NOVARTIS

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Home > News > Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah™ (tisagenlecleucel, CTL019), for children and young adults with B-cell ALL that is

Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah™ (tisagenlecleucel, CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice

Aug 30, 2017

- - First-in-class therapy showed an 83% (52/63) overall remission rate in this patient population with limited treatment options and historically poor outcomes1,2
- - Novel approach to cancer treatment is the result of pioneering CAR-T cell therapy collaboration with University of Pennsylvania
- - Reproducible, flexible and validated manufacturing process builds on years of global clinical trial experience at our facility in New Jersey, US
- - Novartis also announces innovative collaboration with the US Centers for Medicare and Medicaid Services

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Kymriah® (tisagenlecleucel), first-in-class CAR-T therapy from Novartis, receives second FDA approval to treat appropriate r/r patients with large B-cell lymphoma

MAY 1, 2018

- *Kymriah demonstrated an overall response rate of 50%, with median duration of response not yet reached at the time of data cut-off, indicating sustainability of response*[1]
- *Kymriah is the only CAR-T therapy FDA-approved for two distinct indications – in non-Hodgkin lymphoma (NHL) and B-cell acute lymphoblastic leukemia (ALL)*
- *Novartis has established leadership based on first-to-launch CAR-T therapy experience, existing treatment center network and payor environment understanding, which helps to support access and anticipated patient demand*
- *Novartis continues to collaborate with the Centers for Medicare and Medicaid Services (CMS) on various value-based pricing initiatives*

FOR MEDIA USE ONLY

Liz Barrett, CEO, Novartis Oncology

Basel, May 1, 2018 – Novartis today announced the US Food and Drug Administration (FDA) has approved Kymriah® (tisagenlecleucel) suspension for intravenous infusion for its

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FDA approves Novartis Kymriah® CAR-T cell therapy for adult patients with relapsed or refractory follicular lymphoma

May 28, 2022

- *68% of patients receiving Kymriah in the ELARA trial experienced complete response, with an 86% overall response rate, along with a remarkable safety profile*[1]
- *Sustained clinical benefit from Kymriah treatment demonstrated – of patients who achieved a complete response, 85% were still in response at 12 months*[1]
- *Kymriah can be administered in the outpatient setting, offering increased flexibility and potentially reducing the burden of therapy for patients and their care teams*[1,2]
- *Kymriah is now FDA approved in three indications and remains the only CAR-T cell therapy approved in both adult and pediatric settings*[1]

INTERNAL

Single-arm study design

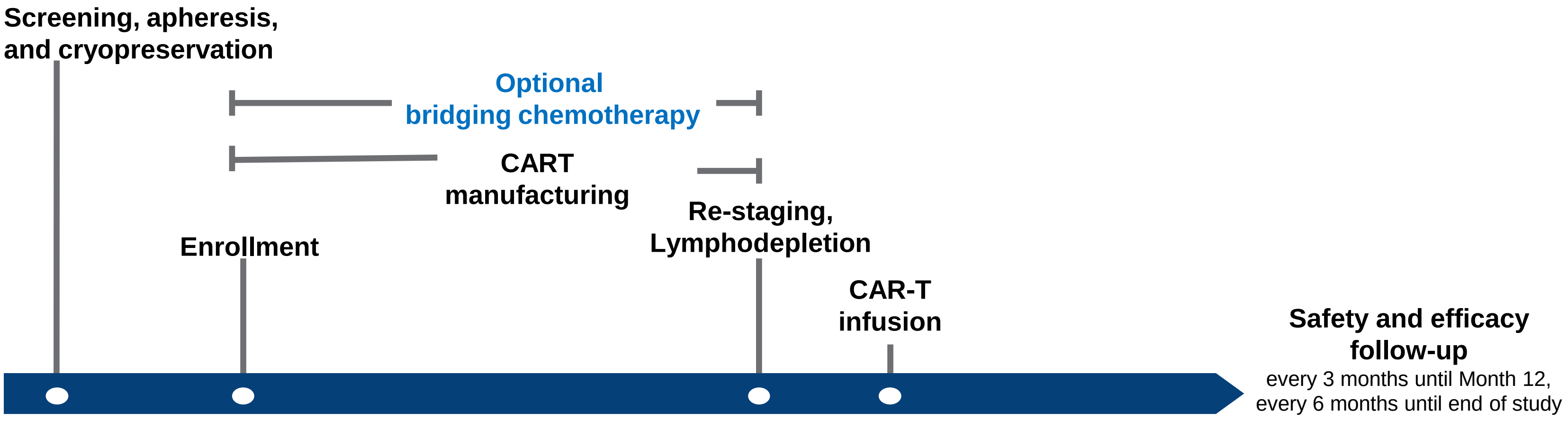
Phase II, single arm, open-label, multi-center clinical trial to determine the efficacy and safety of tisa-cel in patients with relapsed or refractory ALL, DLBCL or FL

Primary endpoint:

- ORR or CR rate by IRC

Secondary endpoints:

- DOR, PFS, OS, PK, Safety ..



