



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

Response to Public Comments on Draft Evidence Report

March 17, 2022

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Manufacturers		
Amgen		
1.	<p>The device failure rate is over-estimated, which misaligns with the available evidence and underrepresents the value of Neulasta.</p> <ul style="list-style-type: none"> 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. <p>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 <i>Draft Evidence Report</i> (6.9% of cycles) is taken from a study with a very low sample size in which Townley <i>et al.</i> 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. Several other sources suggest an even lower likelihood of device failure, ranging from 0.1% to 1.92%.</p> <p>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 ‘<i>Academic in Confidence</i>’ as they were also submitted to a health authority and accepted for presentation at an upcoming 2022 scientific conference</p>	<p>Thank you for the additional information regarding the Onpro failure rate. We look forward to seeing the published data. Our results come from a peer reviewed paper that summarized published failure rates. We did not feel that it was necessary to update the text. Importantly, it is not part of the modeling and does not impact our assessment of the net health benefit and cost effectiveness of the drugs that are the focus of the review.</p>
2.	<p>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.</p> <ul style="list-style-type: none"> We request that ICER adjust the rating to “Insufficient”, until additional data are available. 	<p>Thank you for the suggestion. We considered the FDA determination and after discussion with our full team, we continue to feel that the available evidence for plinabulin is consistent with a C++ rating.</p>

<p>ICER’s draft report should align with the FDA’s recent determination that data for plinabulin was “not sufficiently robust to demonstrate benefit.” 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.</p>	
<p>3. 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.</p> <p>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. In the period between Q3 2018 and Q2 2020 the average selling price (ASP) of Neulasta® fell by 16%.</p> <p>In prior assessments, multiple manufacturers have expressed concerns about the inclusion of a markup in the model 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. <i>We echo those prior comments here: Amgen does not set, control nor have any input into a facility markup.</i> Additionally, as ICER indicates, the scenario in which the markup is applied, has little impact on the assessment of plinabulin. It is reasonable to</p>	<p>We acknowledge that individual payers and health systems have negotiated reimbursement for G-CSF which may be different than in the base case (ASP) and the G-CSF markup scenario. During the course of this evaluation, we heard from payer stakeholders that a higher markup reflects what at least some payers see as a reasonable scenario to include from the health system perspective. This estimate reflects actual data received for G-CSF products. It is not clear what will happen with the new products, but including a markup on these would be conjecture at this point.</p>

	<p>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 <i>must</i> 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.</p>	
<p>G1 Therapeutics</p>		
<p>1.</p>	<p>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.</p> <p>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.</p> <ul style="list-style-type: none"> • 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. 	<p>Thank you for your comment. We respectfully disagree. We believe that death, hospitalizations, and SAEs are some of the most important outcomes to patients with cancer undergoing chemotherapy. They matter to patients and potentially capture unmeasured adverse effects of the novel therapy.</p>

2.	<ul style="list-style-type: none"> 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. (Weiss, Goldschmidt et al. 2021) 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). In this study, prognostic factors for survival were not balanced between the two arms. This was noted in the discussion section of the G1T28-03 publication. More patients in 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). This imbalance is likely unfavorable to trilaciclib for both survival and AEs, as the trilaciclib patients were notably more frail. 	Thank you for the feedback. Since all three trials were randomized, we feel that the pooled data in the cited publication represent a fair assessment of the adverse events compared with placebo.
3.	<ul style="list-style-type: none"> 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. Patients receiving placebo experienced more <i>recurring</i> 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), 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 (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. 	Thank you for that clarification. We agree and have added the sentence “However, the rate of hospitalizations was lower in the trilaciclib group (7.9 per 100 cycles versus 15 per 100 cycles) suggesting that some patients in the placebo group were hospitalized multiple times.”
4.	<p>The clinical evidence rating for trilaciclib should be changed to A, due to the high certainty of the evidence and substantial benefit.</p> <ul style="list-style-type: none"> 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. 	Thank you for describing your judgement about the evidence rating. Given that ES-SCLC has an extremely high mortality (see Kaplan Meier curves for mortality, particularly in the paper presenting pooled data), we would typically want to see a total mortality benefit to judge that the net health

