PharmacoEconomics - Open (2023) 7:393–404
https://doi.org/10.1007/s41669-023-00398-y

ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Letermovir for Cytomegalovirus Prophylaxis Compared with Pre-Emptive Therapy in Allogeneic Hematopoietic Stem Cell Transplant Recipients in the United States

Aryana Sepassi[1] · Ila M. Saunders[2] · Mark Bounthavong[2,3] · Randy A. Taplitz[4] · Cathy Logan[5] · Jonathan H. Watanabe[1]

Accepted: 13 February 2023 / Published online: 25 February 2023

Abstract

Purpose The aim of this study was to assess the cost effectiveness of letermovir prophylaxis with the option for subsequent pre-emptive therapy (PET) for the prevention of cytomegalovirus (CMV) infection compared with a PET-only scenario in adult allogeneic hematopoietic stem cell transplant (allo-HCT) recipients in the United States over a 10-year time horizon.

Materials and Methods A publicly available decision tree model was constructed using a commercial third-party payer perspective to simulate an allo-HCT recipient's clinical trajectory in the first-year post-transplant, followed by entry to a Markov model to simulate years 2 through 10. Clinical inputs and utility estimates were derived from published literature. Costs were derived from published literature and US Department of Veterans Affairs Federal Supply Schedule drug pricing. Outcomes assessed included life expectancy, quality-adjusted life-years (QALYs), direct medical costs, and the incremental cost-effectiveness ratio (ICER). One-way and probabilistic sensitivity analyses (PSA) were performed to test the robustness of the findings.

Results Compared with PET alone, letermovir prophylaxis was projected to increase life-years per person (4.99 vs. 4.70 life-years), and increase QALYs (3.29 vs. 3.08) and costs (US$83.411 vs. US$70,698), yielding an ICER of US$59,356 per QALY gained. One-way sensitivity analyses indicated our model was sensitive to mortality (ICER: $164,771/QALY) and utility (letermovir ICER: $117,447/QALY; PET ICER: $107,290/QALY) in the first-year post-transplant. In 57.1% of the PSA simulations, letermovir was a cost-effective option using a willingness-to-pay threshold of US$100,000 per QALY.

Conclusions Letermovir prophylaxis is cost effective compared with PET alone with a willingness-to-pay threshold of US$100,000 per QALY gained. Sensitivity analysis results indicate future research is required to understand the impact of mortality and quality of life in the first-year post-transplant to arrive at a conclusive decision on letermovir adoption.

✉ Aryana Sepassi
asepassi@hs.uci.edu

1 Department of Clinical Pharmacy Practice, University of California, Irvine School of Pharmacy and Pharmaceutical Sciences, Irvine, CA, USA

2 Division of Clinical Pharmacy, University of California, San Diego Skaggs School of Pharmacy & Pharmaceutical Sciences, La Jolla, CA, USA

3 Department of Veteran Affairs, Health Economic Resource Center, Menlo Park, CA, USA

4 Department of Medicine, City of Hope, Duarte, CA, USA

5 Division of Infectious Diseases and Global Health, University of California, San Diego, La Jolla, CA, USA

1 Introduction

Immunosuppression in cancer patients following allogeneic hematopoietic stem cell transplantation (allo-HCT) leaves patients susceptible to a host of opportunistic infections such as cytomegalovirus (CMV), which may lead to asymptomatic CMV infection (viremia) and, subsequently, CMV end-organ disease. CMV viremia is prevalent in 40–90% of seropositive allo-HCT recipients and may increase the risk of all-cause mortality by 86% compared with those without CMV [1–5]. CMV viremia, defined as the isolation of CMV by culture, may cause patients to present as asymptomatic. If left unmitigated, viremia may progress to CMV end-organ

Key Points for Decision Makers

Letermovir stands as a cost-effective option for prophylaxis against cytomegalovirus compared with pre-emptive therapy alone in allogeneic hematopoietic stem-cell transplant patients over a 10-year time period post-transplant.

The demonstrated cost-effectiveness of letermovir was contingent on the quality of life and mortality of patients at the first-year post-transplant. Decision makers need to weigh the risks of these uncertainties against demonstrated benefits when considering letermovir use.

Future research should focus on reducing the uncertainty surrounding mortality and quality of life, in addition to accounting for potential risks due to the development of viral resistance to letermovir.

disease, which involves the manifestation of clinical signs or symptoms in various organ systems of the body [6]. Despite available treatment, non-relapse mortality related to CMV disease remains as high as 45–60% [6–11]. The economic burden of CMV end-organ disease may be sizeable due to its severe and acute clinical presentation, with payers incurring incremental costs of US$160,000 per CMV disease patient per year [12]. Due to the high risk of mortality associated with CMV end-organ disease, prevention of initial CMV viremia is necessary to mitigate these negative downstream events and costs.

Antiviral prophylaxis with pre-emptive therapy (PET) or use of PET alone are the two predominant treatment strategies used to prevent CMV infection and subsequent disease in allo-HCT recipients [13]. Both strategies have demonstrated effectiveness in reducing CMV-related morbidity and mortality [14–16]. Prophylaxis involves administration of an antiviral agent to all allo-HCT recipients, irrespective of CMV serostatus or viral burden [15]. Patients exhibiting signs or symptoms of CMV viremia while on prophylaxis will have their prophylactic antiviral discontinued and replaced with antivirals used for PET. In contrast, the PET-alone strategy utilizes a monitoring approach at regular intervals post-transplant, where PET antivirals are administered only when viral load measurements exceed a predetermined, institution-specific threshold. The PET-alone strategy is preferred due to the high risk of costly and detrimental adverse events from prophylactic antivirals, such as neutropenia or clinically significant myelosuppression, as is the case with ganciclovir [16]. However, the PET-alone strategy relies heavily on early detection of CMV viremia through viral load monitoring, requiring patients to remain adherent to frequent polymerase chain reaction (PCR) testing procedures [14]. Moreover, viremic patients utilizing PET may also suffer the same adverse events as those receiving prophylaxis once therapy is initiated [14, 16]. Despite these limitations, upwards of 68% of institutions providing allo-HCT exclusively utilize PET-alone as a CMV prevention strategy [17].

In 2017, the antiviral letermovir was approved by the US Food and Drug Administration for CMV prophylaxis in CMV-seropositive adult allo-HCT recipients [18]. The safety profile demonstrated in the phase III clinical trial for letermovir addressed concerns regarding the risk of severe toxicities of traditional antiviral agents, with rates of myelotoxicity and nephrotoxicity similar to that of placebo [19]. Furthermore, letermovir was effective at reducing the rate of clinically significant CMV infection compared with placebo 24 weeks post-transplant [19]. However, letermovir is significantly more costly per dose than traditional antiviral agents used in a PET-only strategy. It is unclear whether the high drug cost of letermovir is offset by a reduction in downstream costs associated with negative outcomes compared with a PET-alone scenario. Therefore, an assessment of overall value utilizing updated data is required to determine whether use of this agent is cost effective compared with a conventional PET-alone strategy from an unsponsored perspective with integration of updated data. The objective of this study was to evaluate the cost effectiveness of letermovir prophylaxis compared with PET-alone in the prevention of CMV viremia and related outcomes in an adult cohort of allo-HCT recipients in the United States using a commercial payer perspective.

