancer Network (NCCN) guidelines (hematopoietic growth factors and small cell lung cancer) within 6 weeks of approval.
 - A new technology add-on payment was granted by the Centers for Medicare & Medicaid Services, where a *substantial* clinical benefit is one of the criteria for evaluation.⁸
 - G1 shared with ICER a recently conducted real world evidence study in the process of being published (in confidence). The trilaciclib patient group (n=21) demonstrated lower red blood cell and platelet transfusions, lower G-CSF usage, and lower all-cause hospitalizations within 21 days post chemotherapy initiation (none during day 8-16 post-chemotherapy initiation). This additional data and evidence from the real world should increase the appraised level of certainty, warranting an 'A' clinical evidence rating.
- 3. Duration of the disutility impact from grade ≥3 myelosuppressive AEs is underestimated in the draft report and should be applied to the whole 3-week period.

The ICER model assumes that the disutility impact of grade ≥ 3 AEs is limited to the period in which the AE is occurring. However, based on the following considerations, it is appropriate to apply the disutility of a given AE for the entirety of the 3-week cycle in which it occurs.

- Health-related quality of life effects extend beyond the duration of an AE: Disutilities of grade ≥3 AEs in the ICER model were sourced from vignette-based utility studies by Nafees 2008⁹ and Tolley 2013.¹⁰ In Nafees 2008⁹, the authors state explicitly that the "health states were designed to describe a **three-week period**." Consistent with this intent, the descriptions of neutropenia and febrile neutropenia (FN) both include aspects of these AEs that would continue until the start of the next 3-week cycle (e.g., "You don't visit family and friends often because of the risk of infection", "You are at risk of it happening again following your next cycle of treatment"). The patient's impending risk of another AE episode extends to the beginning of the next 3-week treatment cycle—this is an inseparable part of the overall disutility impact, and it is therefore inconsistent to apply this AE disutility to a time increment smaller than a whole 3-week cycle.
- The vignette for thrombocytopenia in Tolley 2013¹⁰ similarly describes ongoing lifestyle effects of the AE ("Due to the nose bleeds Joan has to spend half a day in hospital having a blood transfusion. This works for a while but the nose bleeds come back so she has to receive further transfusions once a week for the first 2 months of treatment"). As the model accounts for recurring AEs (i.e., a patient can have up to 1 AE of each type per 3-week cycle), the disutility of thrombocytopenia should be applied to a 3-week cycle per event.



- **FN disutility from Nafees 2008 represents disutility following (not during) FN:** In Nafees 2008⁹, the vignette for FN described the FN-related hospitalization and mortality risk in the past tense ("You had a blood disorder which led to your being hospitalized for about 5 days with a fever and severe flu like symptoms. You received treatment because this blood disorder could have caused you to die within a few days of onset"). The vignette is otherwise written in present tense. The resulting estimate of FN disutility thus represents the disutility that applies in the aftermath of a FN hospitalization until the start of the next treatment cycle. This interpretation may explain why the disutility estimates for FN and non-febrile neutropenia were nearly equivalent, despite FN being more severe and life-threatening. Applying this post-FN disutility for a whole 3-week cycle would still be conservative, as the disutility experienced *during* the hospitalized portion of the cycle would presumably be even larger.
- Input from Dr. Andrew Lloyd, who co-authored Lloyd 2006¹¹ (a utility study in breast cancer that was a precursor to Nafees 2008⁹) and Nafees 2017¹² (an update of Nafees 2008): Dr. Lloyd stated that it was a conscious decision for the vignettes to describe the patient experience over a full 3-week cycle, taking into account that patients will not be experiencing the acute effects of the AE for that entire period. The descriptions did not focus only on the acute period. He confirmed that the resulting disutilities should be applied for the entire 3-week period, not just the acute period of the AE.
- 4. ICER should incorporate more recent data into its estimates of disutility for myelosuppressive events. Nafees 2017^{12} (an update and expansion of Nafees 2008, both in metastatic non-small cell lung cancer) is another relevant literature source for disutilities of grade ≥ 3 myelosuppressive AEs. In contrast to the original UK-only study (N=100), Nafees 2017 included a larger, multi-national sample of respondents (total N=451) and added a health state for grade ≥ 3 bleeding (i.e., grade ≥ 3 thrombocytopenia). The new study also diverged from the original study by using time tradeoff (TTO) rather than standard gamble; the authors noted that health technology appraisal agencies and researchers typically prefer TTO (the valuation method behind the EQ-5D, the generic utility measure preferred by ICER¹³ and NICE¹⁴).
 - G1 recommends that ICER incorporate this more recent data into the disutility inputs for myelosuppressive AEs. Each AE disutility can be derived as a weighted average of the disutilities obtained from ICER's current source and Nafees 2017. Appendix Table 5 shows the calculation of disutilities when pooling ICER's current sources with either: the global estimates from Nafees 2017 (second-to-last column); or the UK-specific estimates from Nafees 2017 (last column).
 - The grade ≥3 anemia disutility of -0.073 (as reported by ICER's current source, Chouaid 2017¹⁵) originates from the disutility for grade ≥3 fatigue estimated by Nafees 2008. This disutility of fatigue has been used to approximate that of anemia in multiple NICE submissions, such as TA310 in 2014 and TA181 in 2009. G1 therefore agrees with the appropriateness of Nafees 2008 to inform the disutility of grade ≥3 anemia, and by extension, the more recent Nafees 2017 inputs should also be incorporated for anemia.
- 5. Proportions of myelosuppressive AEs requiring hospitalization should be sourced from real-world studies rather than trial data.

Trial data provide lower bounds for the proportions of myelosuppressive AEs requiring hospitalization and should not be regarded as the best available evidence for these parameters. In response to the model analysis plan, G1 raised several caveats regarding the use of trial-based hospitalization data in the model, including the expectation that hospitalizations may not have been fully captured. The priority of the Phase 2 trials was primarily to evaluate safety and efficacy for regulatory purposes; therefore, the health care resource use endpoints do not meet the robust requirements for HTA evaluations.

• Hospitalization parameters can instead be computed using episode-level resource use data from Rashid 2016,¹⁶ the study that ICER uses as source of inpatient/outpatient costs per anemia event (Appendix Table 6). G1 recommends that ICER use this source for both arms, which is a conservative approach given trial data suggested proportion of AE requiring hospitalization was lower in the trilaciclib arm.



