Lessons learnt from long-term outcomes of CAR T therapies, HTA and RWE implications

Kite, a Gilead company
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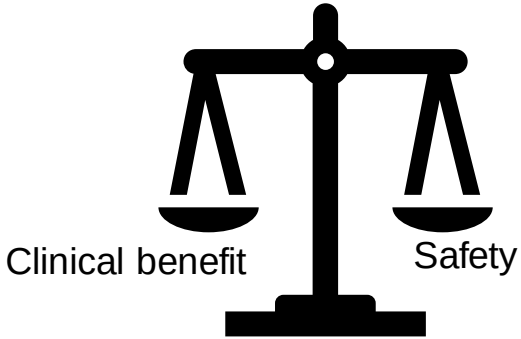
Health Technology Assessment aims to understand whether a technology is likely to be value for money

Regulatory

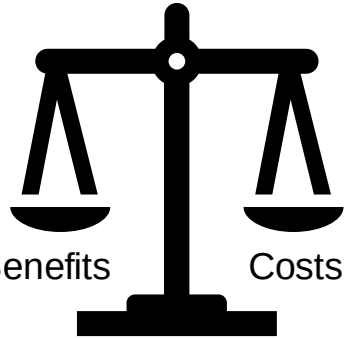


"Is it safe and effective?"

FDA

MHRA

Health Technology Assessment



"Is it value for money?"

Economic evaluation

Benefit assessment

NICE National Institute for Health and Care Excellence

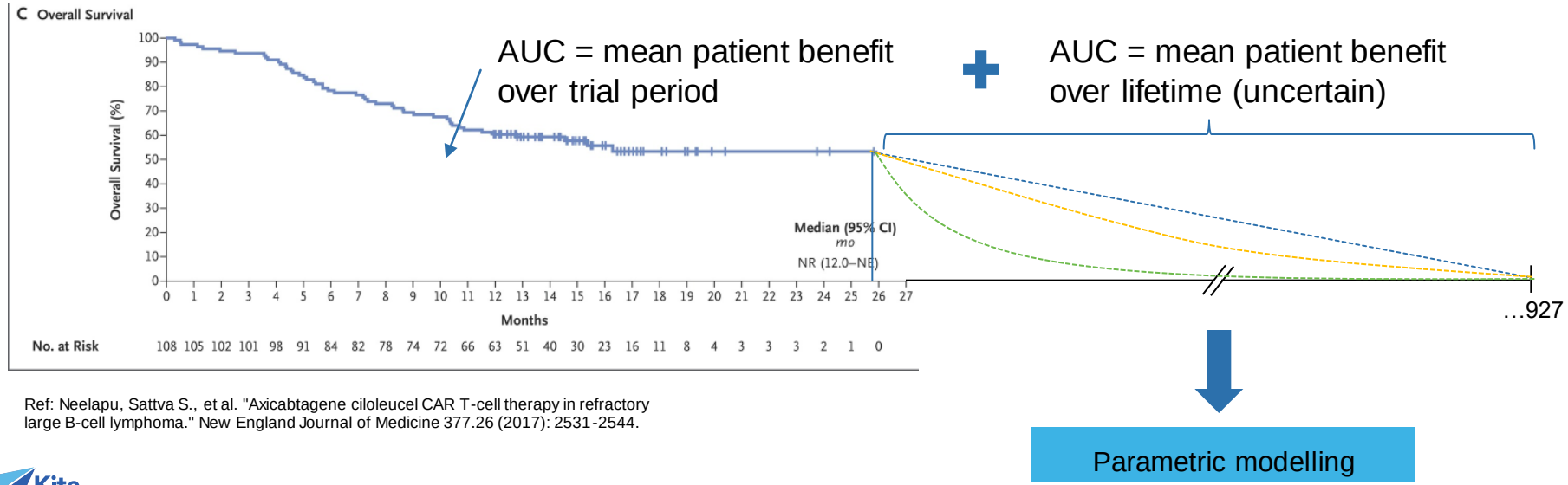
Statens legemiddelverk
Norwegian Medicines Agency

HAS
HAUTE AUTORITÉ DE SANTÉ

Gemeinsamer Bundesausschuss

Economic evaluation requires estimation of lifetime costs and benefits

To understand the trade-offs, we must be able to quantify the lifetime benefits vs the life time costs. However, we only have data for a very small part of a patients lifetime:



Ref: Neelapu, Sattva S., et al. "Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma." New England Journal of Medicine 377.26 (2017): 2531-2544.