Selected challenges and considerations

Analysis considerations of CAR-T single-arm study

1.1. Patient population and extended K-M method

2.2. Utilize real-world data as external control

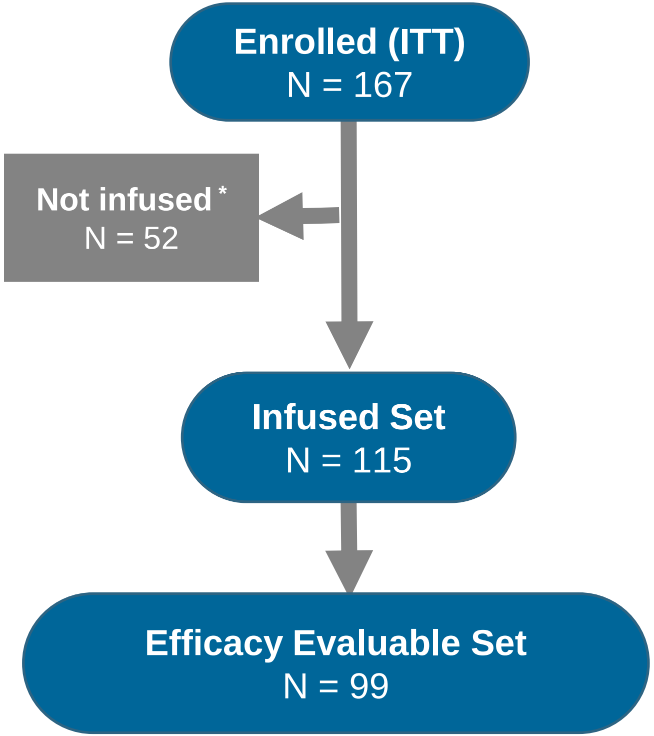
Analysis considerations of CAR-T randomized trial

3. Explore the use of principal stratum strategy

Analysis considerations of CAR-T single-arm study

1. Patient population and extended K-M method

Patient population (before ICH E9 Estimand)



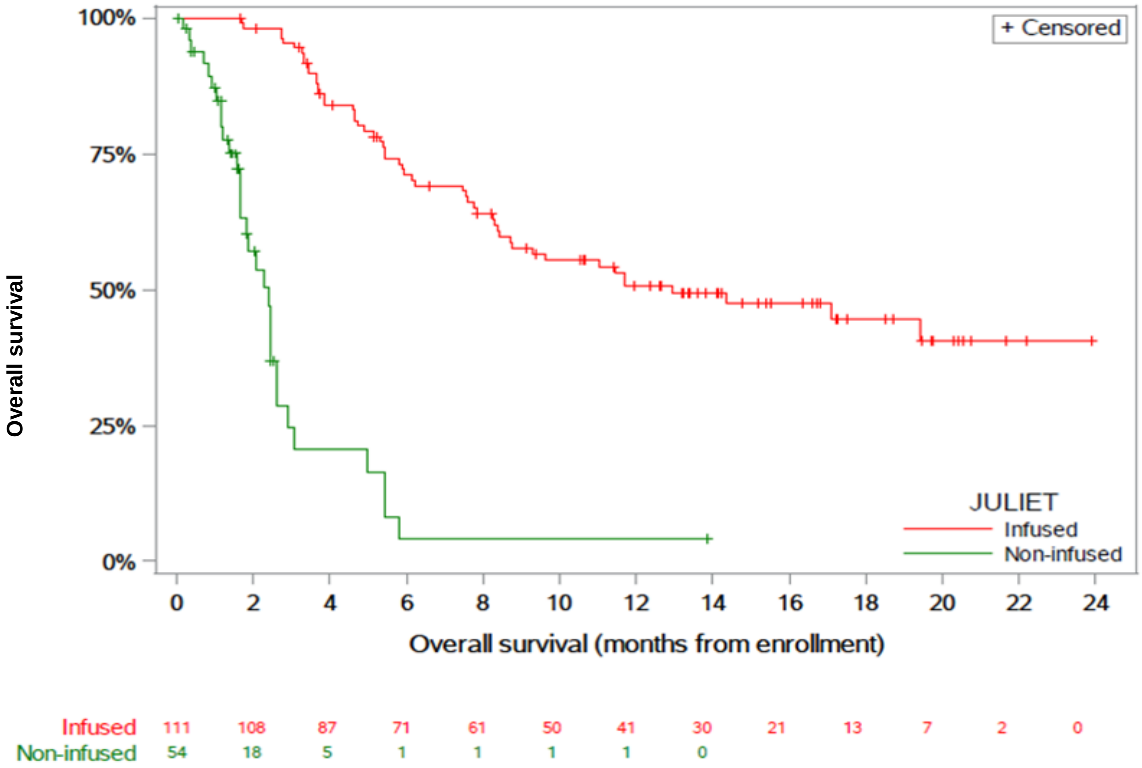
	Enrolled patients N=167	Infused patients N=115
Primary endpoint[1]	**N=147**	**N=99**
Overall response rate (ORR) (CR+PR)[2], n (%) 95% CI	**54 (36.7)** (28.9, 45.1)	**54 (54.5)** (44.2, 64.6)
CR, n (%)	41 (27.9)	41 (41.4)
PR, n (%)	13 (8.8)	13 (13.1)
Response at month 3	N=147	N=99
ORR (%)	40 (27.2)	40 (40.4)
CR (%)	34 (23.1)	34 (34.3)
Response at month 6	N=147	N=99
ORR (%)	34 (23.1)	34 (34.3)
CR (%)	31 (21.1)	31 (31.3)
Duration of response (DOR)[3]	**N=54**	**N=54**
Median (months) (95% CI)	Not reached (10.0, NE[5])	Not reached (10.0, NE[5])
% relapse free probability at 12 months	63.4	63.4
% relapse free probability at 24 months	60.8	60.8
% relapse free probability at 36 months	60.8	60.8
% relapse free probability at 54 months	60.8	60.8
Other secondary endpoints	**N=167**	**N=115**
Overall survival (OS)[4]		
% survival probability at 12 months	41.0	48.2
% survival probability at 36 months	29.4	36.6
% survival probability at 60 months	25.5	31.7
Median (months) (95% CI)	8.2 (5.8, 11.7)	11.1 (6.6, 23.9)

