The Potential Impact of CAR T-Cell Treatment Delays on Society

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ABSTRACT

OBJECTIVES: To date, breakthrough chimeric antigen receptor (CAR) T-cell therapies, such as tisagenlecleucel, indicated for pediatric acute lymphoblastic leukemia (pALL) and diffuse large B-cell lymphoma (DLBCL), and axicabtagene ciloleucel, indicated for DLBCL, although clinically effective, have been limited by treatment delays. Our study measured the social value of CAR T-cell therapy (CAR T) for relapsed or refractory pALL and DLBCL in the United States and quantified social value lost due to treatment delays.

STUDY DESIGN: We used an economic framework for therapy valuation, measuring social value as the sum of consumer surplus and manufacturer profit. Consumer surplus is the difference between the value of health gains from a therapy and its incremental cost, while accounting for indirect costs and benefits to patients.

METHODS: For 20 incident cohorts of pALL (n = 20 × 400 = 8000) and DLBCL (n = 20 × 5902 = 118,040), we quantified patient value, calculated as the value of additional quality-adjusted life-years gained with CAR T, minus the incremental cost of CAR T compared with standard of care (SOC). We calculated manufacturer profits using a range of production costs given uncertainties in the production process. Patient value and manufacturer profits were summed to obtain total social value. We measured social value lost from treatment delays, assuming that patients received the SOC while awaiting CAR T-cell treatment.

RESULTS: Depending on production costs, as much as $6.5 billion and $34.8 billion in social value was generated for patients with pALL and DLBCL, respectively. However, with 1, 2, or 6 months of treatment delay (assuming $200,000 production costs), the pALL population lost 9.8%, 36.2%, and 67.3% of social value, respectively, whereas the DLBCL population lost 4.2%, 11.5%, and 46.0%, relative to no delay.

CONCLUSIONS: The social value of CAR T is significantly limited by treatment delays. Efficient payment mechanisms, adequate capital, and payment policy reform are urgently needed to increase patient access and maximize the value of CAR T.

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Although there have been major advances in treatments for hematologic cancers such as pediatric acute lymphoblastic leukemia (pALL) and diffuse large B-cell lymphoma (DLBCL),[1-3] efficacious treatments have historically remained limited for the population with relapsed or refractory disease.[3,4] However, chimeric antigen receptor (CAR) T-cell therapies, such as tisagenlecleucel and axicabtagene ciloleucel, offer a possible cure for these patients.[5-9] A recent review by the Institute for Clinical and Economic Review (ICER)[10] concluded that tisagenlecleucel for pALL and axicabtagene ciloleucel for DLBCL are cost-effective treatments with incremental costs per quality-adjusted life-year (QALY) of $45,971 and $136,078, respectively.

Despite the recent approval of breakthrough therapies using CAR T cells in the United States, patients have faced barriers to treatment, including manufacturing challenges and a lack of formal coverage policies for CAR T-cell therapy (CAR T) in an inpatient setting,[11,12] with delays as long as 90 days.[11] Given the aggressive nature of relapsed/refractory disease, patients eligible for CAR T may have to settle for less efficacious third- or fourth-line therapies[10,13] or even die while waiting for CAR T reimbursement approval.[11]

Cost-effectiveness analyses, like the ICER report, are useful for informing how resources may be allocated to treatments with the greatest QALY gains; however, stakeholders must consider the trade-off between treatment access today and incentivizing future treatment innovation. Social value analyses can complement cost-effectiveness analyses by shedding light on the access/innovation trade-off. Both types of analyses can inform coverage decisions, but they provide insight into different trade-offs that decision makers must weigh.

In this study, we measured the social value of treating pALL and DLBCL with CAR T in the United States and the social value lost from treatment delays as reported in the media.[11,12,14-16] Social value analyses are used to quantify a therapy's economic value from a societal perspective[17] and determine the share of that value accruing to the manufacturer and patients. Expanded patient access and greater health benefits increase social value, whereas a greater requirement of society's resources to produce the therapy (ie, higher production costs) reduces it. The higher the share of social

TAKEAWAY POINTS

- Chimeric antigen receptor (CAR) T-cell therapies can provide significant benefit to patients with relapsed/refractory pediatric acute lymphoblastic leukemia (pALL) and diffuse large B-cell lymphoma (DLBCL) and to US society, generating up to $6.5 billion and $34.8 billion of social value for patients with pALL and DLBCL, respectively.
- However, with 1, 2, or 6 months of treatment delay, patients with pALL lost 9.8%, 36.2%, and 67.3% of social value, respectively; patients with DLBCL lost 4.2%, 11.5%, and 46.0% of social value, respectively.
- The magnitude of CAR T-cell therapy's value depends on timely patient access. Efficient payment mechanisms, adequate physical and human capital, and payment policy reform could help reduce treatment delays.

value accruing to the manufacturer, the stronger the incentives for innovation. However, when treatment is delayed, social value is lost for both patients and manufacturers: Patients lose access to health gains from the treatment, and manufacturer profit is reduced.

METHODS

An economic framework for therapy valuation was used. Specifically, we measured social value as the sum of consumer surplus and manufacturer profit.[17] In the health context, consumer surplus measures the difference between the value of the health gains from a therapy and its incremental cost to the patient. It also accounts for indirect costs and benefits to patients. We calculated the economic benefit of tisagenlecleucel for pALL relative to standard of care (SOC), clofarabine monotherapy, and of axicabtagene ciloleucel for DLBCL relative to salvage chemotherapy.[10] In each case, social value was estimated for 20 incident cohorts in the United States over a lifetime horizon. In each year, a new incident cohort entered the model and the existing prevalent cohorts aged an additional year. Each cohort's survival followed that of the average patient for each treatment. We explain our calculations using tisagenlecleucel as an example; calculations for axicabtagene ciloleucel were similar, unless otherwise noted.

We obtained clinical and cost parameters from the literature and ICER's assessment of CAR T (**Table 1**[10,18-26]).[10] ICER reported that 400 incident cases of relapsed or refractory pALL occur annually and estimated that the average patient with pALL treated with CAR T would gain 7.9 discounted life-years (12.1 undiscounted) and 7.2 discounted QALYs (10.9 undiscounted) over SOC. Costs to the patient of tisagenlecleucel and SOC were obtained from the literature.[20] Other treatment-associated costs were obtained from ICER's report and can be found in Table 1.[10,18-26]

We measured patient value, also known as consumer surplus, which is the difference between how much a consumer is willing to pay for a good or service and its price. We first estimated the health value that patients obtained, calculated as the value of QALYs gained with tisagenlecleucel compared with SOC, valuing each QALY gained at $150,000 (a midrange value from the literature).[18] To obtain patient value, the incremental cost of tisagenlecleucel relative to SOC was subtracted from the health value.

Next, we estimated productivity gains from tisagenlecleucel. Because the value of QALYs gained to patients includes the value

TABLE 1. Parameter Values for Social Value Model[10,18-26,a]

Input Parameter	Tisagenlecleucel (pALL)		Axicabtagene Ciloleucel (DLBCL)	
	Parameter Value	Source	Parameter Value	Source
Patient Health Parameters				
Number of incident patients who are eligible for treatment annually	400	10	5902	10
Number of annual incident cohorts considered	20	Modeling decision	20	Modeling decision
Average patient age in years at time of treatment initiation	11.5	10	58	10
Comparator selected	Clofarabine monotherapy	Modeling decision (following ICER)	Salvage chemotherapy	Modeling decision (following ICER)
Number of undiscounted life-years on treatment	12.12	10	8.15	10
Number of undiscounted life-years on comparator	2.49	10	3.35	10
Number of undiscounted QALYs on treatment	10.88	10	6.51	10
Number of undiscounted QALYs on comparator	2.15	10	2.57	10
Economic value of a QALY	$150,000	18,19	$150,000	18,19
Price of treatment	$475,000	20	$373,000	20
Price of comparator therapy	$163,686	10	$40,142	10
All other costs of treatment (aside from the drug itself)	$261,265	10	$178,642	10
All other costs of comparator therapy (aside from the drug itself)	$173,570	10	$114,743	10

(continued)

TABLE 1. *(Continued)* Parameter Values for Social Value Model[10,18-26,a]

Input Parameter	Tisagenlecleucel (pALL)		Axicabtagene Ciloleucel (DLBCL)	
	Parameter Value	Source	Parameter Value	Source
All Other Costs Include				
Chemotherapy treatment costs of CAR T	$15,309	10	$0	10
Palliative chemotherapy treatment costs of CAR T	$2648	10	$3748	10
Palliative chemotherapy treatment costs of comparator	$3973	10	$6103	10
Pretreatment costs of CAR T	$2979	10	$4585	10
Pretreatment costs of comparator	$0	10	$0	10
Stem cell transplant costs of CAR T	$47,744	10	$13,345	10
Stem cell transplant costs of comparator	$64,648	10	$62,094	10
Adverse event costs of CAR T	$33,534	10	$16,029	10
Adverse event costs of comparator	$0	10	$7046	10
Administration/monitoring costs of CAR T	$111,548	10	$44,165	10
Administration/monitoring costs of comparator	$93,032	10	$1045	10
Future healthcare costs of CAR T	$45,901	10	$95,223	10
Future healthcare costs of comparator	$9069	10	$36,286	10
End-of-life costs of CAR T	$1602	10	$1547	10
End-of-life costs of comparator	$2848	10	$2169	10
Patient Productivity Parameters				
US employment rate	Varies by age and gender. See eAppendix Table for complete parameters.	21	Varies by age and gender. See eAppendix Table for complete parameters.	21
US average annual income, per capita	Varies by age and gender. See eAppendix Table for complete parameters.	22	Varies by age and gender. See eAppendix Table for complete parameters.	22
Manufacturer Parameters				
Treatment production costs[b]	$100,000-$300,000	Assumption	$100,000-$300,000	Assumption
Year of US treatment launch	2018	Assumption	2018	Assumption
Year of assumed US treatment price reduction	2030	Assumption	2030	Assumption
Reduction in treatment price	30%	23-25	30%	23-25
General Parameters				
Discount rate	3.0%	26	3.0%	26

CAR T indicates chimeric antigen receptor T-cell therapy; DLBCL, diffuse large B-cell lymphoma; ICER, Institute for Clinical and Economic Review; pALL, pediatric acute lymphoblastic leukemia; QALY, quality-adjusted life-year.

