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Economic Evaluation

Value of Reducing Wait Times for Chimeric Antigen Receptor T-Cell Treatment: Evidence From Randomized Controlled Trial Data on Tisagenlecleucel for Diffuse Large B-Cell Lymphoma

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ABSTRACT

Objectives: This study aimed to quantify the value of reducing chimeric antigen receptor T-cell (CAR-T) treatment wait times on patients with refractory and relapsed aggressive blood cancer who can newly gain access to treatment or access treatment earlier in their disease course.

Methods: Using data from the JULIET clinical trial, we first identified the number of additional patients with diffuse large B-cell lymphoma that would have been treated with tisagenlecleucel CAR-T therapy if wait times were shortened. For these patients, we estimated mortality benefits using literature estimates of CAR-T effectiveness. Next, among patients who already received CAR-T, we estimated tumor burden progression over time using a linear probability regression model. The primary outcome variable was an indicator for having above-normal lactate dehydrogenase, and we controlled for time, use of bridging therapy, and time-invariant patient characteristics. The regression results, along with literature estimates relating lactate dehydrogenase to CAR-T effectiveness, were used to compute the survival benefits of earlier CAR-T treatment.

Results: Reducing wait times by 2 months increased the number of eligible patients receiving CAR-T by at least 10.7%. For patients already receiving tisagenlecleucel CAR-T, a 2-month reduction in wait times generated a 3.3% increase in survival gains per treated patient. Thus, among patients seeking treatment, the combined treatment efficacy increased by 14%, with approximately one-quarter of survival benefits accruing to existing patients receiving faster treatment.

Conclusions: Delays affected not only access to CAR-T treatments but also treatment effectiveness. Our results highlight the survival benefits of expediting treatment access and may help explain some observed differences in CAR-T effectiveness across countries.

Keywords: access, chimeric antigen receptor T-cell therapies, survival gains, treatment efficacy, wait time.

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Introduction

Precision medicines—which tailor treatment based on an individual's variability in genes, environment, and lifestyle—have transformed disease prognoses and treatment for previously intractable diseases. For example, chimeric antigen receptor T-cell (CAR-T) therapies have led to complete remission among cancer patients who have not responded to existing therapies. CAR-T therapies take a patient's T-cells (part of the immune system) and genetically engineer them to produce CARs that target specific antigens on the surface of tumor cells. These manufactured tumor-targeting CAR-T cells are then infused into the patient.

Nevertheless, clinical benefits from such precision medicines may be reduced if there are delays in accessing treatment. Delays can occur through several pathways. Community-based physicians may delay the referral of patients because of concerns over the high one-time cost of treatment, the logistics of administering a therapy, and potentially severe side effects.[1] Health insurers may enforce strict previous authorization protocols, leading to lost time waiting for approvals. Manufacturers may experience delays when producing a patient-specific batch of therapy, and transportation of those cells may also require time. Alternatively, treatment centers may have long waiting lists when demand for treatments outstrip. Even after patients make it off the waiting list, additional delays may arise because of limited facility capacity and the lack of available inpatient beds.

Regardless of the reason for delay, reducing the wait time for these new therapies may improve both access and survival, particularly for patients with aggressive diseases. In this article, we focused on quantifying the value of faster access to specifically tisagenlecleucel, a CAR-T treatments approved for patients with relapsed or refractory blood cancers.[2]

Using simulation models based on salvage chemotherapy and literature estimates, a handful of existing studies have considered

how reductions in CAR-T delays will increase the number of patients accessing treatment.[3,4] We built on this work by using individual-level clinical trial data to consider not only access but also survival changes as a result of tisagenlecleucel treatment timing. Our study emphasized the importance of expediting access to existing CAR-T therapies, and it highlighted how differences in wait time may explain differences in observed CAR-T outcomes across countries with varying delays in access timing.