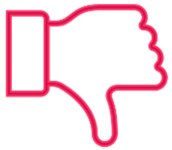
[1] The primary endpoint was analysed on all patients whose Kymriah was manufactured at the Novartis US facility.

* Manufacturing failure and drop-outs prior to CAR-T infusion

INTERNAL

Overall survival by infusion status (naïve)



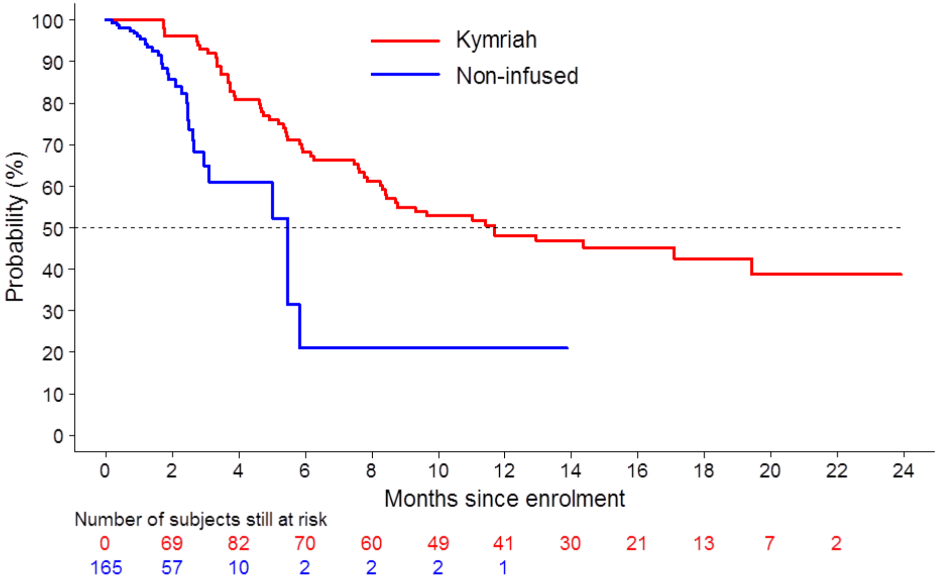


The standard Kaplan-Meier method (left) treated infusion status as a fixed variable

- Not appropriate in our setting
- Would over-estimate treatment effect

Overall survival was defined as time from date of enrollment to the date of death for enrolled set.

Overall survival by infusion status using extended K-M estimator



- **Snapinn et al in 2005** developed an extended K-M estimator to allow for cohorts defined by time-dependent variable

- Define CAR-T infusion status $\boldsymbol{C}(t)$ =
$$\begin{cases} 0, & if\ the\ patient\ has\ not\ received\ Kymriah\ at\ time\ t \\ 1, & if\ the\ patient\ has\ received\ Kymriah\ at\ time\ t \end{cases}$$

- Update the infused and non-infused cohorts at each event time t_j

INTERNAL

Analysis considerations of CAR-T single-arm study

2. Utilize real-world data as external control

External control requested by HAs

Need for external control with **patient-level data** highlighted by the Norwegian Health Authority (Tisa-cel rapporteur country) during protocol review of ELARA trial in 2018:

3 Question #2

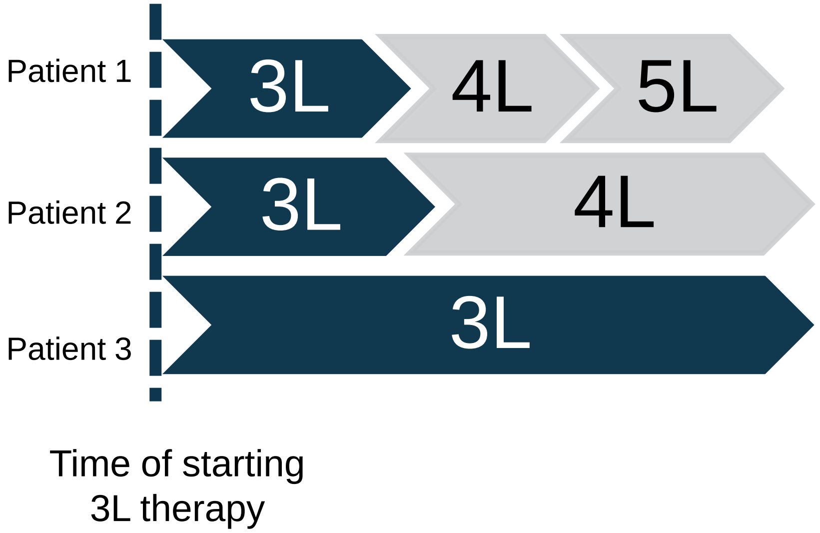
Being a single-arm trial, we assume that, prior to any comparative analyses, the external control will be pre-specified and consist of a population (e.g. from registries or historical trials) where there is access to individual patient-level data. Furthermore, the selection criteria of the external control should match with the selection criteria for the patient population proposed in this trial, to make the two populations as similar as possible. If matching on patient characteristics to the