2 Methods

We conducted a cost-effectiveness analysis of letermovir prophylaxis with an option for PET compared with PET-alone. Costs were estimated from the commercial US healthcare payer perspective. Health outcomes were valued as quality-adjusted life-years (QALYs) with a 10-year time horizon starting from the date of transplant. We used a 10-year time horizon for this patient population to account for full immune reconstitution in allo-HCT recipients at the 10th-year post-transplant in addition to the lack of published survival data in allo-HCT recipients past 10 years post-transplant [20].

2.1 Model Structure

We employed a decision analytic approach to model the disease course of CMV post-transplant based on a previously published model using a third-party payer perspective [21]. A decision tree was constructed to simulate the first year of a hypothetical post allo-HCT adult patient cohort with subsequent entry into a Markov model for post-transplant years 2 through 10 (Fig. 1). The model compared patients receiving letermovir prophylaxis with the option to subsequently receive PET with patients receiving PET alone. Herein, 'PET-alone' refers to patients who did not receive any prophylactic therapy but did undergo PCR testing for CMV viral load at regular intervals. These patients would receive PET antiviral therapy upon developing CMV viremia. 'Letermovir prophylaxis' refers to patients who received letermovir antiviral therapy and initiated PET upon the presence of CMV viremia. Patients were at risk of developing CMV viremia starting from day 1 post-transplant, defined as detectable plasma CMV by PCR testing. Upon detection, CMV viremia was treating using PET [19, 22].

We assumed patients utilized valganciclovir for PET in our deterministic analysis. For the intervention arm, patients were assumed to receive letermovir prophylaxis up to day 100 post-transplant [19]. For the PET-alone arm, patients were assumed to visit their provider at weekly intervals for PCR monitoring of viral load. Patients were determined to have CMV viremia if they reached a PCR threshold of at least 150 copies/mL for high-risk patients, and > 300 copies/mL for low-risk patients (definitions for risk categories may be found in the electronic supplementary material [ESM]) [19]. We assumed these patients were at risk of experiencing neutropenia as an adverse drug event, and of CMV end-organ disease with subsequent complications, defined as acute graft-versus-host disease (GVHD) or CMV-related rehospitalization. In the decision tree, patients either terminally survived or died; those who survived entered into a Markov model for years 2–10 post-transplant. The Markov model had two health states (alive and dead) utilizing monthly cycles. As a minority of patients relapse after allo-HCT, we assumed patients would live in complete remission of their original cancer after receipt of allo-HCT [24–26]. Costs and utility benefits of survival were annually discounted using a 3% rate, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine [23]. All analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Additional model assumptions can be found in the ESM. External validation of the model with an independent expert reviewer who was unaffiliated with this study reinforced the robustness of the model structure and underlying methodology and found no significant problems. The model is publicly available and can be found at https://github.com/arysepassi/letermovir_cea/tree/main.

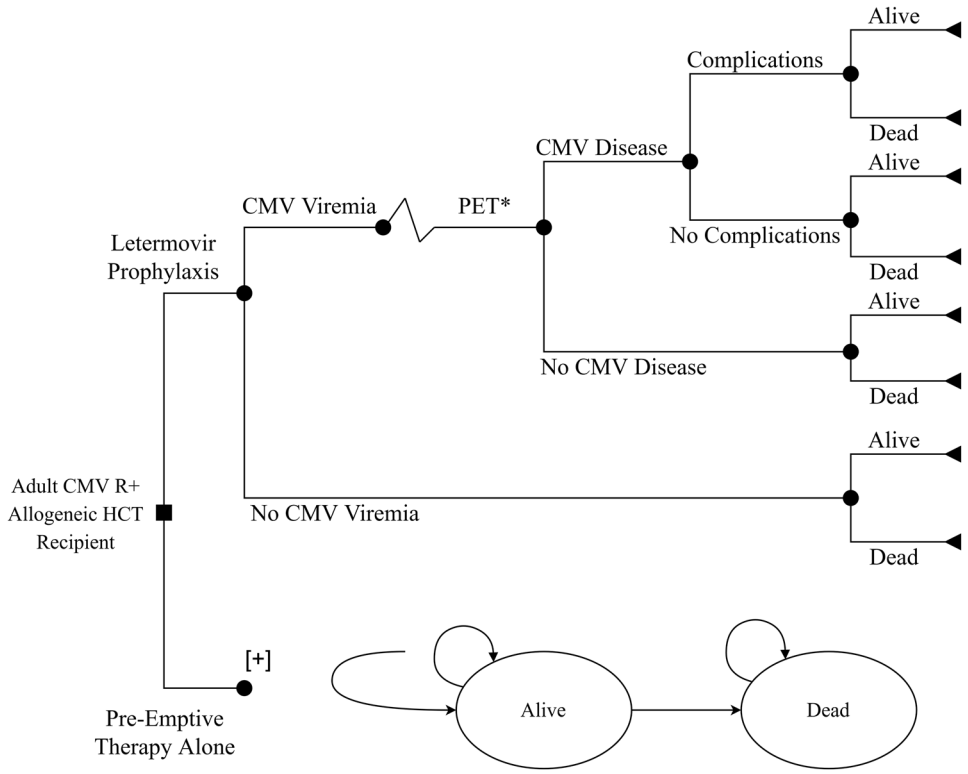

Fig. 1 Decision tree and Markov model for seropositive allogeneic hematopoietic stem cell transplant recipients post-transplant. All patients who develop CMV viremia are assumed to initiate pre-emptive therapy with valganciclovir, followed by subsequent risks of CMV disease and CMV-related complications, ending in survival or death by year 1. For years 2 through 10, survivors enter the 'Alive' health state indicated on the bottom right, with yearly risk of death. *PET* pre-emptive therapy, *CMV* cytomegalovirus, *HCT* hematopoietic stem cell transplant, + indicates the shown decision tree branches as replicated for the 'Pre-Emptive Therapy Alone' arm

2.2 Patient Population

We modeled a patient cohort based on data presented in the letermovir phase III clinical trial [19]. A total of 565 adult CMV-seropositive allo-HCT recipients at high- or low-risk of CMV reactivation were randomized to receive either letermovir or placebo, orally or intravenously, through week 14 post-transplant. High-risk patients included those with unrelated donors, related donors with mismatching gene loci, those with haploidentical donors, those receiving umbilical cord blood as the stem cell source, those receiving ex-vivo T-cell-depleted grafts, and those having GVHD of grade II or higher who required the use of corticosteroids at baseline [19].

