blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Don't keep me waiting: estimating the lifetime impact of reduced vein-to-vein time on 3L + LBCL patient outcomes in the US

Tracking no: ADV-2023-012240R1

Sachin Vadgama (Kite, A Gilead Company, United States) Marcelo Pasquini (Center for International Bone and Marrow Transplant Research, Medical College of Wisconsin, United States) Richard Maziarz (Knight Cancer Institute, United States) Zhen-Huan Hu (Kite, a Gilead Company, United States) Markqayne Ray (Kite, A Gilead Company, United States) Harry Smith (Kite, A Gilead Company, United Kingdom) Ash Bullement (Delta Hat, United Kingdom) Mark Edmondson-Jones (Delta Hat, United Kingdom) Will Sullivan (Delta Hat Limited, United States) Guillaume Cartron (CHU Montpellier UMR5535, France)

Abstract:
Chimeric antigen receptor (CAR) T-cell therapies have revolutionized the treatment of hematological cancers. Production requires a complex logistical process from leukapheresis to patient infusion, the vein-to-vein time (V2VT), during which a patients clinical condition may deteriorate. This study was designed to estimate the benefits of reduced V2VT for third-line+ (3L+) relapsed/refractory large B-cell lymphoma (r/r LBCL) patients treated with CAR T. A mathematical model was developed to estimate the lifetime outcomes of a hypothetical cohort of patients who had either a 'long' or 'short' V2VT. Life-years (LYs), quality-adjusted life years (QALYs), and costs were estimated. Scenario analyses were performed to assess the robustness of results to key assumptions. The results of the model show that reducing V2VT from 54 days (tisa-cel median V2VT; JULIET) to 24 days (axi-cel median V2VT; ZUMA-1) led to a 3.2-year gain in life expectancy (4.2 vs 7.7 LYs), and 2.4 additional QALYs (3.2 vs 5.6) per patient. Furthermore, a shorter V2VT was shown to be cost-effective under conventional willingness-to-pay thresholds in the United States. Results are driven by a higher infusion rate and and a better efficacy of CAR T-cell therapy for those infused. Scenario analyses using a smaller difference in V2VT (24 vs 36 days) produced consistent results. Our study is the first to quantify lifetime V2VT-related outcomes for 3L+ r/r LBCL patients treated with CAR T utilizing currently available evidence. Shorter V2VTs led to improved outcomes, demonstrating the importance of timely infusion achievable by faster manufacturing times and optimization of hospital delivery.

Conflict of interest: COI declared - see note

COI notes: R.T.M. is an advisor or consultant for AlloVir, Artiva, CRISPR Therapeutics, Incyte, and Novartis; reports honoraria from Bristol Myers Squibb/Celgene, Incyte, Intellia, and Kite; received research support from Allovir and Novartis; participates in data and safety monitoring boards for Athersys, Novartis, Century Therapeutics, and VorPharma; and has a patent with Athersys. AB, WS, and MEJ were all employees of Delta Hat at time of manuscript development. Delta Hat received consulting fees for the development of the model and associated analyses described within this manuscript. SV, ZHH, MR, HS are employees of and stockholders of Kite, A Gilead Company. GC received consulting fees and honoraria from Roche, Bristol Myers Squibb, Onwards Therapeutics, MedxCell, EmerCell, MabQ, Sanofi, Abbvie, Takeda, Roche, Janssen, Roche, Novartis and Myltenyi. M.L.: honoraria or travel grants from Pfizer, Novartis, Gilead and Bristol Myers Squibb. MP. has received honoraria from Pfizer and consulting fees from Medigene. M.R.M.V.D. has received research support from Seres Therapeutics; has consulted, received honorarium from or participated in advisory boards for Seres Therapeutics, Flagship Ventures, Novartis, Evelo, Jazz Pharmaceuticals, Therakos, Amgen, Merck & Co, Acute Leukemia Forum (ALF), and DKMS Medical Council (Board); and has IP Licensing with Seres Therapeutics and Juno Therapeutics. K.V.K. has received support for site participation in clinical trials from Kite, Adaptimmune, Atara, and Juno and has served as an ad hoc consultant to Kite/Gilead, Juno/Celgene, Novartis, Atara and Merck. AB and MEJ are employees of Delta Hat. At the time of writing, WS was also an employee of Delta Hat. Delta Hat received consulting fees for the development of the model and associated analyses described within this manuscript. SV, ZHH, MR, HS are employees of and stockholders of Kite, A Gilead Company. GC received consulting fees and honoraria from Roche, Bristol Myers Squibb, Onwards Therapeutics, MedxCell, EmerCell, MabQ, Sanofi, Abbvie, Takeda, Roche, Janssen, Roche, Novartis and Myltenyi. M.L.: honoraria or travel grants from Pfizer, Novartis, Gilead and Bristol Myers Squibb. MP. has received honoraria from Pfizer and consulting fees from Medigene. M.R.M.V.D. has received research support from Seres Therapeutics; has consulted, received honorarium from or participated in advisory boards for Seres Therapeutics, Flagship Ventures, Novartis, Evelo, Jazz Pharmaceuticals, Therakos, Amgen, Merck & Co, Acute Leukemia Forum (ALF), and DKMS Medical Council (Board); and has IP Licensing with Seres Therapeutics and Juno Therapeutics. K.V.K. has received support for site participation in clinical trials from Kite, Adaptimmune, Atara, and Juno and has served as an ad hoc consultant to Kite/Gilead, Juno/Celgene, Novartis, Atara and Merck.

Preprint server: No;

Author contributions and disclosures: SV conceived of the presented idea, designed the model and provided study management. RTM, GC, MP, MR, ZHH, HS and SV contributed to aspects of the concept/design of the study and data interpretation, and critically reviewed, revised, and approved the manuscript content for publication. MR, KH and HS, provided data needed for the model. AB and WS drafted the manuscript and constructed the model used to inform the analysis. MEJ developed the regression analysis used to relate vein-to-vein time to the probability of infusion.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Emails to the corresponding author.

Clinical trial registration information (if any):

Title page (Unblinded)

Working title: 'Don't keep me waiting': estimating the lifetime impact of reduced vein-to-vein time on 3L+ LBCL patient outcomes in the US

Sachin Vadgama[1], Marcelo C Pasquini[2], Richard T Maziarz[3], Zhen-Huan Hu [4], Mark Ray [4], Harry Smith [1], Ash Bullement [5], Mark Edmondson-Jones[5], Will Sullivan [5], Guillaume Cartron

[1]Kite, a Gilead Company, Stockley Park, Uxbridge, UK
[2]Center for International Blood and Marrow Transplant Research (CIBMTR), US Medical College of Wisconsin Clinical Cancer Center, Milwaukee, WI, USA
[3]Knight Cancer Institute, Portland, OR, USA
[4]Kite, A Gilead Company, Santa Monica, CA, USA
[5]Delta Hat Limited, Nottingham, UK
[6]CHU Montpellier, Hematology, Montpellier, France

Corresponding author: Sachin Vadgama (sachin.vadgama@gilead.com, +44 20 8587 2368)

Data Sharing: Emails to the corresponding author.

