

October 8, 2024

Sarah K. Emond, MPP  
President and Chief Executive Officer  
Institute for Clinical and Economic Review  
Two Liberty Square, Ninth Floor  
Boston, MA 02109

Dear Ms. Emond,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment of tabellecleucel for Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV +PTLD).

ICER acknowledges the severe toll EBV+PTLD takes on both patients and caregivers and the reality that current treatments can come with a host of side effects that further impact quality of life. PIPC encourages ICER to take the following comments into consideration.

**Caregiver impact should be included in the model.**

ICER chooses not to include caregiver costs in the model, despite acknowledging in the opening of the report that caregiver burden is high given the severity of disease and the side effects of currently available treatments. The literature supports this assertion that caregiver burden for PTLT is substantial.<sup>1</sup> The modified societal perspective ICER employs uses a proxy version of caregiver cost, while neglecting to incorporate caregiver quality-of-life. PIPC asserts that ICER should be incorporating both direct costs and caregiver quality of life and that both should be included in ICER's base case model.

**ICER's model does not reflect the reported results in the trial data it has chosen to use.**

The ICER model assumes that the survival benefit for tabellecleucel is the same for patients with hematopoietic stem cell transplantation (HSCT) and solid organ transplant (SOT). However, the evidence the report relies on clearly states that the survival benefit is different. The ALLELE RCT reports Median survival was 18.4 months in all patients and 16.4 months in SOT, which suggests survival would be higher in HSCT.

ICER should adhere to the rates of utilization in the trial data it has chosen to use instead of extrapolating its own assumption about dosing. The ICER report states that all patients given tabellecleucel are assumed to receive 3 cycles of treatment. The source of the efficacy data suggests all patients that received at least 1 cycle of tabellecleucel - with a maximum of 3 - were included in the trial results.<sup>1</sup> despite this data, the ICER model assumes *all* patients received all 3

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<sup>1</sup> Deng LX, Sharma A, Gedallovich SM, Tandon P, Hansen L, Lai JC. Caregiver burden in adult solid organ transplantation. *Transplantation*. 2023 Jul 1;107(7):1482-91.

cycles. The dosing in the model should reflect the source of the efficacy data.<sup>1,4</sup> If the mean/median dosage for those patients treated was between 1 and 3 cycles, then the costs should reflect that, as the efficacy data reflects the actual, not preferred, rate of utilization/dosing. We urge ICER to revisit the model to reflect the actual level of utilization that generated the efficacy results from the RCT, not a hypothetical treatment regimen.

### **ICER’s oversimplification risks distorting the actual costs of the treatment being evaluated versus that of usual care.**

In the description of the ICER model the report states that they assume that ‘*after treatment failure with tabellecleucel (or usual care) there is only one subsequent treatment.*’ It is not reasonable to apply this rule equally with respect to subsequent treatment costs for patients who remain alive after successful treatment with tabellecleucel and usual care.

The basic assumption is not accurate based on the literature suggesting that only a fraction of patients undergo subsequent treatments upon treatment failure in usual care.<sup>2 3</sup> This assumption is contrary to the goal of assessing the treatment’s clinical efficacy. The reason cost of treatment will accrue more rapidly for patients being treated with tabellecleucel is that a much higher proportion of patients being treated remain alive at each timepoint throughout the time horizon of the model than those in the usual care arm. The goal should be to keep patients alive for longer, so a modeling construct should not work against that goal.

### **ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.**

Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions,<sup>4</sup> and people with disabilities.<sup>5</sup> There is widespread recognition that the use of the QALY is discriminatory, reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.<sup>6</sup> The recent nondiscrimination regulations governing Section 504 of the

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<sup>2</sup> Socié G, Barba P, Barlev A, Sanz J, García-Cadenas I, Chevallier P, Fagioli F, Guzman-Becerra N, Kumar D, Ljungman P, Pigneux A. Outcomes for patients with EBV-positive PTLD post-allogeneic HCT after failure of rituximab-containing therapy. *Bone marrow transplantation*. 2024 Jan;59(1):52-8.

<sup>3</sup> Dharnidharka V, Thirumalai D, Jaeger U, Zhao W, Dierickx D, Xun P, Minga P, Sawas A, Sadetsky N, Chauvet P, Sundaram E. Clinical outcomes of solid organ transplant patients with Epstein-Barr virus-driven (EBV+) post-transplant lymphoproliferative disorder (PTLD) who fail rituximab plus chemotherapy: a multinational, retrospective chart review study. *Blood*. 2021 Nov 23;138:2528.