[a]QALYs and life-years were converted to undiscounted values from the discounted values presented in the ICER report.[10]

[b]Base-case production cost was assumed to be $200,000 in sensitivity analyses.

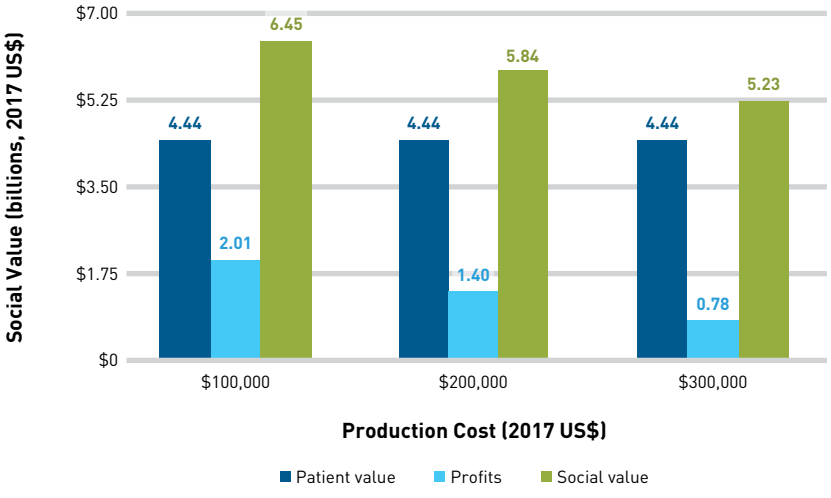
of the labor and leisure they afford, some of the health value from tisagenlecleucel is attributable to productivity gains. Nationally representative data on employment and wages by age and sex from the Bureau of Labor Statistics and the US Census Bureau were used to calculate productivity gains.[21,22]

The manufacturer profits were calculated next. We considered a range of production costs from $100,000 to $300,000 to reflect uncertainty and likely changes in the production process over time. The midpoint value, $200,000, was taken as the base-case value for sensitivity analysis. Given uncertainty about the future price of tisagenlecleucel with loss of exclusivity and competitor entry, we simplistically assumed a 30% price reduction in 2030 based on estimates from the literature.[27] Finally, total social value was calculated by summing the patient value and manufacturer profit.

We calculated social value lost from treatment delays for the first pALL cohort. We examined the first cohort rather than all 20 cohorts given uncertainty around the extent of treatment delays in the future. We assumed that patients would take the SOC treatment while waiting for tisagenlecleucel and would initiate tisagenlecleucel treatment if they survived long enough to receive it. Survival of patients treated with clofarabine monotherapy was obtained from clinical trial data.[28] For the first cohort, life-years, QALYs, and productivity were calculated conditional on patients receiving treatment after 1, 2, and 6 months of delay. Incremental value lost was calculated as the difference between the value obtained by patients who were treated immediately (0-month delay) and those who experienced delays.

The steps above were repeated to measure the value of axicabtagene ciloleucel for the treatment of 20 incident cohorts of patients with

FIGURE 1. Social Value and Its Distribution to Patients and the Manufacturer, by Production Cost of Tisagenlecleucel[a]



[a]Social value reported here is aggregated over 20 cohorts of patients with pediatric acute lymphoblastic leukemia (N = 8000).

DLBCL, using a clinical trial for salvage chemotherapy[13] as the SOC comparator in the treatment delays analysis. Table 1[10,18-26] contains the parameters used in the calculations for patients with DLBCL. All health and monetary values were discounted at a rate of 3.0% and costs were inflated to 2017 US dollars. Additional detail is available in the **eAppendix** (available at **ajmc.com**).

We ran sensitivity analyses to test how consumer surplus, manufacturer profit, and social value changed by varying key model inputs. In 1-way sensitivity analyses, we adjusted the number of patients eligible for treatment, economic value of a QALY, price of CAR T, production costs, and future reduction in CAR T price individually from minimum to maximum values. We also varied life-year and QALY gains concurrently by ±50% and potential patient income by ±20%. In multiway sensitivity analyses, we conducted 1000 Monte Carlo simulations to vary each of the above parameters concurrently by selecting values of each parameter from its distribution, which measured the sensitivity of social value, manufacturer profit, and consumer surplus to the model assumptions. Each parameter was assumed to follow a beta distribution.

RESULTS

pALL

In the population with pALL (n = 20 × 400 = 8000), considering production costs of $100,000, $200,000, and $300,000 and a price of $475,000, we found that the total social values of tisagenlecleucel at each production cost were $6.5 billion, $5.8 billion, and $5.2 billion, respectively (**Figure 1**). The value accruing to patients was $4.4 billion regardless of production costs, representing 68.9%, 76.1%, and 85.0% of total social value, respectively. This translates to 48,485 life-years, 44,010 QALYs (worth $6.6 billion), and $352.0 million in productivity (worth 5.3% of QALY gains). The remaining 15.0% to 31.1% of total social value accrued to manufacturers.

Assuming no treatment delays, patients with pALL in the first cohort gained 2872 total QALYs. The value of those QALY gains totaled $430.8 million, of which $23.0 million (5.3%) was attributable to added patient productivity from employment gains. Accounting for the cost of acquiring CAR T, the total patient value was $271.2 million and the total social value was $381.2 million. This translates to 7.2 QALYs (worth $1.1 million), $57,423 in added productivity, and a social value of $952,991 per patient.

However, with 1, 2, or 6 months of treatment delay (assuming $200,000 production costs), the first pALL cohort lost 9.8%, 36.2%, and 67.3% of social value, respectively, relative to no treatment delays. Contributing to this were losses of 311, 1146, and 2128 total life-years; 282, 1040, and 1932 total QALYs; and $2.3 million, $8.3 million, and $15.4 million in total productivity, respectively. Each patient lost 0.8, 2.9, and 5.3 life-years; 0.7, 2.6, and 4.8 QALYs; $5638, $20,796, and $38,622 in productivity (**Figure 2**[13,28]); and $93,560, $345,133, and $640,967 in social value, respectively. The loss of social value stems primarily from a high mortality rate in patients receiving SOC while awaiting treatment with tisagenlecleucel.[28]

DLBCL

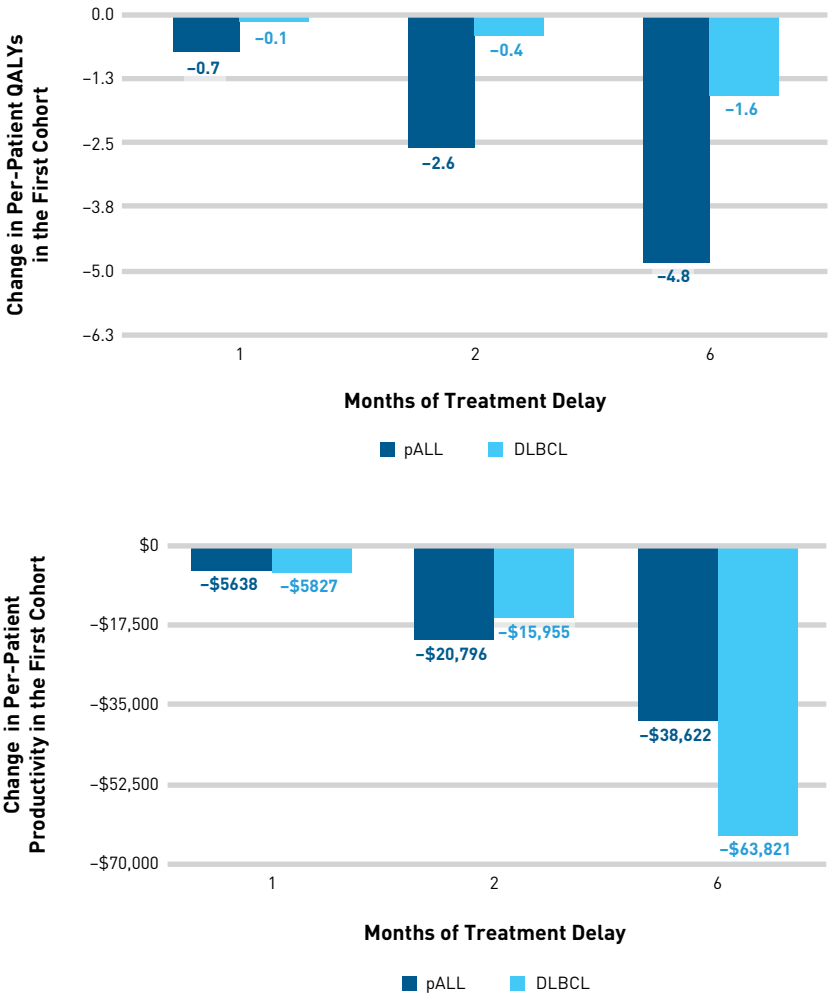
In the population with DLBCL (n = 20 × 5902 = 118,040), given production costs of $100,000, $200,000, and $300,000 and a price of $373,000, the total social values of axicabtagene ciloleucel were $34.8 billion, $25.8 billion, and $16.7 billion, respectively (**Figure 3**). The value accruing to patients was $13.5 billion regardless of production costs, which represents 38.7%, 52.2%, and 80.5% of total social value, respectively. This translates to gains of 372,617 life-years, 306,595 QALYs (worth $46.0 billion), and $12.5 billion in productivity (worth 27.3% of QALY gains). The remaining 19.5% to 61.3% of total social value accrued to manufacturers.