- G1 notes that a real-world study based on SEER-Medicare data among SCLC patients receiving chemotherapy reported that 71.7% patients had at least one medical claim for anemia, and 52.8% had at least one inpatient claim for anemia. Among patients with at least one anemia episode, 74% (=52.8/71.7) had at least one hospitalization related to anemia.¹⁷ Similarly, 45.2% had at least one medical claim for neutropenia, and 33.3% had at least one inpatient claim for neutropenia. Among patients with at least one neutropenia episode, 74% (=33.3/45.2) had at least one hospitalization related to neutropenia. 27% had at least one medical claim for thrombocytopenia, and 17% had at least one inpatient claim for thrombocytopenia. Among patients with at least one inpatient claim for thrombocytopenia. Among patients with at least one thrombocytopenia episode, 63% (=17/27) had at least one hospitalization related to thrombocytopenia. These rates are higher than the Rashid source and can be taken as validation that values from the Rashid would be conservative.
- 6. In the 1L population, the proportions of patients requiring G-CSF therapies should be based on pooled 1L trial results, which suggest a larger difference in G-CSF use.

For consistency with other 1L clinical inputs used, the proportions of patients who receive G-CSF therapy in each arm should be based on pooled data (shown in Appendix Table 7), rather than on Daniel 2020 alone.

7. Proportions of patients requiring ESAs should be directly based on observed trial data (similar to the approach used for G-CSF), rather than being modeled via severe anemia events.

Use of ESAs is underestimated in the current ICER model relative to the observed ESA use. G1 provided the ESA use in each trilaciclib trial in Appendix Table 8.

8. In the 1L population, it is not clinically plausible for the probability of FN conditional on having severe neutropenia to be higher for trilaciclib than placebo.

Across all three pivotal trials of trilaciclib in ES-SCLC, patients with grade 4 myelosuppressive AEs represented a larger percentage of all patients with grade 3-4 myelosuppressive AEs in the placebo arm than in the trilaciclib arm (Appendix Table 9). Thus, in addition to the impact of trilaciclib in preventing grade \geq 3 myelosuppressive AEs that did occur were generally of lower severity with trilaciclib than placebo—a treatment benefit that is not explicitly captured in the model.

- Based on these findings, it is reasonable to expect that FN (the most severe form of neutropenia) will represent a smaller percentage of all severe neutropenia events with trilaciclib than placebo. Results from Hart 2020 (2L setting) align with this, with FN representing 4.9% (2/41) of severe neutropenia events for trilaciclib and 14.3% (7/49) for placebo. Note that grade 4 neutropenia as a percent of grade 3-4 neutropenia was approximately 3-fold higher for placebo than trilaciclib in both the 1L trials (i.e., 64% / 20% = 3.2) and the 2L trial (i.e., 83% / 32% = 2.6), similar to the relative magnitude of FN as a percent of grade 3-4 neutropenia for placebo vs. trilaciclib in the 2L trial (i.e., 14.3% / 4.9% = 2.9).
- However, based on data shared by G1 from the Weiss 2019 and Daniel 2020 studies, ICER assumes that the proportion of severe neutropenia events that are FN is 5.3% (1/19) for trilaciclib and 2.7% (3/113) for placebo in the 1L population. Due to the infrequency of severe neutropenia among trilaciclib-treated patients in 1L, the 5.3% figure was calculated based on a small number of events and should be used with caution. Data from the placebo arms of the 1L and 2L trials suggest that FN as a percentage of grade ≥3 neutropenia should be higher in the 2L than 1L setting. Yet for trilaciclib, FN as a percentage of grade ≥3 neutropenia is estimated to be slightly higher in the 1L than 2L setting (5.3% vs. 4.9%), even though grade 4 neutropenia as a percentage of grade ≥3 neutropenia was higher in the 2L setting.
- G1 understands ICER's preference for using observed trial data where possible. However, given the body of evidence from all three trials, G1 encourages ICER to consider an alternative base-case assumption that 2.7% of grade ≥3 neutropenia events are FN in both arms for the 1L population.
- 9. Report incremental cost per severe myelosuppressive event avoided as an additional output.



ICER is overly focused on neutropenia, while trilaciclib addresses all myelosuppressive cytopenias. This results in a clinically unwarranted narrow portrayal of trilaciclib benefits; for example, Table 3.3 illustrates neutropenia only. Further, Table 4.8 displays results as cost per FN event avoided. We suggest adjusting the report accordingly and reporting incremental cost per severe myelosuppressive event avoided as an additional output (which would appropriately reflect the clinical benefit of trilaciclib) in Table 4.8.

10. Based on the magnitude of indirect costs relative to direct costs, and the impact of treatment on these costs, the societal perspective should be used as a co-base case.

Based on Liou 2007¹⁸, indirect costs, such as paid caregivers and caregiver work loss, account for 34–44% of the total cost of managing neutropenia and more than 50% of the total cost of managing thrombocytopenia. Use of the societal perspective here is in-line with ICER's stated methods and process.

11. Listed below are factual inaccuracies that should be corrected or addressed, and speculative statements that we request to be omitted.