Methods

Data Sources

We relied on individual-level data from the clinical trial JULIET, the pivotal trial for approving tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).[5] These patients were "ineligible for or had disease progression after autologous hematopoietic stem-cell transplantation."[6] For each patient, we observed patient treatment history before CAR-T infusion, including the use of "bridging" chemotherapy, which can forestall or slow disease progression for patients awaiting CAR-T infusion. Importantly, the data included information on the dates of trial enrollment, of CAR-T infusion, of death, and of trial dropout. Other than death, trial dropout occurred because of nonmortality issues such as rapid disease progression, manufacturing delay, or physician or patient decision to withdraw to pursue hospice or an alternative treatment. In our analyses, we accounted for both death and trial dropout before infusion.

For each trial participant, we also observed tumor burden as measured by lactate dehydrogenase (LDH). Although the data offered alternative measures of tumor burden such as total metabolic tumor volume as measured by positron emission tomography or computerized tomography scans, such scans were not mandated before infusion in JULIET. Thus, LDH was uniquely able to capture changes in tumor burden within an individual over time: 92% of trial participants had ≥2 recorded measures of LDH before infusion, whereas only 53% of participants had multiple measures of total metabolic tumor volume. Moreover, the existing literature has demonstrated that LDH is a good predictor of tumor burden in patients with DLBCL and can predict survival among patients treated with chemotherapy.[7-9] Compared with other relevant clinical factors such as age and extranodal sites, LDH is the most predictive prognostic factor of response and survival.[10-12] We classified LDH as low or normal if it was less than the site-specific upper limit of normal, "high × 1" if LDH was between the site-specific upper limit of normal and one times that value, and "high × 2" if LDH was 2 more times higher than the site-specific upper limit of normal. Site-specific limits are presented in Appendix Table A1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.02.007.

Statistical Analysis

Reduced delay in CAR-T treatments can benefit 2 groups of patients: new patients who try to gain access to treatment and existing patients who gain faster to treatment. For the first group, we identified the number of patients who were enrolled in JULIET but never received CAR-T infusion because of death or trial dropout. Among this sample, we fully observed, without censorship, individuals either receiving treatment or not, which allowed us to empirically estimate the probability of remaining enrolled and eligible for treatment over time. Patients who never received treatment were defined as becoming "ineligible." The fraction of clinical trial participants remaining eligible for treatment after a period of time may not faithfully reflect the fraction of real-world patients that would remain eligible after the same period. Nevertheless, mortality will preclude eligibility in both trial and real-world contexts. Therefore, we computed the empirical survival curve that used mortality before infusion as an upper bound on the fraction of real-world patients that would remain eligible after a given period of time. We also calculated the lower bound estimate by examining ineligibility because of both death and trial dropout (for any reason). For a given wait time (τ) since trial enrollment, the empirical survival curve identified the probability (p_τ) that a patient remained eligible for CAR-T infusion. Thus, reducing wait times by τ would allow $(1 - p_\tau)$ additional patients to gain access to CAR-T treatments.

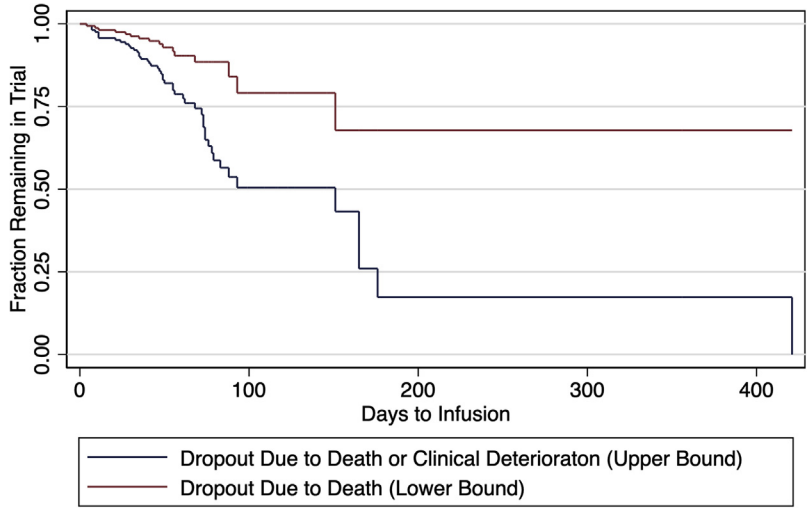
We then relied on literature estimates to identify corresponding gains in discounted life-years and discounted quality-adjusted life-years (QALYs) for patients with DLBCL receiving CAR-T treatment instead of the existing standard of care: $2.96 * (1 - p_\tau)$ and $2.78 * (1 - p_\tau)$, respectively.[13-17] Because existing estimates of life-years and QALYs gained were based on patients who actually received CAR-T treatment, we conducted sensitivity analyses by assuming that previously ineligible patients would accrue 75%, 50%, or 25% of literature-estimated survival gains from CAR-T.