The first cohort of patients with DLBCL gained 20,008 total QALYs, assuming no treatment delays. The value of those QALY gains totaled $3.0 billion, of which $818.9 million (27.3%) was attributable to added patient productivity from employment gains. Accounting for the cost of acquiring CAR T, the total patient value was $659.5 million, and the total social value was $1.68 billion. This translates to 3.39 QALYs (worth $508,500), $138,742 in added productivity, and a social value of $284,743 per patient.

However, with 1, 2, or 6 months of treatment delay (assuming $200,000 production costs), the first DLBCL cohort lost 4.2%, 11.5%, and 46.0% of social value, respectively, relative to no treatment delays.

Contributing to this were losses of 1021, 2796, and 11,185 total life-years; 840, 2301, and 9204 total QALYs; and $34.4 million, $94.2 million, and $376.7 million in total productivity, respectively. Each patient lost 0.2, 0.5, and 1.9 life-years; 0.1, 0.4, and 1.6 QALYs; and $5827, $15,955, and $63,821 in productivity (Figure 2[13,28]), resulting in losses of $11,959, $32,745, and $130,982 in social value, respectively.

FIGURE 2. QALYs and Productivity Lost per Patient From Treatment Delays With CAR T-Cell Therapy for Patients With pALL and DLBCL in the First Cohort, Relative to No Delay[13,28]



CAR indicates chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; pALL, pediatric acute lymphoblastic leukemia; QALY, quality-adjusted life-year.

[a]At 0 months of delay, the average patient with pALL in the first cohort gained 7.2 QALYs and the average patient with DLBCL in the first cohort gained 3.4 QALYs. Values shown represent the value lost relative to no treatment delays. For the pALL cohort, calculations assume that patients received clofarabine monotherapy[28] while awaiting treatment with tisagenlecleucel. For the DLBCL cohort, calculations assume that patients received salvage chemotherapy[13] while awaiting treatment with axicabtagene ciloleucel. At 0 months of delay, the average patient with pALL in the first cohort gained $57,423 in productivity and the average patient with DLBCL in the first cohort gained $138,742 in productivity.

Sensitivity Analyses

In the pALL analysis, results of 1-way sensitivity analyses showed that social value was most sensitive to the discount rate, value of a QALY, and survival gains (**Table 2**). When key parameter assumptions were varied simultaneously to test the sensitivity of the model to those inputs, the social value and patient value results were most sensitive to the discount rate, value of a QALY, and survival gains (**eAppendix Figures 1** and **2**), and the manufacturer profits were most sensitive to the production costs, discount rate, and number of patients eligible for tisagenlecleucel (**eAppendix Figure 3**).

In the DLBCL analysis, results of 1-way sensitivity analyses indicated that social value was most sensitive to the survival gains, value of a QALY, and production costs of axicabtagene ciloleucel (Table 2). These findings are similar in the multiway sensitivity analysis of social value (**eAppendix Figure 4**). Meanwhile, multiway sensitivity analyses indicated that patient value was most sensitive to survival gains, value of a QALY, and discount rate, whereas manufacturer profits were most sensitive to production costs, number of patients eligible for axicabtagene ciloleucel, and discount rate (**eAppendix Figures 5** and **6**).

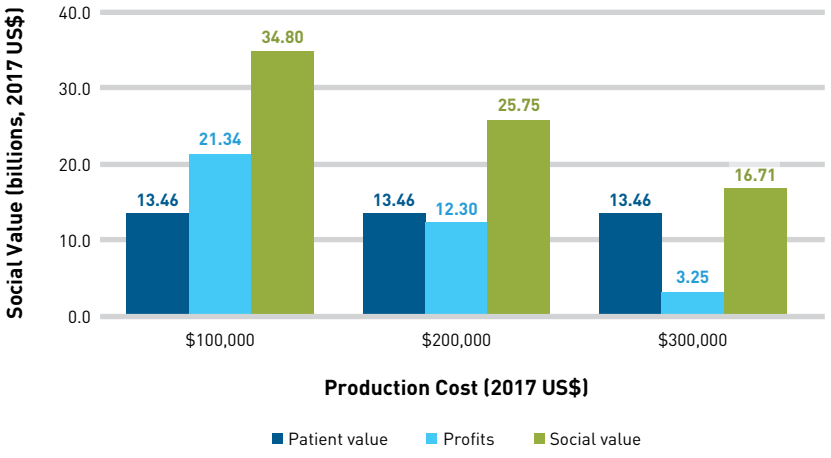
Because the total social value of CAR T is determined by the survival gains and the production costs, it is expected that social value is most sensitive to the aforementioned parameters. Meanwhile, the price of CAR T, future reduction in its price, and patient income had no effect on total social value because the former 2 parameters affect only the patients' and manufacturers' shares of social value, whereas the latter affects only the amount of patient value attributable to productivity.

DISCUSSION

CAR T has provided the hope of a cure to patients who otherwise have limited treatment options and poor prognoses.[29] Patients receiving CAR T are expected to experience meaningful improvements in life expectancy and QALYs, enabling them to contribute to overall productivity and generate social value. In both pALL and DLBCL, patients lost a substantial share of social value with treatment delays.

Various reasons have been reported for the treatment delays.[11,14] One-time curative treatments such as tisagenlecleucel and axicabtagene ciloleucel present a challenge to existing payment systems because their costs accrue up front, whereas benefits accrue over a lifetime, in contrast with other cancer therapies that are administered over an extended time period. To address this challenge, novel

FIGURE 3. Social Value and Its Distribution to Patients and the Manufacturer, by Production Cost of Axicabtagene Ciloleucel[a]



[a]Social value reported here is aggregated over 20 cohorts of patients with diffuse large B-cell lymphoma (N = 118,040).

financing mechanisms, such as an outcomes-based approach to reimbursement for tisagenlecleucel, are currently being discussed.[16,30] One reimbursement approach under consideration would allow participating payers to pay for tisagenlecleucel only when patients respond within 1 month of treatment,[31] allowing payers and manufacturers to share the financial risk. Additionally, aspects of the US healthcare system present challenges to outcomes-based contracts for curative therapies like CAR T. Because the average American changes health insurers every few years,[32] the payers that pay the up-front costs of treatment with CAR T may not be the same ones that cover the cured individual years down the line. Thus, the payer may benefit from only a fraction of the savings, which reduces the incentive to invest in curative therapies.[33] Creative solutions have been proposed to combat this "free-rider" problem.[33,34] Although an outcomes-based contract developed for CAR T may help reduce payers' risk of paying for nonresponse, the issue of up-front costs disincentivizing innovation remains.

Further, the development of formal policies to cover CAR T has been slow. Currently, reimbursement is frequently done on an individual basis,[12] with hospitals facing high financial risk to treat patients with CAR T without a guarantee of payment from insurers.[35] Although larger health plans are often better equipped than smaller regional plans to handle such requests, reviewing each case individually lengthens the authorization process.[12] In some cases, waiting for CAR T reimbursement approval may take up to 90 days, which may be longer than a patient's survival.[11] Some payers, such as Medicare, have had success securing coverage of CAR T in the outpatient setting[12]; however, challenges remain to provide sufficient reimbursement to hospitals to administer the treatment in an inpatient setting. Even with the recent approval of the new technology add-on payment of up to $186,500 per patient,[36] intended to mitigate the additional costs of treatment, the reimbursement promised may fall short of the additional costs. When faced with high financial risk in the event that the costs of treating patients with CAR T exceed this payment cap, hospitals face disincentives for CAR T adoption. Thus, such policies may limit access for patients.

Additionally, CAR T is produced through a complex and individualized process[37] that may be challenging to scale quickly. Efforts are currently under way to minimize delays caused by inefficiencies in production.[38-40] Timely administration also necessitates that treatment centers be equipped with the proper equipment and human capital. Educating community oncologists is especially important in maximizing the efficacy and safety of CAR T, as patients are usually referred to their local oncologists for follow-up care after receiving treatment at the specified transplant centers.[41] Professional organizations, such as the American Society of Hematology and the Foundation for the Accreditation of Cellular Therapy, are in the process of developing guidelines on CAR T.[41,42]

Our social value analysis indicates that facilitating timely patient access is a key consideration in determining an optimal financing approach. For patients with rapidly progressing cancer and high mortality rates,[13,28] delaying treatment comes at a high cost. The case of CAR T provides a lesson to payers, policy makers, and innovators for incentivizing innovation and providing access to other curative therapies. In particular, therapies providing large QALY gains, such as curative therapies, bring large social value to society. Allowing innovators to share in that value incentivizes the development of future cures. However, stakeholders must work together to facilitate prompt patient access to such therapies. Efficient payment mechanisms, sufficient technological capabilities, adequate capital and human capital, and payment policy reform are required to minimize treatment delays for patients. Others have also argued that the price of CAR T should be lowered.[43] These considerations are particularly important given other new or curative therapies in the pipeline, such as voretigene neparvovec-rzyl for mutation-associated retinal dystrophy,[44] SPK-9001 for hemophilia,[45] and LentiGlobin BB305 for sickle cell disease and beta-thalassemia.[46]

Limitations

Our study is based upon the overall experience of patients with pALL and DLBCL and does not account for heterogeneity in patient experiences. We excluded caregiver burden from this analysis, but a reduction could be expected using CAR T-cell therapies, as they may offer patients a possible remission with fewer treatments and adverse events. Additionally, our study examined the impact of treatment delays of various lengths in only the first cohort of

TABLE 2. One-Way Sensitivity Analyses[a]