<sup>4</sup> Paulden M. Recent amendments to NICE’s value-based assessment of health technologies: implicitly inequitable?. *Expert review of pharmacoeconomics & outcomes research*. 2017 May 4;17(3):239-42.

<sup>5</sup> Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. *Health economics*. 1999 Feb;8(1):25-39.

<sup>6</sup> [https://www.ncd.gov/sites/default/files/NCD\\_Quality\\_Adjusted\\_Life\\_Report\\_508.pdf](https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf)

Rehabilitation Act also bar the use of discriminatory measures such as QALYs in decisions impacting access to care among entities receiving federal financial assistance.

We share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities.<sup>7</sup> It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions for patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, older adults, and certain communities of color.<sup>8</sup> With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.

**ICER continues to assume a linear relationship between severity of disease and utility increments. This is an outdated approach to cost-effectiveness analysis.**

As PIPC has included in past ICER comments, the field of cost-effectiveness analysis is evolving. If ICER seeks to provide credible assessments, it is imperative that its methods also evolve. There has been a widespread questioning of several of the assumptions that cost utility analysis is built on.<sup>9</sup> This argument has been most prominent with respect to the reliance on the assumption that every unit of health gain – measured here in health-related quality of life - is equal in value.<sup>10</sup> In other words, a single unit of health generates the same utility whether that health is accrued to someone who is suffering considerable disease burden, or to someone who is suffering minimal disease burden.<sup>11</sup> In fact, several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very reason,

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<sup>7</sup> DiStefano MJ, Zemplyeni A, Anderson KE, Mendola ND, Nair KV, McQueen RB. Alternative approaches to measuring value: an update on innovative methods in the context of the United States Medicare drug price negotiation program. *Expert Rev Pharmacoecon Outcomes Res.* 2024 Feb;24(2):171-180. doi: 10.1080/14737167.2023.2283584. Epub 2024 Jan 25. PMID: 37961908.

<sup>8</sup> Mike Paulden, Chris Sampson, James F. O'Mahony, Eldon Spackman, Christopher McCabe, Jeff Round, Tristan Snowsill, Logical Inconsistencies in the Health Years in Total and Equal Value of Life-Years Gained, *Value in Health*, Volume 27, Issue 3, 2024, Pages 356-366.

<sup>9</sup> Beresniak A, Medina-Lara A, Auray JP, De Wever A, Praet JC, Tarricone R, Torbica A, Dupont D, Lamure M, Duru G. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. *Pharmacoeconomics.* 2015 Jan 1;33(1):61-9.

<sup>10</sup> Sund B, Svensson M. Estimating a constant WTP for a QALY—a mission impossible? *The European Journal of Health Economics.* 2018 Jul;19(6):871-80.

<sup>11</sup> MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). *Social Science & Medicine.* 2018 Aug 1;211:359-66.

and incorporate the role of severity adjacent to the results to make a more context-relevant models.<sup>12,13</sup>

A system of evaluation that treats therapeutic innovations in these disease spaces as of similar relative value for unit of health gain in less severe conditions - and for patients who have minimal disease burden - is thought by many to be inherently unfair and skewed in the wrong direction. This has obvious relevance to patients with EBV+PTSLD as the health utility value of non-responder states is below 0.4 – which is severe disease.<sup>14</sup>

## Conclusion

ICER's assessments continue to rely on flawed metrics and dated constructs of cost-effectiveness. PIPC urges ICER to engage directly with patients and people with disabilities and amend its modeling choices to ensure their needs are met.

Sincerely,



Tony Coelho  
Chairman  
Partnership to Improve Patient Care

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<sup>12</sup> Barra, M. and K. Rand-Hendriksen, *A missing cornerstone in the Norwegian Priority Commission's weighting scheme—Sub-treatment balancedness is a necessary property for priority setting criteria*. *Nordic Journal of Health Economics*, 2016. 4(2): p. pp. 8-23.

<sup>13</sup> Swedish Parliamentary Priorities Commission, *Priorities in health care: ethics, economy, implementation*. 1995, Stockholm: Swedish Government.

<sup>14</sup> Skedgel C, Henderson N, Towse A, Mott D, Green C. Considering severity in health technology assessment: can we do better?. *Value in Health*. 2022 Aug 1;25(8):1399-403.