Yescarta: the first CAR T to be approved in Europe in Aug 2018 for 3L+ DLBCL & PMBCL

- Individualized therapy - Own immune cells are trained to fight cancer
- Unprecedented efficacy in patients out of options (SoC median survival=6m)
- One off treatment with curative potential
- Small patient numbers and treatment in highly specialized hospitals

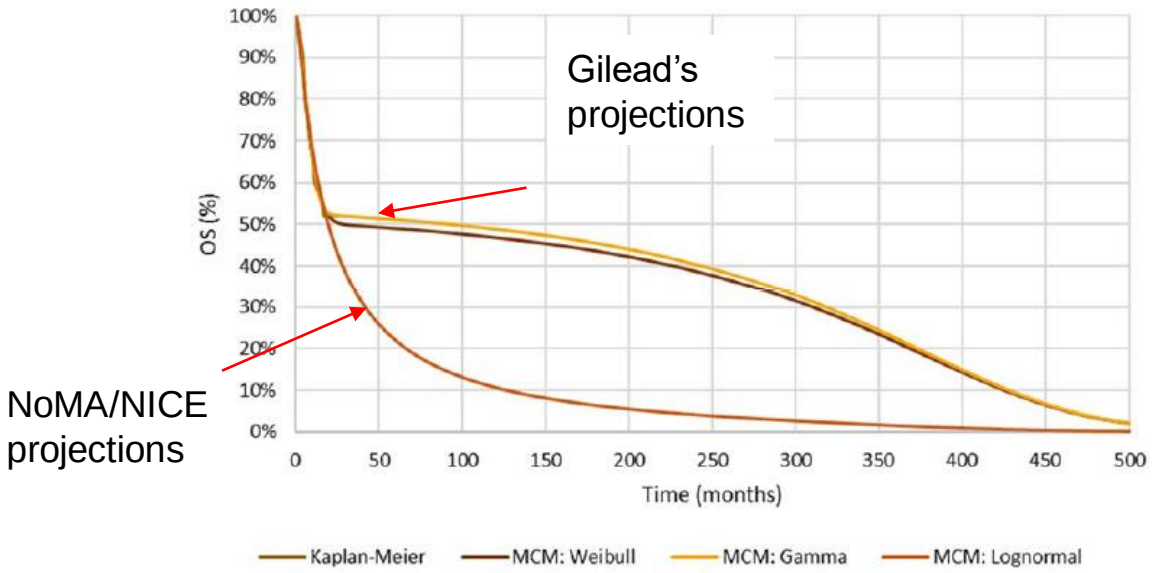
However, HTA bodies sceptical of long-term OS leading to delays in access.

For example, the Norwegian HTA body initially rejected Yescarta on the basis of:

"Additional follow-up data are needed to evaluate the long-term outcomes with axi-cel and reduce the large amount of uncertainty in the current analysis"

Ref:https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/K/Yescarta_DLBCL_2019.pdf

Figure 20: Overall survival for axi-cel: KM with mixture cure model parametric curves