The second group of patients who can benefit from reduced wait times consists of patients who already received CAR-T but may experience improved outcomes if they had received treatment earlier (and in a potentially better health state). This hypothesis is supported by a literature establishing better treatment outcomes among patients with DLBCL with lower levels of LDH, which suggests lower tumor burden. In JULIET, patients with high × 1 LDH at baseline had 12-month progression-free survival (PFS) and overall survival (OS) rates from CAR-T that were 19 and 25 percentage points lower, respectively, than those with normal LDH at baseline.[18] Similar reductions in survival outcomes have been observed among patients with high ×1 LDH receiving chemotherapy.[11]

To identify how wait time affects tumor burden and in turn survival outcomes, we used a linear probability model to identify the likelihood of increasing from low or normal LDH at baseline (ie, time of trial enrollment) to above-normal LDH over time. Using panel data at the patient visit level, we specified our main dependent variable as an indicator equal to one if an individual's LDH was above normal at a given visit and zero otherwise. Our main independent variable was the number of days that had lapsed between baseline date and visit date. Because bridging chemotherapy was used to reduce tumor burden while waiting for CAR-T infusion, we additionally included an indicator equal to one if bridging therapy occurred before the visit date. We also allowed the evolution of LDH to vary before and after bridging therapy receipt, by including an interaction term between the bridging indicator and the number of days that had elapsed. Finally, we included individual fixed effects to remove variation from person-specific differences, such as demographics and baseline health status.

We tested the robustness of our results to 4 alternative modeling choices: (1) a linear probability model with a cubic polynomial in time, (2) an ordinary least squares regression with a continuous (rather than categorical) measure of LDH as the dependent variable, (3) an ordered logit regression that differentiated between increasing from normal LDH to high × 1 or greater than high ×2 (as specified in the Data Sources section), and (4) our main model except we fixed the above-normal indicator to vary based on site-specific measurements of the upper limit of normal 280 units per liter (as opposed to site-specific limits of normal, as we specified in the Data Sources section).[11,18] Mathematical details

Figure 1. Proportion of patients who remain eligible for CAR-T infusion over time. Note: Data from the JULIET clinical trial. Figure shows Kaplan-Meier estimate of the fraction of patients who remained eligible for infusion. Lower bound estimate follows patients who became ineligible for infusion because of death; upper bound estimate follows patients who became ineligible for infusion because of death or nonmortality dropout issue.



CAR-T indicates chimeric antigen receptor T-cell.

for these models, as well as additional justification, are provided in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.02.007.

Our regression estimates identified the relationship between wait times and the probability of above-normal LDH. We then applied the aforementioned literature estimates of how above-normal LDH affects OS and PFS benefits of CAR-T.[18] We assessed the difference in survival because of faster access by calculating the difference between the observed survival curve in JULIET among patients with normal LDH at baseline and the hypothetical survival curve had these patients experienced a reduction in wait time. The area between the 2 survival curves—calculated as the sum of survival differences over the observed data—identified the cumulative survival gain from retaining normal LDH levels before CAR-T infusion.[19]

Finally, we identified changes in treatment efficacy for the intent-to-treat (ITT) population. Assuming patients who do not receive CAR-T receive the standard of care (chemotherapy), the percent change in survival because of reduced delay for the ITT population could be written as the sum of the percent change of people gaining access to CAR-T and the percent change in efficacy among patients gaining faster access. We calculated the percent change of people gaining access to CAR-T by dividing $(1 - p_\tau)$ by the share of patients receiving CAR-T treatment. Additional mathematical details are provided in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.02.007.

