Impact of Increasing Wait Times on the Cost-Effectiveness of Chimeric Antigen Receptor (CAR) T-Cell Therapy in large B-cell lymphoma: A Discrete Event Simulation Model

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Overview

- Background
- Impact of increasing wait times on 1 year mortality
  - Methods
  - Results
- Impact of increasing wait times on System-level Cost-effectiveness analysis
  - Methods
  - Results
- Limitation and Conclusion

Background

Background – CAR-T cell therapy

- The development of chimeric antigen receptor (CAR) T-cells has transformed oncology treatment, offering the potential to cure certain cancers.
- CAR T-cell therapy genetically engineers a patient's own T-cells by transforming the cell surface to incorporate a new protein capable of targeting the CD19 anti

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Leukapheresis → Manufacturing Process → Infusion

- These cells are then transported to a facility that genetically engineers these T-cells into CAR T-cells.
- Retroviruses are used to insert the DNA of the chimeric antigen receptor protein into the DNA of the patient's cells.
- These cells are amplified by several million-fold, before they are transfused back into the patient.

Background – Clinical Trials for DLBCL

	ZUMA-1 PHASE 2 TRIAL(N=101) Neelapu S et al. NEJM 2017	JULIET PHASE 2 TRIAL (N= 93) Schuster et al. NEJM 2018
Patients	101 adults w DLBCL, PMBCL, or transformed FL Median age 58 yrs (23-76) Median follow up 15 months	93 adults with relapsed/refractory DLBCL Median age 56 years (22-76) Median follow up 14 months
Product	Axicabtagene Ciloleucel Gamma-retrovirus; CD28 co-stim domain	Tisagenlecleucel CTL019
CAR T-Cell Therapy	Fludarabine 30 mg/m^2 daily x 3 Cylophosphamide 500 mg/m^2 daily x 3 Axi-cel (target 2.0x10^6 cells/kg) Maximum 2.0 x 10^8 total cells	Fludarabine 25 mg/m^2 daily x 3 Cylophosphamide 250 mg/m^2 daily x 3 Or Bendamustine 90 mg/m²/day × 2 days CAR-positive viable T-cells Median dose 3.0 x 10^8 cells
Efficacy	ORR 82% ; CR 54% PFS 44% at 12 months OS 59% at 12 months	ORR 52% CR 40%; PR 12%
Toxicity	Grade 3 or 4 AEs: 95% CRS: 93% (13% Grade 3 or higher) Neurotoxicity: 64% (28% Grade 3 or higher) TRM: 2 pts	Grade 3 or 4 AEs: 86% CRS: 58% (22% Grade 3 or higher) Neurotoxicity: 21% (12% Grade 3 or higher) TRM: 0 pts

Background – ZUMA-1

- In this Phase 2 trial, axi-cel was successfully manufactured in 110 patients (99%) and 101 patients received axi-cel (91%).
- Median time from leukapheresis to delivery of axi-cel to the treating facility was 17 days.
- Response was evaluated one month after infusion, with objective response (complete and partial response) as the primary outcome.
- At the updated data cut-off at a median of 15.4 months of follow-up, 42% remained in response, including 40% with a complete response.
- Common adverse events included cytokine release syndrome of 93% of patients with most cases being Grade 1 or 2 severity (80%), and neurologic events in 64% of patients, with 28% being Grade 3 or higher.

Background - Hypothesis

- CAR T-cell therapy is resource intensive and potentially limited to centers of excellence when firstly funded.
- Demand will be high in the beginning, limited capacity may prolong wait-times.
- Currently, there is lack of data to inform the limits of an acceptable CAR-T wait-time.

Objective

- Using mathematical simulation models to estimate the hypothetical effectiveness of CAR T-cell therapy with increasing wait-times.