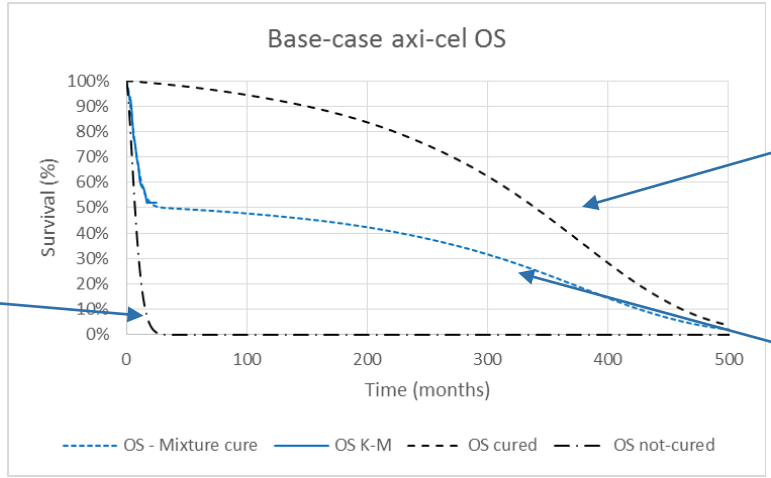
Key: MCM, mixture cure model.

Cure modelling is clinically plausible in LBCL

- LBCL is a curable disease, and CAR T is potentially curative
- Statistical models exist which are able to estimate a ‘statistically’ cured and uncured population from the underlying data
- We can use these models to predict long-term survival
- However, these models have not been validated in the context of LBCL and CAR T