Results

Part 1: New Patients Gaining Access to CAR-T

The empirical survival function of the proportion of patients who remained eligible for CAR-T infusion is presented in Figure 1. Of 167 patients, 52 patients in our sample did not receive CAR-T infusion because of death (N = 16) or nonmortality dropout issue (N = 36) before infusion. By 2 weeks after trial enrollment, 98.1% to 95.7% of patient remained eligible for infusion. In other words, 1.9% of patients had died, and 4.3% of patients had either died or dropped out because of a nonmortality dropout. After 1 month, we estimated that 96.9% to 93.1% of patients remained eligible for infusion. After 2 months, 90.3% to 78.7% of patients remained eligible, and by 3 months, only 88.5% to 56.6% of patients remained eligible. The Kaplan-Meier analysis indicated that dropout held steady after about 6 months, at which point an estimated 17.3% of the sample had died and an additional 14.9% (ie, 32.2%-17.3%) had dropped out because of a nonmortality-related issue. We note that these estimates also bound the cumulative incidence function of death or dropout before infusion (described and shown in Appendix Fig. B1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.02.007).

Table 1[13-17] translated these rates of patient dropout into survival gains if wait times could be reduced. By applying literature-based gains in life-years and QALYs of CAR-T over its comparator, we found that, among a pool of 100 eligible patients, a 2-week reduction in wait times would generate 2 to 5 additional life-years and 5 to 12 additional QALYs. Reducing wait times by 1 month would allow an additional 3.1 to 6.1 patients to access CAR-T treatment, totaling 9 to 18 additional life-years or 9 to 17 additional QALYs.[14-18] Finally, if wait times could be decreased by 2 months, almost 10 fewer patients of 100 eligible patients would have died while waiting for CAR-T infusion, generating 29 additional life-years or 27 QALYs. An additional 12 patients (ie, 21.3-9.7 from columns [1] and [4]) would have avoided a nonmortality dropout issue, leading to an additional 34 life-years gained (ie, 63.05-28.71 from columns [2] and [5]) or 32 QALYs gained (ie, 59.21-26.97 from columns [3] and [6]), if these events accurately reflect loss of eligibility in real-world patient populations too.

Survival gains among the newly eligible may be lower because patients receiving CAR-T therapy may be sicker than those who became ineligible before infusion. Although we cannot observe survival gains among patients who did not receive CAR-T, we provided in Table 2 a conservative range of estimates on life-years and QALYs gained should patients from our lower bound estimate (ie, based on dying before treatment) receive only 75%, 50%, or 25% of CAR-T's estimated survival gains. If wait times were reduced by 2 weeks, the 1.9 patients gaining access to treatment would gain 1 to 4 additional life-years or QALYs. With 1-month reduction in wait times, the 3.1 patients gaining access to treatment would

Table 1. Survival gains from increasing patients accessing CAR-T therapies.

Reduced delay	Lower bound			Upper bound		
	Additional patients per 100 eligible patients (1)	Life-years gained per 100 eligible patients (2)	QALYs gained per 100 eligible patients (3)	Additional patients per 100 eligible patients (4)	Life-years gained per 100 eligible patients (5)	QALYs gained per 100 eligible patients (6)
1 day	0	0	0	0	0	0
1 week	0.60	1.78	1.67	1.80	5.33	5.00
2 weeks	1.90	5.62	5.28	4.30	12.73	11.95
3 weeks	2.50	7.40	6.95	4.90	14.50	13.62
4 weeks	3.10	9.18	8.62	6.10	18.06	16.96
5 weeks	4.50	13.32	12.51	10.00	29.60	27.80
6 weeks	5.20	15.39	14.46	12.70	37.59	35.31
7 weeks	7.10	21.02	19.74	17.00	50.32	47.26
8 weeks	9.70	28.71	26.97	21.30	63.05	59.21