Running head
CAR T vein-to-vein times and impacts on survival

Key words
- CAR T
- Vein to vein time
- Time to infusion
- QALY

Abstract (249 words, free form)
Chimeric antigen receptor (CAR) T-cell therapies have revolutionized the treatment of hematological cancers. Production requires a complex logistical process from leukapheresis to patient infusion, the vein-to-vein time (V2VT), during which a patients clinical condition may deteriorate. This study was designed to estimate the benefits of reduced V2VT for third-line+ (3L+) relapsed/refractory large B-cell lymphoma (r/r LBCL) patients treated with CAR T. A mathematical model was developed to estimate the lifetime outcomes of a hypothetical cohort of patients who had either a 'long' or 'short' V2VT. Life-years (LYs), quality-adjusted life years (QALYs), and costs were estimated. Scenario analyses were performed to assess the robustness of results to key assumptions. The results of the model show that reducing V2VT from 54 days (tisa-cel median V2VT; JULIET) to 24 days (axi-cel median V2VT; ZUMA-1) led to a 3.2-year gain in life expectancy (4.2 vs 7.7 LYs), and 2.4 additional QALYs (3.2 vs 5.6) per patient. Furthermore, a shorter V2VT was shown to be cost-effective under conventional willingness-to-pay thresholds in the United States. Results are driven by a higher infusion rate and and a better efficacy of CAR T-cell therapy for those infused. Scenario analyses using a smaller difference in V2VT (24 vs 36 days) produced consistent results. Our study is the first to quantify lifetime V2VT-related outcomes for 3L+ r/r LBCL patients treated with CAR T utilizing currently available evidence. Shorter V2VTs led to improved outcomes, demonstrating the importance of timely infusion achievable by faster manufacturing times and optimization of hospital delivery.

Key points
- This modelling study shows that V2VT is an important predictor of outcomes, and reducing V2VT can substantially improve life expectancy.
- More real-world data are needed on long-term outcomes associated with varying V2VT

Main body (4,026 words)

1. Introduction

Chimeric antigen receptor (CAR) T-cell therapies are genetically modified autologous T-cells programmed to express a CAR to target and destroy cancer cells. They have revolutionized the treatment of certain hematological cancers.[1] The production of CAR T-cells requires a multistep process, including leukapheresis (i.e., collection of white blood cells from the patient), manufacturing, bidirectional transport, and storage, before infusion.[2] Figure 1, inspired by a diagram by Locke *et al.*, depicts an overview of the CAR T-cell patient's journey.

[Figure 1 here]

Vein-to-vein time (V2VT), highlighted in the image, is observable and measured routinely in datasets and trials.[3–5] Whilst waiting for a CAR T infusion, a patient's condition may deteriorate; thus it is essential that the manufacturing process should be:

- **Rapid**, as patients often have aggressive disease requiring prompt treatment,
- **Robust** and **reproducible**, as patients may be lymphopenic (i.e., a lack of lymphocytes), and there may be variability in the starting leukapheresis material, and
- **Reliable**, to avoid the need to repeat leukapheresis.

Some patients who undergo leukapheresis ultimately may not receive a CAR T infusion, highlighting the potential importance of minimizing avoidable delays in V2VT; for example, owing to manufacturing failure and disease progression; for patient outcomes.[6]

Emergent research has attempted to identify a link between V2VT and short-to-medium-term outcomes. Tully *et al.*, (2019) developed a discrete event simulation to investigate the

relationship between CAR T wait times and 1-year mortality rate.[7] Locke *et al.*, (2022) estimated the impact of V2VT on survival after axicabtagene ciloleucel treatment, using data collected in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry.[6] These two studies are currently the extent of the published research investigating the specific link between V2VT and long-term patient outcomes (i.e., over a lifetime horizon). The estimation of *long-term* survival outcomes is important to fully understand the consequences of any potentially avoidable delays in V2VT.

This study aims to compare potential lifetime outcomes of a hypothetical cohort of relapsed/refractory (R/R) large B-cell lymphoma (LBCL) patients treated with CAR T at third-line or later (3L+) with differing V2VTs.

2. Methods

To accomplish the aim of this study, we estimated expected future life-years (LYs) and quality-adjusted life years (QALYs) for two groups with different V2VTs being compared ('long' vs 'short' V2VT –[see section 2.2 for more details]) over a lifetime horizon using a model. These measures (LYs and QALYs) represent remaining life expectancy (i.e., LY) and remaining health-related quality of life (HRQL) adjusted life expectancy (i.e., QALY). LYs and QALYs are measures of health [used by the Institute of Clinical and Economic Review (ICER) and others] to measure health benefit in health technology assessments. Importantly, for a life-extending treatment, it is necessary to estimate both over a lifetime horizon to fully understand potential implications, which requires extrapolation of incomplete survival data. To give a sense of economic as well as clinical implications, total lifetime cost implications of V2VT delays were also estimated.

2.1. Model overview

A cohort-level decision-analytic model was developed in Microsoft Excel® to map the consequences associated with a 'long' or 'short' V2VT, for R/R LBCL patients intended to be treated with CAR T.[8] A schematic of the model is provided in Figure 2.

[Figure 2 here]

A hypothetical cohort of eligible patients entered the model at leukapheresis and were assigned either a 'long' or 'short' V2VT. The probability of successful infusion was estimated as a function of V2VT, as described later; in this way the assigned V2VT determines the probability of infusion success. The sub-cohort predicted to be successfully infused in each case arm followed one survival projection, and those predicted to not be infused followed a different (poorer) survival projection. The extrapolation portion of the model is comparable to a typical partitioned survival analysis commonly used in HTA for cancer treatments, though with only two health states: 'alive' and 'dead'.

2.2. Data inputs

The study model was established based on published clinical evidence for (i) V2VT from registrational studies of CAR T therapies in R/R LBCL and (ii) analyses of outcomes for similar patients in routine clinical practice, some of whom received CAR T. The analysis was built around evidence from these clinical studies, supplemented by targeted searches for cost, patient health-related quality of life and other data described throughout this section.

V2VT and infusion success

We used data from three pivotal clinical trials of populations with 3L+ R/R LBCL:

- **ZUMA-1:** a Phase I/II study of axicabtagene ciloleucel (Yescarta®, axi-cel) in refractory LBCL (NCT02348216).[4]

- **JULIET:** a Phase II study of tisagenlecleucel (Kymriah®, tisa-cel) for patients with R/R diffuse LBCL (NCT02445248).[3]
- **TRANSCEND-NHL-001:** a Phase I study of lisocabtagene maraleucel (Breyanzi®, liso-cel) for patients with R/R LBCL (NCT02631044).[5]

From these studies, we extracted published data on numbers of patients enrolled and infused and V2VT among those infused; these data are shown in Table 1. The additional information in Table 1 is reported V2VT dispersion data.

[Table 1 here]

To estimate the probability of infusion success, a range of statistical models were fitted to the data summarized in Table 1, to estimate the potential relationship between V2VT, and the likelihood of patients being ultimately infused. Of note, the regression analysis assumed that the attrition of patients from enrolment to infusion serves as a proxy for infusion success. This is because of a lack of reported data specifically for the number of patients that undergo leukapheresis to inform the regression analysis.

Figure 3 shows the estimated relationship between V2VT and probability of infusion success, across a range of statistical methods. The methods explored ranged from simple regression on the median to methods that estimate the underlying V2VT distribution. Of note, Figure 3 presents *estimated* interquartile ranges (heavier, darker blue range), and *estimated* 95% ranges (lighter, blue range); *estimated* since these data were not reported for all studies, to aid with the regression model fitting. For simplicity, the base-case analysis used results from the simple linear model (LM), with alternative models tested in sensitivity analyses.

[Figure 3 here]

The data in Table 1 also define the difference between "short" and "long" V2VT in the analysis. The median V2VT in ZUMA-1, 24 days, was assumed to represent a short V2VT, while the median V2VT in the JULIET study, 54 days, was used as proxy for long V2VT. Alternative V2VT definitions were explored in scenario analyses. The distinction between short and long V2VT drives differences in outcomes across arms of the analysis, through the predicted difference in infusion success chance, as described in this sub-section, and further consequences described in the remainder of this section.

Survival for non-infused and infused patients

Once the cohort was partitioned into "infused" and "not infused" sub-cohorts, each sub-cohort was assumed to follow an infusion-outcome-dependent survival projection for the remainder of the lifetime horizon.