- The inclusion of trilaciclib in two NCCN guidelines should be reported in the guideline review section.
- The primary endpoints for the Daniel 2020 and Hart 2021 studies (should be duration of severe neutropenia in cycle 1 and percentage of patients with severe neutropenia during the treatment period) are described incorrectly in Table 3.1 and in the supplemental tables. In addition, secondary endpoints are incomplete.
- Key trial results are reported for 2L trilaciclib in Table 3.5 but there is no 1L table shown. In addition, the dose reduction row in Table 3.5 is incorrect and should read 18.8% for trilaciclib and 31.0% for placebo.
- G1 notes errors in some ICER model formulas. These were reported separately to ICER in confidence.
- Trilaciclib should not be compared to pegfilgrastim or plinabulin in any capacity within the report. While ICER acknowledged that trilaciclib and plinabulin were evaluated in different patient populations, and the interventions were not explicitly compared, listing the key results within the same tables and discussing the consistency of the results (page ES2) implies an unwarranted comparison. Suggest splitting the report into two major parallel sections, one for trilaciclib and one for plinabulin.
- On page E35, trilaciclib is compared to G-CSF. The two treatments are used differently and should not be compared. Trilaciclib proactively protects against CIM, while G-CSF is for neutropenia management and is given in a reactive way *after* chemotherapy damage has occurred.
- On page ES1, the indication statement is quoted incorrectly as "the incidence of myelosuppression (neutropenia, anemia)". Please delete "(neutropenia, anemia)" as this is not in the indication statement.
- The statement "trilaciclib mechanism of action could lead to reduced chemotherapy efficacy for some cancers" is speculative, unexplained, outside the scope of this assessment, and should be removed.
- One expert reviewer, Dr. Lee Schwartzberg, reports a consulting relationship with BeyondSpring, the manufacturer of plinabulin. This conflict of interest may bias the review and should be a noted limitation.
- Table 5.2 should consider that trilaciclib has substantial potential to improve patients' abilities to achieve major life goals. This is supported by patient testimony (submitted as evidence in confidence). In addition, patients receiving trilaciclib can improve patients' abilities to manage and sustain myelotoxic treatment and are less likely to experience dose reduction (Appendix Table 10).
- Table D12 shows treatment-related AEs for the Weiss 2019 study as "Not Reported." Note that treatmentemergent AEs are given in Table 5 of the supplemental information for Weiss 2019: Overall: placebo 94.6% vs trilaciclib 89.5%. Grade ≥3: placebo 75.7% vs trilaciclib 28.9%.
- Table D14 for the Daniel 2020 study labels both arms "placebo," however the right-hand column should be labeled as the trilaciclib arm. Furthermore, anemia TOI events are incorrectly shown as 27 in both arms; this should read 19 for the trilaciclib arm.
- Table E2 gives overall BSA for the pooled 1L trials as 1.90, however this is the average BSA for the Weiss 2019 study only. Please correct this with BSA across both studies.



• Table E6 reported median PFS as 5.6 months for 1L clinical inputs. This should be 5.4 months based on the Daniel 2020 study (5.4 months for placebo and 5.9 months for trilaciclib).



Appendix

Table 1. Serious adverse event rates in 1L and 2L trilaciclib trials

	Placebo	Trilaciclib
G1T28-02 (Placebo N=37, Trilaciclib N=38) ¹⁹	9 (24.3 %)	11 (28.9 %)
G1T28-03 (Placebo N=28, Trilaciclib N=32) ²	7 (25.0 %)	12 (37.5 %)
G1T28-05 (Placebo N=53, Trilaciclib N=52) ⁴	14 (26.4 %)	13 (25.0 %)
Pooled (Placebo N=118, Trilaciclib N=122) ¹	30 (25.4 %)	36 (29.5 %)

Note: as per the prescribing information,⁵ serious adverse reactions reported in >3% of patients for trilaciclib (across the three trials) were respiratory failure, hemorrhage, and thrombosis.

Table 2. Distribution of prognostic factor categories by treatment group in G1T28-03²

	Trilaciclib prior to topotecan 1.5 mg/m ² (n = 32)	Placebo prior to topotecan 1.5 mg/m ² (n = 29)
0 or 1 prognostic factor, n (%)	5 (15.6)	8 (27.6)
2 or 3 prognostic factors, n (%)	17 (53.1)	16 (55.2)
4 or 5 prognostic factors, n (%)	10 (31.3)	5 (17.2)

Note: no patient had more than 5 prognostic factors.



Table 3. Hospitalization across trilaciclib clinical trials

	G1T	28-05 ³	G1T28-0 poo	02 and -05 bled ⁴	G1T2	28-03 ²	G1T28-02, - pool	-05 and -03 led ¹
	Trilaciclib	Placebo	Trilaciclib	Placebo	Trilaciclib	Placebo	Trilaciclib	Placebo
All-cause hospitalization								
Patients with at least one event (%)	23.1	26.4	22.2	25.6	31.3	25.0	24.6	25.4
Events per 100 cycles	10.8	12.5	8.7	11.1	7.9	15.0	8.4 ⁴	12.0^{4}
CIM-related hospitalization								
Patients with at least one event %	3.8	9.4	2.2	10.0	9.44	21.4 ⁴	4.1^{4}	12.74
Events per 100 cycles	1.0	4.5	0.5	3.8	2.0^{4}	8.9 ⁴	0.9^{4}	4.9 ⁴



Table 4. Number of patients with TEAE leading to death

	Placebo	Trilaciclib
G1T28-02 (Placebo N=37,Trilaciclib N=38) ⁴	0	1 (2.6%)
G1T28-03 (Placebo N=28,Trilaciclib N=32) ²	1 (3.6 %)	3 (9.4 %)
G1T28-05 (Placebo N=53,Trilaciclib N=52) ⁴	2 (3.8 %)	2 (3.8%)
Pooled (Placebo N=118, Trilaciclib N=122) ⁴	3 (2.5 %)	6 (4.9 %)

Table 5. AE disutilities for myelosuppressive AEs

AE type (grade ≥3)	Current source [a]			Nafees 2017 (global), [b]		Nafees 2017 (UK), [c]		Pooled disutility,	Pooled disutility,	
	Source	Disutility	N	Disutility	N	Disutility	N	[u] & [v]	[u] & [c]	
Febrile neutropenia	Nafees 2008	-0.090	100	-0.47	451	-0.50	75	-0.401	-0.266	
Non-febrile neutropenia	Nafees 2008	-0.090	100	-0.35	451	-0.46	75	-0.303	-0.248	
Anemia (based on	Nafees 2008/	-0.073	100	-0.29	451	-0.41	75	-0.251	-0.218	
fatigue)	Chouaid 2017									
Thrombocytopenia	Tolley 2013 ¹⁰	-0.108	110	-0.25	451	-0.20	75	-0.222	-0.145	



Table 6. Calculated episode-level resource use from Rashid 2016

AE type	% of episodes managed by hospitalization	Calculation details (based on episode-level results in Table 3 of Rashid 2016) ¹⁶
Neutropenia	26%	= (16+63) / (187+16+10+23+63)
Anemia	18%	= (46+18+155) / (901+46+33+82+18+155)
Thrombocytopenia	18%	= (7+17) / (101+7+8+17)

Table 7. Proportion of patients using G-CSF in pooled 1L trilaciclib trials (G1T28-02 and G1T28-05)⁴