Note. Data from JULIET. Columns (1) and (4) are one minus the Kaplan-Meier estimated probability of remaining eligible for infusion. Lower bound refers to patients who became ineligible for infusion because of death. Upper bound refers to patients who became ineligible for infusion because of death or nonmortality dropout issue. Life-years and QALYs gained assume CAR-T generates 2.96 life-years and 2.78 QALYs over the next best alternative.[13-17]
CAR-T indicates chimeric antigen receptor T-cell; QALY, quality-adjusted life-year.

experience 2 to 7 additional life-years or 2 to 6 QALYs if treatment benefits were only 25% or 75%, respectively. With 2 months, the respective survival benefits among 10 patients ranged from 7 to 22 life-years or 7 to 20 QALYs.

Part 2: Existing Patients Accessing CAR-T Faster

In Table 3, we estimated the rate of tumor burden progression from low or normal LDH at baseline to above-normal LDH among patients who received the CAR-T infusion. Column (1), which did not account for individual fixed effects, indicated that the probability of having above-normal LDH increased by 0.0018 per day. Limiting variation to changes in LDH within an individual over time did not significantly change the estimated rate of tumor growth (ie, 0.0026 per day in column [2]). Estimates were also robust to accounting for the use of bridging chemotherapy (ie, 0.0025 per day in column [3]). Although patients with above-normal LDH were more likely to receive bridging chemotherapy, the use of bridging did not decrease the rate of tumor burden growth in a statistically significant manner.

Our estimated rate of tumor growth was robust to alternative model specifications. Shown in Appendix Table B1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.02.007, the cubic polynomial in time produced insignificant coefficients on wait time squared and wait time cubed. Appendix Table B2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.02.007 considered how continuous LDH changes over time: on average, LDH increased by 0.362 units per liter per day. With the median site-specific limit of normal defined as 220 units per liter, this result suggested that, for patients with the lowest LDH, the likelihood of having above-normal LDH would increase by 0.002 per day (ie, 0.362/220), which corresponds closely to our preferred baseline estimate shown in column 3 of Table 3 (ie, 0.0025 per day). Appendix Table B3 in Supplemental

Table 2. Lower bound sensitivity analyses of survival gains from increasing patients accessing CAR-T therapies.

Reduced delay	Survival gained			QALYs gained		
	75% of benefits (1)	50% of benefits (2)	25% of benefits (3)	75% of benefits (4)	50% of benefits (5)	25% of benefits (6)
1 day	0	0	0	0	0	0
1 week	1.33	0.89	0.44	1.25	0.83	0.42
2 weeks	4.22	2.81	1.41	3.96	2.64	1.32
3 weeks	5.55	3.70	1.85	5.21	3.48	1.74
4 weeks	6.88	4.59	2.29	6.46	4.31	2.15
5 weeks	9.99	6.66	3.33	9.38	6.26	3.13
6 weeks	11.54	7.70	3.85	10.84	7.23	3.61
7 weeks	15.76	10.51	5.25	14.80	9.87	4.93
8 weeks	21.53	14.36	7.18	20.22	13.48	6.74

Note. Data from JULIET. Estimates in columns (1) and (4) assume that the lower bound of patients (ie, shown in the first column of Table 1) who gain access to CAR-T will receive only 75% of CAR-T survival gains. Columns (2) and (5) assume 50% of CAR-T survival gains are realized, and columns (3) and (6) assume 25% of CAR-T survival gains are realized.
CAR-T indicates chimeric antigen receptor T-cell; QALY, quality-adjusted life-year.

Table 3. Relationship between wait time and having above-normal tumor burden, among patients eligible for CAR-T infusion.