$$S(t) = S^*(t)(\pi + 1 - \pi)S_u(t))$$

π= cure fraction



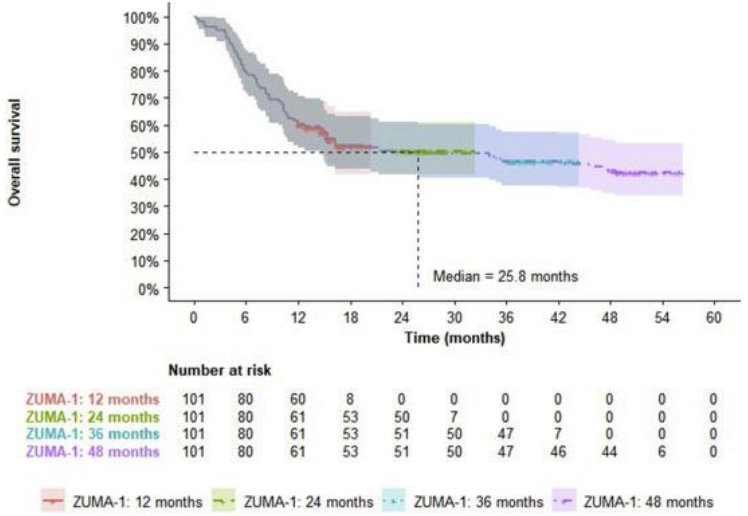
Estimated survival of uncured group

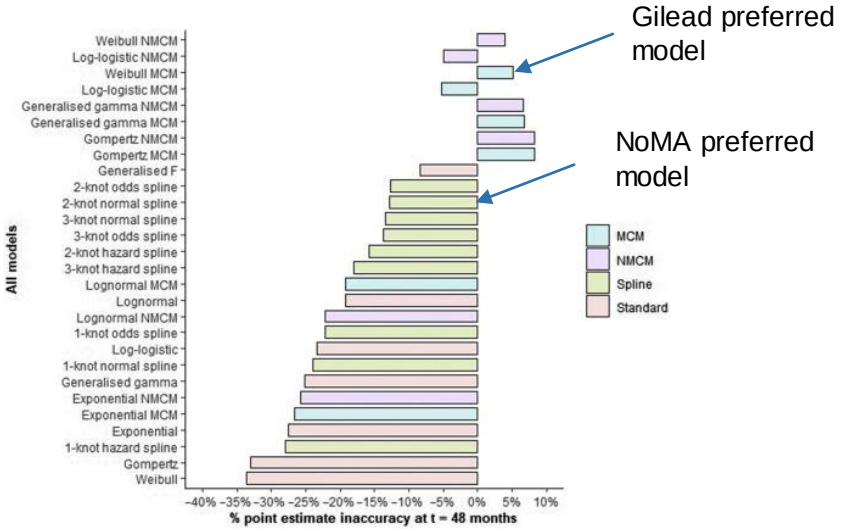
General population mortality

Weighted survival curve

Vadgama et al (2022) showed that MCM models are empirically valid in LBCL

- Cure models, along with 2 other classes of models were fitted to the interim OS data (12 month min FU), and their accuracy at predicting the empirical 4 year OS data was evaluated using a range of metrics.
- Cure-based models were able to produce consistent and accurate extrapolations of longer-term survival for patients treated with axicabtagene ciloleucel, even with limited follow-up data
- All cure models converged by 2 years of FU data

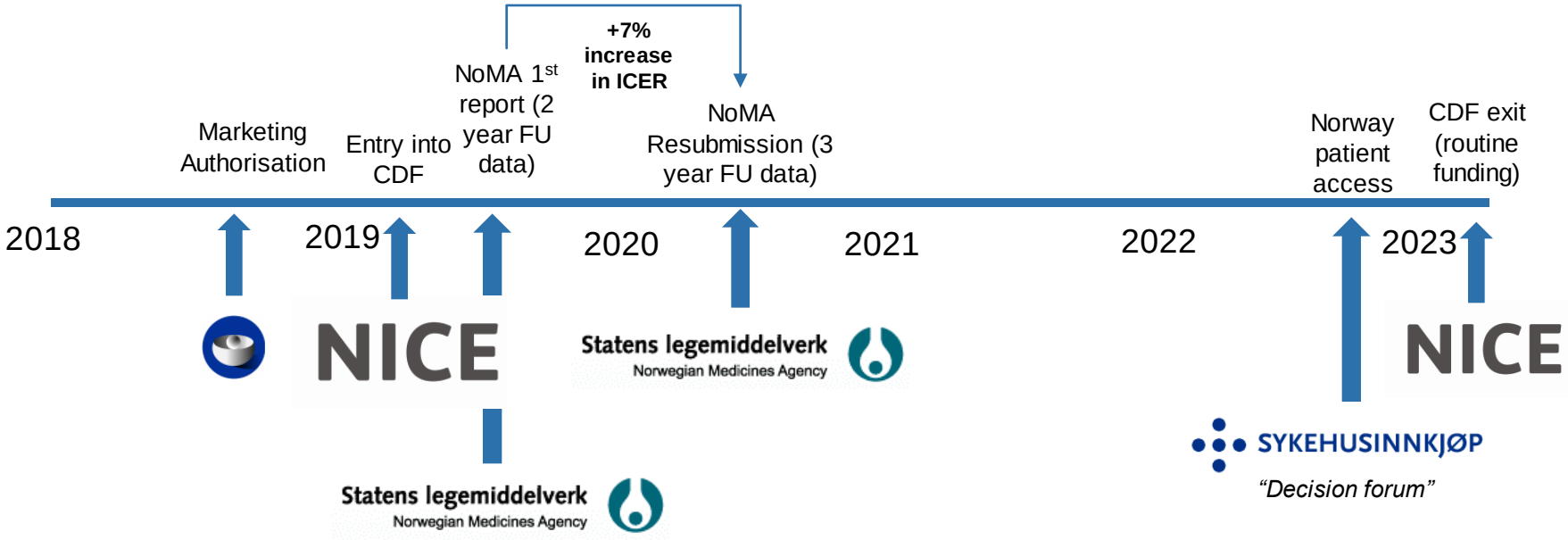




Ref: Vadgama, Sachin, et al. "Predicting survival for chimeric antigen receptor T-cell therapy: a validation of survival models using follow-up data from ZUMA-1." Value in Health 25.6 (2022): 1010-1017.