	<ul style="list-style-type: none"> • ES-SCLC is a highly fatal disease associated with significant morbidity and limited life expectancy. <ul style="list-style-type: none"> ○ 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. 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 <i>substantial</i> clinical benefit is one of the criteria for evaluation. • 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. 	<p>benefits are substantial. But as noted in the report, there is not even a trend towards a mortality benefit. In addition, with a small sample of randomized data and some inconsistency in other measures of clinical benefit, we continue to feel that a C+ rating is justified.</p>
<p>5.</p>	<p>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.</p> <p>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.</p> <ul style="list-style-type: none"> • 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 2008(Nafees, Stafford et al. 	<p>We thank G1 for bringing to our attention that the health state utility estimates in Nafees 2008 and Tolley 2013 were designed to describe a 3-week period. The model inputs have been revised to reflect a decrement in utility lasting one full cycle (21 days).</p>

2008) and Tolley 2013.(Tolley, Goad et al. 2013) In Nafees 2008(Nafees, Stafford et al. 2008), 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 2013 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 2008, 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.

	<ul style="list-style-type: none"> • Input from Dr. Andrew Lloyd, who co-authored Lloyd 2006 (a utility study in breast cancer that was a precursor to Nafees 2008) and Nafees 2017 (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. 	
6.	<p>ICER should incorporate more recent data into its estimates of disutility for myelosuppressive events.</p> <p>Nafees 2017 (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 ICER and NICE).</p> <ul style="list-style-type: none"> • 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 2017) 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 	<p>We acknowledge that multiple sources of utility data are available in published literature for adverse events in lung cancer, each with limitations (Paracha 2018). In the revised model, we have changed the utility inputs to use the more recent disutility estimates from Nafees 2017, with fatigue used as a proxy for anemia.</p>

	<p>anemia, and by extension, the more recent Nafees 2017 inputs should also be incorporated for anemia.</p>	
<p>7.</p>	<p>Proportions of myelosuppressive AEs requiring hospitalization should be sourced from real-world studies rather than trial data.</p> <p>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.</p> <ul style="list-style-type: none"> • Hospitalization parameters can instead be computed using episode-level resource use data from Rashid 2016, 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.(Epstein, Nelms et al. 2021) 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 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. 	<p>The trilaciclib trials collected hospitalization data due to myelosuppressive events by treatment arm, which have been published as additional endpoints from the trials. Despite limitations with potential missingness and geographical variation in practice patterns, we consider these data to be best available direct evidence for the impact of trilaciclib on HCRU associated with myelosuppressive events.</p> <p>We appreciate the RWE submission and continued evidence generation regarding the burden of myelosuppressive events in this population. It is unclear from the poster what coding methodology was used for identification of cases and inpatient claims attributable to myelosuppression. The finding that 74.3% of patients have an inpatient claim for myelosuppression may be due to an overestimation of the proportion of inpatient claims truly attributable to the event, if all diagnosis codes in any position are considered.</p> <p>We have added an additional scenario analysis using episode-level resource data from Rashid 2016. Because the cost of multiple events in the model is additive, the episode-level resource use for single events in Rashid was used rather than a pooled estimate based on single and multiple events as submitted in Appendix Table 6, to avoid double counting of costs.</p>