Variables	LDH		
	(1)	(2)	(3)
Days	0.00182*	0.00261*	0.00249*
	(0.000627)	(0.000629)	(0.000878)
Days† 1 (bridging)			−0.00479
			(0.0115)
1 (bridging)			−0.0289
			(0.221)
Individual FE	N	Y	Y
No. of individuals	42	42	42
No. of observations	108	108	108

Note. Data from JULIET. Sample includes patients who received CAR-T infusion and had normal LDH—defined using site-specific measures of the upper limit of normal—at baseline. Each column shows estimates from an ordinary least squares regression. Standard errors shown in parentheses.
CAR-T indicates chimeric antigen receptor T-cell; FE, fixed effect; LDH, lactate dehydrogenase; N, no; Y, yes.
*Significance at 1% level.
†Significance at 10% level.

Materials found at https://doi.org/10.1016/j.jval.2022.02.007 illustrated the effect of wait times on the probability of maintaining normal LDH over high ×1 LDH or high ×2 and over LDH. We found that the probability of having normal LDH decreased by 0.002, whereas the probability of having above-normal LDH increased by 0.001 to 0.002 per day (ie, 0.079/8 weeks). Our preferred baseline estimate again falls within this range. Finally, in Appendix Table B4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.02.007, we showed the results when defining above-normal LDH using absolute levels of normal. With this alternative definition, the probability of having above-normal LDH increased by 0.0013 per day, which is marginally higher than our preferred baseline estimate. Nevertheless, this alternative specification relied on a smaller sample of patients: fewer patients had normal LDH at baseline with the site-specific classification.

From literature estimates in Appendix Table B5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.02.007, we ascertained that having above-normal LDH reduces the 12-month PFS likelihood by 19 percentage points and the 12-month OS likelihood by 25 percentage points.[13] Thus, a reduction in delay by 1 day, which reduced the probability of having above-normal LDH by 0.0025, would be associated with 0.05 percentage point increase in 12-month PFS and a 0.06 percentage point increase in 12-month OS (Table 4). Survival gains increased with bigger reductions in delay. With 1- and 2-month reductions in wait time, the 12-month PFS would increase by 1.36 and 2.72 percentage points, respectively, and the 12-month OS would increase by 01.76 and 3.51 percentage points, respectively.

To better understand the value of these survival gains, we estimated in Table 5 the difference between the observed Kaplan-Meier survival curve for patients with low or normal LDH at baseline and hypothetical survival curves if wait times could be reduced. For each treated patient, the 3-year restricted mean survival time—calculated by the area under the survival curve—was 2.04 life-years. If wait times could be reduced by 2 weeks, the survival gain per 100 treated patient was 1.7 life-years. Similarly,

Table 4. Impact of reduced delay on PFS and OS after CAR-T infusion.

Reduced delay	Probability of having above-normal LDH (1)	Percentage point change in PFS at 12 months (%) (2)	Percentage point change in OS at 12 months (%) (3)
1 day	0.0025	0.05	0.06
1 week	0.017	0.34	0.44
2 weeks	0.035	0.68	0.88
3 weeks	0.052	1.02	1.32
4 weeks	0.070	1.36	1.76
5 weeks	0.087	1.70	2.19
6 weeks	0.105	2.04	2.63
7 weeks	0.122	2.38	3.07
8 weeks	0.139	2.72	3.51

Note. Data from JULIET and Westin (2019). Percentage point changes come from multiplying likelihood of above-normal LDH with changes in survival. At 12 months, mean PFS and OS reduction because of high ×1 LDH relative to normal LDH are 19 percentage points and 25 percentage points, respectively.
CAR-T indicates chimeric antigen receptor T-cell; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

Table 5. Impact of reduced delay on progression-free survival and overall survival after CAR-T infusion.