For the post-infusion component of the model, data from three recent publications were harnessed:

- **Bachy *et al.*, (2022):** Reported overall survival (OS) survival projections separately for 3L+ LBCL patients with a CAR T product order (i) who did not proceed to infusion, from the point of order and (ii) who did proceed to infusion, from the point of infusion.[9] The analyses are based on data from the French DESCAR-T registry, and include patients with axi-cel and tisagenlecleucel (tisa-cel) orders between December 2019 and October 2021.
- **Kuhnl *et al.*, (2022):** Similarly, reported OS Kaplan-Meier data for 3L+ LBCL patients approved for CAR T treatment by the National CAR-T Clinical Panel (NCCP, for England) (i) who did not proceed to infusion, from the point of approval and (ii) who did proceed to infusion, from the point of infusion.[10] The analyses are

based on data from patients submitted for NCCP CAR T (axi-cel or tisa-cel) approval between December 2018 and November 2020.

- **Locke *et al.*, (2022):** Reported OS projections for 3L+ LBCL patients who received axi-cel commercially in the US between October 2017 and August 2020, using data from CIBMTR.[6] Unlike the previous two studies, Locke *et al.* explicitly sought to evaluate the effect of V2VT upon patient outcomes, and present survival projections as outputs from multivariate logistic and Cox regression analyses. Specifically, Locke *et al.* present OS projections from point of infusion stratified by V2VT categories, and hazard ratios associated with different categories.

Though the data from Bachy *et al*. and Kunhl *et al*. report outcomes stratified by different CAR T product, for simplicity we assumed no differences in efficacy between axi-cel and other CAR T-cell therapies, which can be considered a conservative assumption.[9–15]

As a first step in harnessing the published survival data, survival plots in each study were digitized to create pseudo-patient-level data, using the WebPlotDigitizer software and the re-creation algorithm of Guyot *et al.*, (2012).[16,17] Parametric survival models were then fitted to re-created patient-level data. A range of parametric models were considered as per National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Document 21 guidelines, including 'standard' parametric models, restricted cubic spline-based models (or 'flexible' parametric models), and mixture-cure models.[18]

In the base-case analysis, as the sample of patients recruited in Bachy *et al.* represent a more recent cohort than those recruited in Kuhnl *et al.* (approximately 1 year difference in enrollment periods), survival for non-infused patients (from CAR T approval) was based on recreated data from Bachy *et al.*, with use of recreated data from Kunhl *et al.* tested in scenario analysis. Survival from infusion for infused patients was based on data from Locke

et al. in the base case, given the ability to link V2VT to post-infusion outcomes with this source. Specifically, recreated data from Locke et al. projections for OS for patients with V2VT <36 days were used alongside an HR from the same study to produce survival projections for patients with V2VT ≥36 days.[6] For robustness, an alternative V2VT categorization approach from Locke *et al.* was explored in scenario analysis.

A log-normal model was assumed for survival outcomes for non-infused patients in the base case analysis, based on Bayesian Information Criterion goodness of fit statistics across tested models. For successfully infused patients, a mixture-cure survival model structure was assumed, in line with expectations that a proportion of patients may achieve long-term survivorship comparable to the age-adjusted disease-free population, owing to the curative potential of CAR T therapy in this setting. Specifically, a log-normal mixture cure model (MCM) was assumed, for consistency in structural assumptions across non-infused patient outcomes and outcomes for the uncured fraction of infused patients. For the fraction of infused patients estimated to be cured, US age and sex matched general population survival data from the Human Mortality Database were used.[19]

The base-case survival projections for infused/ non-infused patients are presented in Figure 4. Alternative structural assumptions were tested in scenario analyses and the analytic model retained the functionality to test the range of survival models fitted to each dataset.

[Figure 4 here]

Health-related quality of life

To predict expected patient QALYs in addition to LYs, patient utility is defined as a measure of value a patient derives from their HRQL, where a utility of 1 is associated with full health, and a utility of 0 is associated with death. An average lifetime utility value for the modelled cohort was estimated using data reported by Lin *et al*, (2018).[20] In this study, utility values of

0.782 and 0.729 for patients with and without disease progression (respectively) were reported. To retain simplicity of the model, we did not 'partition' patients by progression status. As such, an average of these values (0.756) was assumed to apply across the model's lifetime horizon as a measure of the average utility experienced by patients. This is expected to represent an underestimate of the average utility value, since patients are expected to spend more time without disease progression than with disease progression.

Costs

Exploratory cost and cost-effectiveness analyses took a 2022 US healthcare payer perspective. The cost assumed for CAR T acquisition is $462,000, based on Kite pricing at time of writing. The cost assumed for leukapheresis and hospitalisation was $54,450.47, based on the ICER review of axi-cel and tisa-cel, uplifted to 2022 prices using US Bureau of Statistics Consumer Price Index data.[21,22]

Aside from CAR T acquisition, leukapheresis, and hospitalization costs, ongoing healthcare costs were considered. An estimate of $11,890 healthcare costs per month for diffuse LBCL patients was reported by a burden-of-illness study that analyzed costs from diagnosis onwards.[23] In this indicative analysis, after uplifting the $11,890 monthly estimate to 2022 prices to $14,791.75, we assumed this cost applies in full only to patients who are not infused. For patients who are infused, we assumed 50% of this monthly estimate ($7,395.88 per month) for the first year, then 25% ($3,697.94 per month) for the next three years, then 5% ($739.59 per month) from 5 years post-infusion onwards. Additional costs, such as the 'cost of waiting' for patients that are not infused and end-of-life care were not included. However, the omission of these costs means that current estimates of cost-effectiveness are likely conservative.

Key settings and other assumptions

We assumed a baseline age of 60 years and a time horizon of 40 years, tracking the cohort to an upper limit of age 100 years in monthly model cycles. In presentation of LY and QALY results in isolation, the analysis assumed no time-preference discounting of future costs and health outcomes in order to provide accurate differences in lifetime patient mortality and QALYs. However, in the exploratory cost-effectiveness analysis, a 3% per annum discount rate was assumed for cost and health outcomes, to fully capture the opportunity costs of longer vein-to-vein times, in line with ICER methods.

For reference and clarity, base-case settings and assumptions are provided (Supplementary Appendix), alongside population, incidence and eligibility assumptions used to estimate the number of US 3L+ R/R LBCL patients likely to receive CAR T treatment in a given year.

2.3. Model outputs

The base case analysis produced predicted probability of infusion success for long and short V2VTs, and total expected per-patient costs, QALYs and LYs associated with long and short V2VTs, respectively. These results were used to calculate incremental per-patient QALY and LY gains predicted to be associated with reducing V2VT from a long V2VT (54 days) to a short V2VT (24 days). The population-level analysis produced similar outputs to the base-case analysis, scaled up to the estimated annual CAR T-eligible 3L+ LBCL US population level.

The indicative cost-effectiveness analysis compared the cost-effectiveness of a ‘short’ vs ‘long’ V2VT and outputs total and incremental per-patient costs, QALYs and LYs, as per the base-case analysis, except with the inclusion of cost outputs and application of time-preference discounting assumptions described in 2.2.

We perform numerous sensitivity and scenario analyses to test the impact upon headline results of different data and assumption choices in order to fully explore robustness of the results, as described throughout 2.2.

3. Results

3.1. Base case results

The modeled difference in V2VT led to a 3.2-year gain in life expectancy (4.2 vs 7.7 LYs), and an additional 2.4 undiscounted QALYs (3.2 vs 5.6) per patient. Based on the regression model, a reduction in V2VT from 54 to 24 days improved the probability of being successfully infused by 23.3% (from 66.6% to 89.8%). Using a smaller difference in V2VT (24 vs 37 days) produced 2.5 and 1.9 additional LYs and QALYs, respectively. The resultant survival extrapolations for these comparisons are provided in Figure 5.