Parameter	Trilaciclib	Placebo
Proportion of patients using G-CSF	21.7%	54.4%

Table 8. Proportion of patients using ESAs in trilaciclib trials

Davamatar	1L: G1T28-05	5 & G1T28-02 ⁴	1L: G1T	² 28-05 ³	2L: G1T28-03 ²	
rarameter	Trilaciclib	Placebo	Trilaciclib	Placebo	Trilaciclib	Placebo
Proportion of patients using ESAs	4.3%	8.9%	5.6%	11.3%	3.1%	20.7%



Table 9. Patients with grade 3/4 myelosuppressive AEs across trilaciclib clinical trials

		Trilacic	lib		<u>Pla</u>	<u>cebo</u>
Trial / AE type	No. patients with grade 3 event	No. patients with grade 4 event	% with grade 4 event among those with grade 3-4 events	No. patients with grade 3 event	No. patients with grade 4 event	% with grade 4 event among those with grade 3-4 events
	[a]	[b]	=[a]/([a]+[b])*100%	[c]	[d]	=[c]/([c]+[d])*100%
Pooled Daniel 2020 & Weiss 2019	9 studies ⁴					
Anemia	14	0	0%	22	1	4%
Neutropenia	12	3	20%	18	32	64%
Thrombocytopenia	3	0	0%	11	7	39%
Daniel 2021 study (based on 2	Table 2 in publicati	$(on)^3$				
Anemia	9	0	0%	15	1	6%
Neutropenia	9	1	10%	7	18	72%
Thrombocytopenia	0	0	N/A, no events	8	7	47%
Weiss 2019 study (based on F	igure 3 in publicati	on) ¹⁹				
Anemia	5	0	0%	7	0	0%
Neutropenia	3	2	40%	11	14	56%
Thrombocytopenia	3	0	0%	3	0	0%



Hart 2020 study (based on Table 2 in publication)² Anemia 9 0 0% 0% 17 0 Neutropenia 15 4 20 7 32% 83% Thrombocytopenia 8 9 53% 5 11 69%

Note: this table was prepared for illustrative purposes using published trial results, and does not include recurrent AEs.



Table 10. Dose reductions in trilaciclib trials

Devementar	1L: G1'	1L: G1T2	8-02 ¹⁹	2L: G1T28-03 ²		
rarameter	Trilaciclib	Placebo	Trilaciclib Placebo Trilaciclib		Placebo	
Dose reductions (%)	Etoposide 5.8% Carboplatin 1.9%	Etoposide 26.4% Carboplatin 24.5%	7.9%	35.1%	18.8%	31.0%



References

1. 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*. Sep 2021;22(5):449-460. doi:10.1016/j.cllc.2021.03.010

2. 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.* Jan 2021;38(1):350-365. doi:10.1007/s12325-020-01538-0

3. 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*. Dec 21 2020;doi:10.1002/ijc.33453

4. G1 Therapeutics Inc. Data on file. 2022.

5. G1 Therapeutics Inc. Cosela (trilaciclib) [prescribing information]. 2021.

6. FDA approves drug to reduce bone marrow suppression caused by chemotherapy. February 12, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-drug-reduce-bone-marrow-suppressioncaused-chemotherapy

7. Dhillon S. Trilaciclib: first approval. *Drugs*. May 2021;81(7):867-874. doi:10.1007/s40265-021-01508 y

8. G1 Therapeutics granted new technology add-on payment (NTAP) for Cosela (trilaciclib) by Centers for Medicare & Medicaid Services (CMS). August 4, 2021. <u>http://investor.g1therapeutics.com/news-releases/news-release-details/g1-therapeutics-granted-new-technology-add-payment-ntap-coselatm</u>

9. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. Oct 21 2008;6:84. doi:10.1186/1477-7525-6-84

10. 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*. Oct 2013;14(5):749-59. doi:10.1007/s10198-012-0419-2

11. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer*. Sep 18 2006;95(6):683-90. doi:10.1038/sj.bjc.6603326

12. 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*. Oct 2017;13(5):e195-e203. doi:10.1111/ajco.12477

13. Institute for Clinical and Economic Review. *ICER's reference case for economic evaluations: principles and rationale*. 2020. <u>https://icer.org/wp-content/uploads/2020/10/ICER_Reference_Case_013120.pdf</u>

14. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [PMG9]*. 2013. <u>https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781</u>

15. Chouaid C, Luciani L, LeLay K, et al. Cost-effectiveness analysis of afatinib versus gefitinib for firstline treatment of advanced EGFR-mutated advanced non-small cell lung cancers. *J Thorac Oncol*. Oct 2017;12(10):1496-1502. doi:10.1016/j.jtho.2017.07.013



16. 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. doi:10.2147/BCTT.S105618

17. Epstein R, Nelms J, Moran D, Girman C, Krenitsky J, Chioda M. Trends in prevalence, treatment patterns, myelosuppression, and burden on the health care system among patients with small cell lung cancer: a SEER-Medicare analysis. Poster presented at: Virtual ISPOR Annual Meeting; May 17-20 2021; https://www.gltherapeutics.com/file.cfm/34/docs/ISPOR_SEER-Medicare%20Poster_5May2021.pdf

18. Liou SY, Stephens JM, Carpiuc KT, Feng W, Botteman MF, Hay JW. Economic burden of haematological adverse effects in cancer patients: a systematic review. *Clin Drug Investig*. 2007;27(6):381-96. doi:10.2165/00044011-200727060-00002

19. 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*. Oct 1 2019;30(10):1613-1621. doi:10.1093/annonc/mdz278



February 22, 2022

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

Re: Draft Evidence Report for Chemotherapy-Induced Neutropenia

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft evidence report on plinabulin and trilaciclib for chemotherapy-induced neutropenia. This letter also includes comments about the unusual process ICER has followed for this review.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient-centered care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of health care providers committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

Evidence Report and Review Process Comments

ICER has announced its intent to issue a final evidence report in this review without first holding a public hearing, a highly unusual decision. It is disappointing to see ICER moving forward in this manner after denying patients and advocacy organizations the public opportunity to participate in the only open component of ICER's assessment process.

Review of Treatments Prior to FDA Approval

Trilaciclib and plinabulin are two novel treatments for cancer patients facing neutropenia caused by cancer treatment with cytotoxic chemotherapy. These two agents use different

mechanisms of action, yet both serve to combat and decrease the incidence of neutropenia.