Parameter	Minimum	Base Case	Maximum	10th Percentile	Median	90th Percentile
Tisagenlecleucel (pALL)						
Number of patients who are eligible for tisagenlecleucel	320	400	480	$5,235,900,585	$5,844,835,975	$6,408,004,754
Undiscounted tisagenlecleucel life-years[b]	6.1	12.1	18.2	$3,902,075,156	$5,715,291,306	$7,589,316,440
Undiscounted tisagenlecleucel QALYs[b]	5.4	10.9	16.3			
Economic value of a QALY	$100,000	$150,000	$200,000	$4,708,152,755	$5,811,974,663	$6,952,581,546
Adjustment factor for income[c]	0.8	1.0	1.2	No effect on total social value, although it does affect the share of patients' value attributable to productivity		
Production costs of tisagenlecleucel[d]	$100,000	$200,000	$300,000	$5,531,215,603	$5,828,326,243	$5,861,898,538
Reduction in price after loss of exclusivity	15%	30%	45%	No effect on total social value, although it does affect the distribution of value between patients and the manufacturer		
Discount rate	0.0%	3.0%	6.0%	$4,660,770,983	$5,861,252,743	$7,521,321,059
Axicabtagene Ciloleucel (DLBCL)						
Number of patients who are eligible for axicabtagene ciloleucel	4722	5902	7082	$23,092,403,318	$25,695,368,452	$28,321,162,184
Undiscounted axicabtagene ciloleucel life-years[b]	4.08	8.15	12.23	$6,495,269,609	$25,529,199,097	$42,271,585,179
Undiscounted axicabtagene ciloleucel QALYs[b]	3.26	6.51	9.77			
Economic value of a QALY	$100,000	$150,000	$200,000	$17,698,649,172	$25,940,482,025	$33,097,508,858
Adjustment factor for income[c]	0.8	1.0	1.2	No effect on total social value, although it does affect the share of patients' value attributable to productivity		
Production costs of axicabtagene ciloleucel[d]	$100,000	$200,000	$300,000	$21,123,684,105	$25,527,875,927	$30,479,957,449
Reduction in price after loss of exclusivity	15%	30%	45%	No effect on total social value, although it does affect the distribution of value between patients and the manufacturer		
Discount rate	0.0%	3.0%	6.0%	$22,843,843,068	$25,663,296,112	$29,161,235,763

DLBCL indicates diffuse large B-cell lymphoma; pALL, pediatric acute lymphoblastic leukemia; QALY, quality-adjusted life-year.

[a]Results were obtained from 1000 Monte Carlo simulations; parameters follow a beta distribution.

[b]Because of the uncertainty in long-run survival of patients treated with chimeric antigen receptor T-cell therapy, minimum and maximum life-years and QALYs were determined by varying the base-case parameter ±50%.

[c]Adjustment factor for income adjusts income for each age and gender by ±20%.

[d]Base-case production cost was assumed to be $200,000 in sensitivity analyses.

patients. It is uncertain how treatment delays may change in the future. Because of a lack of clinical data, we were also unable to account in our analysis for potential reductions in CAR T efficacy due to treatment delays. To the extent that delayed treatment reduces CAR T efficacy, our estimates of the social value lost because of treatment delays are conservative.

Moreover, the total cost of treatment with CAR T is not yet clear[20] and may change over time. The average total costs of tisagenlecleucel used in our analysis ($736,265; obtained from the ICER report[10]) included the average costs required by patients with pALL over the course of their treatment history (costs of CAR T, chemotherapy treatment, palliative chemotherapy, pretreatment, stem cell transplantation, adverse events, administration and monitoring, future healthcare, and end-of-life costs). This estimate substantially exceeded the average cost of treatment in the literature, which considered physician costs for leukapheresis and administration of lymphodepletion therapy, facilities, CAR T, drugs other than CAR T, facility fees for hospitalizations for cytokine release syndrome, and physician costs. These estimates ranged from $432,131 to $510,963 with the outcomes-based pricing arrangement.[20]

The average total cost of axicabtagene ciloleucel used in our analysis ($551,642) included costs accrued by patients over their treatment history (described above) and exceeded the $402,647 estimate reported by Hernandez et al in 2018.[20]

CONCLUSIONS

CAR T-cell therapies have the potential to provide significant benefit to patients with pALL and DLBCL and to society in the United States, particularly through gains in survival and productivity. However, the magnitude of benefit depends upon the ability of patients to access these treatments promptly. ■

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Social Value of CAR T-Cell Therapy and Consequences of Treatment Delays

eAppendix

Additional Details on Study Methods

The objectives of this study were to calculate the social value of tisagenlecleucel and axicabtagene ciloleucel for the treatment of relapsed or refractory pALL and DLBCL in the US, respectively, as well as the share of that value accruing to the manufacturer and patients. We accomplished these objectives in four steps. We use tisagenlecleucel as an example of how we performed our calculations; axicabtagene ciloleucel was handled analogously. First, we calculated the net health benefits from the use of tisagenlecleucel ("Step 1"). Second, we calculated the productivity value of tisagenlecleucel, in terms of the additional productivity patients may attain through the use of tisagenlecleucel ("Step 2"). Third, we estimated the manufacturer's profits from tisagenlecleucel ("Step 3"). Last, we calculated the shares of social value accruing to the manufacturer and patients ("Step 4"). Detail on each of these steps is provided below. All values were calculated at the per capita level to reflect the individual patient and at the aggregate level to reflect an annual cohort of patients in the US. Throughout all steps, monetary values were inflation-adjusted to 2017 US dollars using the Consumer Prices Index (CPI).[1] Following ICER convention, an annual discount rate of 3.0% was applied to costs and health outcomes.[2]

Step 1: Value Net Health Benefits.

The net health benefits of tisagenlecleucel were expressed in QALYs and valued by applying a standard economic value per QALY from the literature. Specifically, following ICER (2018) [2], we measured gains in QALYs with tisagenlecleucel relative to those experienced with clofarabine monotherapy.

QALYs gained from tisagenlecleucel were valued at a standard economic value of a QALY taken from the literature. Economists value a statistical life year (or QALY) using various techniques, including survey-based methods such as conjoint analysis or contingent valuation, and revealed preference methods which measure how individuals trade financial gain for mortality risk in the real world setting. (For example, a job which requires a greater risk of death due to its safety conditions, such as mining, will typically require a wage premium compared to a similar job in safer conditions.) The value of a statistical life year represents the value that an individual implicitly places on living an additional year. It incorporates the value of both leisure and working time and is net of the costs associated with living an additional year (including healthcare costs). Following ICER (2018) [2], in the base case we assumed a value of $150,000 per QALY.

We obtained the health value of tisagenlecleucel by multiplying the health gain by the value of a QALY as follows:

$$\Delta health\_value\_pc = \Delta QALYs \times value$$

Here $\Delta health\_value\_pc$ represents the per capita economic value of the net health benefits of tisagenlecleucel, compared to clofarabine use (in the base case); $\Delta QALYs$ represents the (discounted) QALYs the patient can expect to gain through the use of tisagenlecleucel relative to clofarabine; and *value* represents the economic value of a QALY.

Once the per capita health value was obtained, we obtained the aggregate health value as follows:

$$\Delta health\_value = \Delta health\_value\_pc \times patients$$

Here, $\Delta health\_value$ represents the aggregate change in health value from the use of tisagenlecleucel, and $patients$ represents the number of patients expected to be eligible to take tisagenlecleucel in a given year.

Since more than one incident cohort of tisagenlecleucel patients was considered, the health value was summed across cohorts as follows:

$$total\_health\_value = \sum_{t=1}^{T} health\_value_t * \left(\frac{1}{1+r}\right)^{t-1}$$

Here *t* represents a given cohort, *T* is the total number of cohorts considered, and *r* is the discount rate.

Step 2: Value Productivity Benefits.

In this step we quantified the productivity gained through the use of tisagenlecleucel. It should be noted that part of the value of an additional year of life is the productivity it brings, and therefore, the value of the patient's productivity is already included in the value of a QALY. Therefore, the patient's productivity gains estimated in this step could be compared to the overall value of the QALYs gained computed in the first step; however, the productivity benefits are a line item under the value of the health benefits, and are not additive with the health benefits.

To estimate the productivity benefits of tisagenlecleucel to the patient, we considered the years of life a child gains, as well as their expected earnings in those years. Specifically, we defined the per capita productivity gain from tisagenlecleucel as follows:

$$\Delta patient\_productivity\_pc = \Delta child\_income$$

That is, the per capita change in productivity from tisagenlecleucel, $\Delta patient\_productivity\_pc$, was equal to the change in income of the child who is spared an early death and therefore goes on to a productive work life ($\Delta child\_income$).

The gain in the child's income from the use of tisagenlecleucel was estimated based on projected working years and average annual income in those years. Specifically, we defined the gain in the child's income based on the additional life years the child could expect with tisagenlecleucel ($life\_years\_CART$), the additional life years expected with the prior standard of care ($life\_years\_SOC$, in the base case taken to be clofarabine), the discount rate *r* (assumed to be 3.5% in the base case), and the child's income in each year $income_t$.

$$\Delta child\_income = \sum_{t=1}^{life\_years\_CART} \left(\frac{1}{1+r}\right)^{t-1} \times income_t - \sum_{t=1}^{life\_years\_SOC} \left(\frac{1}{1+r}\right)^{t-1} \times income_t$$

For the purposes of this calculation, we assumed that the child taking tisagenlecleucel is the age of the average patient given in the economic model of ICER (2018) [2], i.e., 14 years. Therefore, the index *t* in the above equation counts years of the patient's life from beginning treatment with tisagenlecleucel or the comparator onward through the patient's remaining life expectancy. Because the US restricts the number of hours that children under 16 years of age may work [3], we conservatively assumed zero income at ages 14 and 15. From age 16 onward, we used average US income. We adjusted for employment rates and income by age and gender, to reflect the fact

that, say, a 40 year-old is more likely to be employed and to have a higher income than, say, a 20 year-old.

We conservatively used current income figures and did not adjust for economic growth expected over the child's lifetime. Although omitting economic growth is an unrealistically pessimistic assumption, it is better aligned with our conventional approach to take a fixed value of a life-year. Otherwise, the productivity value of an additional year of a child's life would soon outstrip the total value of that life-year, even though productivity is only one component of a life-year's value. (One could argue that this highlights the deficiency of the concept of a fixed value of a life-year, but that is beyond the scope of the current study.)

