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Assessment of Utilities for Adverse Events (AEs) Associated With Chimeric Antigen Receptor (CAR) T Cell Therapy in Large B-Cell Lymphoma (LBCL)

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Introduction

- Chimeric antigen receptor (CAR) T cell immunotherapy is a therapeutic approach that involves genetically modifying the patients' own immune cells ex vivo in order to direct these cells to a tumor target and eliminate tumor cells[1]
- In 2017, the US Food and Drug Administration approved 2 CD19-targeted CAR T cell therapies: tisagenlecleucel for the treatment of adult patients with relapsed/refractory (R/R) LBCL, and children and young adults with R/R B-cell acute lymphoblastic leukemia (ALL); and axicabtagene ciloleucel for the treatment of adult patients with R/R LBCL
- CAR T cell therapy is associated with 2 specific toxicities, cytokine release syndrome (CRS) and neurological events (NEs)[2]
- CRS occurs when excessive cytokines are released by an overactive immune system.[3] CRS can range from mild, requiring only symptomatic treatment, to life threatening, requiring invasive treatments, such as ventilation support.[3] The most severe symptoms of CRS are fever, hypoxia, and hypotension.[3] Other symptoms include rash, nausea/vomiting, and rigors[3]
- NEs can occur with or without CRS. Symptoms include confusion, aphasia, headache, seizures, tremor, and hallucinations[4]
- Lisocabtagene maraleucel (liso-cel), an investigational, CD19-directed, defined composition, 4-1BB CAR T cell product administered at equal target doses of CD8+ and CD4+ CAR+ T cells[5] has a favorable adverse event (AE) profile
- There are currently no reliable data on utility associated with severe CRS/NEs

Objective

- To obtain utility values associated with CAR T cell therapy-related AEs (CRS and NEs) so that future economic models comparing CAR T cell therapies can include these disutilities

Methods

Figure 1. Sample Health States

Health State A: Base DLBCL without AEs

Disease	• You have a life-threatening condition in which **your white blood cells replicate and grow abnormally**. These white blood cells are part of the immune system that usually protects the body against disease ○ These white blood cells are **replicating too often** and **spreading throughout your body** • You have **significant chronic fatigue** • Your lymph nodes in your **neck, armpit, and groin** are **swollen**. You have pain in these swollen areas • There are **minimal options** for curative treatment. Without treatment, this condition will become more severe
Impact	• You find it **very difficult to work** • You have **significant difficulty performing most day-to-day tasks**, such as **housework, exercising,** and **going to social engagements**

Treatment	• Your treatment involves **removing your normal white blood cells** and modifying them in a laboratory so that they can treat your condition. Then, the modified white blood cells are **infused back into your body**. This involves the following steps:
	1. You undergo **extraction of your white blood cells.**
	  ○ This may be done with a **large needle** placed in **veins in each arm** to extract and return blood from your body
	  ○ The procedure lasts **2–4 hours**. You do not stay overnight in hospital
	2. **Three weeks later**, you undergo a **3-day** course of moderately strong **chemotherapy** to make your body more receptive to new white blood cells.
	  ○ This is an **outpatient** procedure. Each **daily treatment** lasts **6 hours**. This treatment is administered with an **intravenous (IV) infusion,** which means that fluid is inserted through a tube into a vein in your arm
	  ○ This treatment is relatively mild and **does not cause substantial hair loss** but can cause **some fatigue** and **nausea**. The treatment can also make you more susceptible to **infection and bleeding**
	3. **Three to seven days** later, you are **admitted to hospital** to receive your modified white blood cells.
	  ○ This is a **5-minute IV infusion**

Follow-Up	• You remain in hospital for **about 10 days** for monitoring • After you are released from hospital, you have **6 clinic appointments** over the next **2 weeks**. Your doctor monitors basic vital signs, performs physical exams, and asks questions about how you are feeling • For about 2 weeks after you are released from hospital, you will need someone to help care for you at home • You begin to feel better about **3 weeks** after the infusion. Symptoms such as fatigue and pain begin to improve • You continue to have appointments for **scans** at **months 1, 3, 6, and 9** following the infusion • You should **not drive** for the first **2 months** after the infusion because of possible neurological side effects. You have some restrictions on travel during this time • **Three months** after the infusion, you **return to work and most symptoms have resolved**. At **month 6,** you have **no further restrictions**. However, you still take precautions and medications to prevent infection
Timeline of the First Four Months	