- This will provide valuable information to both clinicians and health policy decision-makers to account for resource allocation

Methods:

Impact of Increasing Wait Times on 1-year Mortality

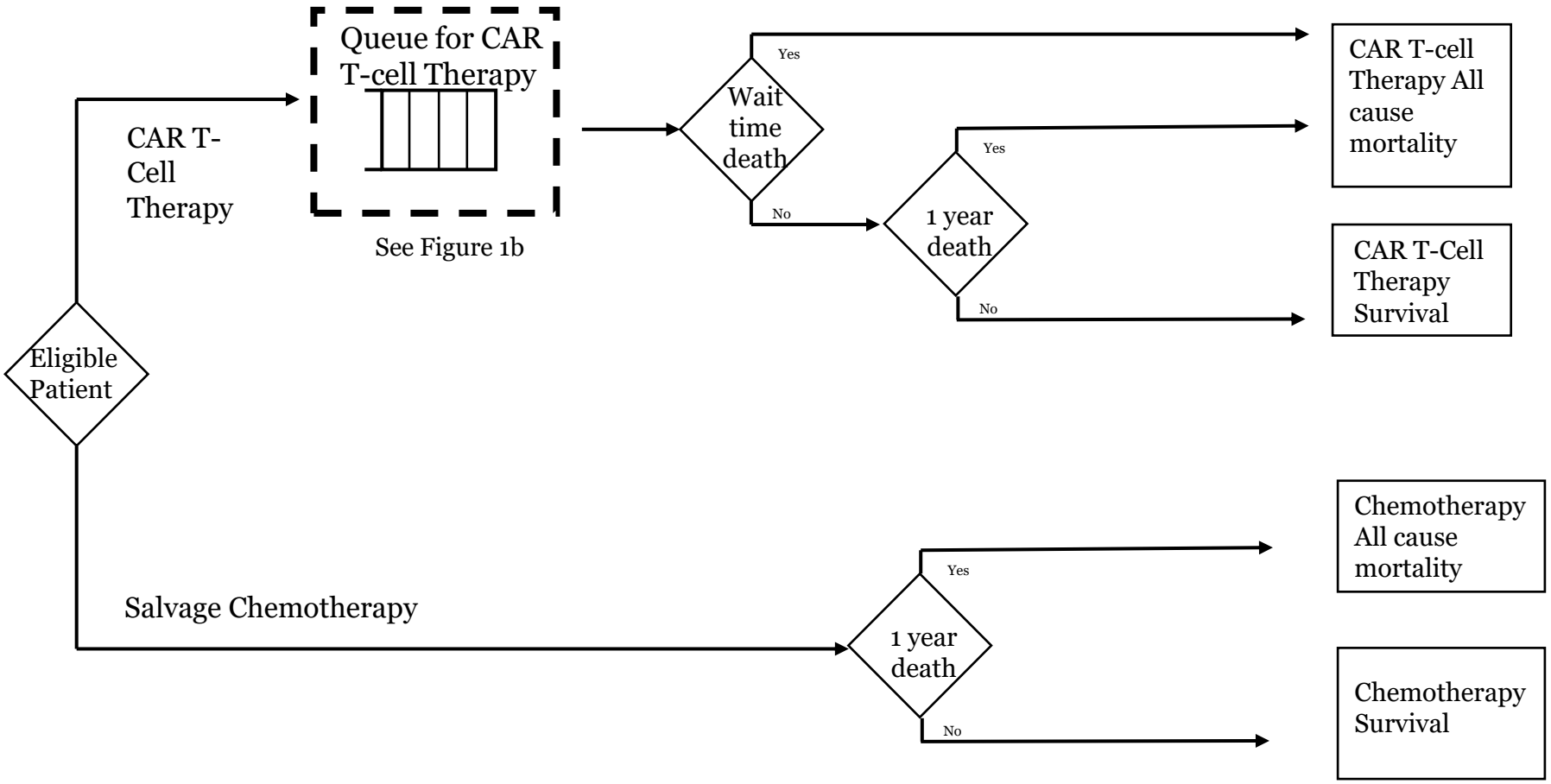
Methods: Population and Inception time

- Our study population represents the individuals who underwent the ZUMA-1 study. (i.e. patient who are relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
- These are patients who've already received second-line chemotherapy and are preparing to undergo CAR T-cell Therapy.
- The average age is 58 years.
- Inception time point:
  - We begin our model with the patient having completed all necessary diagnostic tests and deemed appropriate to begin CAR T-cell Therapy.
- The delay in time for treatment represents the amount of time the CAR T-cell Therapy population must wait to receive their therapy, and the corresponding one-year outcomes were based on the one-year period from the inception point.
- Important assumption:
  - The model assumes that patients will undergo chemotherapy treatment while they wait for their CAR T-cell therapy and will follow the OS and PFS chemotherapy curves while awaiting CAR T-cell Therapy treatment.