[Figure 5 here]

The total population of US CAR T-eligible 3L+ R/R LBCL patients was estimated by ICER to be 5,902 per year.[21] Using the epidemiological model, if all patients in the US were to receive a 'short' V2VT vs 'long' V2VT, an additional 18,875 LYs and 14,260 additional QALYs would be generated every year. Using a smaller difference in V2VT (24 vs 37 days), the per-patients results equate to population level gains of 14,526 LYs and 10,974 QALYs. Equivalent results for smaller populations (e.g., at a local hospital level), and/or to reflect smaller uptake, can be estimated by a simple multiplication of the per-patient results.

3.2. Sensitivity analyses

As described throughout the methods section, scenario analyses were used to test the sensitivity of results to various assumptions in the base case analysis. These scenario analyses and their results are summarized in Table 2. Across tested scenarios, shorter V2VT is

associated with better health outcomes, though the magnitude of predicted health benefit varies with different assumptions. The predicted health benefit associated with a shorter V2VT is notably reduced if either the probability of successful infusion or the survival projection post-infusion is assumed to be uncorrelated with V2VT.

[Table 2 here]

3.3. Indicative cost-effectiveness results

Using annual discount rates of 3% for costs and outcomes, reducing V2VT from 54 to 24 days leads to improved health outcomes at an anticipated cost of $92,587 for every QALY gained. The increase costs are due to a higher proportion of patients receiving CAR T as typically CAR T costs are billed after a successful infusion. These results are below the ICER threshold range of $100,000 to $150,000 per QALY gained, suggesting such an improvement in V2VT is expected to be cost-effective in the US setting.[21]

4. Discussion

In clinical practice, there are multiple factors that can impact V2VT for patients receiving CAR T therapy, and delays during this multi-step process may impact patient outcomes. We believe our study model is the first to quantify the potential lifetime health consequences of reducing V2VT for 3L+ R/R LBCL patients intended to be treated with CAR T. Within this, we believe this is also the first study to estimate a formal relationship between study-level V2VT and infusion success. Further contributions from this study include the harnessing of recently published outcomes evidence, estimation of the impact of reducing V2VT upon expected patient quality of life-adjusted survival and derivation of cost-effectiveness implications.

The design of the decision-analytic model underling this study is intentionally simple and its description herein is intended to be transparent, serving as a foundation from which further work can be conducted; for instance, in assessing the expected benefits of newer experimental products with the potential to dramatically reduce expected time from apheresis to infusion. A modular approach was taken to identify and incorporate input data from a range of sources, which means it is possible to investigate uncertainty easily for specific aspects of the model. This is because it is not possible for a single study to provide all the necessary data to inform this type of analysis (as doing so would require designing a study with intentionally delayed time to administration of treatment, which introduces a number of ethical issues). Moreover, should further data be later made available, such sources can readily be included within the analysis (without requiring other components of the model to be re-analyzed).

We identified cost inputs from published literature as well as reporting produced by HTA bodies, such as NICE and ICER. Morrison *et al.*, (2018) found that costs decreased after the first year following diagnosis, and so use of this cost without accounting for changes over time may lead to an overestimate for 3L+ LBCL patients. Further, ongoing costs post CAR T infusion have been estimated to be low, across NICE appraisals of CAR T therapies in 3L+ LBCL and in the ICER review of axi-cel and tisa-cel.[21,24,25] Specifically, the ICER modelling group assumed ongoing medical management costs decreased in stages, first upon assessment of CAR T response, then at one year following response assessment, then at 5 years following response assessment, from which point only minimal ongoing costs are assumed. Similarly, NICE appraisals of axi-cel and tisa-cel assumed minimal ongoing healthcare costs after 5 years, from which point patients are effectively assumed to be cured. This mirrors the approach taken in our study (to capture decreasing costs over time), but is nevertheless an area of uncertainty within our costing analysis.

Relatedly, our model assumes that all CAR T-cell therapy administration takes place in an inpatient setting. In reality, some patients could be infused with some CAR T-cell therapies in an outpatient setting, which is expected to be less costly. Therefore, all other things held equal, the incremental costs projected by our modelling associated with V2VT would reduce if a proportion of patients are assumed to be treated in an outpatient rather than an inpatient setting.

We have undertaken extensive sensitivity analyses to contextualize the base-case analysis results in the context of limited data. Specifically, we have explored alternative regression analyses for V2VT versus infusion probability, various parametric survival models for survival for both infused and non-infused patients and tested different data sources. These sensitivity analyses demonstrate a consistent benefit associated with reduced V2VT, supporting our headline results.

Key limitations include the limited granularity of data to fully interrogate relationship between time elapsed prior to infusion and survival, and reliance on data from a range of sources, each associated with its own limitations. There would clearly be ethical issues in purposefully delaying infusion to investigate the relationship between V2VT and survival in a controlled setting, and so studies such as this will likely always need to rely on real-world analyses.

We believe our results support a call for increased clinical and research attention on 'brain-to-vein' time (i.e., the time from referral to infusion); delays from referral to CAR T order will logically have similar implications to delays from order to infusion. Ultimately, the results of our analysis demonstrate that outcomes for non-infused patients are substantially poorer than those for infused patients, and so infusion success is of critical importance for survival outcomes. Median estimates of survival for non-infused patients used to inform the model

were in the region of 2-to-3 months, compared with 6.3 months in the historical SCHOLAR-1 cohort study – in other words, patients that are not infused have a worse outcome versus the historical standard of care in the pre-CAR-T era.

In some countries (for example, the UK), there is a relatively high uptake of bridging therapy as a debulking strategy prior to CAR T infusion. For example, Kuhnl *et al.*, (2022) reported that 86.7% of patients received bridging therapy.[10] Similarly, in Bachy *et al.*, (2022) reported 82.7% of patients receiving bridging therapy.[9] This is understood to be driven by the infusion date being *intentionally* delayed to maximize the effect of the bridging therapy before infusion. Such *intentional* delays are different to the *avoidable* delays that comprise the focus of our analysis. The potential role of bridging therapy and its associated impact on the results of our analysis are unclear, though this limitation was mitigated somewhat by considering a sensitivity analysis only from the point of infusion.

Our analysis assumes the same efficacy for all CAR T products, since the focus of our study was on the impact of V2VT. In reality, it is expected that there may be some differences in outcomes that arise as a function of both V2VT *and* different efficacy for specific products. For example, one real-world comparison by Bachy *et al.*, (2022) suggested differences in efficacy and safety between axi-cel and tisa- cel.[9] CAR T efficacy may be influenced by a multitude of factors, such as viral vector, culture, novel activation domains, bicistronic constructs, etc.; however, these were not explored in this study owing to a lack of current or anticipated future head-to-head studies comparing different CAR T products. It remains challenging to disentangle the effects of V2VT and the specific CAR T product on post-infusion survival.

5. Conclusions

We find that V2VT may be an important predictor of outcomes and aiming for short manufacturing, product release, shipping and infusion times may be key to further improve outcomes for patients treated with CAR T. We predicted life expectancy gains in the region of 3 years associated with shortening V2VT. At a population level, over 18,000 LYs could be gained each year if all 3L+ R/R LBCL CAR T-intended patients in the US received a short V2VT versus the longer dates modeled in this study. Furthermore, indicative economic results show reducing V2VT to be a cost-effective treatment strategy, in the US setting.

Data on the relationship between V2VT and long-term patient outcomes are sparse. Further data collection and reporting for V2VT in general would aid additional research, including proxy measures for patients who are not infused. This would allow for specific investigations to be undertaken, including the reasons why V2VT can vary across individuals, regions, and the impact of bridging strategies.

Manuscript information

Author Contributions

SV conceieved of the presented idea, designed the model and provided study management.

RTM, GC, MP, MR, ZHH, HS and SV contributed to aspects of the concept/design of the study and data interpretation, and critically reviewed, revised, and approved the manuscript content for publication. MR, KH and HS, provided data needed for the model.

AB and WS drafted the manuscript and constructed the model used to inform the analysis. MEJ developed the regression analysis used to relate vein-to-vein time to the probability of infusion.