2.3 Model Inputs—Clinical

All model inputs are listed in Table 1. We used evidence specific to allo-HCT recipients treated in the US for all model data. Clinical parameters were mostly derived from phase III clinical trial data [19]. Data regarding CMV viremia were extracted from the week 24 follow-up point of the trial [27]. We utilized data obtained at the week 48 follow-up point from the phase III trial for CMV end-organ disease and year 1 survival [19, 27]. This was done to ensure our estimates were as close to 1-year post-transplant as possible. Week 48 data missing from the published phase III clinical trial were extracted from a published report of the Canadian Agency for Drugs and Technologies in Health (CADTH) on the clinical effectiveness of letermovir [27].

We assumed that all patients receiving PET received valganciclovir, in accordance with trends and recommendations from the literature [28]. To account for any differences in treatment modalities, we performed a scenario analysis assuming that 50% of patients received valganciclovir, 39% received ganciclovir, and 10% received foscarnet [19]. Using published guidelines, the dose and frequency of valganciclovir was set at 900 mg orally twice daily for 14 days as induction therapy, followed by 450 mg orally twice daily up to 36 days (the average length of PET described in the phase III trial) [29]. We assumed all patients using PET were at risk of developing neutropenia as a potential adverse event [30]. CMV complication rates of acute GVHD and CMV-related rehospitalization were extracted from the phase III clinical trial results at 48 weeks (rates can be found in the ESM) [27]. We assumed that patients would independently experience CMV-related rehospitalization or acute GVHD, as data of overlapping event rates in the allo-HCT population are unavailable to date.

2.4 Model Inputs—Long-Term Survival

Survival data for the patient population were modeled using three sources of data and fitted using smoothed spline curves with three knots to estimate long-term life expectancy. The survival curves were constructed in a stepwise manner using the best available long-term data that best matched the model population. Survival data from months 0–12 post-transplant were obtained from the phase III clinical trial for letermovir [19]. Data for survival from the beginning of year 2 until year 10 were extrapolated using data from a published study in a cohort of allo-HCT recipients followed up to 5 years post-transplant [31]. Data from the Kaplan–Meier curve of the study were extracted using the 'digitize' package in R (Boston, MA, USA) and were used to reconstruct individual patient-level data using methods adapted from Guyot et al. [32, 33]. These data were used to fit various parametric survival curves, including exponential, Weibull, log-normal, log-logistic, gamma, Gompertz, and generalized gamma distributions using the 'flexsurv' package in R (Boston, MA, USA) [34]. The fit of the models to the extracted data was analyzed using the Akaike Information Criteria (AIC) and visual inspection of function tails to determine clinical plausibility of the estimated fit (see the ESM). Based on these criteria, Gompertz distribution yielded the best fit.

The survival curve for years 2 through 10 was applied to both the intervention and control groups using the Gompertz distribution (Eq. 1):

$$S(t) = e^{\left(\left(\frac{-\delta}{\kappa}\right)\times e^{((\kappa\times t)-1)}\right)} \quad (1)$$

where δ and κ denote parameters from the Gompertz distribution and t denotes the month when the Gompertz distribution was fitted to the Kaplan–Meier curve. A visual representation of the Gompertz curve fit to the Kaplan–Meier curve and other fitted distributions is provided in the ESM. The same extrapolated curve was fitted to both treatment groups beginning at year 2 and throughout the post-transplant period (months 13–120). Survival estimates for month 120 (year 10) and on post-transplant were obtained using adjusted annual relative mortality risks applied to life expectancies of the general population from 2017 US life tables. We utilized a relative mortality risk observed in a retrospective observational study of patients who received an allo-HCT at age 45 years or older, which closely matched that of the original letermovir phase III trial population [35]. The survival model constructed from these three data sources was then fitted to a smoothed spline model using three splines with 13 degrees of freedom for curve smoothing using the 'splines' and 'ISLRA' packages in R (Boston, MA, USA) [36, 37].

To test the robustness of changes to long-term life expectancy, we performed a sensitivity analysis using different

Table 1 List of utilized parameters

Parameter	Deterministic value	Low range	High range	Description	Distribution	Source
Clinical inputs						
Viremia, LET	0.16	0.14	0.18	Probability of CMV viremia with letermovir at week 24	Beta	Marty et al. [19]
Viremia, PET	0.40	0.36	0.44	Probability of CMV viremia with PET alone at week 24	Beta	Marty et al. [19]
CMV disease, LET	0.015	0.008	0.022	Probability of CMV disease with letermovir at week 48	Beta	CADTH report [24]
CMV disease, PET	0.018	0.008	0.028	Probability of CMV disease with PET alone at week 48	Beta	CADTH report [24]
Year 1 survival, LET	0.81	0.79	0.83	Probability of survival with letermovir at week 48	Beta	Ljungman et al. [22]
Year 1 survival, PET	0.77	0.73	0.80	Probability of survival with PET alone at week 48	Beta	Ljungman et al. [22]
Neutropenia	0.47	0.37	0.56	Probability of neutropenia with valganciclovir/PET	Beta	Zavras et al. [27]
CMV complications[a], LET	0.86	0.76	0.96	Probability of experiencing a CMV-related complication with letermovir	Beta	Marty et al. [19]
CMV complications, PET	0.90	0.81	0.99	Probability of experiencing a CMV-related complication with PET alone	Beta	Marty et al. [19]
Cost inputs						
Cost of letermovir	US$12,182	US$9746	US$14,618	Cost of 100 days of letermovir therapy at 480 mg daily	Gamma	VA FSS pricing [35]
Cost of PET[b]	US$1237	US$990	US$1485	Cost of PET using valganciclovir	Gamma	VA FSS pricing [35]
Cost of GVHD	US$18,605	US$14,884	US$22,326	Cost of treating an acute GVHD event	Gamma	Yu et al. [32]
Cost of rehospitalization	US$45,002	US$36,002	US$54,002	Cost of a CMV-related rehospitalization	Gamma	El Haddad et al. [37]
Cost of CMV disease	US$98,442	US$78,754	US$118,130	Cost of experiencing CMV end-organ disease	Gamma	Scheflout et al. [36]
Monthly cost, year 2 post allo-HCT	US$8625	US$6900	US$10,350	Cost of care for second-year post allo-HCT	Gamma	Zhou et al. [40]
Utility inputs						
Year 1, LET	0.724	0.579	0.869	Weighted baseline utility with LET prophylaxis	Beta	CADTH report [24]
Year 1, PET	0.728	0.582	0.874	Weighted baseline utility with PET alone	Beta	CADTH report [24]
Year 2+	0.760	0.686	0.850	Yearly utility for either intervention, year 2 post-allo HCT and on	Beta	Castejon et al. [42]

LET letermovir prophylaxis, *PET* pre-emptive therapy alone (no prophylaxis scenario), *CMV* cytomegalovirus, *CADTH* Canadian Agency for Drugs and Technologies in Health, *PCR* polymerase chain reaction, *GVHD* graft-versus-host disease, *VA* Veterans Affairs, *FSS* Federal Supply Schedule

[a]CMV complications are defined as either acute GVHD or CMV-related rehospitalization

[b]Includes the cost of weekly CMV DNA PCR testing and complete blood count + differential laboratory examinations

survival curves (e.g., Weibull, log-normal, generalized Gamma) during years 2 through 10 post-transplant to evaluate impact on long-term mortality and incremental cost-effectiveness ratio (ICER) compared with the deterministic analysis. Additionally, we performed a sensitivity analysis assuming a 30% reduction in all monthly death risks from years 2–10 post-transplant and on, to compensate for potentially overestimating mortality.