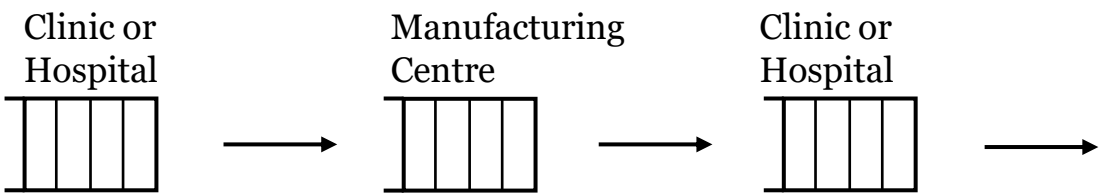
Methods: Decision Model

- Discrete event simulation (DES) is a form of computer-based modeling that provides an intuitive and flexible approach to represent a complex system.
  - It can represent complex relationships among individuals, populations and their environment.
- Most early applications involved analyses of systems with constrained resources, where the general aim was to improve the organization of delivered services.
  - DES models are used widely in service facilities, production and material handling systems when congestion or competition for scarce resources can occur.
- More recently, DES has increasingly been applied to evaluate specific technologies in the context of health technology assessment.
  - DES models can simulate individual patients as they transit through the health care system, with transitions dependent on both patient characteristics and the availability of resources.
  - Models can determine if queues will develop due to resource constraints, and can also evaluate the impact of wait-time strategies.

Methods: DES


Queue for CAR T-cell Therapy
CAR T-Cell Therapy
See Figure 1b
Wait time death
Yes
No
1 year death
Yes
No
CAR T-cell Therapy All cause mortality
CAR T-Cell Therapy Survival
Eligible Patient
Salvage Chemotherapy
1 year death
Yes
No
Chemotherapy All cause mortality
Chemotherapy Survival

Methods: Wait time contributors



Approval and Leukapheresis
- Average reimbursement approval time
- Average wait time for facilities
- Facility capacity (Personnel/ Equipment
- Patient travel time
- Leukapheresis time
- Centres available

Manufacturing Parameters
- Time to engineer cells.
- Facility capacity (Personnel/ Equipment)
- Manufacturing Failure rate
- Delivery time receive from clinic
- Centres available

Infusion Centre and Monitoring
- Delivery time receive from manufacturing centre
- Duration during patient monitoring
- Wait time for infusion
- Facility capacity (Personnel/ Equipment)

Parameters impacting delay of treatment
Patient uses standard chemotherapy treatment until end of delay

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ZUMA-1: From Leukapheresis to time engineered cells are ready to be infused: 2-3 weeks