Health State C: Grade 2 CRS Added to Health State A[a]

Adverse Event	• About **2 days** after your treatment, you develop a **fever** and begin to feel some **fatigue and flu-like symptoms** • Your **blood pressure drops**, and you have mild **trouble breathing** • You are given **IV antibiotics** to prevent infection every 8 hours for 30 minutes each time • You are given **IV fluids to raise your blood pressure**, and an **oxygen tube on your face below your nose** to help you breathe • This event resolves after **about 7 days**. You spend a total of **14 days** in hospital

[a]This is an excerpt from health state C. This text describing an adverse event was added to health state A along with adjustments to the follow-up and timeline.

Health State E: Grade 1/2 NEs Added to Health State A[b]

Adverse Event	• About **7 days** after your treatment, you begin to feel some mild **confusion** • You struggle to **remember basic details** (eg, what day it is) • You develop a **mild tremor** in your hands • You have some **difficulty finding words when speaking**. You forget some names of common objects and people who are close to you • This event resolves after **about 5 days**, and you are released from hospital **15 days** after initial treatment

[b]This is an excerpt from health state E. This text describing an adverse event was added to health state A along with adjustments to the follow-up and timeline.

Study Design

- Vignette-based time trade-off (TTO) utility interviews[6] were conducted with a sample of general public respondents in 2 locations in the United Kingdom: Edinburgh and London
- Six health states were presented during the utility interviews: 1 state described CAR T cell therapy for DLBCL with no AEs; 3 states described CAR T cell therapy for DLBCL with varying grades of CRS; and 2 states described CAR T cell therapy for DLBCL with varying grades of NEs. All health states also included the same background information about DLBCL

Participants

- All participants were required to be (1) at least 18 years of age; (2) able to understand the assessment procedures as judged by the investigator; (3) able and willing to give written informed consent; (4) able to complete the protocol requirements; and (5) a UK resident
  - Participants were recruited through newspaper and online classified advertisements

Health State Development and Pilot Study

- Health states were drafted based on: (1) literature review covering DLBCL symptoms, CAR T cell therapy, quality of life impact, and AEs associated with CAR T cell therapy; (2) multiple rounds of interviews with DLBCL and CAR T cell experts, including 2 physicians with oncology specialties and 2 nurse practitioners with personal experience administering liso-cel
- Draft health states and utility assessment methods were tested in a pilot study in London with 22 general population participants (50.0% male; mean age, 44.0 years). Minor edits to health state formatting and word choice were made based on pilot participant feedback

Procedures

- After an introductory ranking task, participants completed the TTO task to value the 6 health states. All health states were on a 1-year time horizon and described CAR T cell therapy, applicable AEs, and recovery, followed by a period of good health