8.	<p>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.</p> <p>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.</p>	<p>These model inputs have been revised to rely on pooled estimates rather than Daniel 2020 alone.</p>
9.	<p>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.</p> <p>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.</p>	<p>We have revised the model to consider use of ESA directly, by treatment arm, rather than by the proportion of anemia events which are managed by ESAs.</p>
10.	<p>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.</p> <p>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 ≥ 3 myelosuppressive AEs, the grade ≥ 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.</p> <ul style="list-style-type: none"> 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 	<p>It is a limitation of our model that Grade 3 and 4 AEs are not differentiated. Data to differentiate utility decrement and cost between Grade 3 and Grade 4 is limited.</p> <p>Data directly from the clinical trials was used consistently throughout the model. Due to the event rate and relatively small trial size, some individual proportions are generated by small patient counts. We have accounted for this uncertainty in the sensitivity analyses, where the 95% CI and SEs are calculated based on the numerator and denominator from the trials.</p> <p>The proportion of neutropenia which is febrile neutropenia is an important model parameter and is applied to the proportion of patients who experience severe neutropenia, by trial arm. We note that while the proportion that is FN is 5.3% (1/19) for trilaciclib and 2.7% (3/113) for placebo in the 1L population, the absolute number of FN episodes that the model estimates is lower in the trilaciclib arm (0.011 for trilaciclib vs 0.034 for placebo).</p>

	<p>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.</p> <ul style="list-style-type: none"> 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. 	
11.	<p>Report incremental cost per severe myelosuppressive event avoided as an additional output.</p> <p>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.</p>	We have revised the report to include the cost per severe myelosuppressive event avoided in the analysis of trilaciclib.
12.	<p>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.</p> <p>Based on Liou 2007, 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.</p>	In the revised model, inclusion of indirect costs changes the incremental cost per QALY by more than 20% in the 1L ES-SCLC population. Therefore, we have included the societal perspective as a co-base case in the 1L population.
13.	<p>Listed below are factual inaccuracies that should be corrected or addressed, and speculative statements that we request to be omitted.</p>	We have corrected the cited errors in the model calculations and inputs.
#	Comment	ICER Response
Clinicians		
Dr. Jeffrey Crawford		

<p>1. 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.</p> <p>The clinical trial data for trilaciclib validates very nicely the reduction in neutropenia, anemia and thrombocytopenia, with the use of trilaciclib 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.</p> <p>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 well-being, 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.</p>	<p>Thank you. We appreciate the importance of quality-of-life outcomes for patients. We have added paragraphs to the main report describing the quality-of-life results using the FACT-G quality of life instrument, as that is the broadest measure of quality of life that has been reported from the trials. We also referenced the Supplemental Tables with all of the published quality of life scales and subscales.</p> <p>We had reviewed the Figure that you included: it reports the results of a specialized quality of life scale - the Functional Assessment of Cancer Therapy-Anemia. This is not a measure of overall health related quality of life, like the SF-36, EQ-5D, or the FACT-G. In addition, the analysis was atypical. Usually the change in quality of life score or the absolute quality of life score is compared at different time points. The authors report a time to event analysis.</p>
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2.	<p>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.</p>	<p>Thank you for sharing your personal and practice experience with trilaciclib. We encourage you to publish your findings when sufficient numbers of patients receive the drug.</p>
<p>Dr. Keith Crawford</p>		
1.	<p>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.</p> <p>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 chemotherapy-induced 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.</p>	<p>As we state in the review, we do not think that it is appropriate to directly compare the two agents (scrutinize the clinical therapy between these two therapies) for several important reasons. First, they have been studied in different patient populations (different underlying cancer diagnoses and different chemotherapy combinations). Second, one is used without G-CSF, the other with G-CSF.</p> <p>We feel that given the current state of the evidence for the two drugs, it would be misleading and could potentially lead to poor patient care if we directly compared the two agents.</p> <p>We also note that trilaciclib was added to the project during the scoping phase, so the FDA’s decision to deny plinabulin was a completely separate issue.</p>