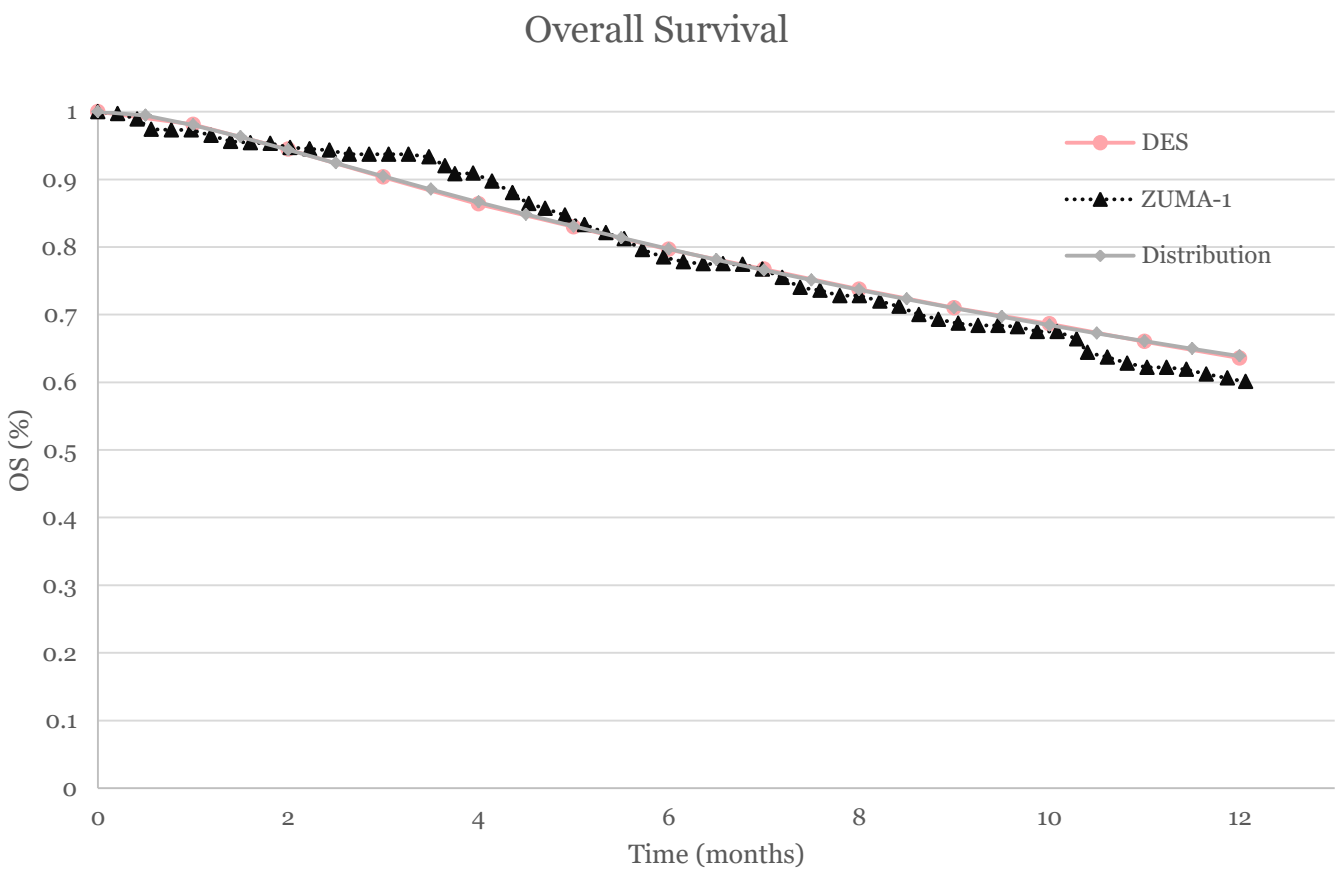
Methods: Input Parameters

- Main Input parameters:
  - CAR-T-cell Therapy arm: ZUMA-1
  - Chemotherapy arm: SCHOLAR-1
    - SCHOLAR-1: Retrospective Study contains relapsed or refractory DLBCL (N = 424)
- Digitalization and Reconstructing the KM curves: Survival curves of the ZUMA-1 and SCHOLAR-1 were digitized and Kaplan-Meier curves were reconstructed using an algorithm designed by Guyot et. al.
- Extrapolation: Parametric fits
  - OS and PFS curves of the ZUMA-1
  - OS curve of the SCHOLAR-1
  - Based on the best model fit using AIC/BIC information.