Disclosure of Conflicts of Interest

R.T.M. is an advisor or consultant for AlloVir, Artiva, CRISPR Therapeutics, Incyte, and Novartis; reports honoraria from Bristol Myers Squibb/Celgene, Incyte, Intellia, and Kite; received research support from Allovir and Novartis; participates in data and safety monitoring boards for Athersys, Novartis, Century Therapeutics, and VorPharma; and has a patent with Athersys.

AB, WS, and MEJ were all employees of Delta Hat at time of manuscript development. Delta Hat received consulting fees for the development of the model and associated analyses described within this manuscript.

SV, ZHH, MR, HS are employees of and stockholders of Kite, A Gilead Company.

GC received consulting fees and honoraria from Roche, Bristol Myers Squibb, Onwards Therapeutics, MedxCell, EmerCell, MabQ, Sanofi, Abbvie, Takeda, Roche, Janssen, Roche, Novartis and Myltenyi. M.L.: honoraria or travel grants from Pfizer, Novartis, Gilead and Bristol Myers Squibb.

MP. has received honoraria from Pfizer and consulting fees from Medigene. M.R.M.V.D. has received research support from Seres Therapeutics; has consulted, received honorarium from or participated in advisory boards for Seres Therapeutics, Flagship Ventures, Novartis, Evelo, Jazz Pharmaceuticals, Therakos, Amgen, Merck & Co, Acute Leukemia Forum (ALF), and DKMS Medical Council (Board); and has IP Licensing with Seres Therapeutics and Juno Therapeutics. K.V.K. has received support for site participation in clinical trials from Kite, Adaptimmune, Atara, and Juno and has served as an ad hoc consultant to Kite/Gilead, Juno/Celgene, Novartis, Atara and Merck.

References

1. Ivica NA, Young CM. Tracking the CAR-T Revolution: Analysis of Clinical Trials of CAR-T and TCR-T Therapies for the Treatment of Cancer (1997–2020). *Healthcare*. 2021;9(8):1062. doi:10.3390/healthcare9081062

2. Levine BL, Miskin J, Wonnacott K, Keir C. Global Manufacturing of CAR T Cell Therapy. *Mol Ther Methods Clin Dev*. 2016;4:92-101. doi:10.1016/j.omtm.2016.12.006

3. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;380(1):45-56. doi:10.1056/NEJMoa1804980

4. electronic medicines compendium (emc). Yescarta - Summary of Product Characteristics (SmPC). Published June 28, 2023. Accessed October 16, 2023. https://www.medicines.org.uk/emc/product/9439/smpc/print

5. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *The Lancet*. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0

6. Locke FL, Hu ZH, Siddiqi T, et al. Real-World Impact of Time from Leukapheresis to Infusion (Vein-to-Vein Time) in Patients with Relapsed or Refractory (r/r) Large B-Cell Lymphoma (LBCL) Treated with Axicabtagene Ciloleucel. *Blood*. 2022;140(Supplement 1):7512-7515. doi:10.1182/blood-2022-155603

7. Tully S, Feng Z, Grindrod K, McFarlane T, Chan KKW, Wong WWL. Impact of Increasing Wait Times on Overall Mortality of Chimeric Antigen Receptor T-Cell Therapy in Large B-Cell Lymphoma: A Discrete Event Simulation Model. *JCO Clin Cancer Inform*. 2019;3:1-9. doi:10.1200/CCI.19.00086

8. Microsoft Corporation. Microsoft Excel. Published online 2018. https://office.microsoft.com/excel

9. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med*. 2022;28(10):2145-2154. doi:10.1038/s41591-022-01969-y

10. Kuhnl A, Roddie C, Kirkwood AA, et al. A national service for delivering CD19 CAR-Tin large B-cell lymphoma - The UK real-world experience. *Br J Haematol*. 2022;198(3):492-502. doi:10.1111/bjh.18209

11. Riedell PA, Hwang WT, Nastoupil LJ, et al. Patterns of Use, Outcomes, and Resource Utilization among Recipients of Commercial Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B Cell Lymphomas. *Transplant Cell Ther*. 2022;28(10):669-676. doi:10.1016/j.jtct.2022.07.011

12. Kwon M, Iacoboni G, Reguera JL, et al. Axicabtagene ciloleucel compared to tisagenlecleucel for the treatment of aggressive B-cell lymphoma. *Haematologica*. 2023;108(1):110-121. doi:10.3324/haematol.2022.280805

13. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. *Blood*. 2022;140(4):349-358. doi:10.1182/blood.2021015209

14. Chacim S, Monjardino T, Cunha JL, et al. Costs, effectiveness, and safety associated with Chimeric Antigen Receptor (CAR) T-cell therapy: Results from a comprehensive cancer center. *PLOS ONE*. 2022;17(12):e0278950. doi:10.1371/journal.pone.0278950

15. Oluwole OO, Jansen JP, Lin VW, et al. Comparing Efficacy, Safety, and Preinfusion Period of Axicabtagene Ciloleucel versus Tisagenlecleucel in Relapsed/Refractory Large B Cell Lymphoma. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. 2020;26(9):1581-1588. doi:10.1016/j.bbmt.2020.06.008

16. Rohatgi A. WebPlotDigitizer. Published online 2022. Accessed October 16, 2023. http://arohatgi.info/WebPlotDigitizer

17. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12(1):9. doi:10.1186/1471-2288-12-9

18. Rutherford MJ, Lambert PC, Sweeting MJ, et al. NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis. Published January 23, 2020. Accessed October 16, 2023. http://nicedsu.org.uk/wp-content/uploads/2020/11/NICE-DSU-Flex-Surv-TSD-21_Final_alt_text.pdf

19. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). The Human Mortality Database. Published 2020. Accessed November 18, 2020. www.mortality.org or www.humanmortality.de

20. Lin VW, Jiang Y, Chuang LH, Navale L, Cheng P, Purdum A. P889: Health Utilities for Patients with Relapsed or Refractory Large B-Cell Lymphoma (R/R-LBCL): Ad Hoc Analysis From an Axicabtagene Ciloleucel (Axi-cel) Safety Management Study. *Bone Marrow Transplant*. 2019;53(1):878-887. doi:10.1038/s41409-018-0325-z

21. Institute for Clinical and Economic Review (ICER). Chimeric Antigen Receptor T-Cell Therapy for BCell Cancers: Effectiveness and Value: Final Evidence Report. Published March 23, 2018. Accessed October 16, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_CAR_T_Final_Evidence_Report_032318.pdf

22. Lyman GH, Nguyen A, Snyder S, Gitlin M, Chung KC. Economic Evaluation of Chimeric Antigen Receptor T-Cell Therapy by Site of Care Among Patients With Relapsed or Refractory Large B-Cell Lymphoma. *JAMA Netw Open*. 2020;3(4):e202072. doi:10.1001/jamanetworkopen.2020.2072

23. Morrison VA, Bell JA, Hamilton L, et al. Economic burden of patients with diffuse large B-cell and follicular lymphoma treated in the USA. *Future Oncol*. 2018;14(25):2627-2642. doi:10.2217/fon-2018-0267

24. National Institute for Health and Care Excellence (NICE). TA872: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Published February 28, 2023. Accessed October 16, 2023. https://www.nice.org.uk/guidance/ta872

25. National Institute for Health and Care Excellence (NICE). TA554: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years. Published December 21, 2018. Accessed October 16, 2023. https://www.nice.org.uk/guidance/TA554

Tables and Figures

Table 1: Available data from pivotal clinical trials of populations with 3L+ r/r LBCL regarding V2VT

Study	N	Infused (n, %)	Median V2VT	Additional information
ZUMA-1[4]	111	101, 91%	24 days	V2VT range: 16 to 73 days
JULIET[3]	165	111, 67%	54 days	90% of patients infused between 30 and 92 days
TRANSCEND-NHL-001[5]	344	269, 78%	37 days	V2VT range: 27 to 224 days

Key: V2VT, vein-to-vein time.