Reduced delay	3-year restricted mean survival time per 100 treated patients (1)	Life-years gained per 100 treated patients (2)	Percent change in efficacy per treated patients (%) (3)
1 day	204.01	0.12	0.06
1 week	204.73	0.84	0.41
2 weeks	205.57	1.68	0.82
3 weeks	206.41	2.52	1.24
4 weeks	207.25	3.36	1.65
5 weeks	208.09	4.20	2.06
6 weeks	208.93	5.04	2.47
7 weeks	209.77	5.88	2.89
8 weeks	210.61	6.73	3.30

Note. Data from JULIET and Westin (2019). The 3-year restricted mean survival time per 100 patients is 203.89 years, calculated as the area under the Kaplan-Meier survival curve after infusion for 100 patients with below normal or normal LDH at baseline. Column (1) shows the area under the survival curve for patients, as a result of reduced wait time. Column (2) shows the difference between column (1) and 203.89. Column (3) shows the percent change in efficacy, calculated as column (2) divided by 203.89.
CAR-T indicates chimeric antigen receptor T-cell; LDH, lactate dehydrogenase.

survival gains were 3.4 to 6.7 life-years with 1 to 2 months, respectively, of reduced wait times. These gains represented a 1.7% to 3.3% increase in treatment efficacy.

Part 3: Survival Gain Among the ITT Population

With the results earlier, we calculated the total survival gain among the ITT population. We found that expediting access to CAR-T treatments by either 2 weeks, 1 month, or 2 months increased total treatment efficacy by 3%, 5%, or 14%, respectively, with more than a quarter of the gain in survival coming from patients receiving faster access to CAR-T. These estimates came from summing the percent change in patients newly gaining access to CAR-T with the percent increase in efficacy among patients who gained faster access to CAR-T. For the first component, we noted that 90.4% of all patients received CAR-T (ie, 16 of 167 patients died before CAR-T). Thus, reducing CAR-T delays increased the patients gaining access by 3.4% to 10.7% (eg, 9.7 percentage points in Table 1 [13-17] divided by 90.4). The second component came directly from column (3) of Table 5.

Discussion

We found meaningful gains in survival from reducing delays in accessing CAR-T treatment. Faster access increased the number of eligible patients who would remain healthy enough to receive the CAR-T infusion. Our estimates for this group of patients were comparable with related estimates in the literature. Using Monte Carlo simulations based on death rates from a retrospective chemotherapy trial, Tully et al[4] estimated that delaying access to CAR-T by 1 month causes mortality to increase by 13%, and a 2-month delay causes mortality to increase by 21%. These align with our findings that 3% to 6% patients would gain eligibility should access expedite by 1 month and 10% to 20% should access expedite by 2 months.[4] Thornton Snider et al (2019)[3] studied axicabtagene ciloleucel, a different CAR-T therapy for patients with DLBCL, and found that a 1-month delay resulted in 0.1 QALYs lost and a 2-month delay led to 0.4 QALYs lost. In our context, reducing wait times by 1 month generated 9 to 17 QALYS per 100 eligible patients or, in other words, an average of 0.09 to 0.17 QALYs per patient; 2 months of wait similarly generated 0.27 to 0.59 QALYs per eligible patient.

We additionally demonstrated survival gains from existing patients accessing CAR-T with a lower tumor burden level. To the best of our knowledge, this study is the first to assess how CAR-T treatment timing affects treatment efficacy. A few studies have considered LDH changes over time after chemotherapy, and they find marginally faster LDH progression over time.[20,21] In our context, we estimated lower rates of tumor burden progression, with 15% and 22% of patients with DLBCL moving from low or normal LDH to above-normal LDH in 2 and 3 months, respectively. We note that although within-person measurements of LDH in JULIET are as long 6 months apart, the median time between observations was 2 months, suggesting that our estimates of tumor burden progression were most accurate for shorter time periods. Even with these modest changes in tumor burden, gains in survival from treating patients with lower tumor burden account for more than one-quarter of the total survival gains among the ITT population.