Proposed two sources of real-world to support a comprehensive efficacy assessment of tisa-cel in r/r FL patients

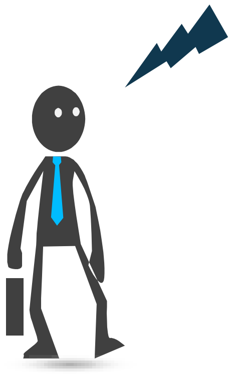
Selection of index line

Longitudinal data across several lines of therapies available in RWD sources

Patients in RWD can meet the eligibility criteria of at ELARA multiple lines of therapy



- Use data from all lines?
- Use earliest/latest lines ?
- Randomly select one line?



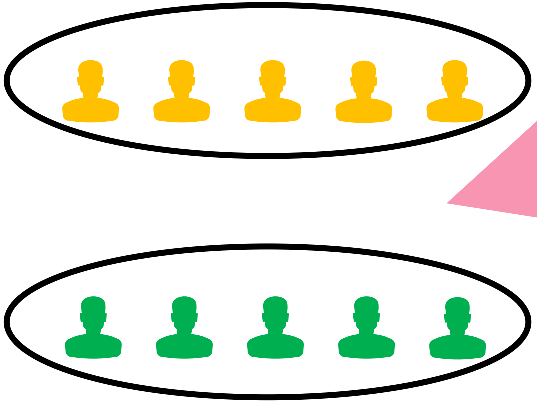
Design-associated biases

Single arm trial data

Observed outcomes on drug

External control RWD

Observed outcomes on control



Potential biases could impact our causal inference. *± E.g.

- Confounding bias
- Selection bias
- Assessment bias
- Different endpoint bias
- Immortal time bias
- Efficacy / effectiveness gap
- Drift in SoC over time

Take steps to eliminate or mitigate potential biases through the careful design *and* analysis of the effectiveness comparison between single arm trial data and its external control data

* Burger et al. *Pharmaceutical Statistics*, 2021

± Catalogue of Bias Link

Target trial & Estimand frameworks

- ICH E9(R1) estimand provides a structured framework to clinical trial design, conduct, analysis and interpretation
- Target trial emulation framework can be used to extend the ICH E9(R1) estimand thinking process to studies using RWD, but doesn't include intercurrent events

- Provides formal frameworks to identify and avoid common methodological pitfalls of study design and statistical analysis
- Facilitates transparent communication about potential limitations

Applying target trial & estimand frameworks

Question: ***What's the treatment effect of prescribing tisa-cel vs SoC in the patient population who participated in the ELARA trial?*** – average treatment effect on treated (ATT)

Attribute	Target RCT	Emulated trial		Our strategy
		ELARA	RWD	
Population /Eligibility criteria	ELARA inclusion/exclusion (I/E) criteria	Same as target RCT	ELARA I/E criteria that are feasible to apply retrospectively	Be transparent and summarize all criteria that were not feasible to apply in RWD
Treatment/ Treatment strategy	**CAR-T treatment strategy** vs **Current SoC**	CAR-T treatment strategy as target RCT	Current SoC	✓
Treatment assignment	Block randomized to either CAR-T arm or SoC arm	Emulate simple randomization		Propose statistical methods to emulate randomization
Variables	OS is time to death from any cause	Same as in target RCT		✓
	CR best overall response of complete remission per Lugano criteria	Same as target RCT	CR and progression based on real-world response criteria	Subgroup analysis ≥ 2014 was conducted as year of introduction of Lugano response criteria
	PFS is time to first progression or death from any cause	Same as target RCT	Progression dates unavailable for many patients	To consider new anticancer therapy as PFS event and pre-specify in SAP

Applying target trial & estimand frameworks

Attribute	Target RCT	Emulated trial: ELARA	Emulated trial: RWD	Our strategy
Start of follow-up	Start: date of randomization	Start: enrollment, regarded as prescription date	Start: start date of SoC treatment • Multiple line of therapy	Propose statistical method to select index line
Intercurrent event(s)	**IE: new anti-cancer therapy** OS: Treatment policy strategy CR: ICE reflected in Variable PFS: Hypothetical strategy	Same as target RCT for OS and CR PFS: Composite strategy		✓
Causal effect	**ATT:** Effect of prescribing tisagenlecleucel vs SoC in patients meeting ELARA inclusion/exclusion criteria	Same as in target RCT		✓
Summary measure	Binary endpoints: Difference in marginal response probabilities on CAR-T vs SoC Time-to-event (TTE) endpoints: Marginal HR	Same as in target RCT		✓
Analysis	Binary: Difference in response rates TTE: Cox regression	Binary: Difference in weighted proportions of responders TTE: HR obtained from a weighted Cox regression		✓

Novel approach to select line of therapy

Step1. Estimation of propensity scores per patient per line
(as each patient has new set of ‘baseline’ covariates at start of each line)

Step 2. Selection of one eligible line per patient in external cohort
- The **highest** propensity score per patient is chosen, i.e. line where the patient is mostly closely aligned with that ELARA population.