Trilaciclib was approved by the U.S. Food and Drug Administration in February 2021 and is currently available for patient use. Plinabulin has not yet been approved by the FDA. Rather, the federal agency requested that the manufacturer complete an additional trial prior to reconsideration.

IfPA has previously raised concerns about ICER's habit of prematurely initiating reviews. The FDA's approval should be complete before ICER initiates a value assessment. Federal officials review all available data before making a determination about the safety and efficacy of new treatments. It is their job to decide whether a breakthrough medication should be approved for use. In some cases, as with plinabulin, federal officials may determine that more data is needed. Decisions like these render ICER's assumptions and calculations incomplete. This can be avoided in the future by reviewing only federally approved drugs and devices.

Process Irregularities

Rather than suspend or pause this review due to the unforeseen circumstance surrounding plinabulin, ICER instead announced it will fast track and finalize the review with process changes.

While altering a well-documented process midway through is cause for concern, the cancellation of the only public meeting is particularly alarming. The public meeting would have given the cancer community an opportunity to hear and see the process unfold. It would have also provided a platform for stakeholders to express their experiences and raise concerns directly to reviewers.

With a disease like cancer, it is unrealistic to expect a panel or review board to include all stakeholders. However, the opportunity to participate in a public meeting, which allows patients, providers and other invested parties to provide their unique viewpoints, can be valuable for reviewers. This importance is elevated when dealing with diseases like cancer, where clear disparities and inequities exist. Due to the removal of the public meeting, those who want to offer comments – about the review or the unseemly process changes – are left with submitting a written comment as their only option.

Patients, especially those from the communities who are most affected by cancer, should be offered more opportunities, not fewer, to comment on processes that could affect their long-term access to new treatments. The data is clear that the current standard of care for the side effects of chemotherapy, including neutropenia, is not sufficient. Over 60,000

patients are hospitalized, at a cost of more than \$2.7 billion, and more than 4,000 die of febrile neutropenia annually.^{1, 2}

The new drugs assessed in this ICER review could provide an opportunity for cancer patients to expand their treatment options. Plinabulin is the first drug submitted for FDA approval that would address neutropenia during the first week of chemotherapy, providing an innovative option to the current G-CSF standard of care.³ While the value of increasing treatment options is difficult to quantify, it must not be dismissed. Neither should patients. They deserve the opportunity to publicly share their concerns about the seriousness of chemotherapy side effects as well as their optimism about the potential lifesaving benefits of a new medication.

ICER's reports, once finalized, live in the public domain and are used by many groups. Among those most interested in ICER's findings are health insurers, both public and commercial. It is no secret that ICER's reviews are referenced as evidence to justify utilization management techniques like prior authorization or to place medications on unaffordable specialty tiers. These barriers serve to limit patients access to novel treatments.

To diminish patients' participation in a process that could eventually be used against them is, simply stated, wrong.

Conclusion

Removing the most direct opportunity for patients to contribute to this review flies in the face of ICER's pledge to incorporate more patient input. ICER's review, despite its shortcomings, has the potential to impact cancer patients' access to novel treatments. For these reasons, IfPA urges ICER to consider these concerns as it moves forward with finalizing the evidence report.

If IfPA can provide further information or aid the Institute for Clinical and Economic Review in any way, please contact IfPA at 202-951-7097.

Sincerely,

Unidere un po winskun

Michelle M. D. Winokur, DrPH Executive Director Institute for Patient Access

¹ https://www.cdc.gov/cancer/dcpc/research/articles/neutropenia.htm
²

https://www.cdc.gov/cancer/dcpc/research/articles/neutropenia.htm#:~:text=Th e%20total%20cost%20for%20adults,for%20children%20(%241.6%20billion). ³ https://beyondspringpharma.com/pipeline/plinabulin/

UNIVERSITY OF MINNESOTA

Twin Cities Campus College of Pharmacy Graduate Program in Social & Administrative Pharmacy 7-155 Weaver-Densford Hall 308 Harvard Street S.E. Minneapolis, MN 55455

Dr S D Pearson President Institute for Clinical and Economic Review Two Liberty Square, 9th Floor BOSTON MA 02109

20 February 2022

PUBLIC COMMENT FOR REVIEW OF NOVEL AGENTS TO PREVENT CHEMOTHERAPY INDUCED NEUTROPENIA AND OTHER MYELOSUPPRESSIVE EFFECTS

I refer to your recently released Draft Evidence Report for trilaciclib and plinabulin to prevent chemotherapy induced neutropenia¹.

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science ². That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. The QALY, as you have been informed on a number of occasions, is a mathematically impossible construct with a paper in *F1000Research* and a letter to *Value in Health* pointing this out ^{3 4}.

More recently the attempt to bolster the standing of assumption driven simulations has been through the release in January last of the CHEERS 22⁵. Again, the modeling proposed fails the standards detailed above for your reference case. Of interest, however, is the neglect in CHEERS 22 of the information needs of formulary committees; the focus appears to be on submissions to academic journals. This assumes that the respective editors, many of who have endorsed this guidance, are willing to publish papers on imaginary value claims. As these value claims are assumption driven, we can presumably look forward to a plethora of such claims, including papers based on ICER models. I am not sure, from a professional perspective in health technology assessment that this gets us very far. As I have noted on previous occasions, surely if we accept the standards of normal science we should be looking to a research program that is predicated on the discovery of new, yet provisional facts on therapy benefits. Simply recycling assumptions with off-the-shelf simulation software provided by academic groups seems a somewhat barren endeavor where the claims for cost-effectiveness are, by design, non-evaluable.

My focus in this submission is on the use of utilities in your model for these two agents. This is important because, as demonstrated, the utilities are ordinal and not ratio measures and cannot support QALYs. If you want to support a QALY then your instrument must be designed to have single attribute, bounded ratio properties (i.e., a true zero, capped at unity).