Methods: Analysis

- Fully probabilistic individual level model
  - For each CAR-T-cell Therapy wait-time:
    - 10,000 1st order Monte-Carlo simulations.
    - 100 2nd order Monte-Carlo simulations for parameter uncertainty.
  - Acceptability Curve
    - Proportion of 100 2nd order simulations in which CAR-T vs. chemotherapy had lower mortality.
- For mortality illustration
  - 1-year time horizon
  - Wait-times ranging between 1 to 9 months

Results - Validation



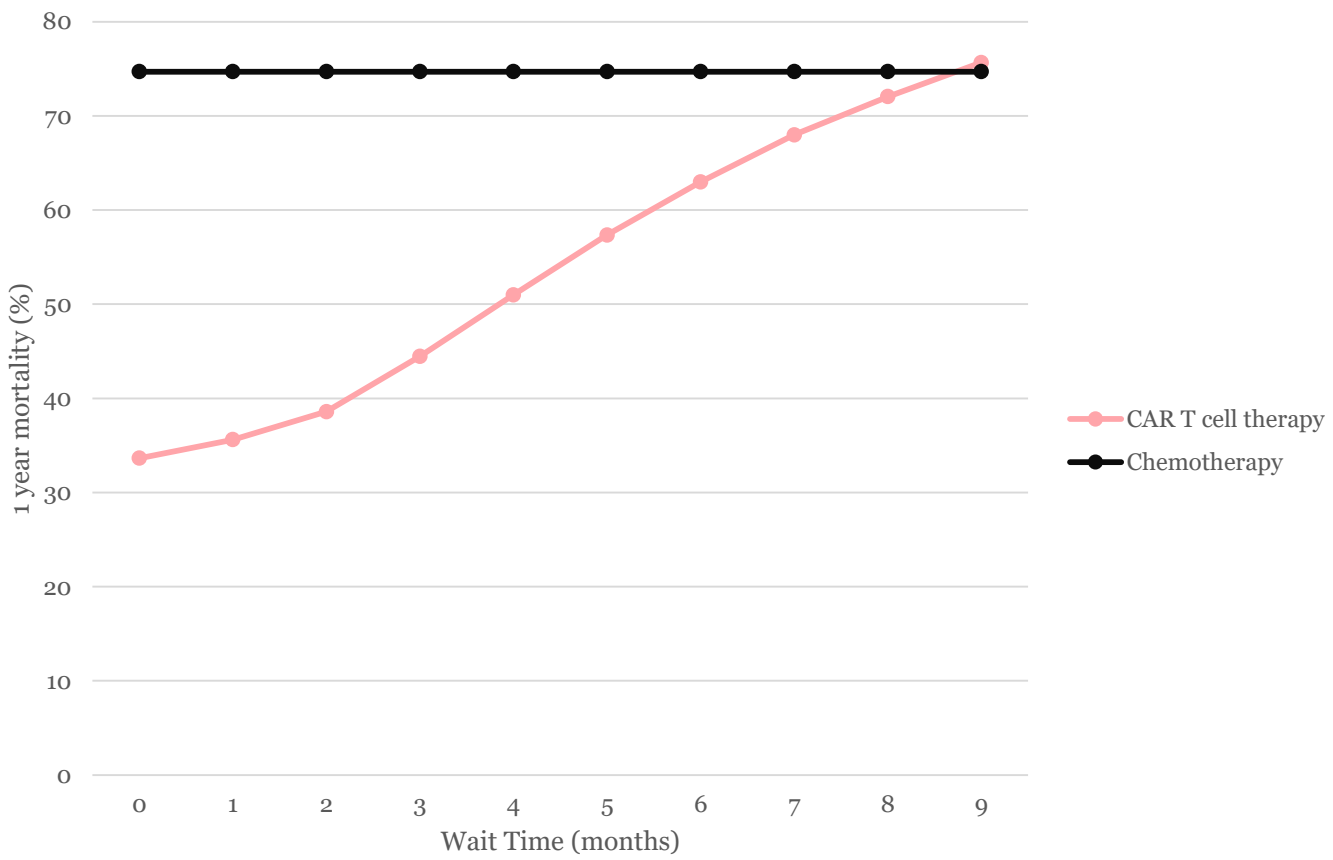
Results:

Impact of Increasing Wait Times on 1-year Mortality

Results – 1 year mortality

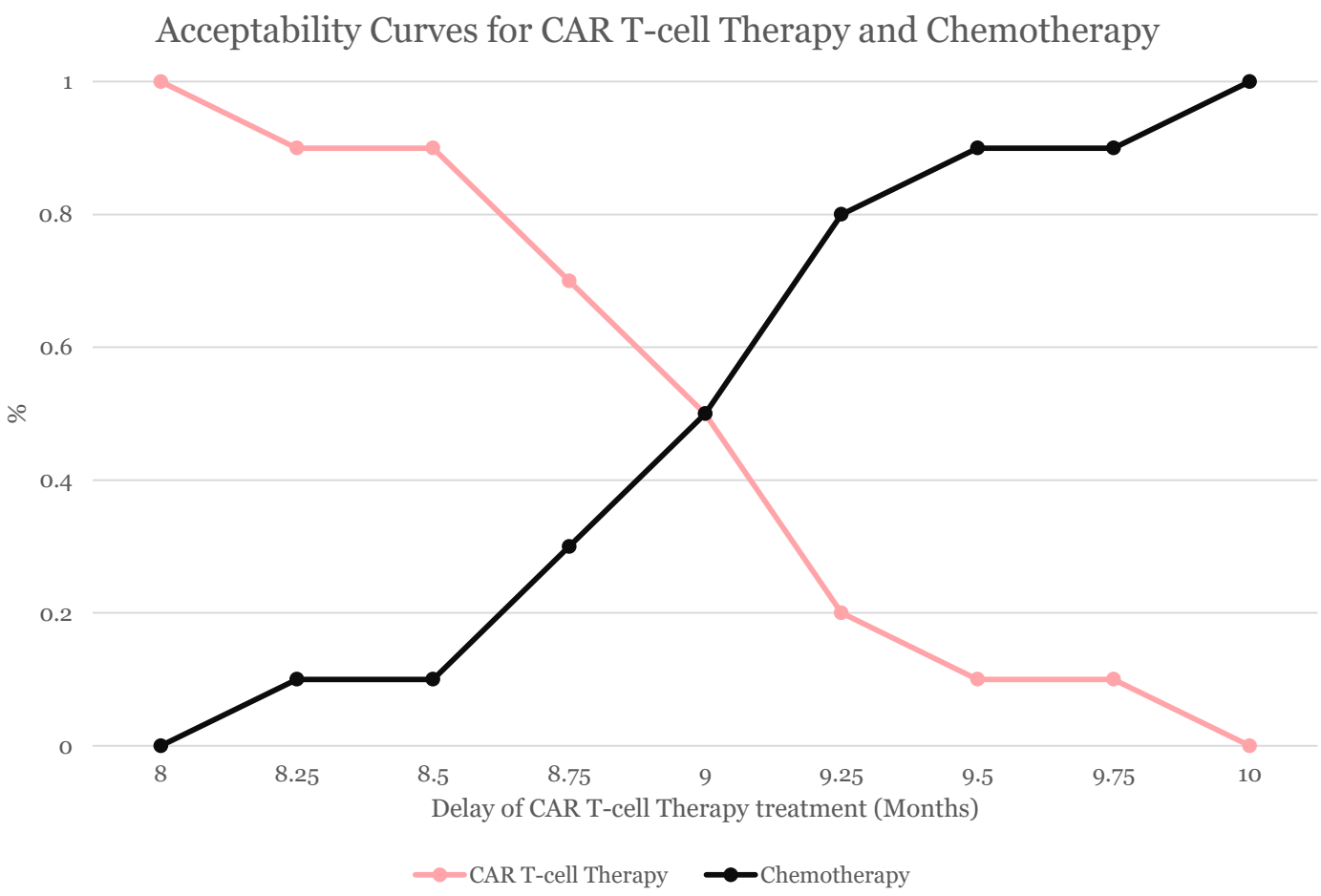
CAR-T wait time	CAR-T 1 year death (%) (95% C.I)	Chemotherapy 1 year death(%) (95% C.I.)
No delay	33.65 (33.15-34.13)	74.69(74.26-75.1)
1 month	35.61(35.05-36.17)	74.69(74.26-75.1)
2 months	38.59(38.2-38.97)	74.69(74.26-75.1)
3 months	44.47(44.28-44.65)	74.69(74.26-75.1)
4 months	51.00 (50.79-51.19)	74.69(74.26-75.1)
5 months	57.35(57.13-57.57)	74.69(74.26-75.1)
6 months	62.99(62.64-63.32)	74.69(74.26-75.1)
7 months	67.99(67.33-68.64)	74.69(74.26-75.1)
8 months	72.05(71.33-72.76)	74.69(74.26-75.1)
9 months	75.66(75.11-76.19)	74.69(74.26-75.1)