External Cohort

Real-world patient ID	LoT where SOC is given	Propensity score
1	3	0.67
1	4	0.49
1	5	0.68
2	4	0.56
2	5	0.75
3	3	0.77
....	....	....

Propensity score = probability a patient would have been enrolled in ELARA

External Cohort

Real-world patient ID	LoT where SOC is given	Propensity score
1	3	0.67
1	4	0.49
1	5	0.68
2	4	0.56
2	5	0.75
3	3	0.77
....	....	....

Higher propensity score = more similar to ELARA patients

Hampson LV, **Chu J**, et al. *Statistics in Biopharmaceutical Research* (2023). https://doi.org/10.1080/19466315.2023.2190931

Utilizing PS to mitigate confounding bias

ATT: “What is the effect of prescribing tisa-cel (vs SoC) on efficacy in the population who participated in ELARA?”

→Weight each patient in the external cohort based on their odds of being in ELARA

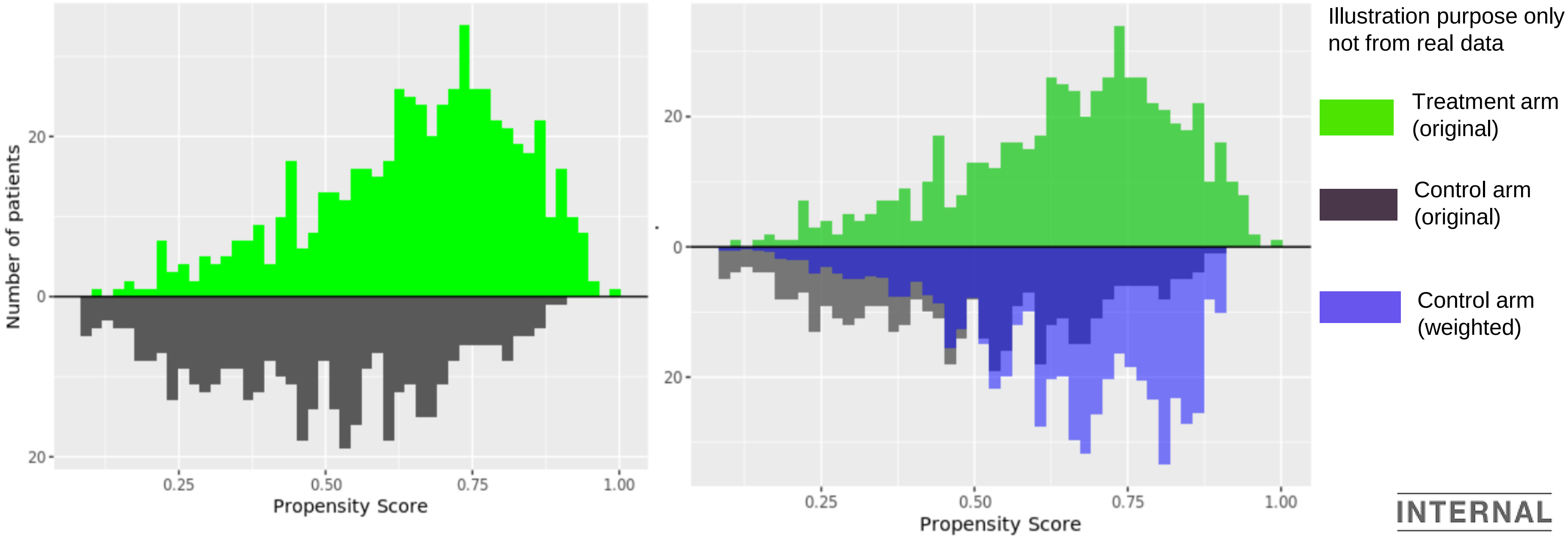
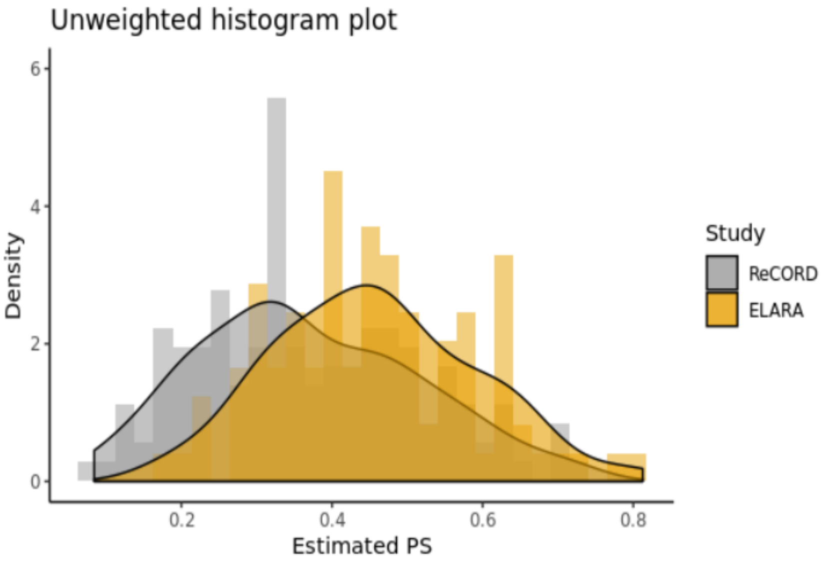
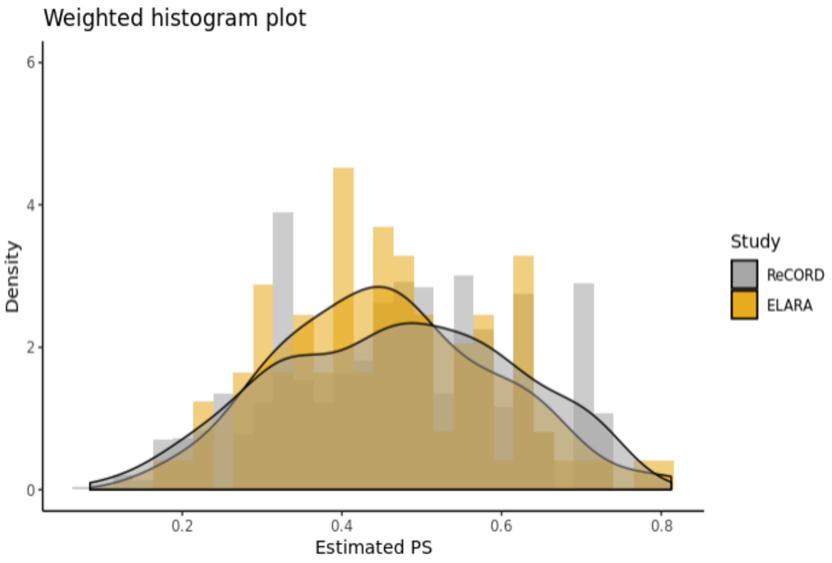