Once we obtained an estimate of the per capita productivity impact of tisagenlecleucel for patients, we obtained the aggregate productivity effect for patients as follows:

$$\Delta patient\_productivity = \Delta patient\_productivity\_pc \times patients$$

This provided the estimated productivity effect to the patients of giving tisagenlecleucel to an annual cohort of patients in the US. This estimate of the effects of tisagenlecleucel on the patients' productivity could be compared to the economic value of the QALYs gained to better understand how productivity contributes to the value of tisagenlecleucel to patients.

Of course, the patients' own productivity is not the only productivity to be affected by the use of tisagenlecleucel or clofarabine. Caregivers' productivity is also affected; however, we lacked data to include these effects in our model.

More than one incident cohort of tisagenlecleucel patients was considered, so the patient effects were summed across cohorts as follows:

$$total\_patient\_productivity\_gain = \sum_{t=1}^{T} \Delta patient\_productivity_t * \left(\frac{1}{1+r}\right)^{t-1}$$

Here *t* represents a given cohort, *T* is the total number of cohorts considered, and *r* is the discount rate.

Step 3: Estimate Manufacturer Profits.

To estimate manufacturer profits from tisagenlecleucel, we subtracted per patient production costs from the price, as follows:

$$profit\_pc = price - production\_cost$$

Here $profit\_pc$ represents the per capita profit the manufacturer earns on tisagenlecleucel, $price$ represents the price of tisagenlecleucel in the US, and *production_cost* represents the estimated per-patient production cost.

We estimated the aggregate profits from tisagenlecleucel as follows:

$$profit = profit\_pc \times patients$$

Since more than one incident cohort of tisagenlecleucel patients was considered, the manufacturer profit was summed across cohorts as follows:

$$total\_profit = \sum_{t=1}^{T} profit_t * \left(\frac{1}{1+r}\right)^{t-1}$$

Here *t* represents a given cohort, *T* is the total number of cohorts considered, and *r* is the discount rate.

Step 4: Calculate Total Social Value and Shares of Value.

The social value of tisagenlecleucel primarily stemmed from its survival benefits. (Productivity benefits are included in the value of a QALY and therefore comprise a line item under the net health benefits, rather than an additive source of value.) In this step we decomposed the social value of tisagenlecleucel into the shares accruing to the manufacturer and the patients/consumers. More precisely, the social value of tisagenlecleucel was calculated as follows:

$$social\_value \equiv total\_surplus = producer\_surplus + consumer\_surplus$$

That is, the social value of tisagenlecleucel was defined equal to the total surplus from tisagenlecleucel, which was in turn composed of the producer surplus plus the consumer surplus. The producer surplus is simply the total manufacturer profit, as estimated in Step 3.

The per capita consumer surplus is defined as follows:

$$consumer\_surplus\_pc = \Delta health\_value\_pc - (price - cost\_offsets)$$

In other words, our measure of the patient's effective price reflected cost offsets. Specifically, we measured the price net of any cost offsets from the use of tisagenlecleucel. In this case, the medical costs associated with tisagenlecleucel treatment are higher than those associated with clofarabine monotherapy. Therefore the costs offsets actually increase the effective price of treatment with tisagenlecleucel.

This formula was calculated using the change in health value estimated in Step 1 and the price of tisagenlecleucel from Step 3.

The aggregate consumer surplus was defined as:

$$consumer\_surplus = consumer\_surplus\_pc \times patients$$

Once the social value was defined, manufacturer profits were compared to the total social value of tisagenlecleucel, as follows:

$$manufacturer\_share = \frac{producer\_surplus}{total\_surplus} = \frac{profit}{social\_value}$$

That is, the manufacturer's share of total value was equal to the producer surplus divided by the total surplus, or equivalently, to the manufacturer's profit divided by the total social value of tisagenlecleucel.

Step 5: Calculate Total Loss of Social Value from Treatment Delays

Lastly, we calculated the social value lost from treatment delays. To do so, we first extracted data from the survival curve of patients from the Jeha et al. [4] and SCHOLAR-1 [5] clinical trials

for pALL and DLBCL, respectively. This provided us with a probability of survival at each month, m, leading up to treatment with CAR-T, $p(survival_m)$. Note that the probability of surviving to receive CAR-T therapy differs for each indication as the probability of survival to month *m* was based upon two different clinical trials.

For each cohort of patients, we then calculated the social value conditional on living to month m, and assumed that patients received the standard of care treatment leading up to that month, at which point they would be treated with CAR-T therapy and subsequently follow the survival of patients treated with CAR-T.

For t = 0 to 12 months,

$$social\_value_m = social\_value_0 * p(survival_m)$$

That is, the social value after m months of treatment delay is the social value assuming no delays, adjusted for the probability of surviving a delay of m months.

Note that this approach produces a conservative estimate of the social value lost due to treatment delays for two reasons. First, we assume that those patients who survive a delay of *m* months and receive CAR-T will fare just as well as those patients who receive CAR-T immediately, when in reality, the patients' health status may have worsened after the *m*-month delay. Second, we only count the cost of CAR-T in this analysis, but in reality, the delayed patient will incur both the cost of CAR-T and the cost of the interim treatment while waiting for CAR-T. Therefore, compared to no delays, delay likely imposes higher costs and has a larger negative impact on health benefits than our simplified analysis predicts. That is, the true social value losses from delay are likely to be larger than our predictions.

To calculate the social value across multiple cohorts (denoted $total\_social\_value$), we used the following formula:

$$total\_social\_value = \sum_{t=1}^{T} social\_value_m * \left(\frac{1}{1+r}\right)^{t-1}$$

Here *t* represents a given cohort, *T* is the total number of cohorts considered, and *m* is the number of months of treatment delay. Though it is possible to calculate the social value for various cohorts assuming differing lengths of treatment delay, in our analysis we assumed that all cohorts experienced the same length of treatment delay as there is insufficient evidence to estimate how this delay may change in the future.

eAppendix Table. Complete parameter values for social value model

	Tisagenlecleucel (pALL)		*Axicabtagene ciloleucel (DLBCL)*	
Input Parameter	Parameter Value	Source	Parameter Value	Source
Patient Health Parameters				
Number of incident patients who are eligible for treatment	400	[6]	5,902	[6]
Number of annual incident cohorts considered	20	Modeling decision	20	Modeling decision
Average patient age at time of treatment initiation	11.5	[6]	58	[6]
Comparator selected	Clofarabine monotherapy	Modeling decision (following ICER)	Salvage chemotherapy	Modeling decision (following ICER)
Number of undiscounted life years on treatment	12.12	[6]	8.15	[6]
Number of undiscounted life years on comparator	2.49	[6]	3.35	[6]
Number of undiscounted QALYs on treatment	10.88	[6]	6.51	[6]
Number of undiscounted QALYs on comparator	2.15	[6]	2.57	[6]
Economic value of a QALY	$150,000	[7,8]	$150,000	[7,8]
Price of treatment	$475,000	[9]	$373,000	[9]
Price of comparator therapy	$163,686	[6]	$40,142	[6]
All other costs of treatment (aside from the drug itself)	$261,265	[6]	$178,642	[6]
All other costs of comparator therapy (aside from the drug itself)	$173,570	[6]	$114,743	[6]
All other costs include:				
Chemotherapy treatment costs of CAR-T	$15,309	[6]	$0	[6]
Palliative chemotherapy treatment costs of CAR-T	$2,648	[6]	$3,748	[6]

Palliative chemotherapy treatment costs of comparator	$3,973	[6]	$6,103	[6]
Pre-treatment costs of CAR-T	$2,979	[6]	$4,585	[6]
Pre-treatment costs of comparator	$0	[6]	$0	[6]
Stem cell transplant costs of CAR-T	$47,744	[6]	$13,345	[6]
Stem cell transplant costs of comparator	$64,648	[6]	$62,094	[6]
Adverse event costs of CAR-T	$33,534	[6]	$16,029	[6]
Adverse event costs of standard of care comparator	$0	[6]	$7,046	[6]
Administration/monitoring costs of CAR-T	$111,548	[6]	$44,165	[6]
Administration/monitoring costs of comparator	$93,032	[6]	$1,045	[6]
Future healthcare costs of CAR-T	$45,901	[6]	$95,223	[6]
Future healthcare costs of comparator	$9,069	[6]	$36,286	[6]
End of life costs of CAR-T	$1,602	[6]	$1,547	[6]
End of life costs of comparator	$2,848	[6]	$2,169	[6]
Patient Productivity Parameters				
US Male employment rate ages 0-15	0.0%	[10]	0.0%	[10]
US Male employment rate ages 16-19	29.2%	[10]	29.2%	[10]
US Male employment rate ages 20-24	67.9%	[10]	67.9%	[10]
US Male employment rate ages 25-29	83.0%	[10]	83.0%	[10]
US Male employment rate ages 30-34	86.6%	[10]	86.6%	[10]
US Male employment rate ages 35-39	87.9%	[10]	87.9%	[10]
US Male employment rate ages 40-44	87.6%	[10]	87.6%	[10]
US Male employment rate ages 45-49	85.8%	[10]	85.8%	[10]