Results – 1 year mortality



Results – Acceptability Curves

Proportion of 100 2nd order simulations in which CAR-T vs. chemotherapy had lower mortality



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Methods:

Impact of Increasing Wait Times on System-level Cost-Effectiveness

Methods: System-level Cost-effectiveness Analysis

- Model: Same DES
- Main Input parameters:
  - CAR-T-cell Therapy arm: ZUMA-1
  - Chemotherapy arm: SCHOLAR-1
    - SCHOLAR-1: Retrospective Study contains relapsed or refractory DLBCL (N = 424)
- Cost and QALY:
  - Based on Institute for Clinical and Economic Review Report:
    - https://icer-review.org/material/car-t-final-report/
- Using the same assumptions as indicated in the report:
  - Assumptions of "cured" on PFS and OS
  - US perspective
  - Discount rate 3%
  - Life-time horizon

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value

Final Evidence Report

March 23, 2018

Prepared for

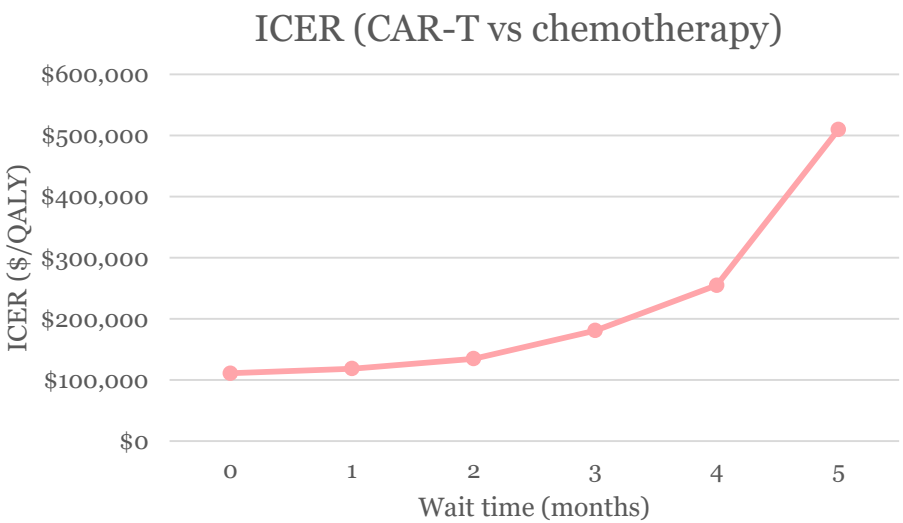
CTAF
CALIFORNIA TECHNOLOGY ASSESSMENT FORUM

Preliminary Results:

Impact of Increasing Wait Times on CEA

Preliminary Results - CEA

CAR-T wait time	Δ Cost (CAR-T vs Chemo)	Δ QALY (CAR-T vs Chemo)	ICER (CAR-T vs Chemo)
No delay	$392,230	3.54	$110,799
1 month	$352,015	2.97	$118,524
2 months	$315,469	2.34	$134,816
3 months	$282,015	1.56	$180,779
4 months	$232,043	0.91	$254,992
5 months	$183,463	0.36	$509,619
6 months	$142,033	-0.02	Dominated