Illustration purpose only not from real data

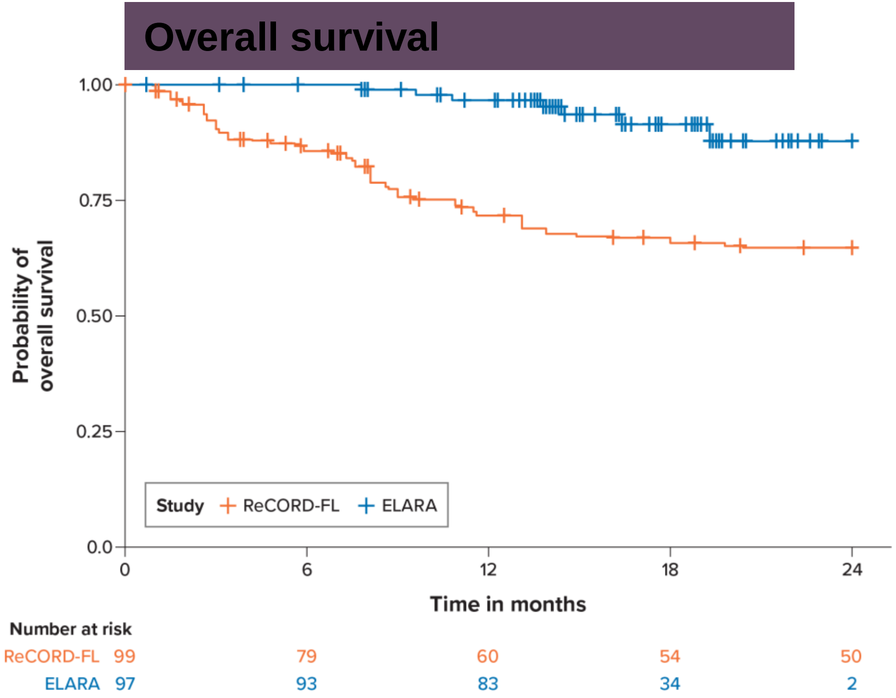
Diagnostics: how successful were we at emulating randomization?