US Male employment rate ages 50-54	81.9%	[10]	81.9%	[10]
US Male employment rate ages 55-59	75.6%	[10]	75.6%	[10]
US Male employment rate ages 60-64	60.4%	[10]	60.4%	[10]
US Male employment rate ages 65-69	36.0%	[10]	36.0%	[10]
US Male employment rate ages 70-74	22.8%	[10]	22.8%	[10]
US Male employment rate ages 75+	11.2%	[10]	11.2%	[10]
US Female employment rate ages 0-15	0.0%	[10]	0.0%	[10]
US Female employment rate ages 16-19	31.4%	[10]	31.4%	[10]
US Female employment rate ages 20-24	64.2%	[10]	64.2%	[10]
US Female employment rate ages 25-29	72.8%	[10]	72.8%	[10]
US Female employment rate ages 30-34	71.2%	[10]	71.2%	[10]
US Female employment rate ages 35-39	71.5%	[10]	71.5%	[10]
US Female employment rate ages 40-44	72.9%	[10]	72.9%	[10]
US Female employment rate ages 45-49	73.2%	[10]	73.2%	[10]
US Female employment rate ages 50-54	70.9%	[10]	70.9%	[10]
US Female employment rate ages 55-59	64.1%	[10]	64.1%	[10]
US Female employment rate ages 60-64	49.6%	[10]	49.6%	[10]
US Female employment rate ages 65-69	27.0%	[10]	27.0%	[10]
US Female employment rate ages 70-74	15.5%	[10]	15.5%	[10]
US Female employment rate ages 75+	5.8%	[10]	5.8%	[10]
US Male average annual income per capita ages 0-14	$0	Assumption	$0	Assumption
US Male average annual income per capita ages 15-19	$21,188	[11]	$21,188	[11]

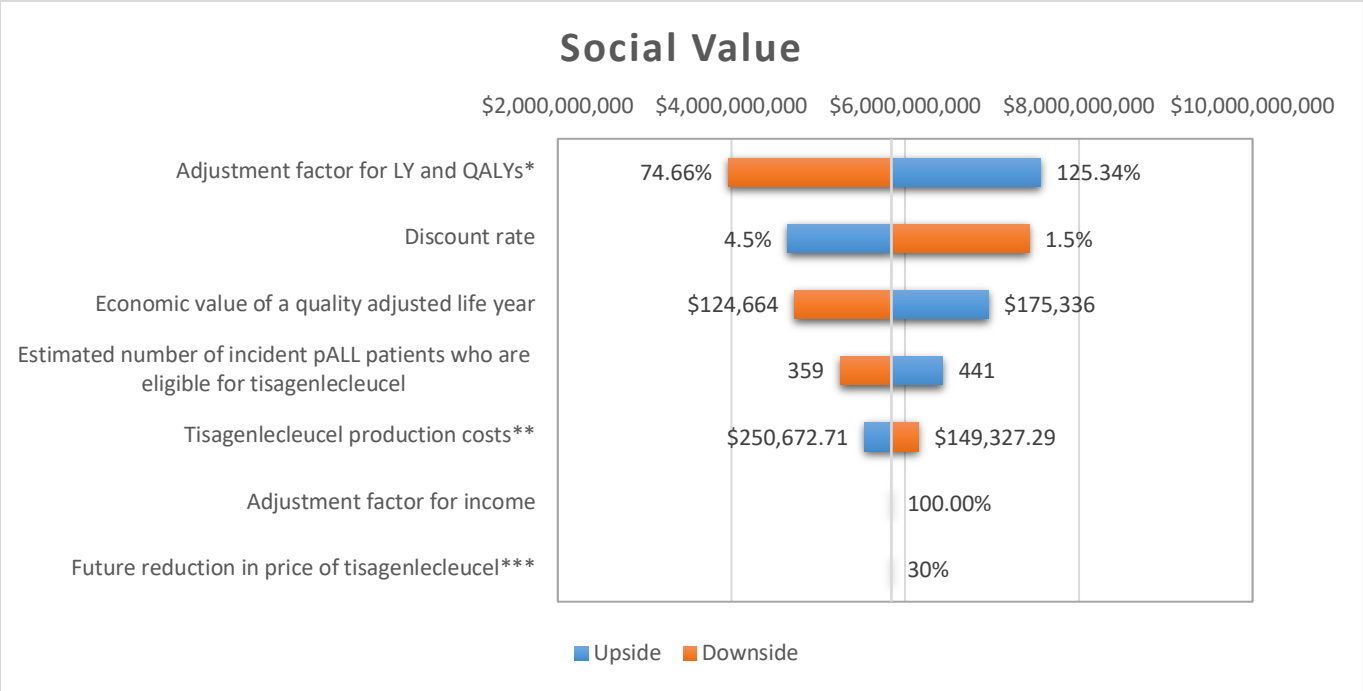
US Male average annual income per capita ages 20-24	$21,188	[11]	$21,188	[11]
US Male average annual income per capita ages 25-29	$60,290	[11]	$60,290	[11]
US Male average annual income per capita ages 30-34	$60,290	[11]	$60,290	[11]
US Male average annual income per capita ages 35-39	$60,290	[11]	$60,290	[11]
US Male average annual income per capita ages 40-44	$60,290	[11]	$60,290	[11]
US Male average annual income per capita ages 45-49	$74,231	[11]	$74,231	[11]
US Male average annual income per capita ages 50-54	$74,231	[11]	$74,231	[11]
US Male average annual income per capita ages 55-59	$74,231	[11]	$74,231	[11]
US Male average annual income per capita ages 60-64	$74,231	[11]	$74,231	[11]
US Male average annual income per capita ages 65-69	$60,852	[11]	$60,852	[11]
US Male average annual income per capita ages 70-74	$60,852	[11]	$60,852	[11]
US Male average annual income per capita ages 75+	$60,852	[11]	$60,852	[11]
US Female average annual income per capita ages 0-14	$0	Assumption	$0	Assumption
US Female average annual income per capita ages 15-19	$15,403	[11]	$15,403	[11]
US Female average annual income per capita ages 20-24	$15,403	[11]	$15,403	[11]

US Female average annual income per capita ages 25-29	$42,686	[11]	$42,686	[11]
US Female average annual income per capita ages 30-34	$42,686	[11]	$42,686	[11]
US Female average annual income per capita ages 35-39	$42,686	[11]	$42,686	[11]
US Female average annual income per capita ages 40-44	$42,686	[11]	$42,686	[11]
US Female average annual income per capita ages 45-49	$49,333	[11]	$49,333	[11]
US Female average annual income per capita ages 50-54	$49,333	[11]	$49,333	[11]
US Female average annual income per capita ages 55-59	$49,333	[11]	$49,333	[11]
US Female average annual income per capita ages 60-64	$49,333	[11]	$49,333	[11]
US Female average annual income per capita ages 65-69	$33,734	[11]	$33,734	[11]
US Female average annual income per capita ages 70-74	$33,734	[11]	$33,734	[11]
US Female average annual income per capita ages 75+	$33,734	[11]	$33,734	[11]
Manufacturer Parameters				
Treatment production costs*	$100,000-300,000	Assumption	$100,000-300,000	Assumption
Year of treatment launch in US	2018	Assumption	2018	Assumption
Year of assumed treatment price reduction in US	2030	Assumption	2030	Assumption
Reduction in treatment price	30%	[12-14]	30%	[12-14]
General Parameters				
Discount rate	3.0%	[15]	3.0%	[15]

Notes: pALL = pediatric acute lymphoblastic leukemia; DLBCL = diffuse large B-cell lymphoma; QALY = quality adjusted life year; US = United States; QALYs and life years were converted to undiscounted values from the discounted values presented in the ICER report [6]. Comparators used in the pALL and DLBCL analysis were clofarabine monotherapy and salvage chemotherapy, respectively. [6] *Base case production cost assumed to be $200,000 in sensitivity analyses.

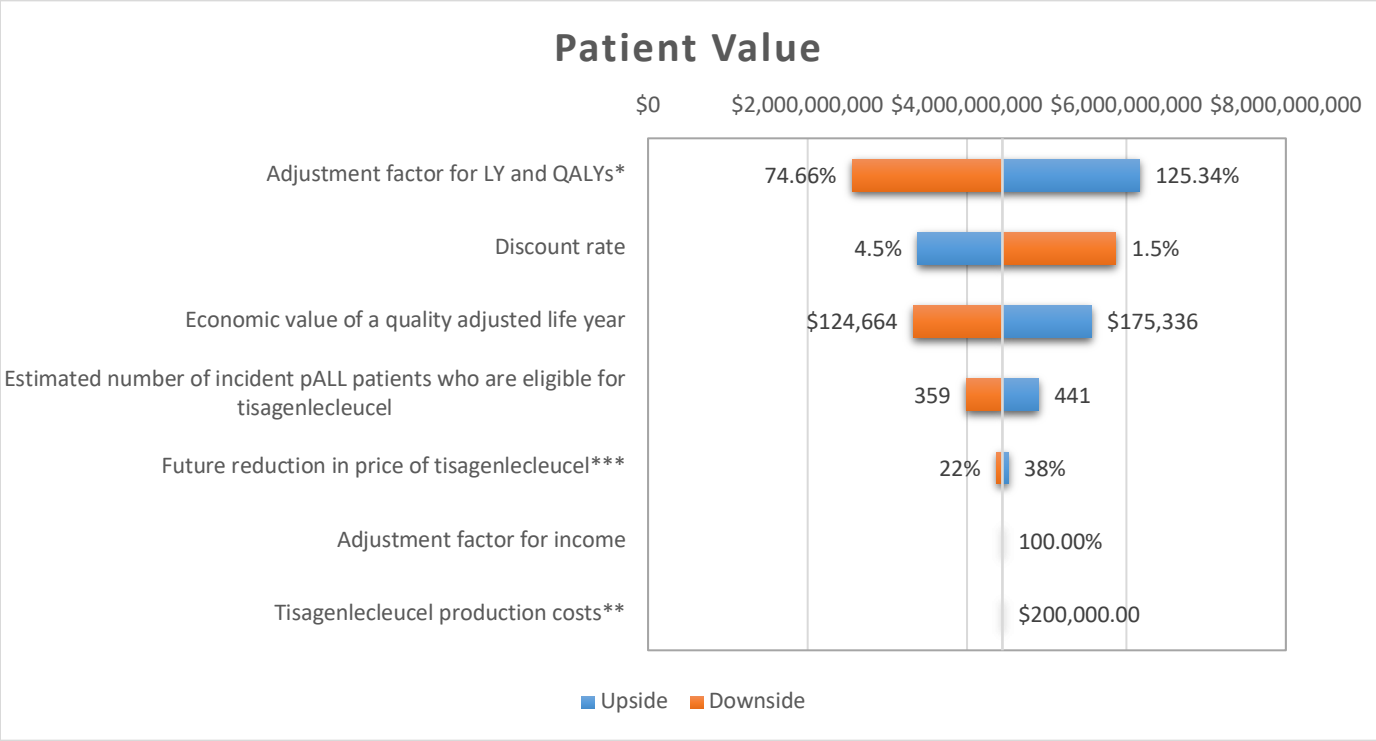
Additional Detail on Study Results

eAppendix Figure 1. Social value sensitivity analyses varying multiple parameters, tisagenlecleucel