<p>2.</p>	<p>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.</p> <p>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.</p>	<p>You are correct that decision-making processes are different in other countries, where health technology assessment using methods very similar to ICER's is a required step before adoption and reimbursement. In the US, pricing is set and marketing occurs immediately after regulatory approval, which is why ICER must link its timelines to the regulatory timetable and occasionally alter its approach when the FDA delays or denies approval.</p> <p>As we have mentioned many times previously, cost-effectiveness analysis using the QALY is the internationally-accepted method for evaluating how price aligns with value. In addition, this is but one component of ICER's approach, which also includes synthesis of the clinical evidence and evaluation of contextual concerns that cannot easily be quantified.</p> <p>Finally, while a public meeting on this topic was not deemed feasible, ICER's process includes multiple formal and informal opportunities for patients and caregivers to engage with our review, and actively reaches out to disease specific patient organizations for input in each review from beginning to end of the process. For each review, we seek out input from the major disease-specific patient advocacy organizations and patients who are living with the condition that is the subject of our review. Our process also includes multiple opportunities for feedback from the broader patient and advocacy communities, including explicit review of early drafts of our report.</p>
<p><i>Florida Cancer Specialists and Research Institute</i></p>		
<p>1.</p>	<p>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.</p> <p>We ran a RWD analysis at FCS to understand the burden of chemotherapy-induced myelosuppression (CIM) in patients with extensive-stage small-cell lung</p>	<p>Thank you for sharing your clinical experience. We encourage you to publish it so that ICER and other groups can include these findings in future comparative effectiveness and cost effectiveness analyses.</p>

<p>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.</p> <p>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.</p> <p>We strongly endorse its continued use, development and hopefully label expansion to other cancer types and other indications.</p>	
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Dr. Jared Weiss

<p>1. 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 myelosuppression, 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</p>	<p>Thank you for your insights and suggestions. See the response above about our additions to the main report highlighting the quality-of-life measures.</p>
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	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.	
#	Comment	ICER Response
Patient/Patient Groups		
Carrie's Touch		
1.	<p>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.</p> <p>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.</p>	<p>Please see above regarding cancellation of the public meeting as well as the multiple opportunities we have preserved for engagement with patients, caregivers, and other key stakeholders.</p>

<p>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.</p>	
<p>Lung Cancer Foundation of America</p>	
<p>1. 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.</p> <p>Montessa L., SCLC lung cancer:</p> <ul style="list-style-type: none"> • “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.” <p>Lysa B., ROS1+ lung cancer:</p> <ul style="list-style-type: none"> • 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.” <p>Terri C., KRAS Lung Cancer Patient, Advocate - Director, Founder, KRAS Kickers:</p> <ul style="list-style-type: none"> • “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?” <p>Gina H., ALK+ non-small cell lung cancer:</p>	<p>Thank you for helping to expand on the patient experience of chemotherapy. However, our review is not focused specifically on chemotherapy. We were trying to capture the particular experiences of patients who suffer neutropenia or other forms of myelosuppression as these are the adverse events that the new therapies are hoping to limit.</p> <p>We added an additional patient story describing her initial experiences with chemotherapy and the contrast in her experience when she received trilaciclib. We think that story captures some of the flavor of the anecdotes that you provided.</p> <p>Of course, each patient is an individual with unique characteristics and unique experiences from chemotherapy. A single evidence assessment can never completely capture the full heterogeneity of the patient experience.</p>

	<p>“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 because 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.</p>	
2.	<p>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.</p> <p>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:</p> <p>“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.”</p>	<p>Thank you. Dorothy T. submitted her own story and we have both responded to her comments and have added her feedback to the section on “Patient and Caregiver Perspectives.”</p>
Tigerlily Foundation		
1.	<p>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.</p>	<p>Thank you for your comment. We wholeheartedly agree that it is essential that clinical trial populations reflect the full</p>