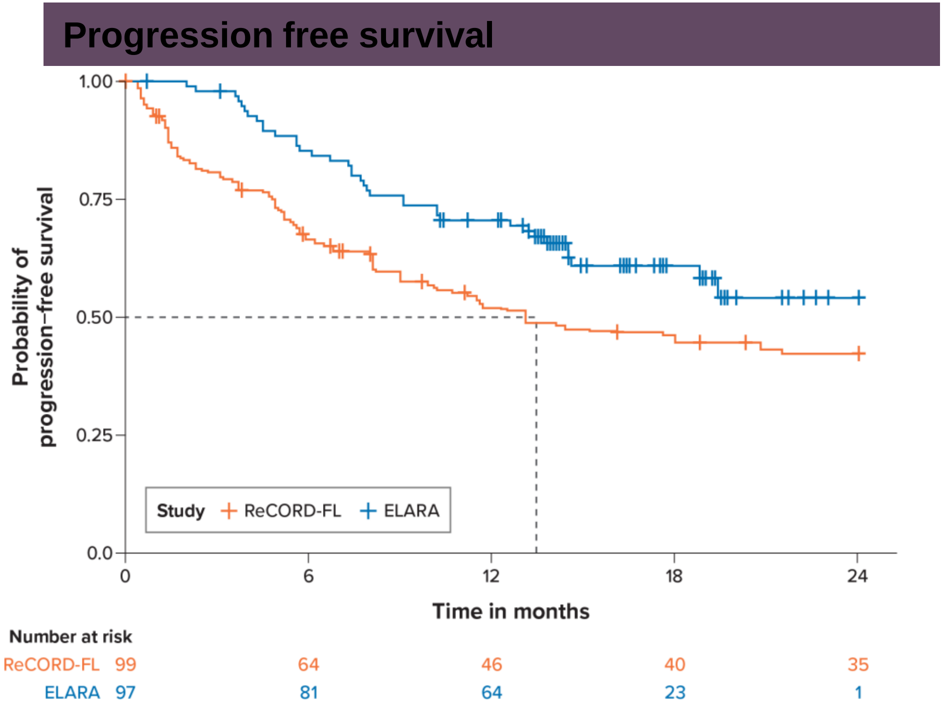
Figures compare the empirical distributions of propensity score estimates in ELARA vs RWD before and after weighting