2.5 Model Input—Costs

All costs were valued in 2021 US dollars ($US) using the medical consumer price index (CPI) [23]. Drug costs were based on Federal Supply Schedule (FSS) pricing publicly provided by the US Department of Veterans Affairs (VA) in accordance with recommendations by the Second Panel in Cost-Effectiveness in Health and Medicine [38, 39]. The cost of letermovir prophylaxis included the costs of both intravenous and oral administration. The Centers for Medicare and Medicaid Services (CMS) fee-for-service pricing was used to determine the cost of an outpatient visit for post-transplant follow-up and PCR monitoring (Current Procedural Terminology [CPT] code 96395). Costs of CMV disease, CMV-related rehospitalization, neutropenia and acute GVHD were extracted from the literature [39–42]. Medical costs of an allo-HCT recipient in their second-year post-transplant were derived using an average of published data from patients seen in outpatient, specialist, and inpatients settings [43].

2.6 Model Inputs—Health-Related Quality of Life

We valued health outcomes using QALYs, a metric that is calculated by weighing expected survival by a utility score that encompasses quality of life and ranges from 0 (death) to 1 (perfect health) [41, 44]. Health utilities included in our analysis were collected using data from a phase III clinical trial that used the EQ-5D-3L scale with UK tariffs to extract utility scores for both letermovir and placebo groups at baseline (immediately post-transplant), week 14, week 24, and week 48 [27]. These utility scores were weighted according to the number of weeks in the year for which they applied and were incorporated as a final weighted utility score for each arm in the model's decision tree. For health utilities past this point, we applied a utility score derived from a study in a set of patients with acute myeloid leukemia (AML) in remission from the United Kingdom that used the time trade-off (TTO) method, on the basis that the majority of allo-HCT recipients originally had AML in the phase III trial for letermovir [45].

2.7 Model Outputs

We assessed total discounted direct costs and QALYs for a 10-year post-transplant time horizon and estimate the ICER comparing letermovir with PET alone. We considered a treatment strategy to be cost effective if the deterministic ICER was less than a willingness-to-pay (WTP) threshold of US$100,000 per additional QALY gained [46].

2.8 Sensitivity Analyses

To assess model uncertainty, we performed a series of one-way sensitivity analyses to determine the influence of individual parameters on the ICER. If data related to variance (e.g., standard error) of the deterministic inputs were reported in the literature, then those data were used to estimate lower and upper bounds (e.g., deterministic ± standard error). If data were not reported in the literature, we used a ± 20% range of the deterministic value. Additionally, we used annual discount rates of 1% and 5% in one-way sensitivity analyses to evaluate their influence on the ICER. We performed a probabilistic sensitivity analysis (PSA) to account for uncertainty across all model parameters simultaneously. Probability and utility inputs were modeled using a beta distribution, and cost inputs were modeled using a gamma distribution. Long-term survival data were adjusted for uncertainty in the PSA using a Cholesky decomposition matrix of the Gompertz distribution. Monte-Carlo simulation was performed with 1000 iterations to achieve convergence in order to determine the impact of parameter uncertainty on costs, QALYs, and ICER estimates. PSA results were used to generate a cost-effectiveness acceptability curve (CEAC) to determine the probability that letermovir prophylaxis was cost effective compared with PET alone at various WTP thresholds.

3 Results

3.1 Deterministic Analysis

In our deterministic analysis, the expected total cost per patient of letermovir prophylaxis for a post allo-HCT recipient was US$12,713 greater compared with PET alone over a 10-year time horizon (US$83,411 vs. US$70,698). Additionally, letermovir prophylaxis was associated with 0.29 additional life-years per patient compared with PET alone (4.99 life-years vs. 4.70 life-years). An estimated 39/100 simulated patients were alive after 10 years post-transplant, closely matching estimates from the published literature [28]. When adjusted with utility weights, the letermovir prophylaxis arm was expected to gain 0.21 QALYs per patient compared with PET alone (3.29 QALYs vs. 3.08 QALYs). Based on these

Table 2 Deterministic and probabilistic results comparing letermovir prophylaxis with pre-emptive therapy alone

Treatment	Total costs (US$)[a]	Per-person cost (US$)	QALYs[b]	Per-person QALYs	Total life-years	Per-person life-years
Deterministic results						
Letermovir prophylaxis	8,385,712	83,857	328.16	3.28	497.76	4.98
PET alone	7,066,095	70,661	306.57	3.07	468.95	4.69
ICER	US$59,356 per additional QALY gained					
	Mean (95% CI)		Minimum		Maximum	SD
Probabilistic results						
Incremental cost	US$9802 (US$9473, US$10,131)		−US$8929		US$27,079	US$5322
Incremental QALYs	0.13 (0.12, 0.14)		−0.40		0.71	0.18
Mean ICER	US$75,497 per additional QALY gained					

CI confidence interval, *SD* standard deviation, *QALY* quality-adjusted life-year, *ICER* incremental cost-effectiveness ratio

[a]Total costs in a 100-patient cohort

findings, letermovir use was reported to be cost effective with an ICER of US$59,356 per QALY gained, assuming a WTP threshold of US$100,000 per QALY.

Table 2 summarizes our main results, including total costs, life-years gained, QALYs, and the deterministic ICER. Of the events captured in the first-year post-transplant (Table 3), letermovir prophylaxis was most impactful in reducing CMV viremia events (incremental −24.0 events). The letermovir prophylaxis strategy was associated with a reduction in events downstream of CMV viremia, including neutropenia (−8.4 events with letermovir), CMV-related rehospitalization (−4.9 events with letermovir), and acute GVHD (−1.4 events with letermovir). This was accompanied by a total cost reduction of US$8333 per person within the first-year post-transplant compared with PET alone.

In our scenario analysis, changing the proportion of patients receiving valganciclovir based on data from Marty et al. (where 51.0% of patients received valganciclovir, 39.0% received ganciclovir, and 10.0% received foscarnet) resulted in an ICER of US$53,822 per QALY gained [19]. This reduced ICER was likely due to the increased cost of PET and reduced number of CMV viremia events in the letermovir intervention compared with PET alone. Results of the long-term survival scenario analysis can be found in the ESM. Overall, the base-case ICERs generated by the different survival distributions ranged between US$53,710 and

Table 3 Estimated event outcomes and costs for deterministic scenario per 100 patients

Outcome	Letermovir prophylaxis (*n* events)	PET alone (*n* events)	Incremental difference (events)	Letermovir prophylaxis (US$)	PET alone (US$)	Incremental difference (costs, US$)
CMV prophylaxis	–	–	–	1,218,201	–	1,218,201
PET[b]	–	–	–	19,795	49,489	−29,694
CMV viremia[a]	16.0	40.0	−24.0	–	–	–
CMV disease	1.5	1.8	−0.3	147,663	177,195	−29,532
Rehospitalization[c]	3.1	8.0	−4.9	139,506	360,016	−220,510
Acute GVHD	48.6	50.0	−1.4	904,194	930,241	−26,047
Neutropenia	5.6	13.9	−8.3	52,679	131,669	−78,990

PET pre-emptive therapy, *CMV* cytomegalovirus, *PCR* polymerase chain reaction, *GVHD* graft-versus-host disease

[a]Defined as exceeding 150 copies/mL (high-risk patients) or 300 copies/mL (low/standard-risk patients) on CMV PCR examination up to week 14 post-transplant

[b]PET with valganciclovir

[c]Defined as CMV-related rehospitalization

US$62,703 per QALY gained. Expected life-years ranged between 3.97 and 5.37 for letermovir prophylaxis and 3.58 and 5.07 for PET alone, while expected QALYs ranged between 2.62 and 3.54 for letermovir prophylaxis and 2.33 and 3.32 for PET alone.