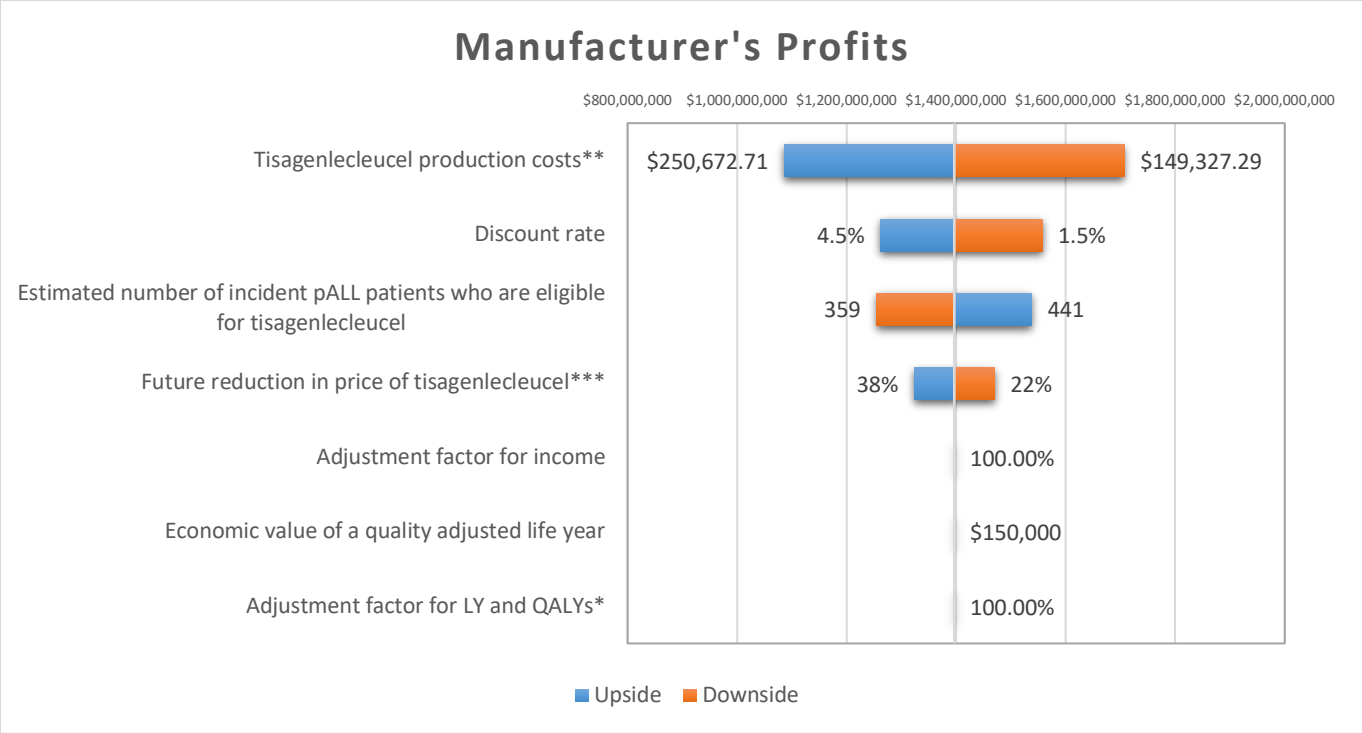
Notes: LY= life years; QALY = quality adjusted life year. Results were obtained from 1,000 Monte Carlo simulations varying all parameters simultaneously; all parameters follow a beta distribution. Increase represents the patient value when the parameter is selected at the upper end of its distribution; decrease represents the patient value when the parameter is selected at the lower end of its distribution. Selecting a parameter at the upper end of the distribution may result in lower patient value (e.g. discount rate); varying the production cost does not affect patient value (although it does affect the manufacturer's profit).*Because of the uncertainty in long run survival of patients treated with tisagenlecleucel, minimum and maximum life years and QALYs were determined by varying the base case parameter ±50% using an adjustment factor to vary both simultaneously. **Base case production cost assumed to be $200,000 in sensitivity analyses. ***We assumed a price reduction would occur in 2030 because of loss of exclusivity or competition. This is an oversimplification of the complicated, unknown price trajectory over time that may occur.

eAppendix Figure 2. Patient value sensitivity analyses varying multiple parameters, tisagenlecleucel



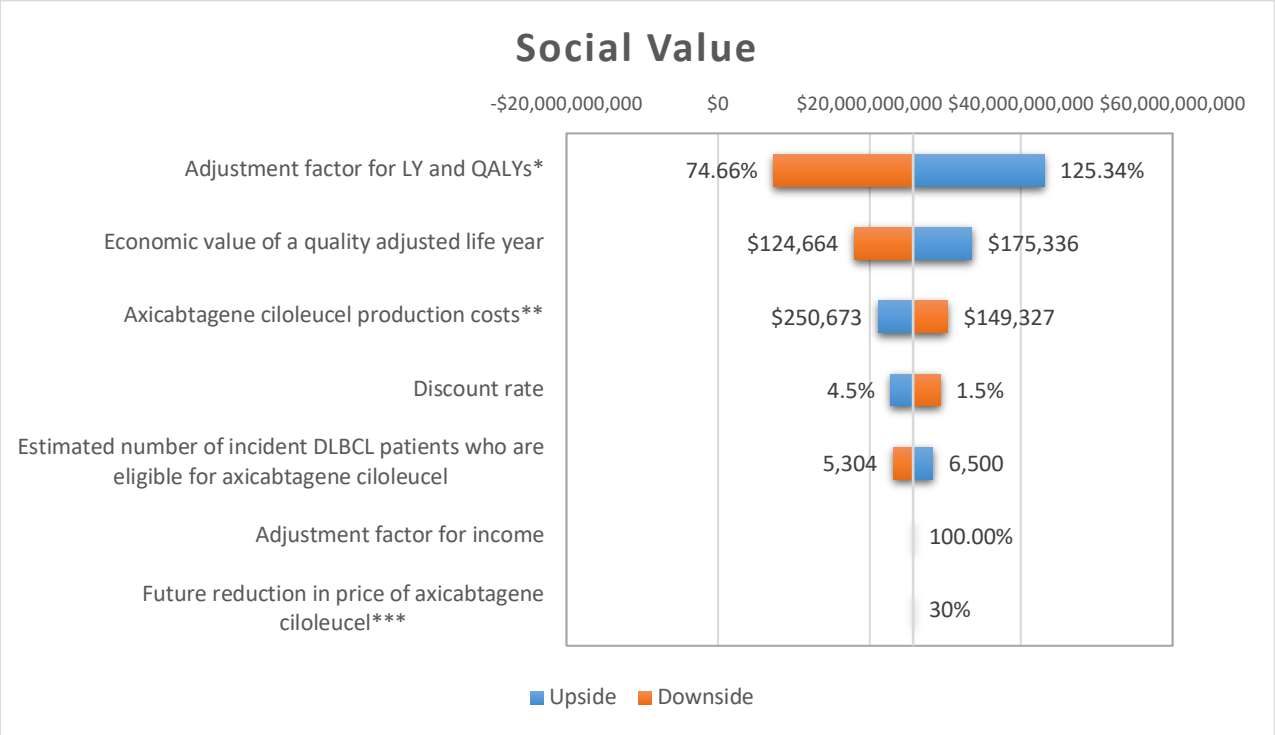
Notes: LY= life years; QALY = quality adjusted life year. Results were obtained from 1,000 Monte Carlo simulations varying all parameters simultaneously; all parameters follow a beta distribution. Increase represents the patient value when the parameter is selected at the upper end of its distribution; decrease represents the patient value when the parameter is selected at the lower end of its distribution. Selecting a parameter at the upper end of the distribution may result in lower patient value (e.g. discount rate); varying the production cost does not affect patient value (although it does affect the manufacturer's profit).*Because of the uncertainty in long run survival of patients treated with tisagenlecleucel, minimum and maximum life years and QALYs were determined by varying the base case parameter ±50% using an adjustment factor to vary both simultaneously. **Base case production cost assumed to be $200,000 in sensitivity analyses. ***We assumed a price reduction would occur in 2030 because of loss of exclusivity or competition. This is an oversimplification of the complicated, unknown price trajectory over time that may occur.

eAppendix Figure 3. Manufacturer profits sensitivity analyses varying multiple parameters, tisagenlecleucel