Table 2: Results from scenario analyses (LYs gained)

Scenario number and description		Rationale	Per-patient	US population
Base case			3.20	18,875
1	Probability of infusion not affected by V2VT	In this scenario, V2VT only impacts post-infusion survival (i.e., not the proportion of patients that receive an infusion).	1.98	11,706
2	Post-infusion survival not affected by V2VT (Bachy *et al.*, [2022])	In this scenario, post-infusion survival is informed by Bachy *et al.*, which does not differentiate survival by V2VT.	0.82	4,826
3	Switch non-infused survival source (Kuhnl *et al.*, [2022])	As above, except using an alternative source for post-infusion survival: Kuhnl *et al.*	3.19	18,832
4	Switch HR cut-offs (to <28 vs ≥28 days to <40 vs ≥40 days)	In the base-case analysis, HR cut-offs of <36 and ≥36 days were used, as a simple means to dichotomize the Locke *et al.* cohort in terms of their survival experience linked to V2VT. In this scenario, alternative cut-offs are used, which breaks the cohort into three groups instead of two.	3.47	20,500
5	Change 'long' V2VT to be 37 days	Alternative 'long' V2VT specified to reflect a smaller reduction for the 'short' V2VT group.	2.46	14,526
6	Change 'short' V2VT to be 30 days	Alternative 'short' V2VT specified to reflect a smaller reduction from the 'long' V2VT group.	2.82	16,661
7	Assume half of the US population	Sensitivity of the population results stress-tested by assuming half of the estimated eligible cohort.	3.20	9,438
8	Assume CIBMT registry population of 1,294 patients	Sensitivity of the population results stress-tested by assuming same population per latest data from CIBMT registry.	3.20	4,138
9	Post-infusion survival model:	Choice of an alternative survival extrapolation for patients that receive CAR T.	1.82	10,761
10	*Lognormal*		2.34	13,801
11	*1 knot(s) normal spline*		3.53	20,813
12	*MCM: Weibull* *MCM: Log-logistic*		3.29	19,435
13	Non-infused survival model	Choice of an alternative survival extrapolation for patients that do not receive CAR T.	3.20	18,861
14	*Log-logistic*		3.20	18,865
15	*1 knot(s) odds spline*		3.06	18,042
16	*MCM: Lognormal* *MCM: Log-logistic*		3.06	18,067
17	V2VT regression model:	Choice of an alternative regression model for estimating the proportion of patients that are infused based on V2VT.	3.14	18,529
18	*Weighted linear*		3.07	18,102
19	*Logistic*		2.68	15,802
20	*Method of moments* *Expectation maximization algorithm*		2.44	14,420
21	Iterative V2VT sampling	In the base-case analysis, all patients were assumed to have the same V2VT. In this scenario, V2VT is sampled from a distribution, with the mean results taken. Further details of this approach are provided in a supplementary appendix.	2.79	16,475

Key: CAR T, chimeric antigen receptor T-cell therapy; HR, hazard ratio; LY, life-year; MCM, mixture-cure model; V2VT, vein-to-vein time.

Figure 1: Patient journey for CAR T

Figure 2: Simple Model schematic

Key: V2VT, vein-to-vein time.
Note: A square node represents a decision node, whereas a circle node represents a probability node.

Figure 3: The relationship between V2VT and probability of infusion based on ZUMA-1, TRANSCEND-NHL and JULIET using a variety of regression models.

Note: lighter blue horizontal range = estimated 95% range; heavier, darker blue range = estimated inter-quartile range; point size proportionate to sample size.

Figure 4: Base-case survival extrapolations for infused and non-infused patients

Key: V2VT, vein-to-vein time.

Figure 5: Base-case survival extrapolations for all patients based on cohort average V2VT and median survival.