3.2 Sensitivity Analyses

According to the one-way sensitivity analyses, the deterministic analysis was sensitive to a mortality rate of PET alone at the end of the first-year post-transplant in addition to weighted utilities at year 1 post-transplant for letermovir and PET, respectively (Fig. 2). Otherwise, the deterministic analysis was robust to all other parameters (ICER range of remaining parameters: US$47,269–US$99,751). The PSA generated a mean ICER of US$75,497 per QALY gained. Incremental costs generated by the PSA ranged from −US$8929 to US$27,079, and incremental QALYs generated ranged from −0.40 to 0.71. The CEAC generated from the results of the PSA indicated that at a WTP threshold of US$100,000 per QALY gained, the probability of letermovir prophylaxis being cost effective compared with PET alone was 57.1% (Fig. 3). The majority of incremental results generated from the PSA fell into the northeast quadrant of the cost-effectiveness plane (74.2%), with 22.8% falling into the northwest quadrant (Fig. 4).

4 Discussion

This was the first cost-effectiveness analysis of letermovir prophylaxis compared with PET alone performed from an unsponsored perspective using novel survival data. We found that letermovir was cost effective in a US healthcare setting using a WTP threshold of US$100,000 per QALY gained. This was largely due to cost offsets from reduced use of PET after CMV viremia, CMV end-organ disease, CMV-related rehospitalizations, and PET-related neutropenia. Moreover, improvements in mortality and health-related quality of life contributed to the cost effectiveness of letermovir compared with PET alone. Our PSA results indicated that the presence of parameter uncertainty evidenced a 57.5% probability of letermovir remaining cost effective at a standard WTP threshold. However, this likelihood increased well past the US$100,000 per QALY threshold, plateauing at around 60%. Although key decision makers may be constrained to various WTP thresholds per QALY, the CEAC indicates that there is some degree of certainty of letermovir as the cost-effective option past a threshold of US$100,000 per QALY gained. We hypothesize that this uncertainty is due to sensitivity

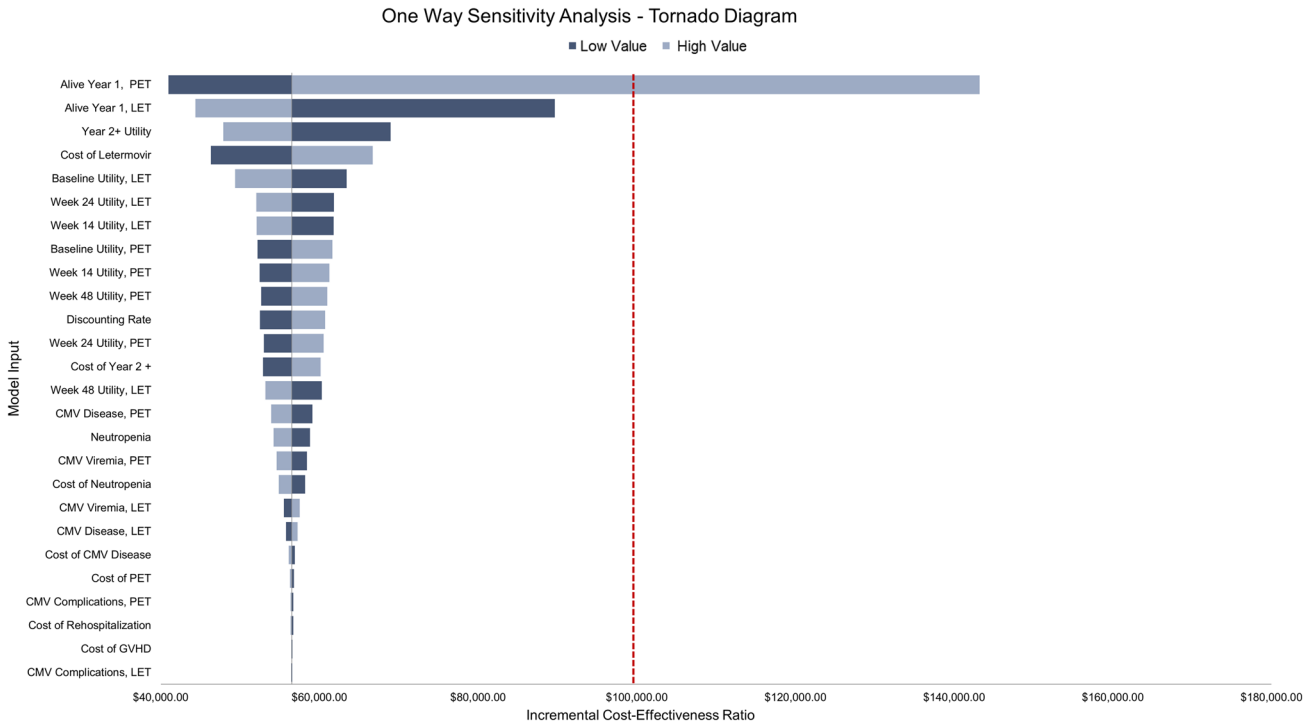

Fig. 2 Tornado diagram of incremental cost-effectiveness ratios assessing letermovir prophylaxis versus pre-emptive therapy alone in a series of one-way sensitivity analysis values. A willingness-to-pay threshold of US$100,000 per QALY gained is displayed using a red dotted line. *PET* pre-emptive therapy alone, *LET* letermovir prophylaxis, *GVHD* graft-versus-host disease, *CMV* cytomegalovirus