Interim funding models allow quicker patient access whilst tackling uncertainty in the health economic evaluation

- HTA bodies were understandably sceptical of the curative potential of axi-cel (Yescarta)
- NICE provides a framework when there is uncertainty in the evidence, which meets the needs of patient access, whilst collecting further evidence.
- NoMa did not have such frameworks which may have led to access delays



Key take aways

- Addressing uncertainty is important for HTA, but this must be balanced with the risk of slower patient access and subsequent consequences to health care burden
- Cure models are a validated statistical tool in predicting long-term OS for axi-cel treated LBCL patients
- Collecting OS data beyond 2 years did not substantially change the cost-effectiveness estimates
- Innovative funding models may be a useful funding mechanism to allow managed patient access

Kite
A GILEAD Company

Challenges With Long Term CAR-T Follow-up

- Payer-mandated PAES
- Patient burden and loss to follow-up
- Statistical considerations of 15y follow-up
- Conclusions

Challenges Underlying Payer-mandated PAES

Payers can request RWD collection through registries for orphan drugs, medicines that have a conditional marketing authorisation or products that receive a marketing authorisation under exceptional circumstances. Once a registry study is initiated, the drug subject to the measure may then only be prescribed to patients enrolled in the registry. There are a few challenges though:

- Adequate comparators can be difficult to identify in oncology or rare diseases
- A PAES with control arm requires excellent data quality to be able to control for known confounders

"The GBA has now gained a good three years of experience in real-world data collection. Even though it was apparent from the outset that our demands would have to be limited to certain case clusters in the evaluation of new drugs, it has become clear that our assumptions were too optimistic in several respects. First, we underestimated the effort and expense involved for all parties. Second, we significantly overestimated the quality of existing registries—such registry data may be used less frequently than expected. And third, we misjudged the incentive for manufacturers to engage in real-world data collection to obtain a potentially better assessment of their new drug in the medium term based on meaningful data from practice."

GBA's 2022 annual report

Patient burden and long-term follow-up in R/R NHL

There is a regulatory requirement from EMA and FDA to monitor patients who receive cell and gene therapy products for a period of up to 15 years to characterize the long-term safety profile, regardless of disease area.

Attending specialised treatment centers for safety follow-up can place a considerable burden on patients, their caretakers, families, and healthcare providers. As a result, loss-to-follow-up can be high which has a negative impact on overall data quality.

In an analysis of patients who received hematopoietic cell transplantation, enrolled in the CIBMTR registry, and completed their end of Year 2 visit, there was an incremental increase in the proportion of patients who were lost to follow-up between Year 3 to Year 10.

Parameter (n; %)	Adult		Pediatric	
	Allogeneic	Autologous	Allogeneic	Autologous
Number of patients	10,367	7,291	3,865	468
Loss to Follow-up at Year 2	0%	0%	0%	0%
Loss to Follow-up at Year 3	2%	2%	3%	4%
Loss to Follow-up at Year 5	5%	7%	11%	12%
Loss to Follow-up at Year 10	13%	15%	25%	24%