Figure 1

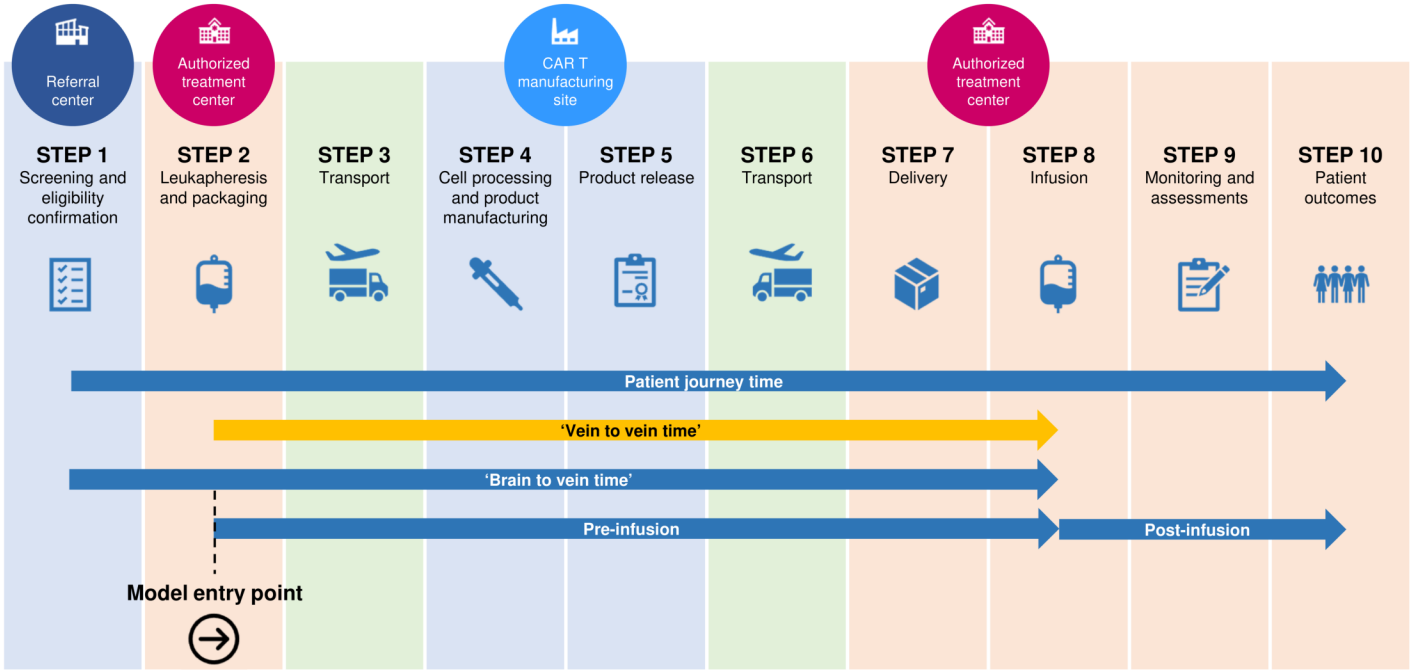


Figure 2

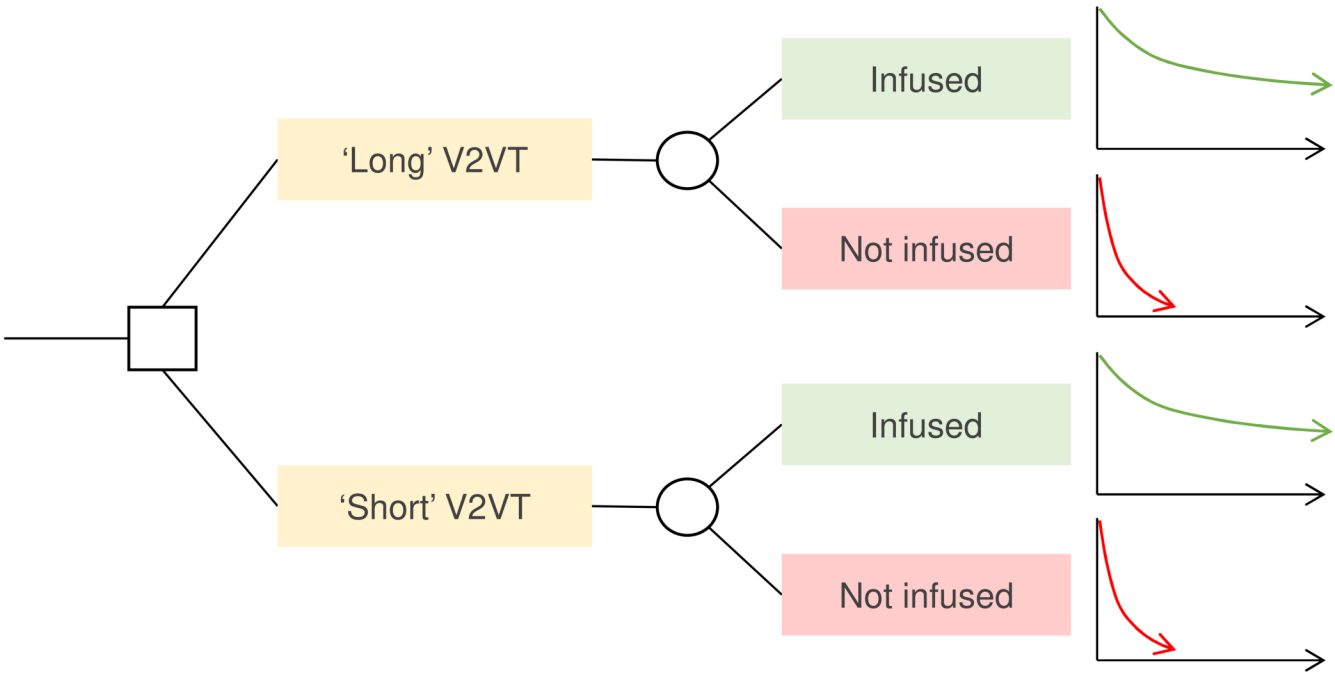


Figure 3

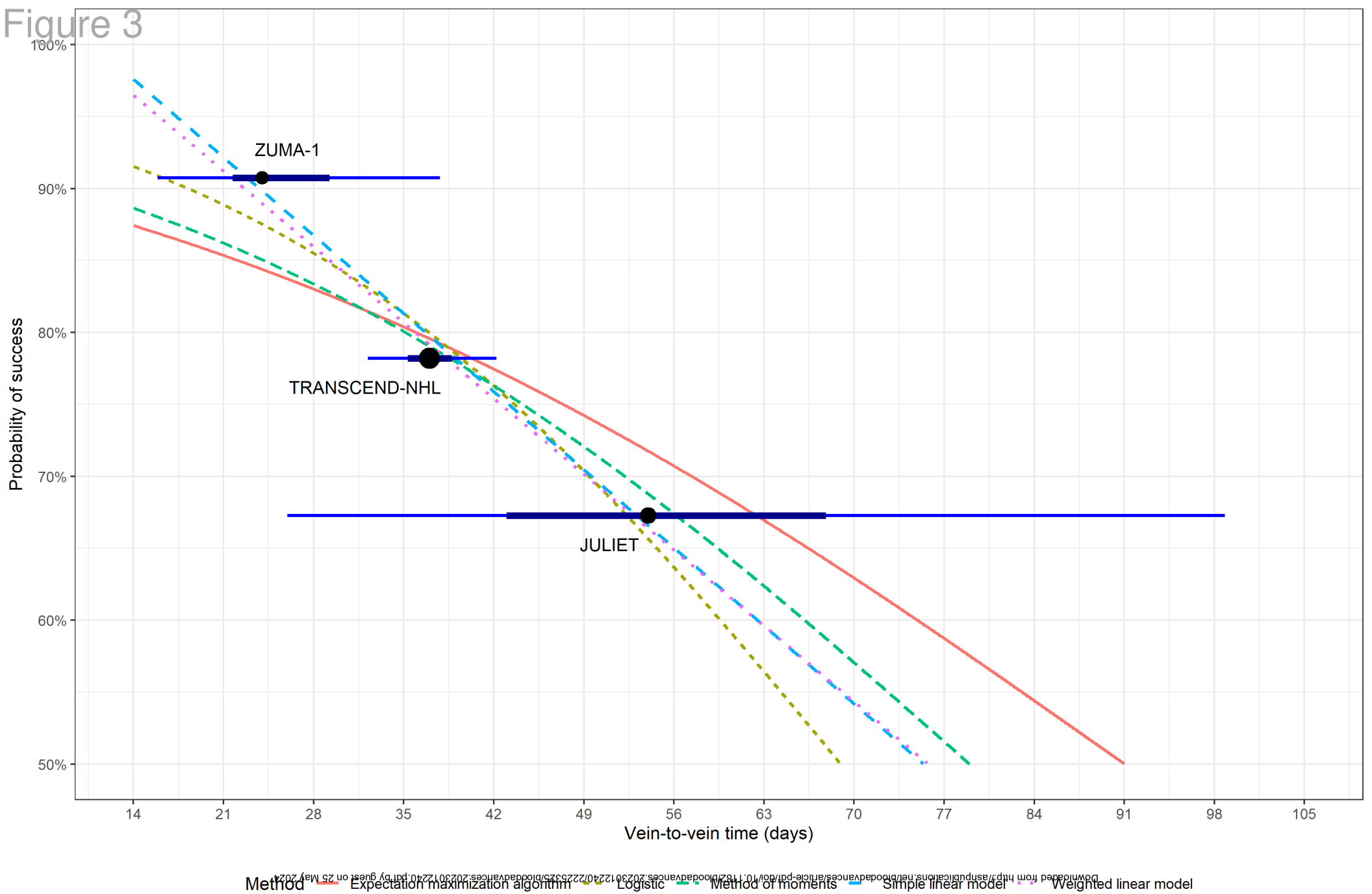


Figure 4

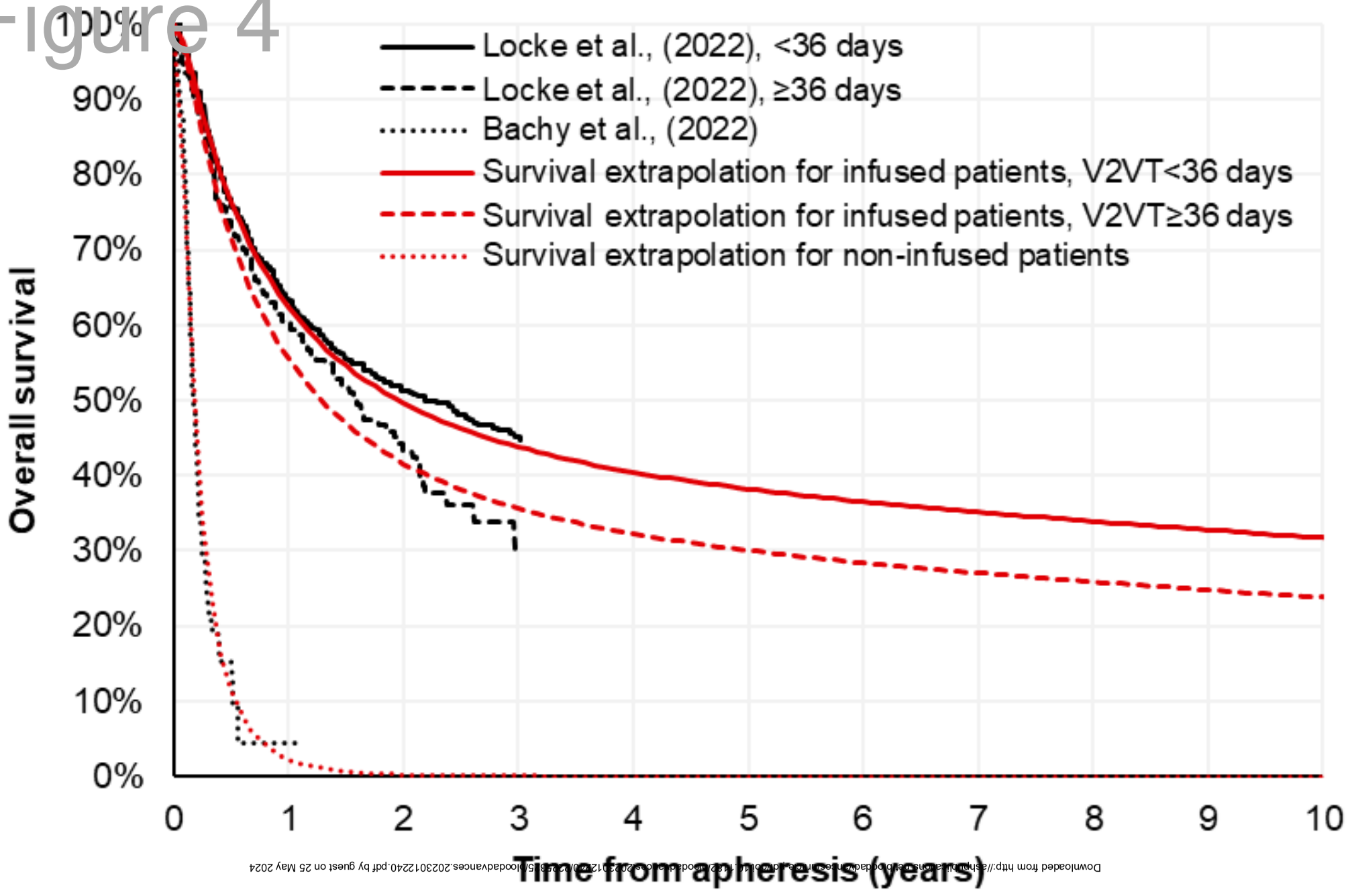
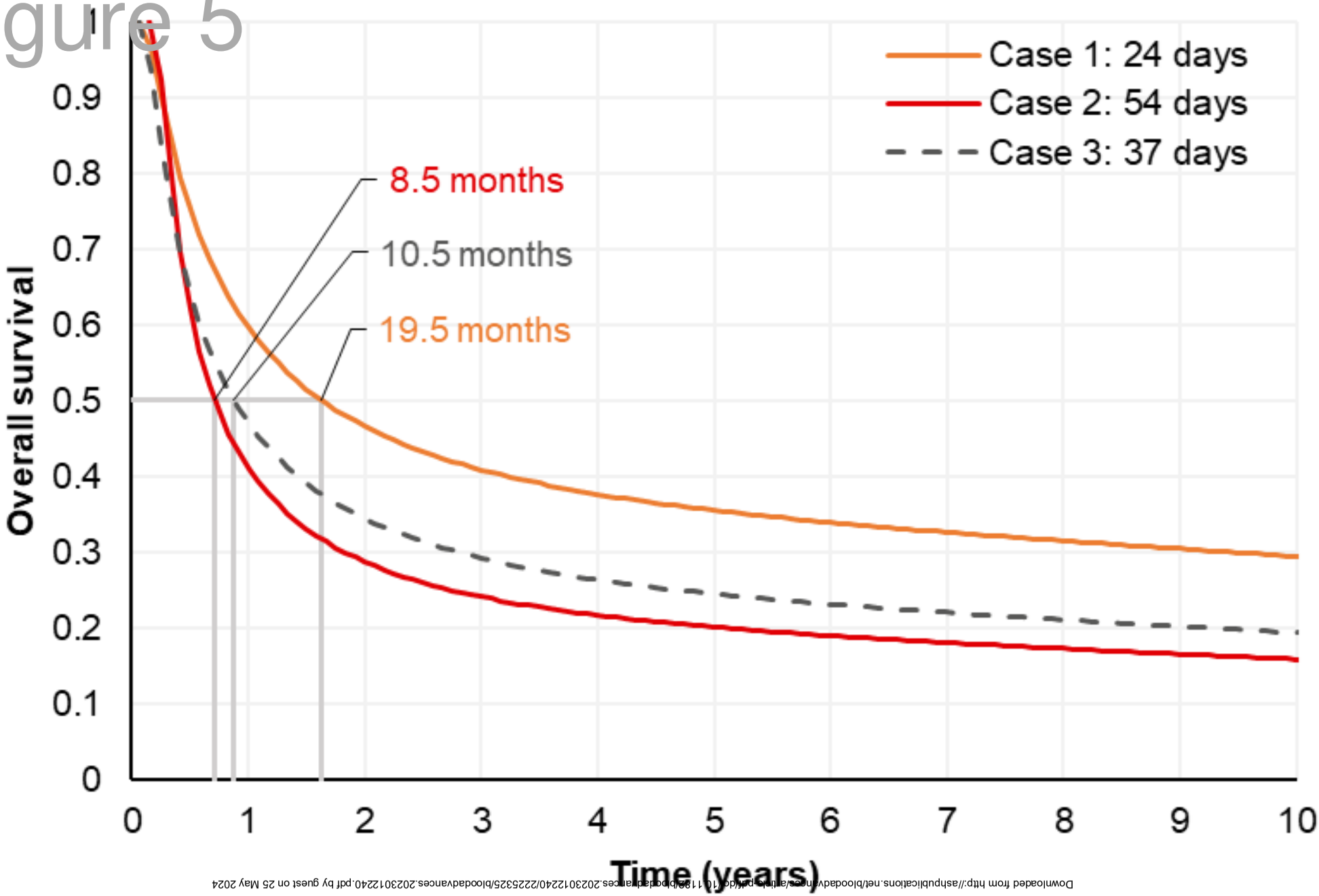
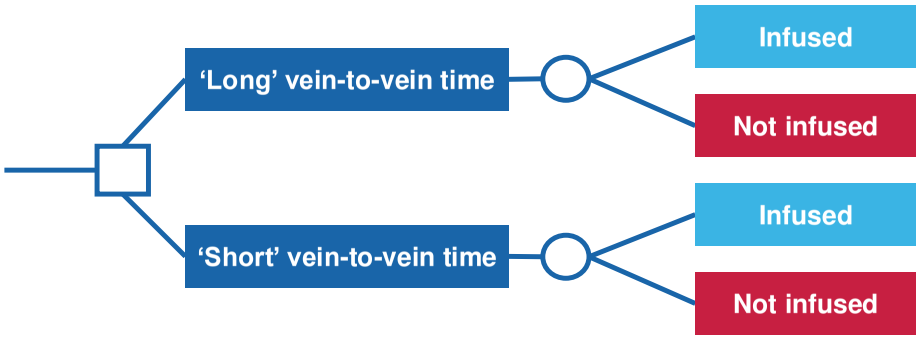
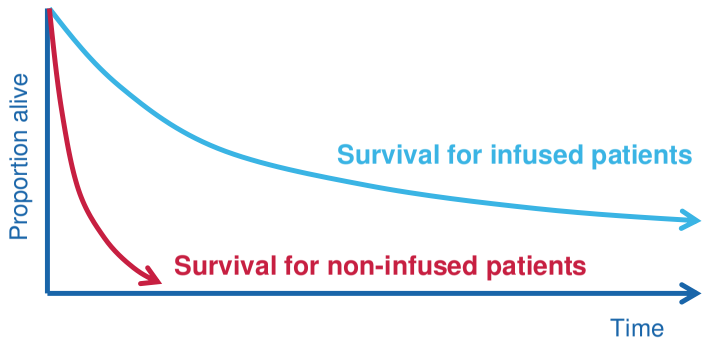


Figure 5







Reduced vein-to-vein time

Improved patient outcomes

- ☑ More likely to remain fit enough for CAR T-cell infusion
- ☑ Improved life expectancy post infusion

Further research recommendations

- Role of bridging therapy
- Patient quality of life implications
- 'Brain-to-vein' time