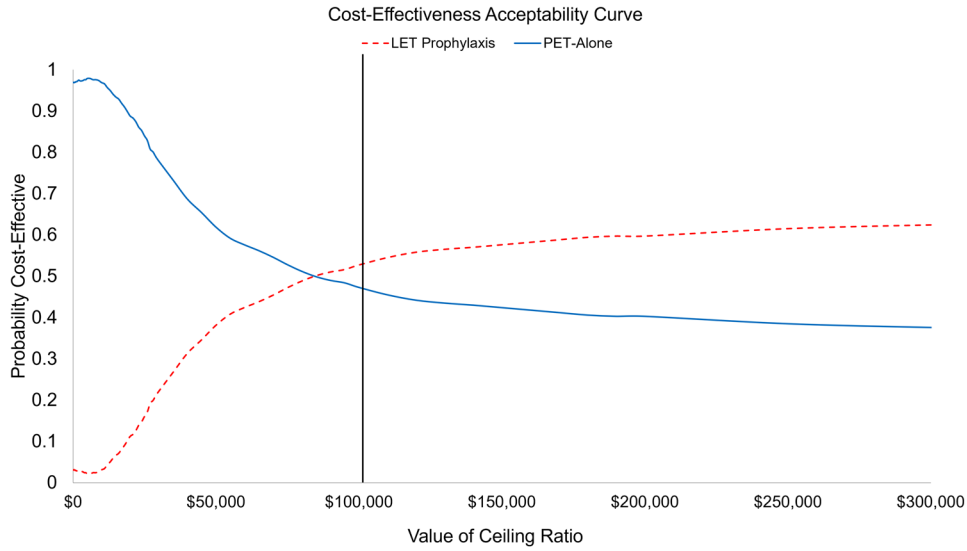

Fig. 3 Probabilistic sensitivity analysis results presented as cost-effectiveness acceptability curves. The vertical black line represents a willingness-to-pay threshold of US$100,000 per QALY gained, the red dotted line represents letermovir prophylaxis, and the blue line represents PET alone. *PET* pre-emptive therapy, *QALY* quality-adjusted life-year

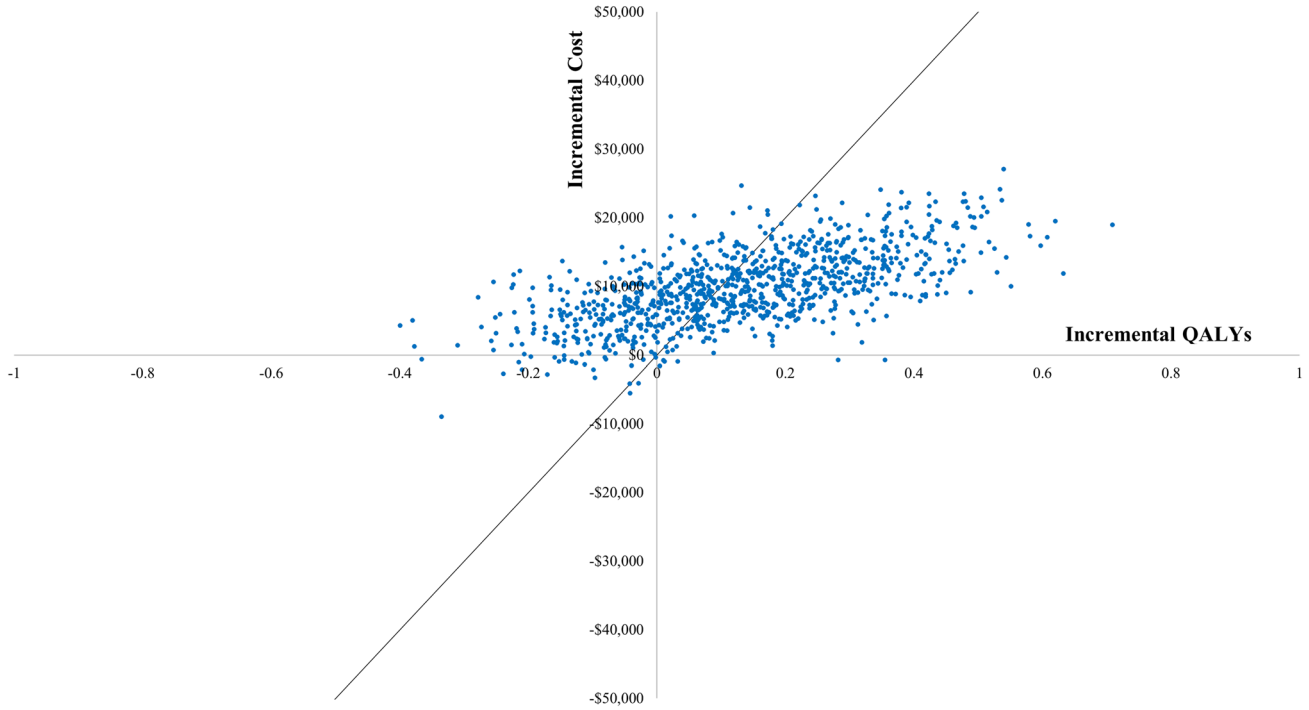

Fig. 4 Probabilistic sensitivity analysis results presented as a cost-effectiveness scatter plane. Each blue dot represents one of 1000 Monte Carlo simulations performed, and the black line represents a willingness-to-pay threshold of US$100,000 per QALY gained. *QALY* quality-adjusted life-year

of the model to mortality of patients at the first-year post-transplant. Uncertainty in models are inevitable; the lack of data on long-term mortality with letermovir limits our ability to make accurate predictions, highlighting the demand for future research to address this gap. Ultimately, key decision makers must interpret our findings in the context of this uncertainty and carefully balance the current demonstrated benefits and costs of letermovir prophylaxis when deciding on post-transplant strategies.

Our results are consistent with other published models assessing letermovir prophylaxis [21, 47, 48]. An industry-sponsored model published using the US third-party payer perspective demonstrated similar results, with sensitivity to mortality rates in the PET-alone group at year 1

post-transplant [21]. These results were consistent with two other industry-sponsored models using Italian- and Hong Kong-specific data [47, 48]. However, these models applied a 24-week survival rate at the first-year post-transplant. To account for the patients who may have died between week 24 and the first year, we utilized a 48-week survival rate. Our decision to utilize survival data at 48 weeks for the decision tree portion of the model was motivated by the observation that a significant proportion of allo-HCT recipients die within the first-year post-transplant. Moreover, we found that the published models utilized survival data obtained from a cohort of patients already alive at 2 years post-transplant and applied it to the model starting at the first-year post-transplant. To account for patients who may have died in the second post-transplant year, we utilized survival data from a cohort of patients studied for a 5-year period starting from the time of transplant. While their results also demonstrated cost effectiveness of the letermovir intervention, their base-case ICER was significantly lower compared with our results, at US$25,046 per QALY gained (vs. $56K per QALY gained, respectively). Aside from our differences in the use of survival data for allo-HCT recipients, certain costs in our models were different from other published models, which may have accounted for discrepancies in ICERs. The costs utilized in our model for certain events (e.g., CMV disease, GVHD) were obtained from various microcosting studies for these events in the allo-HCT population. This allowed for a more holistic estimate of event costs compared with those used in other letermovir models, where only the cost of a therapeutic treatment as considered. As more data continue to be published on the clinical effectiveness of letermovir, we urge investigators to consider other events that significantly affect our results, such as drug-resistant CMV. Current in vitro studies suggest a low genetic barrier to development of letermovir-resistant CMV [49, 50]. Overall, resistant and refractory CMV have been previously associated with significant morbidity and mortality that was not currently captured in this model [51]. The authors of the phase III trial assessing the efficacy of letermovir have acknowledged these risks, stating that CMV-seropositive patients receiving letermovir prophylaxis can experience CMV reactivation and reduced susceptibility to letermovir [19]. We theorize that our model results may be impacted with the consideration and addition of drug-resistant CMV.