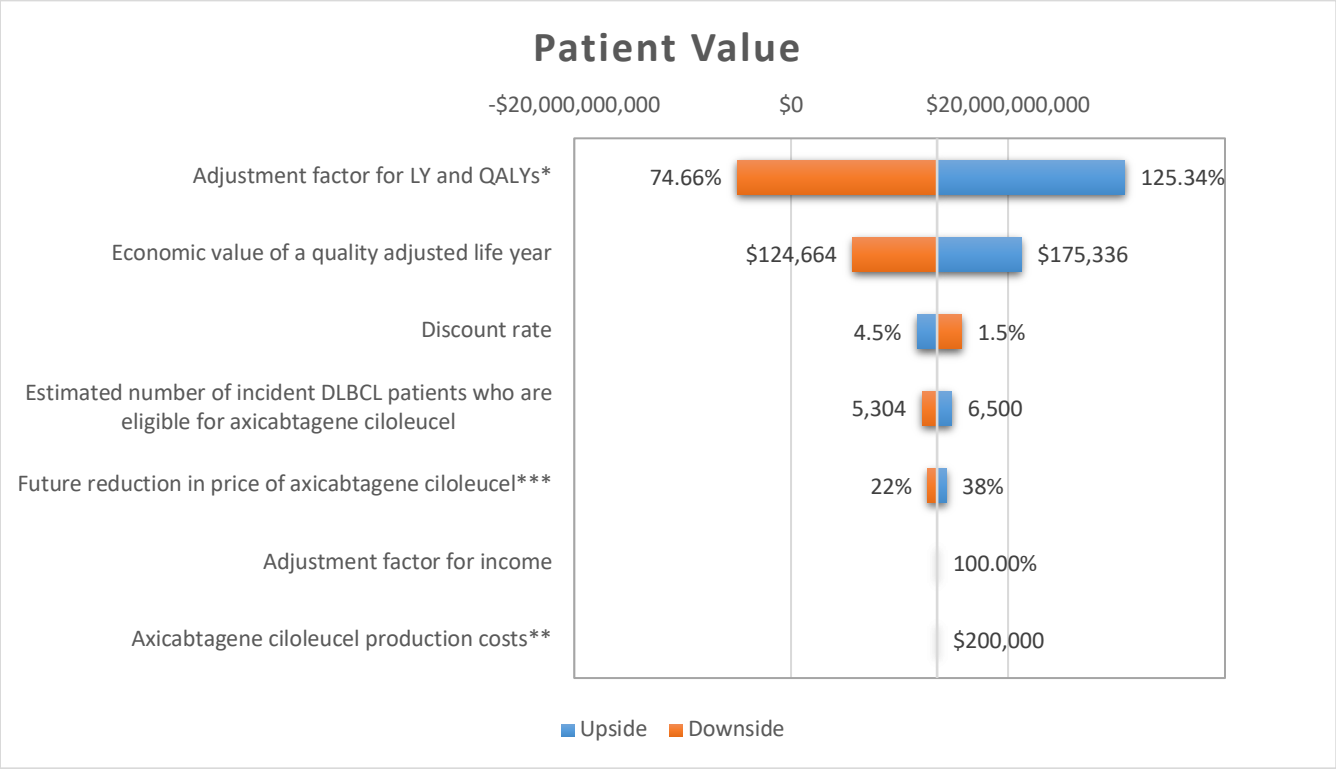
Notes: LY= life years; QALY = quality adjusted life year. Results were obtained from 1,000 Monte Carlo simulations varying all parameters simultaneously; all parameters follow a beta distribution. Increase represents the patient value when the parameter is selected at the upper end of its distribution; decrease represents the patient value when the parameter is selected at the lower end of its distribution. Selecting a parameter at the upper end of the distribution may result in lower patient value (e.g. discount rate); varying the production cost does not affect patient value (although it does affect the manufacturer's profit).*Because of the uncertainty in long run survival of patients treated with tisagenlecleucel, minimum and maximum life years and QALYs were determined by varying the base case parameter ±50% using an adjustment factor to vary both simultaneously. **Base case production cost assumed to be $200,000 in sensitivity analyses. ***We assumed a price reduction would occur in 2030 because of loss of exclusivity or competition. This is an oversimplification of the complicated, unknown price trajectory over time that may occur.

eAppendix Figure 4. Social value sensitivity analyses varying multiple parameters, axicabtagene ciloleucel



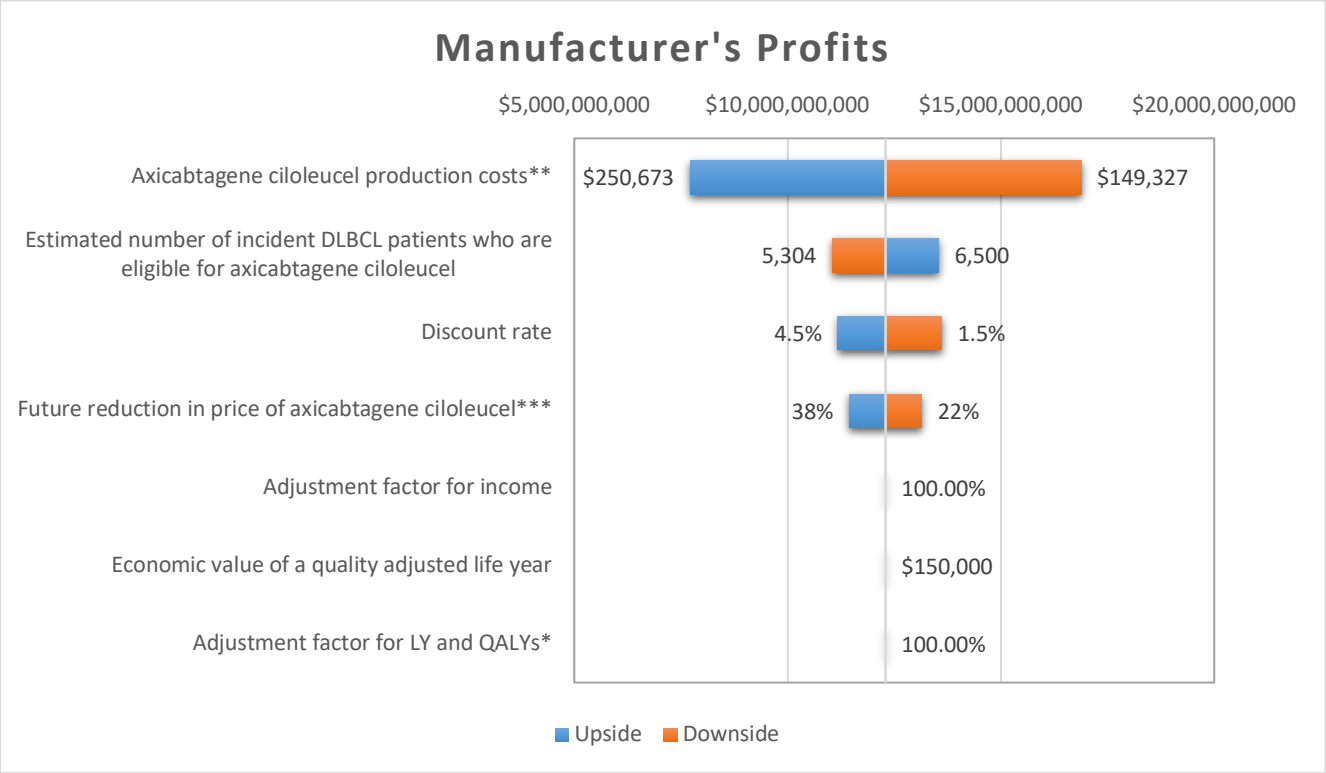
Notes: LY= life years; QALY = quality adjusted life year. Results were obtained from 1,000 Monte Carlo simulations varying all parameters simultaneously; all parameters follow a beta distribution. Increase represents the patient value when the parameter is selected at the upper end of its distribution; decrease represents the patient value when the parameter is selected at the lower end of its distribution. Selecting a parameter at the upper end of the distribution may result in lower patient value (e.g. discount rate); varying the production cost does not affect patient value (although it does affect the manufacturer's profit).*Because of the uncertainty in long run survival of patients treated with axicabtagene ciloleucel, minimum and maximum life years and QALYs were determined by varying the base case parameter ±50% using an adjustment factor to vary both simultaneously. **Base case production cost assumed to be $200,000 in sensitivity analyses. ***We assumed a price reduction would occur in 2030 because of loss of exclusivity or competition. This is an oversimplification of the complicated, unknown price trajectory over time that may occur.

eAppendix Figure 5. Patient value sensitivity analyses varying multiple parameters, axicabtagene ciloleucel



Notes: LY= life years; QALY = quality adjusted life year. Results were obtained from 1,000 Monte Carlo simulations varying all parameters simultaneously; all parameters follow a beta distribution. Increase represents the patient value when the parameter is selected at the upper end of its distribution; decrease represents the patient value when the parameter is selected at the lower end of its distribution. Selecting a parameter at the upper end of the distribution may result in lower patient value (e.g. discount rate); varying the production cost does not affect patient value (although it does affect the manufacturer's profit).*Because of the uncertainty in long run survival of patients treated with axicabtagene ciloleucel, minimum and maximum life years and QALYs were determined by varying the base case parameter ±50% using an adjustment factor to vary both simultaneously. **Base case production cost assumed to be $200,000 in sensitivity analyses. ***We assumed a price reduction would occur in 2030 because of loss of exclusivity or competition. This is an oversimplification of the complicated, unknown price trajectory over time that may occur.

eAppendix Figure 6. Manufacturer's profits sensitivity analyses varying multiple parameters, axicabtagene ciloleucel



Notes: LY= life years; QALY = quality adjusted life year. Results were obtained from 1,000 Monte Carlo simulations varying all parameters simultaneously; all parameters follow a beta distribution. Increase represents the patient value when the parameter is selected at the upper end of its distribution; decrease represents the patient value when the parameter is selected at the lower end of its distribution. Selecting a parameter at the upper end of the distribution may result in lower patient value (e.g. discount rate); varying the production cost does not affect patient value (although it does affect the manufacturer's profit).*Because of the uncertainty in long run survival of patients treated with axicabtagene ciloleucel, minimum and maximum life years and QALYs were determined by varying the base case parameter ±50% using an adjustment factor to vary both simultaneously. **Base case production cost assumed to be $200,000 in sensitivity analyses. ***We assumed a price reduction would occur in 2030 because of loss of exclusivity or competition. This is an oversimplification of the complicated, unknown price trajectory over time that may occur.

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