Results

Table 1. Demographic Characteristics

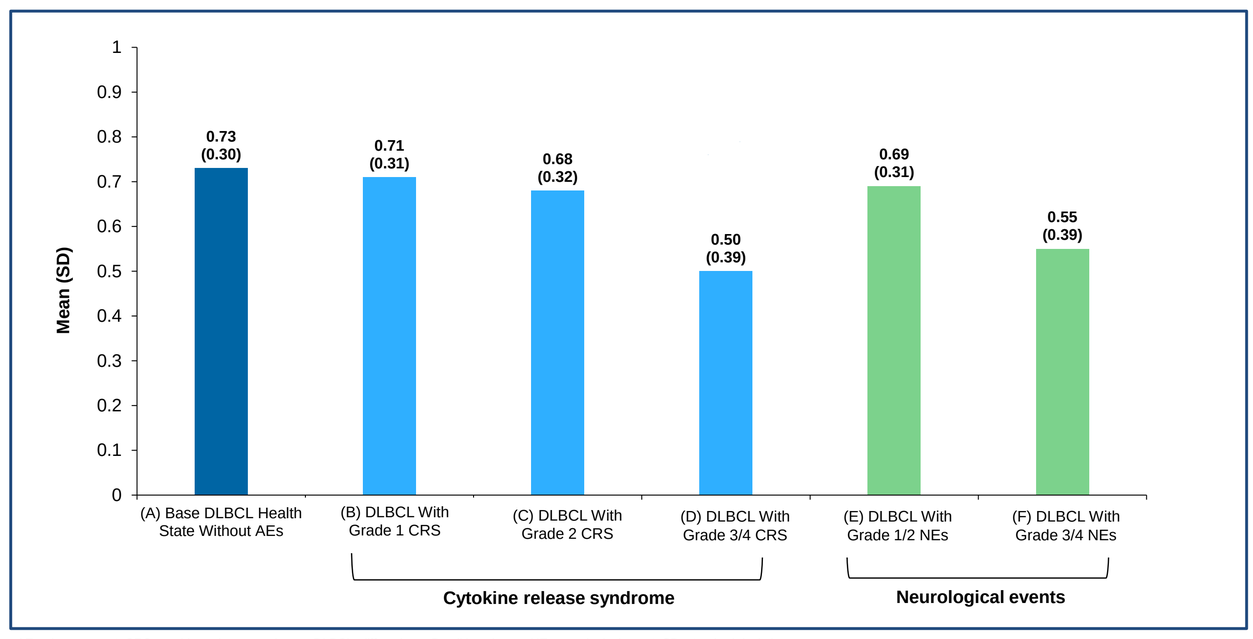
Characteristic	Total Sample (N=218)
Age, mean (SD), years	48.8 (12.7)
Sex, n (%)	
Male	109 (50%)
Female	109 (50%)
Race/ethnicity, n (%)	
White	169 (78%)
African, Caribbean, or black	13 (6%)
Asian	16 (7%)
Mixed ethnicity	15 (7%)
Other	5 (2%)
Employment status,[a] n (%)	
Full-time	88 (40%)
Part-time	65 (30%)
Other	65 (30%)
Education level,[a] n (%)	
No formal qualifications	6 (3%)
GCSE/ordinary levels or equivalent	41 (19%)
Advanced levels or equivalent	43 (20%)
Vocational/work-based qualifications	34 (16%)
University degree	65 (30%)
Postgraduate degree (MA, PhD, PGCE)	29 (13%)

[a]Not mutually exclusive.
GCSE, General Certificate of Secondary Education; NE, neurological event.

Sample Description

- A total of 218 participants completed the interview (113 in London and 105 in Edinburgh). The most commonly reported health conditions in this general population sample were depression (22%), anxiety (20%), diabetes (14%), arthritis (13%), and hypertension (8%). No participant reported a diagnosis of DLBCL

Figure 2. Health State Utilities (N=218)



AE, adverse event; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; NE, neurological event; SD, standard deviation.

Health State Utilities

- The "Base DLBCL" health state had the highest utility (0.73), followed by "grade 1 CRS" (0.71), "grade 1/2 NEs" (0.69), "grade 2 CRS" (0.68), "grade 3/4 NEs" (0.55), and "grade 3/4 CRS" (0.50). There were no significant differences in utilities by age or sex

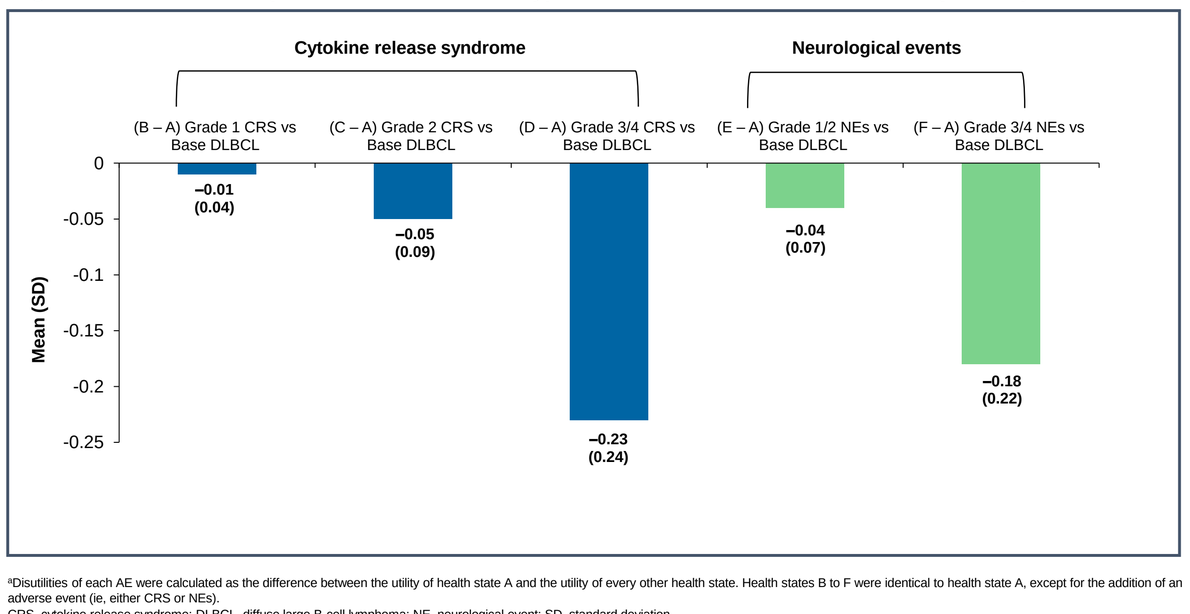
Table 2. Utility Differences (N=218)