Our model had limitations of note. First, our analysis was largely driven by data from the letermovir phase III clinical trial, where certain data were only collected up to week 48 post-transplant [19]. While we assumed that these data would not change at 1 year, this may have overlooked other CMV-related events that may have occurred between the week 48 and 1-year interval. Furthermore, while phase III trial data from a randomized controlled trial may indicate efficacy of an intervention, results may not necessarily translate to effectiveness in the real-world setting. With real-world evidence (RWE)-based studies gaining traction, considerable thought has been put into guidance as to how non-traditional sources of data may be used to support valid inference [53–55]. We encourage investigators to utilize these guidelines to support RWE-based studies evaluating the clinical efficacy of letermovir prophylaxis. We assumed the duration of letermovir therapy to be the same as that observed from the phase III trial; this duration may significantly differ from what is observed in clinical practice today. In addition, our model did not account for other potentially substantial adverse events related to PET, such as acute kidney injury. Our decision to exclude these events was based on the observation that renal injury is not frequently associated with valganciclovir use, but rather foscarnet, which is infrequently used for PET [30]. We did not account for health states outside of life or death in years 2 through 10 post-transplant, excluding events such as cancer recurrence due to a lack of published data, as doing so would require relapse data for each type of cancer for which allo-HCT may be indicated, conditional on having received an allo-HCT. Our model applied weighted utility scores based on the number of weeks post-transplant in the first year. This may have underestimated changes in utility due to different health states, such as the difference in presumed utility between CMV disease or CMV viremia. Further work must be done to quantify quality of life in this patient population to fill this gap. Furthermore, we did not perform a cost-effectiveness analysis using a societal perspective as were unable to find or obtain data related to non-healthcare cost benefits from the use of letermovir, such as productivity gains due to a reduction in CMV-related events. Finally, our source of long-term survival data from year 1 post-transplant onward was derived from a single-center observational study conducted from 2009 to 2013. Additional data are needed on the long-term survival of allo-HCT patients starting from the time of post-transplant.

5 Conclusion

We performed a cost-effectiveness analysis to assess the cost and clinical outcomes of letermovir prophylaxis versus PET only in seropositive adult allo-HCT patients in the US. Our base-case findings indicate that the use of letermovir prophylaxis may be cost effective, with a WTP threshold of US$100,000 per QALY gained. To aid in future decision making, models assessing the use of letermovir prophylaxis should consider data related to drug-resistant CMV infection.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41669-023-00398-y.

Acknowledgements The authors would like to thank Solomon J. Lubinga, PhD, for his assistance in enabling us to generate and incorporate long-term survival data into our model.

Declarations

Author contributions All authors contributed to the study conception and design. Preparation, data collection, and analysis was performed by Aryana Sepassi with supervision from Mark Bounthavong. The first draft of the manuscript was written by Aryana Sepassi, and all authors commented on various versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest Aryana Sepassi, Ila M. Saunders, Mark Bounthavong, Randy A. Taplitz, Cathy Logan, and Jonathan H. Watanabe have no financial or non-financial interests to disclose that are directly or indirectly related to the work submitted, and have no financial support to declare for this study.

Ethics approval This work was determined to be Institutional Review Board (IRB) exempt by the University of California, Irvine IRB.

Consent to participate Not applicable.

Consent for publication (from patients/participants) Not applicable.

Data availability This model and the data used for this model are available at https://github.com/arysepassi/letermovir_cea/tree/main.

Code availability R code used for this model can be found in the ESM. Code is also available at https://github.com/arysepassi/letermovir_cea/tree/main.

References

1. Green ML, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haematopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol. 2016;3(3):e119-127.
2. Huang YT, Neofytos D, Foldi J, et al. Cytomegalovirus infection after CD34(+)-selected hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2016;22(8):1480–6.
3. Milano F, Pergam SA, Xie H, et al. Intensive strategy to prevent CMV disease in seropositive umbilical cord blood transplant recipients. Blood. 2011;118(20):5689–96.
4. De Latour RP, Chevallier P, Blaise D, et al. Clinical and economic impact of treatment CMV infection in adult CMV-seropositive patients after allogeneic hematopoietic cell transplantation. J Med Virol. 2020;92(12):3665–73.
5. McBride J, Sheinson D, Jiang J, et al. Correlation of cytomegalovirus (CMV) disease severity and mortality with CMV viral burden in CMV-seropositive donor and CMV-seronegative solid organ transplant recipients. Open Forum Infect Dis. 2019;6(2):003.
6. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. Clin Infect Dis. 2017;64(1):87–91.
7. Ljungman P, Reusser P, de la Camara R, et al. Management of CMV infections: recommendations from the infectious diseases working party of the EBMT. Bone Marrow Transplant. 2004;33(11):1075–81.
8. Boeckh M, Leisenring W, Riddell SR, et al. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood. 2003;101(2):407–14.
9. Lee HY, Rhee CK, Choi JY, et al. Diagnosis of cytomegalovirus pneumonia by quantitative polymerase chain reaction using bronchial washing fluid from patients with hematologic malignancies. Oncotarget. 2017;8(24):39736–45.
10. Nguyen Q, Estey E, Raad I, et al. Cytomegalovirus pneumonia in adults with leukemia: an emerging problem. Clin Infect Dis. 2001;32:539–45.
11. Erard V, Guthrie KA, Seo S, et al. Reduced mortality of cytomegalovirus pneumonia after hematopoietic cell transplantation due to antiviral therapy and changes in transplantation practices. Clin Infect Dis. 2015;61:31–9.
12. Macalalad AR, Yang H, Zhou Z, et al. Economic consequences of cytomegalovirus disease among stem cell transplant recipients. Allogeneic Transplants. 2015;21(2 Suppl):S296.
13. Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients. Hematol Oncol Clin North Am. 2011;25(1):151–69.
14. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood. 2009;113(23):5711–9.
15. Chen K, Cheng MP, Hammond SP, Einsele H, Marty FM. Antiviral prophylaxis for cytomegalovirus infection in allogeneic hematopoietic cell transplantation. Blood Adv. 2018;2(16):2159–75.
16. Winston DJ, Ho WG, Bartoni K, et al. Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients: results of a placebo-controlled, double-blind trial. Ann Intern Med. 1993;118(3):179–84.
17. Pollack M, Heugel J, Xie H, Leisenring W, Storek J, Young J, et al. An international comparison of current strategies to prevent herpesvirus and fungal infections in hematopoietic cell transplant recipients. Biol Blood Marrow Transplant. 2011;17(5):664–73.
18. US Food and Drug Administration (FDA). PREVYMIS (letermovir) tablets and PREVYMIS (letermovir) injection. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209939orig1s000,209940orig1s000toc.cfm. Accessed 10 Sep 2021.
19. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med. 2017;377:2433–44.
20. Mehta-Shah N, Teja S, Tao Y, et al. Successful treatment of mature T-cell lymphoma with allogeneic stem cell transplantation: the largest multicenter retrospective analysis. Blood. 2017;130(Suppl):4597.
21. Alsumali A, Chemaly RF, Graham J, et al. Cost-effectiveness analysis of cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplant recipients from a US payer perspective. J Med Virol. 2021;93(6):3786–94.