As this requirement may be unfamiliar to ICER let me digress and give a brief outline of the required measurement standards in statistical analysis. Claims for response to therapy must recognize the axioms of fundamental measurement. Following the formalization by Stevens and others in the 1930s and 1940s, scales or levels of evidence used in statistical analyses are classified as nominal, ordinal, interval or ratio ⁶. Each scale has one or more of the following properties: (i) identity where each value has a unique meaning (nominal scale); (ii) magnitude where values on the scale have an ordered relationship with each other but the distance between each is unknown (ordinal scale); (iii) invariance of comparison where scale units are equal in an ordered relationship with an arbitrary zero (interval scale) and (iv) a true zero (or a universal constant) where no value on the scale can take negative scores (ratio scale). Nominal and ordinal scales only support nonparametric statistics. Interval scales can support addition and subtraction while ratio scales support the additional operations of multiplication and division as they have a true zero. This zero point characteristic means it is meaningful to say that the one object is twice as long as another. Given these limitations, the only acceptable empirically evaluable value claims are those designed for single attributes with interval or ratio properties. Multiattribute scales, unless the attributes have bounded ratio properties, are mathematically unacceptable as they lack dimensional homogeneity and construct validity.

While the utility of preference scales are ordinal scores with a limited (nonparametric) application in statistical analysis, in previous correspondence, I have pointed to a somewhat cavalier attitude in your consultant's modeling. This is shown in lumping together preference (or utility) scores from different instruments. This model seems no different with EQ-5D scores (it is not clear is these are EQ-5D-3L or EQ-5D-5L)^{7 8} lumped together with utility scores from a variant of the standard gamble technique ⁹ and time trade off (TTO)¹⁰. There appears to be no attempt to crosswalk or map these to a common base. Caution is required, as stated by Drummond et al in their primer on creating imaginary claims: in response to the question as to which system to use they point out that the decision does matter as *These systems are far from identical. They differ in the dimensions of health they cover, on the number of levels defined on each dimension, the description of those levels, and the severity of the most severe level¹¹. I can only surmise that where utility scores are difficult to find for the model, whatever you can find will suffice irrespective of their origin and health state description.*

If, as you claim, health economists have confidence that the ordinal preference scales have a true zero, then there is the question of negative values or 'states worse than death The fact that the composite scoring algorithms that support ordinal preference scores can generate negative values or states worse than death has been recognized since the algorithms were first applied; the response has been to ignore this unfortunate characteristic or, more bluntly, sweep it under the carpet. In the case of the EQ-5D-3L, for example, the most widely applied composite preference score, the algorithm determines scoring range is from 1 = perfect health to -0.58 (with death = 0). In the case of the application of utilities in model claims there are two questions of interest: (i) what is the distribution of ranked values for a given target patient population and (ii) what is the impact of

negative values (if present) on the overall 'average' EQ-5D-3L score. These are never addressed; least of all in your modeled claims. The average is, of course, disallowed as the score is ordinal (and disallowed also because it is dimensionally heterogeneous), but this is the form in which it is usually presented, with equally disallowed measures of dispersion (e.g., standard deviations, range). Interpreting a positive 'average' preference score which includes negative values is impossible; particularly as the average is meaningless.

It should not be though that negative 'average' ordinal preference scores are relatively infrequent. The best example of the pervasiveness of these negative scores is from the Tufts Medical Center Cost-Effectiveness Analysis (CEA) database. This database was initiated 46 years ago and comprises extracts from studies (now over 8000) that have presented cost-utility analyses. Apart from summarizing preference or utility scores from the various multiattribute instruments, the data base includes a range of impossible mathematical measures to include QALYs, cost-per-QALY claims and incremental cost-per-QALY claims. There are now some 36,000 preference scores for health states; obviously a go-to database for constructing imaginary modeled claims. Unfortunately, no one apparently recognized that these preference scores are composite ordinal 'averages' and that the entire exercise is essentially a waste of time (and mathematically disallowed); except, presumably, for users who believe ordinal preference scores are actually bounded ratio scales in disguise. This belief is challenged by the fact that, from the 100 health state 'average' preference scores on the Tufts CEA website, some 47% present with apparently negative values. The range of composite ordinal negative health states is from -0.01 to -0.55; the range for positive weights is from zero to 0.93. These ranges are questionable because they reflect the different algorithms used.

I realize that these arguments for the failure of preference scores and the QALY are unlikely to shake your belief in mathematically impossible imaginary claims. Even so your response would be welcome. Perhaps you could do better than last time when you simply acknowledged my comments but made no attempt to reply and justify your belief in constructing imaginary claims with ordinal preferences.

As it stands in the case of trilaciclib, your modeled claim (Table ES2) that a cost-per-QALY gained as first line therapy is \$2 million and the cost-QALY for modeled second line therapy is \$1.7 million is not to be taken seriously as they ignore the constraints of fundamental evidence. Similarly, your conclusions that under a range of threshold cost-per-QALY applications ranges from \$630 to \$750 for first line therapy and \$360 to \$520 for second line therapy are also impossible conclusions (Table ES3). While your model supporters may disagree, you are producing claims for pricing that should not even be considered. This is not just a conclusion that comes from the ordinal nature of preferences, but from the development of a lifetime model driven by assumptions that fails the standards of normal science.

Yours sincerely

Paul C. Langley, Ph.D. Adjunct Professor College of Pharmacy University of Minnesota

MINNEAPOLIS MN Email: langley@maimonresearch.com

REFERENCES

¹ Tice JA, Bloudek L, McKenna A, et al. Novel Agents to Prevent Chemotherapy-Induced Neutropenia and Other Myelosuppressive Effects; Draft Evidence Report. Institute for Clinical and Economic Review, January 25, 2022

² Langley P. Nonsense on Stilts – Part 1: The ICER 2020-2023 value assessment framework for constructing imaginary worlds. *InovPharm*. 2020;11(1): No. 12 https://pubs.lib.umn.edu/index.php/innovations/article/view/2444/2348

³ Langley PC and McKenna SP. Measurement, modeling and QALYs [version 1; peer reviewed] *F1000Research* 2020, 9:1048 <u>https://doi.org/10.12688/f1000research.25039.1</u>

⁴ Langley PC, McKenna SP. Fundamental Measurement and Quality Adjusted Life Years. ValueHealth. 2021:24(3)(:451

⁵ Husereau D, Drummond M, Augustovski F et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 22) Statement: Updated reporting guidance for health economic evaluations. *ValueHealth*. 2022;25(1):3-9

⁶ Stevens S. On the theory of scales of measurement. *Science*. 1946;103: 677-80

⁷ 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; September (pre print)

⁸ Chouaid C, Luciani L, LeLay K et al. Cost-effectiveness analysis of afatnib versus gefitinib for firest-line treatment of advanced EGFR-mutated advanced non-small cell lung cancers. *J Thorac Oncol.* 2012; 12(10):1496-1502

⁹ Nafees B, Stafford M, Gavriel S et al. Health state utilities for non-small cell lung cancer. *Health Qual Life* Outcomes. 200;6:84 i

¹⁰ Tolley K, Goad, Yi Y et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ.* 2013;14(5):749-59

¹¹ Drummond M, Sculpher M, Claxton K et al. Methods for the Economic Evaluation of Health Care Programmes (3rd Ed.). New York: Oxford University Press, 2015



February 22, 2022

Dear Institute for Clinical and Economic Review Representatives:

Lung Cancer Foundation of America (LCFA) appreciates the opportunity to submit comment with regard to Chemotherapy-Induced Neutropenia.