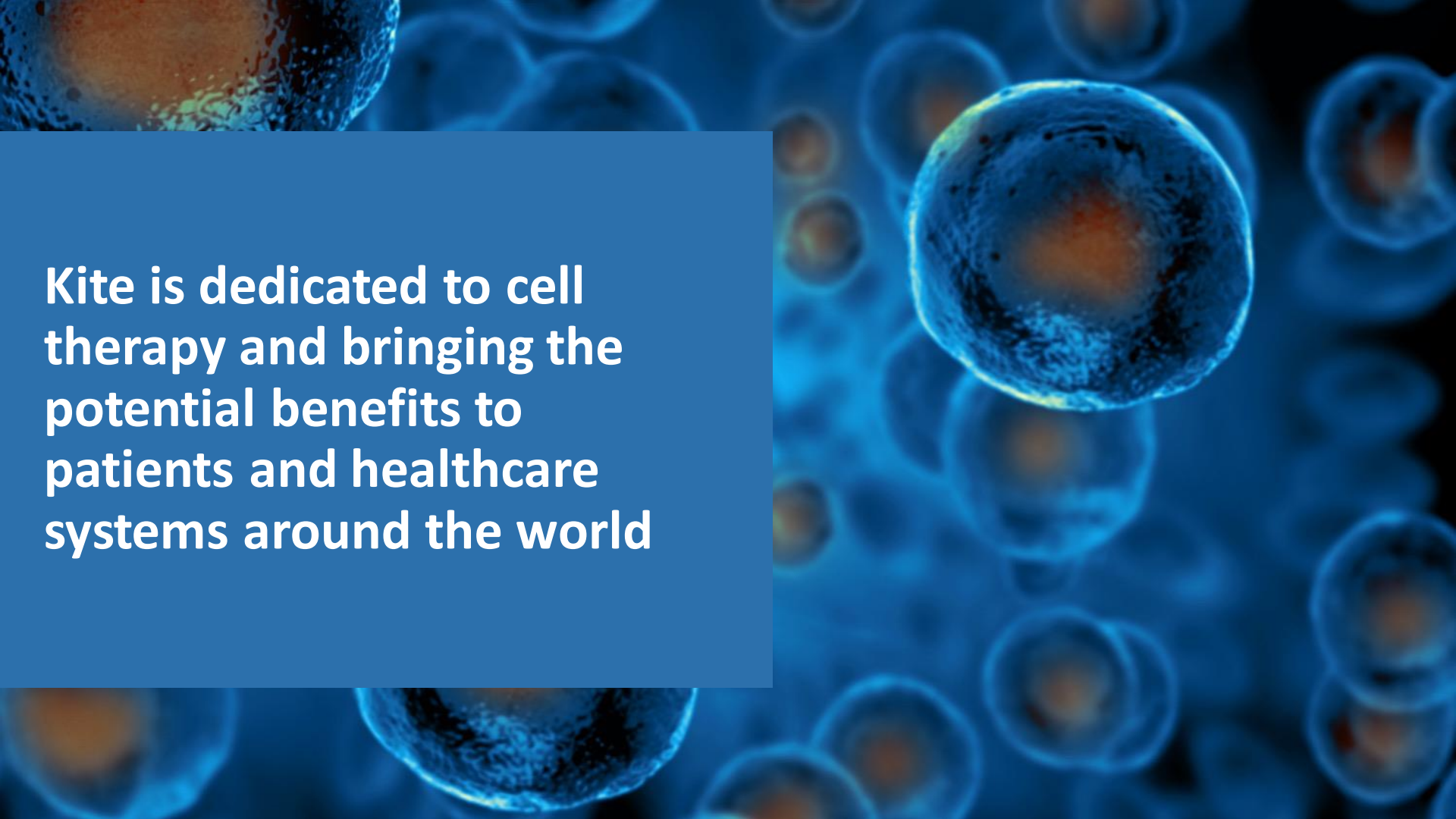
*Adapted from {Buchbinder 2020} on HSCT

Statistical Considerations of Long-term Follow-up

- Interference of earlier/subsequent treatments in oncology
- Timing of the follow-up analysis
- Patient burden and loss to follow-up
- Competing risk of death
- Bias in loss to follow-up

Conclusions

- Where applicable and appropriate, real-world data collected from health care encounters should be considered for long-term safety and effectiveness of patients treated with CAR T-cell therapy.
- There is a need for active pharmacovigilance to assess short- and long-term safety post-approval, and the guidelines for these activities should take into consideration the heterogeneity of patient characteristics and disease prognosis between different therapeutic indications.
- The burden of long-term follow-up on patients, their caretakers, families, and healthcare providers is significant in a prospective cohort study setting where safety information is obtained via primary data collection.
- Long-term follow-up in oncology mandates statistical considerations


Kite is dedicated to cell therapy and bringing the potential benefits to patients and healthcare systems around the world