22. Ljungman P, Schmitt M, Marty FM, et al. A Mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. Clin Infect Dis. 2020;70(8):1525–33.
23. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses. JAMA. 2016;316(10):1093–103.
24. Merryman RW, Kim HT, Zinzani PT, et al. Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. Blood. 2017;120(1):1380–8.
25. Lin CH, Chen TC, Shih YH, et al. Acute myeloid leukemia relapse after allogeneic hematopoietic stem cell transplantation: a retrospective study from a single institution. J Int Med Res. 2022;50(2): 03000605221078466.
26. Horowitz M, Schrieber H, Elder A, et al. Epidemiology and biology of relapse after stem cell transplantation. Bone Marrow Transplant. 2018;53(11):1379–89.
27. Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH common drug review: clinical review report for letermovir (Prevymis). https://cadth.ca/sites/default/files/cdr/clinical/SR0545_Prevymis_CL_Report.pdf. Accessed 1 Aug 2021.
28. Einsele H, Ljungman P, Boeckh M. How I treat CMV reactivation after allogeneic hematopoietic stem cell transplantation. Blood. 2020;135(19):1619–29.
29. Tomblyn M, Chillter T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143–238.
30. Zavras P, Su Y, Fang J, et al. Impact of preemptive therapy for cytomegalovirus on toxicities after allogeneic hematopoietic cell transplantation in clinical practice: a retrospective single-center cohort study. Biol Blood Marrow Transplant. 2020;26(8):1482–91.
31. Saullo JL, Li Y, Messina JA, et al. Cytomegalovirus in allogeneic hematopoietic transplantation: impact on costs and clinical outcomes using a preemptive strategy. Biol Blood Marrow Transplant. 2020;26:568–80.
32. Poisot T. The digitize package: extracting numerical data from scatterplots. R J. 2011;3:25–6.
33. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan–Meier survival curves. BMC Med Res Methodol. 2012;12:9.
34. Jackson C. Flexsurv: a platform for parametric survival modeling in R. J Stat Softw. 2016;70(8):1–33.
35. Bhatia S, Dai C, Landier W, et al. Trends in late mortality and life expectancy after allogeneic blood or marrow transplantation over 4 decade: a blood or marrow transplant survivor study report. JAMA Oncol. 2021;7(11):1626–34.
36. Wang W, Yan J. Shape-restricted regression splines with R package splines2. J Data Sci. 2021;19(3):498–517.
37. James G, Witten D, Hastie T, Tibshirani R. An introduction to statistical learning: with applications in R. 1st ed. Berlin: Springer; 2013.
38. US Department of Veterans Affairs. National Acquisition Center (CSST) Pharmaceutical Catalog Search. https://www.vendorportal.ecms.va.gov/nac/pharma/list. Accessed 1 Aug 2021.
39. Scheflhout J, Brown H, House JA, Raval AD. Cytomegalovirus infection and associated hospitalization and costs among individuals undergoing allogeneic hematopoietic stem cell transplant. Curr Med Res Opin. 2020;36(1):43–50.
40. El Haddad J, Ghantoji SS, Park AK, et al. Clinical and economic burden of pre-emptive therapy of cytomegalovirus infection in hospitalized allogeneic hematopoietic cell transplant recipients. J Med Virol. 2020;92:86–95.
41. Tai E, Guy JR, Dunbar A, Richardson LC. Cost of cancer-related neutropenia or fever hospitalizations, United States, 2012. J Oncol Pract. 2017;13(6):e552–61.
42. Yu J, Judy JT, Parasuraman S, Sinha M, Weisdorf D. Inpatient healthcare resource utilization, costs, and mortality in adult patients with acute graft-versus-host disease, including steroid-refractory of high-risk disease, following allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2020;26:600–5.
43. Zhou J, Nutescu EA, Han J, Calip GS. Clinical trajectories, healthcare resource use, and costs of long-term hematopoietic stem cell transplantation survivors: a latent class analysis. J Cancer Surviv. 2020;14(3):294–304.
44. Torrance GW, Feeny D. Utilities and quality-adjusted life years. Int J Technol Assess Health Care. 1989;5(4):559–75.
45. Castejon N, Cappelleri JC, Cuervo J, Lang K, Mehta P, Mokgokong R, et al. Social preferences for health states associated with acute myeloid leukemia for patients undergoing treatment in the United Kingdom. Health Qual Life Outcomes. 2018;16(1):66.
46. Institute for Clinical and Economic Review (ICER). Overview of the ICER value assessment framework and update for 2017–2019. https://icer.org/wp-content/uploads/2020/10/ICER-value-assessment-framework-Updated-050818.pdf. Accessed 1 Aug 2021.
47. Restelli U, Croce D, Pacelli V, Ciceri F, Girmenia C. Cost-effectiveness analysis of the use of letermovir for the prophylaxis of cytomegalovirus in adult cytomegalovirus seropositive recipients undergoing allogeneic hematopoietic stem cell transplantation in Italy. Infect Drug Resist. 2019;12:1127–38.
48. Chan TSY, Cheng SSY, Chen WT, Hsu DC, Chau RWY, Kang SH, et al. Cost-effectiveness of letermovir as cytomegalovirus prophylaxis in adult recipients of allogeneic hematopoietic stem cell transplantation in Hong Kong. J Med Econ. 2020;23(12):1485–92.
49. Chou S. A third component of the human cytomegalovirus terminase complex is involved in letermovir resistance. Antivir Res. 2017;148:1–4.
50. Piret J, Goyette N, Boivin G. Drug susceptibility and replicative capacity of multi-drug resistance recombinant human cytomegalovirus harboring mutations in UL56 and UL 54 genes. Antimicrob Agents Chemother. 2017;61:e01044-e1117.
51. Yong MK, Shigle TL, Kim YJ, et al. American Society for Transplantation and Cellular Therapy Series: #4—cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation. Cell Ther. 2021;27(12):957–67.
52. Schleiss MR. Letermovir and HCT: too much of a good thing? Immunology and Immunotherapy. Blood. 2021;138(1):1–2.
53. Simon GE, Platt R, Watanabe JH, et al. When can we rely on real-world evidence to evaluate new treatments? Clin Pharmacol Ther. 2022;111(1):30–4.
54. Miksad RA, Abernethy AP. Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality. Clin Pharmacol Ther. 2018;103:202–5.
55. Richesson RL, et al. Electronic health records based phenotyping in next-generation clinical trials: a perspective from the NIH Health Care Systems Collaboratory. J Am Med Inform Assoc. 2013;20:e226-231.