LCFA's mission is the improvement in survivorship of lung cancer patients through the funding of transformative science. While raising funds to support lung cancer research, LCFA will raise the public's awareness and serve as a resource for patients or anyone seeking answers, hope, and access to updated treatment information, scientific investigation, and clinical trials.

As a patient advocacy organization we recognize the challenge in evaluating effectiveness, access, and cost of new and developing health care interventions. We also applaud your commitment to understanding the patient perspectives, and would like to share the following perspectives both from our organization and from our patient speaker's bureau about the debilitating effects of chemotherapy and the unmet need to mitigate them. We are concerned that your draft analysis of Chemotherapy-Induced Neutropenia does not capture the real-world impact of chemotherapy on the lives of cancer patients.

As you know, in patients with extensive stage disease, median survival of 6 to 12 months is reported with currently available therapy, but long-term disease-free survival is rare.Survival rates for non-small cell lung cancer are somewhat higher, but still unacceptably low, especially when compared to breast, prostate and colon cancer survival rates. Time and time again, our patients have told us that quality of life is absolutely critical to making the most of the time they have left with their loved ones. Below are just a few of the anecdotal experiences we hear every day from patients about the huge impact of chemotherapy on their lives:

Montessa L., SCLC lung cancer:

• "Chemo literally knocks me out. It's like walking with legs of cement. I'm not even able to walk up and down a few stairs. I'm always concerned about being near family members as they can easily make me very ill without even knowing. And lots of blood work."

Lysa B., ROS1+ lung cancer:

• Side effects of chemotherapy for me included, "debilitating fatigue for several days; avoiding friends with young kids and large groups because of weakened immune system; and low white blood cell counts that sometimes cause a delay in treatment."

Terri C., KRAS Lung Cancer Patient, Advocate - Director, Founder, KRAS Kickers:

• "Chemo fatigue is like trying to swim in peanut butter in hopes of getting to an island of safety. Shouldn't this be studied, managed to be reduced? or prevented?"

Gina H., ALK+ non-small cell lung cancer:

• "I was diagnosed with stage IV lung cancer in 2015. I was given biomarker testing and my first treatment was a targeted therapy pill. Then I ran out of targeted therapies. In April of 2021 I started chemotherapy. When I got home, the exhaustion hit. Taking a nap was not optional. When I got tired, I had to go down. My immune system was compromised and so I couldn't get out in public, particularly bc of the fear of COVID. After 6 years of living with cancer, chemo made me feel like a cancer patient. Then, a clinical trial opened, and I had a chance to go back on a combination of targeted therapies. I withdrew from the trial after 9 months because the experimental drug made me feel like I couldn't breathe. I went from participating in Cross-Fit in October to not being able to walk up the stairs in November and unable to get off the couch in Dec. Today, I'm actually looking forward to starting chemo to help tame the cancer, and hopefully help my SOB and chest pain. I know it will make me tired, lose my hair, and limit my activities, but I also know it could help me have more time with my family. My quality of life may likely decline, but I'm thankful to be able to have more time with them.

In addition to reducing quality of life, adverse events such as low blood cell counts often require additional treatments and, in severe cases, hospitalizations, which can compromise patient outcomes. Among our goals as an organization is to ensure access to novel drugs, and we feel any obstacles to access would be detrimental to patient well-being.

I'll close with a statement from small-cell lung cancer patient Dorothy T., who describes the dramatic difference a treatment like trilaciclib made the second time she went through chemotherapy:

• "When my lung cancer recurred, I spoke to my doctor about the unbearable experience of chemotherapy. I told him I'd rather die than go through chemo treatments again. He told me about a drug that had been approved to help protect against the worst of the side effects I'd gone through. I can't say enough about the difference it made in my life. I wasn't sick, I wasn't exhausted, and the best part was my cell count didn't go down. It's scary to think I almost decided to give up on treating my lung cancer rather than go through chemotherapy ever again."

Thank you for the opportunity to participate in this review.

Jim Baranski Executive Director jbaranski@LCFAmerica.org 773.968.1308 LCFA EIN: 20-8730839



February 21, 2022

Dear Sir/Madam:

On behalf of the Tigerlily Foundation, I am writing to express my concern about several issues concerning ICER's actions. One of our core mission areas is to serve as an advocacy support for and with patients and we are concerned about how your actions will impact the lives of patients, particularly the underserved. The following outlines our key concerns:

- 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. You are relying on clinical trial data that excludes marginalized groups of patients, as they are not adequately represented in trials, meaning that you are making decisions for millions of people about whether these drugs/treatments are cost effective for white patients only. This is gross negligence on your part and is part of why inherent racism still permeates many of our systems today. Studies and data show diverse patient involvement is key to developing effective treatments and guidance has been developed by government agencies for this very reason. We have collectively worked hard to ensure the patient voice is included throughout this process, including from trial design through after market analysis. Limiting patient access to provide feedback at this stage sets back that momentum and infringes on patient rights. It also sends the message that ICER is above proven best practices.
- **Review of Medications Not Yet Approved by FDA.** There an issue with analyzing drugs/treatments that have not been approved by the FDA for, as the FDA is an entity that is in place to ensure the safety of human beings who use drugs/treatments. In addition, since people of color are not sufficiently represented, the efficacy/safety of such protocols for this population is unclear.
- **Putting Cost Before Human Life**. What you are doing is negligent and setting a scary precedent- putting cost and utilization management before patient needs. Chemotherapy-induced neutropenia is a severe side effect of chemotherapy that increases risk of infection and hospitalization. Not only does this condition affect the patient's ability to adhere to treatment, but negatively impacts quality of life and poses a risk of death. It is unconscionable that you would put money before human life.