	<p>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.</p>	<p>spectrum of patients affected by the disease. In fact, we have a section of our report that highlights populations who are particularly affected by the disease of interest but may be under-represented in the clinical trial data (see recent reports on Lupus Nephritis and Myasthenia Gravis, where this was a particular issue for Black patients.) Please continue to shine light on these structural issues and advocate for change at the level of the FDA, so that manufacturers are sent a clear message that pivotal clinical trials should represent the populations affected by disease.</p> <p>We have added your insights on underrepresentation of Black patients in clinical trials to the “Patient and Caregiver Perspectives” section of the report.</p> <p>Please see our response to the comment above regarding opportunities for public engagement, even without a public meeting on the topic.</p>
<p>2.</p>	<p>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.</p>	<p>We recognize that data are often limited for new treatments. However, patients, clinicians, and insurers are still faced with decisions about how to best use these treatments once they are approved for use by the FDA. Thus, we view comparative effectiveness research and economic modeling as important ways to identify key inputs that impact the effectiveness and cost of a new treatment. Our report highlights the limitations of these data as well.</p>
<p>3.</p>	<p>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.</p>	<p>Health systems that overpay for new treatments face challenges in funding other valuable drugs and services, putting patients at risk. This also leads to inexorably higher insurance premiums, pricing some patients out of the market and harming all of us.</p> <p>Further, as noted above, the cost-effectiveness analyses presented are only one part of this report. It also includes a detailed review of the existing literature as well as input from stakeholders highlighting potential other benefits of these</p>

		agents as well as key contextual factors that should be considered by policymakers.
4.	<p>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 and face many health disparities, and Black women, in particular, 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.</p>	Please see above regarding the multiple opportunities that we have preserved for patients, caregivers, and other members of the community to engage with this topic and report, including the opportunity for public comment on the draft report.
<i>TOUCH The Black Breast Cancer Alliance</i>		
1.	<p>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.</p>	Thank you for your important input. We have added it to the “Patient and Caregiver Perspectives” section.
2.	<p>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.</p> <p>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, that may impact patient care and the exclusion of a drug that could be of significant benefit to a patient.</p>	<p>Please see our response above regarding the multiple opportunities that ICER has preserved for public engagement in the process and report, despite our decision to cancel the public meeting.</p> <p>Please also see our response above regarding our decision not to directly compare these therapies, which are used in different populations and with a different treatment paradigm—direct comparison would be irresponsible.</p> <p>Finally, despite the decision to cancel the public meeting, we felt strongly that stakeholders deserved to see all of the data</p>

	<p>My organization focuses on getting more black women into clinical trials – an ongoing effort. And until minority representation in research increases, advocates like me and 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.</p> <p>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.</p>	<p>generated for these therapies to date as well as our interpretation of it.</p>
<p>Dorothy Turner</p>		
<p>1.</p>	<p>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 eight 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</p>	<p>Thank you for sharing your experiences with cancer and trilaciclib. We have incorporated them into the “Patient and Caregiver Perspectives” section of the report.</p>

	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.	
#	Comment	ICER Response
Other		
Institute for Patient Access		
1.	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.	Please see above regarding cancellation of the public meeting as well as the multiple opportunities we have preserved for engagement with patients, caregivers, and other key stakeholders.
2.	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.	Please see our responses above regarding the need for ICER to tie its process to the FDA regulatory timeline, as well as the interest in making all information on these agents generated to date publicly available.
3.	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.	Please see above regarding meeting cancellation and our preservation of multiple opportunities for patient, caregiver, and other stakeholder engagement with the process and report.
Paul Langley		
1.	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 if these are EQ-5D-3L or EQ-5D-5L) lumped together with utility scores from a variant of the standard gamble technique and time trade off (TTO). There	Thank you, your concerns are noted. As we have expressed before, we (and most health economists) are confident that changes in the EQ-5D (and other multi-attribute utility instruments) do have ratio properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level), with preference weights assigned to different attributes. We fail to see why this should be considered as an

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 level.* 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 thought 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

ordinal (ranked) scale. The dead state represents a natural zero point on a scale of health-related quality of life. Negative utility values on the EQ-5D scale represent states considered worse than dead. We do not find that this lacks face validity. We also appreciate the concerns about relying solely on QALYs. They are only one component of the value assessment, and many of the issues you raise are part of the "Potential Other Benefits and Contextual Considerations" section, which are essential in assessing value.

	<p>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.</p>	
2.	<p>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.</p>	<p>We are unclear which set of “fundamental evidence” you are describing. As mentioned above, cost effectiveness is but one input into ICER’s process, and we urge you to review the uncertainties noted in the clinical evidence as well as the other benefits and contextual considerations.</p>