Health State Comparison	Mean Difference	SD	95% CI
Disutilities of CRS and NEs compared with base DLBCL			
(B–A) Grade 1 CRS vs base DLBCL	−0.01	0.04	−0.02 to −0.01
(C–A) Grade 2 CRS vs base DLBCL	−0.05	0.09	−0.06 to −0.03
(D–A) Grade 3/4 CRS vs base DLBCL	−0.23	0.24	−0.26 to −0.20
(E–A) Grade 1/2 NEs vs base DLBCL	−0.04	0.07	−0.05 to −0.03
(F–A) Grade 3/4 NEs vs base DLBCL	−0.18	0.22	−0.21 to −0.15
Differences between CRS health states			
(C–B) Grade 2 CRS vs grade 1 CRS	−0.03	0.08	−0.04 to −0.02
(D–B) Grade 3/4 CRS vs grade 1 CRS	−0.21	0.24	−0.25 to −0.18
(D–C) Grade 3/4 CRS vs grade 2 CRS	−0.18	0.22	−0.21 to −0.15
Differences between NE health states			
(F–E) Grade 3/4 NEs vs grade 1/2 NEs	−0.14	0.21	−0.16 to −0.11

CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; NE, neurological event; SD, standard deviation.

- All disutility comparisons between health states were statistically significant (all $P<.0001$)

Figure 3. Disutilities[a] (ie, Decreases in Utility) Associated With CRS and NEs (N=218)



[a]Disutilities of each AE were calculated as the difference between the utility of health state A and the utility of every other health state. Health states B to F were identical to health state A, except for the addition of an adverse event (ie, either CRS or NEs).
CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; NE, neurological event; SD, standard deviation.

- When compared with the base health state, grade 1 CRS resulted in a disutility of −0.01, grade 2 CRS resulted in a disutility of −0.05 and grade 3/4 CRS resulted in a disutility of −0.23. Grade 1/2 NEs resulted in a disutility of −0.04 and grade 3/4 NEs resulted in a disutility of −0.18. There were no significant differences in disutilities by age or sex

Limitations

- The vignette-based approach was used because it is often infeasible to derive treatment-associated utilities from a patient sample for a treatment like liso-cel
- Furthermore, the vignette approach can estimate the utility of a temporary health-related event that changes over time
- However, a limitation of the vignette-based utility assessment approach is that the resulting utility scores represent preferences for the specific health states rather than the experience of an actual patient sample
- The extent to which these utilities might differ from values derived from generic preference-based measures completed by patients is unknown

Conclusion

- Among these DLBCL health states, more severe AEs were associated with greater disutility
- Because the health states each represent 1 year and were valued in a TTO task with a 1-year time horizon, the resulting disutility for each AE can be used in cost-utility models as a decrement in quality-adjusted life years
- The health state utilities estimated in this study would be useful in models that examine and compare cost-effectiveness of CAR T cell therapies for DLBCL

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Disclosures

- TAH and LSM are employees of Evidera; MPJ and AP are employees of Bristol-Myers Squibb Company and own Bristol-Myers Squibb Company stock. JG is an employee of Juno Therapeutics, a Bristol-Myers Squibb Company and owns Bristol-Myers Squibb Company stock. DGM has received research funding (paid to his institution) from Juno Therapeutics, Celgene, Kite Pharma; honoraria from Juno Therapeutics, Celgene, Kite Pharma, BioLine RX, Gilead, Genentech, Novartis, and A2 Biotherapeutics; patents/royalties from Juno Therapeutics, and owns stock in A2 Biotherapeutics.
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