• Lack of Patient Engagement in Public Comment. One of the two therapies under your review has not been FDA-approved and has been pulled back from the FDA approval process. Despite this, you are moving forward with your final report – cancelling the only public meeting for your review of two drugs for the prevention of chemotherapy-induced neutropenia – meaning that you are moving forward without providing the cancer community the opportunity to voice their concerns at a public meeting, one of the few opportunities for patient input. Representation is critically important to ensuring that people of all colors, particularly BIPOC populations have access to the best treatments. Not having a voice could mean loss of quality of life, and in some instances, have fatal consequences. We must have agencies and leaders now more than ever to be including patient advocates throughout this process. Black and Brown people, have higher mortality rates from breast cancer. As an advocate for populations such as these, we find it shocking that you would deny human beings the opportunity to have a voice.

We urge ICER to take our comments into consideration and act responsibly.

Sincerely,

wel Storma

Maimah S. Karmo, Founder & President



February 22, 2022

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

Dr. Pearson:

Re: PUBLIC COMMENT: NOVEL AGENTS TO PREVENT CHEMOTHERAPY-INDUCED NEUTROPENIA AND OTHER MYELOSUPPRESSIVE EFFECTS

I am a very blessed 10 year survivor of Triple Negative Breast Cancer. I founded TOUCH, The Black Breast Cancer Alliance to drive the collaborative efforts of patients, survivors, advocates, advocacy organizations, health care professionals, researchers, and pharmaceutical companies to work collectively and with accountability towards the common goal of advancing the science for Black women and eradicate Black Breast Cancer. 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. We cannot afford not to get the best care and opportunities to save our lives.

We believe that true health equity is when HCP's, researcher, medical authorities and organizations that influence health treat everyone they interact with like family. It's as simple as that, the GOLDEN RULE, treat others like you want to be treated, treat others like you would treat your family members.

The cancellation by the Institute for Clinical and Economic Review of the meeting to review the two drugs for the prevention of chemotherapy-induced neutropenia is an unfortunate circumstance. Since the FDA did not approve one of the drugs under review, we are now faced with the fact that the clinical performance between these therapies has not been adequately scrutinized. This is making it difficult to conduct a reliable comparison. Because ICER has continued to move forward with a report containing speculative information, we are now in a situation that can lead to **poor decision making**,

TOUCH, The Black Breast Cancer Alliance 1011 Bay Ridge Ave. Suite 200 Annapolis, MD 21403 <u>www.touchbbca.org</u> 443-758-1924



that may impact patient care and the exclusion of a drug that could be of significant benefit to a patient.

My organization focuses on getting more black women into clinical trials – an ongoing effort. And until minority representation in research increases, advocates like me an my advocacy partners are left conveying our communities' experience through other avenues – like public meetings. We need access to more and different medications to combat breast cancer and its related conditions like neutropenia. Frankly depriving us the public meeting is akin to removing the voice of Black women, who experience the highest rate of breast cancer mortality of any racial or ethnic group.

We are extremely disheartened that ICER's plan to cancel an opportunity to speak out about the experience of living with chemotherapy-induced neutropenia or the value they see in new treatment options will be a detriment not only to the type of treatments available to an individual but also the quality of life of those patients.

As we all "supposedly" strive towards health equity, this is definitely not it.

Sincerely,

Ricki Fairley

Ricki Fairley CEO TOUCH, The Black Breast Cancer Alliance

> TOUCH, The Black Breast Cancer Alliance 1011 Bay Ridge Ave. Suite 200 Annapolis, MD 21403 <u>www.touchbbca.org</u> 443-758-1924

Dear ICER,

I'm a small-cell lung cancer patient, and I'm writing on behalf of COSELA. I know your role is an important one – to evaluate drugs for their benefit and value to patients. I'm here to tell you that you cannot put a price on the benefit that trilaciclib provided to me. When I first had lung cancer several years ago, I was prescribed chemotherapy. It was indescribably awful, like an out-of-body experience. I'd fall on the floor at night going to bathroom. I couldn't take a shower for five days. I couldn't eat anything, and I lost 50 lbs. They admitted me to hospital, and I ended up staying there for 4 days after each treatment. My white cell counts went from 9,000 to 300. The doctor said he was so afraid for me. I really, really thought I was dying. I once said to God, "I'm ready. Take me." After that experience, I said I'd never, ever get chemotherapy again, and I meant it. Last year, I went in for a CT scan and they found a spot on my lung. They told me I'd need chemotherapy again, and I refused at first. I was seeing a new doctor, and he told me about a drug (COSELA) that could help protect me against some of the worst side effects I'd experienced. I can't say enough about the difference it's made. With COSELA, I feel a hundred percent better than I did during the first round of chemo. I might have lost 8 pounds but that's it. I'm eating, I don't look like I'm sick, and I don't feel like I have cancer. It's scary to think I almost decided to give up on treating my cancer rather than go through chemotherapy again. It's important that all patients who need it can get access to this drug, because the difference it can make is truly remarkable.

Thank you,

Dorothy Turner

Dear Sir or Madame,

I read with interest your draft report and write to provide public comment. I was an investigator referenced in your report and, perhaps more importantly, an oncologist with many small cell lung cancer patients. I commend you for the inclusion in your report of patient and caregiver perspectives. I hope that as an oncologist deeply invested in the quality of lives of my patients, that I may be counted as a caregiver and offer a perspective complimentary to that already expressed in your report. This perspective surrounds quality of life. Quality of life is the most important reason that I treat incurable cancers, yet can be very hard to measure and understand. In the office, I go beyond toxicity tables by asking patients open ended questions about how they feel. Over time and experience, this leads to some understanding of an axis of well-being not fully captured by toxicity tables. With regards to myelosupression, any oncologist can tell you that patients feel poorly when their counts are suppressed, and that this does not correlate purely with anemia. The three randomized phase II trials of trilaciclib did collect patient reported outcomes to attempt to quantify the patient experience to the extent possible. These measures showed an improvement in patient-reported quality of life, particularly fatigue. In comparing the patient experience pre-trilaciclib to patients treated with trilaciclib, I see a meaningful improvement in this axis of well-being. I encourage discussion of fatigue and quality of life in your final report.

Best,

Jared Weiss, MD Professor of Medicine Section Chief of thoracic and head/neck oncology at UNC Vice President of cancergrace.org Advocate with Lung Cancer Initiative of NC