Our study had several limitations. First, it is not possible to ascertain the survival gains from CAR-T for patients who died before receiving CAR-T infusions. Instead, we approximated these survival gains using estimates based on patients who have received CAR-T treatment, and we assessed the sensitivity of our results to lower survival estimates. Second, we focused on how treatment affect survival through specifically changes in tumor burden progression. LDH is one of the strongest predictors of survival, and the remaining effect of wait time on mortality independent of LDH is small. Nevertheless, alternative metrics of deteriorating health may generate additional reductions in survival. For example, waiting can also exacerbate mental health concerns, which can further worsen outcomes and increase the value of reducing wait times.[22] Third, we examined survival gains from faster access but note that there may be value generated from alternative sources, including reduced caregiver burden, gains in work productivity, and lower overall costs.[3] These topics are fruitful areas for future research. Fourth, our estimates on survival gains among patients receiving faster access to CAR-T are constrained to the 3-year restricted mean survival time. Because tumor growth is often modeled exponentially, it is possible that longer-term survival gains are in fact larger than our reported estimates: potential reductions in tumor burden become bigger over longer horizons.[23,24]

Finally, our work focuses on analyzing tisagenlecleucel for patients with DLBCL. The impact of reducing wait times among other CAR-T therapies—for example, axicabtagene ciloleucel (Yescarta), lisocabtagene maraleucel (Breyanzi), and brexucabtagene autoleucel (Tecartus)—or other indications—for example, pediatric patients with acute lymphoblastic leukemia—may have different values. Moreover, the reasons for dropout in the clinical trial setting may be different from the real-world setting. If trial dropout reflects the dropout rate among real-world patients, this approach will yield an accurate "treatment on the treated" effect for the real world. If delays for treatment in the real-world affect patients who are on the margin sicker than those dropping out of the clinical trial or if trial dropouts instead receive treatment in the real world, then it is possible that we overstate survival benefits. With additional data on CAR-T eligible patients in the real world—such as through commercial and Medicare data sets and registries, future work should evaluate whether survival benefits from reduced wait times in the clinical trial data are comparable with those benefits in the real world.

Despite these limitations, our findings reveal the critical importance of treatment timing. As noted in the Introduction, treatment delays can occur through several different channels, beginning with physicians' decisions to refer patients to CAR-T treatment. Although the number of oncologists who referred at least 1 patient to CAR-T cell therapy has been growing over time, with 54% in 2017, 71% in 2019, and 91% in 2021, administrative and cost barriers continue to affect timely referrals.[1,25] In 2021, the average sales price for CAR-T therapies ranged from $395 380 to $425 409.[26]

Insurers may also be slow to cover or approve CAR-T treatments. Although tisagenlecleucel was first approved in the United States in August 2017, Medicare did not issue a national coverage determination until 2 years later in August 2019.[27] Some Medicaid programs still do not cover the therapy, and commercial insurers generally offer coverage on an individual basis.[28] The case-by-case approval process can add weeks of delay, particularly among smaller insurers plans where the CAR-T technology or urgency of request is not well understood.[28] In other countries such as the UK and Germany, tumor board approval bodies may add delay.[29-31]

Once treatment begins, manufacturing delays or capacity constraints can add to wait times. In JULIET, the median time from enrollment to infusion was 54 days, but treatment times have improved since this first pivotal clinical trial. Real-world turnaround time is fastest in the United States, with the median time from apheresis—which removes the patient's blood and separates it into components—to CAR-T infusion of approximately 26 to 28 days.[32,33] In Europe, real-world time from apheresis to infusion was 41 days in Germany, 42 days in the United Kingdom, 50 in France, and 53 days in Spain.[31,34-36] Perhaps correspondingly, observed response rates have been inferior in real-world European studies relative to real-world US studies. In the United States, 50% had complete response, whereas complete response rates in Germany, France, and Spain were 25%, 17%, and 26%, respectively.[31,37]

In addition to actively expanding manufacturing capacities, pharmaceutical firms are exploring new technological platforms that can enable next-day manufacturing or off-the-shelf products, which can transform the 2 to 6 week wait times for CAR-T cells to just a few days.[38,39]

Conclusions

Using clinical trial data, we showed that delays in CAR-T treatment not only reduced access for patients who became ineligible for treatment during the waiting period but also lowered treatment efficacy for patients receiving the CAR-T infusion at a worsened health state. Although much policy attention has focused on the development of new treatments, our results point toward the importance of establishing an expedited framework for accessing existing precision medicines.[40]

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.02.007.

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