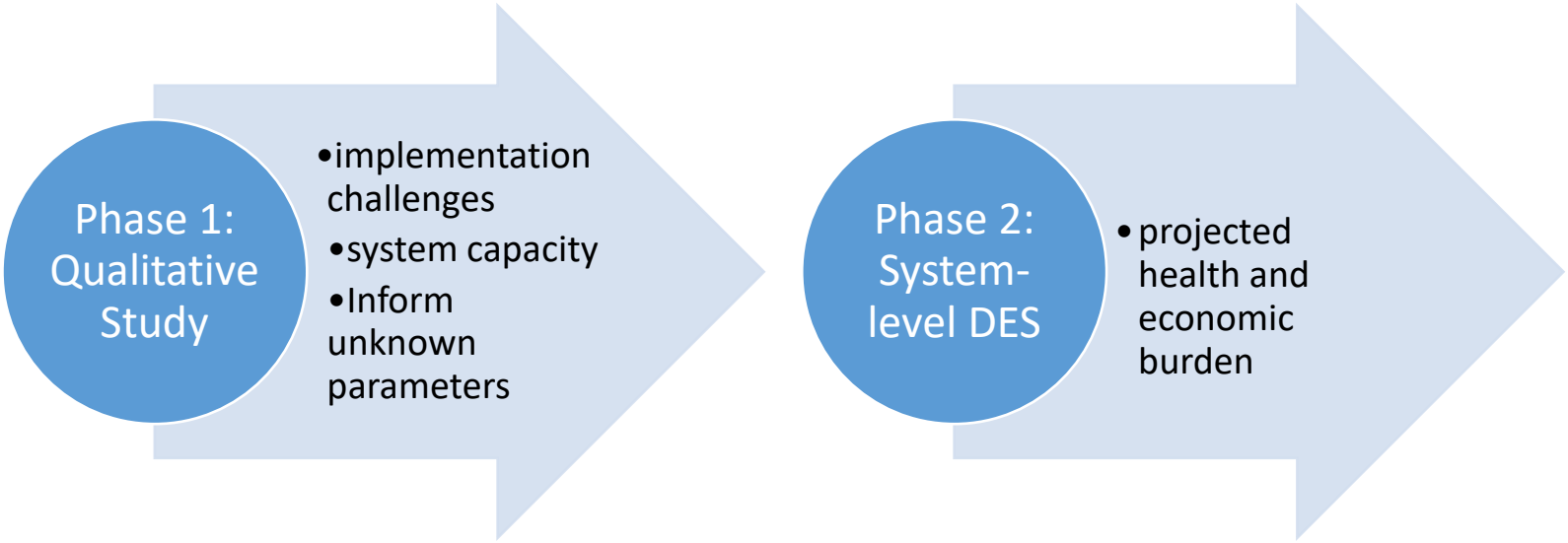
Limitations

- ZUMA-1 and SCHOLAR-1 trials are both single arm studies, with the ZUMA-1 containing a relatively small population.
  - Direct comparative and long-term evidence is lacking.
- No wait-time specific data currently available. We make the best-case scenario assumption on wait-time mortality that a patient who will experience a delay before receiving CAR T-cell Therapy, will immediately begin chemotherapy treatment without any additional delays.
- This research was a modelling exercise, and does not incorporate many of the distinctions of clinical decision-making.
  - Our model should therefore be considered hypothesis-generating and not conclusive

Conclusion

- CAR T-cell Therapy treatment delay has a significant impact on survival outcomes, and that even modest delays in CAR T-cell Therapy significantly hinder its efficacy and system-level cost-effectiveness.
- Wait-time strategies that minimize delays in access to CAR T-cell Therapy will be associated with a reduction of complications during waiting, and improvement of clinical outcomes.
- When policy makers decide to implement CAR T-cell Therapy, information pertaining to the wait-time of treatment must factor into their decision.

Next step


Phase 1: Qualitative Study
•implementation challenges
•system capacity
•Inform unknown parameters
Phase 2: System-level DES
• projected health and economic burden

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BioCanRx
Biotherapeutics for Cancer Treatment
Biothérapies pour le traitement du cancer

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