Kaplan-Meier plots for ELARA vs RWD after weighting





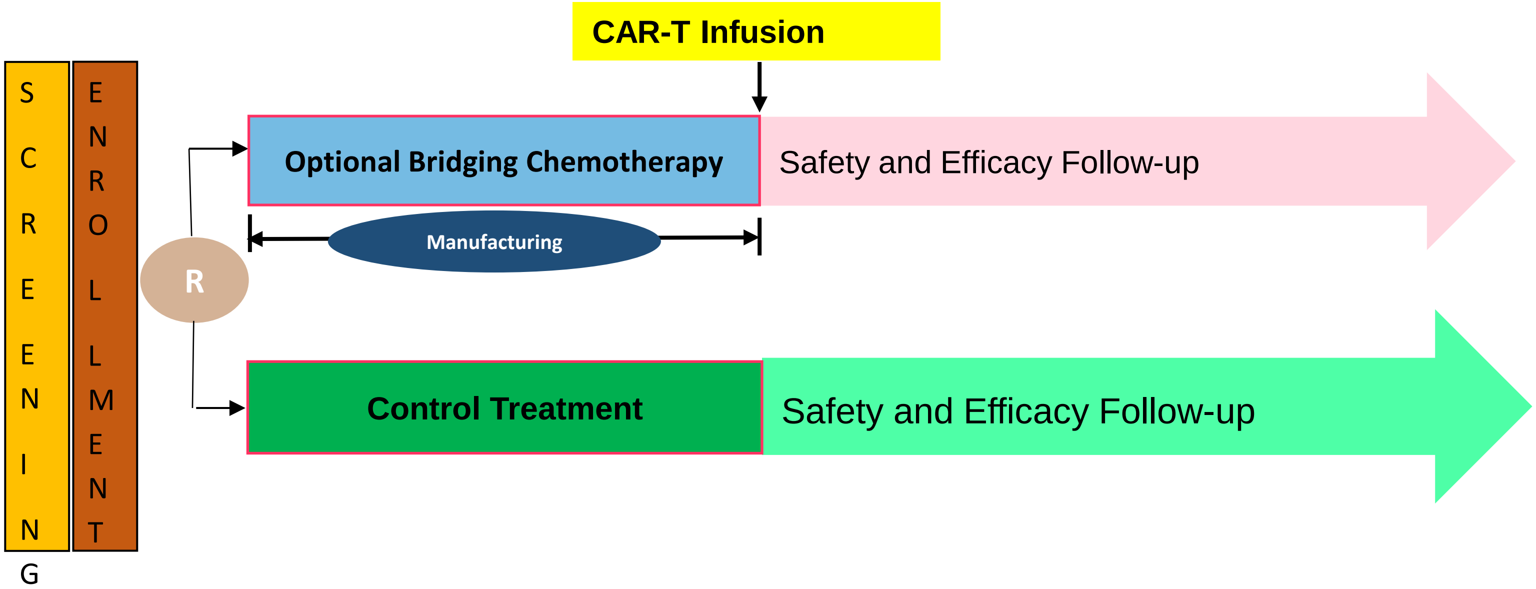
INTERNAL

Analysis considerations of CAR-T randomized trial

3. Explore the use of principle stratum strategy

CAR-T randomized phase III trial

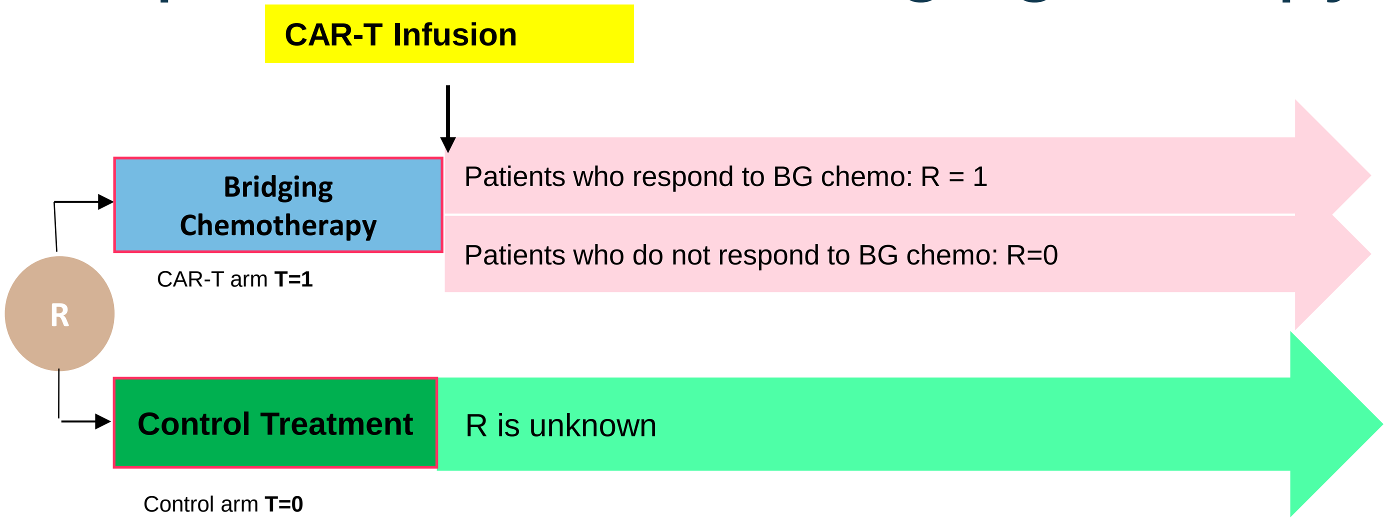
General study design



Primary objective

Compare treatment effect (e.g, OS or PFS) of the two treatment strategies regardless of a patient's response to bridging chemotherapy

Response status to bridging therapy



Question of interest (Secondary):
What is the treatment effect (e.g., OS or PFS) of the CAR-T relative to control in patients <u>who would be in (or not in) remission after bridging if they were given the bridging chemotherapy</u>?

At the end of bridging,

- For CAR-T arm patients, R is observed (either R=1 or 0)
- For control arm patients, **<u>R is unknown</u>**

ICH E9 (R1)* – Principal stratum strategy

Principal stratum strategy

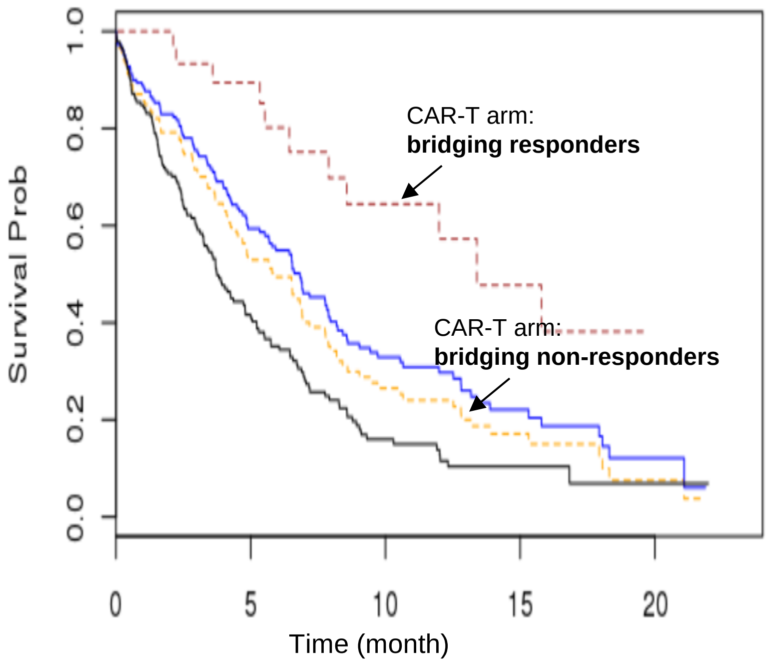
The target population might be taken to be the principal stratum (see Glossary) in which an intercurrent event would not occur. For example, the target population of interest might be taken to be the stratum of patients in which failure to adhere to treatment would not occur. In other words, a principal stratum is a subset of the broader population who would not experience the intercurrent event. The scientific question of interest relates to the treatment effect only within that stratum.

Effects in principal strata should be clearly distinguished from any type of subgroup or per-protocol analyses where membership is based on the trial data. Principal stratification (see Glossary) is defined by a patient's potential intercurrent events on both treatments: for example, patients who would adhere to either treatment. It is not possible in general to identify these subjects directly, either in advance of the trial since the occurrence of the intercurrent event cannot be predicted, or based on the data from a randomised controlled trial because each patient will be observed on one treatment only.

*Estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

A “naive” comparison

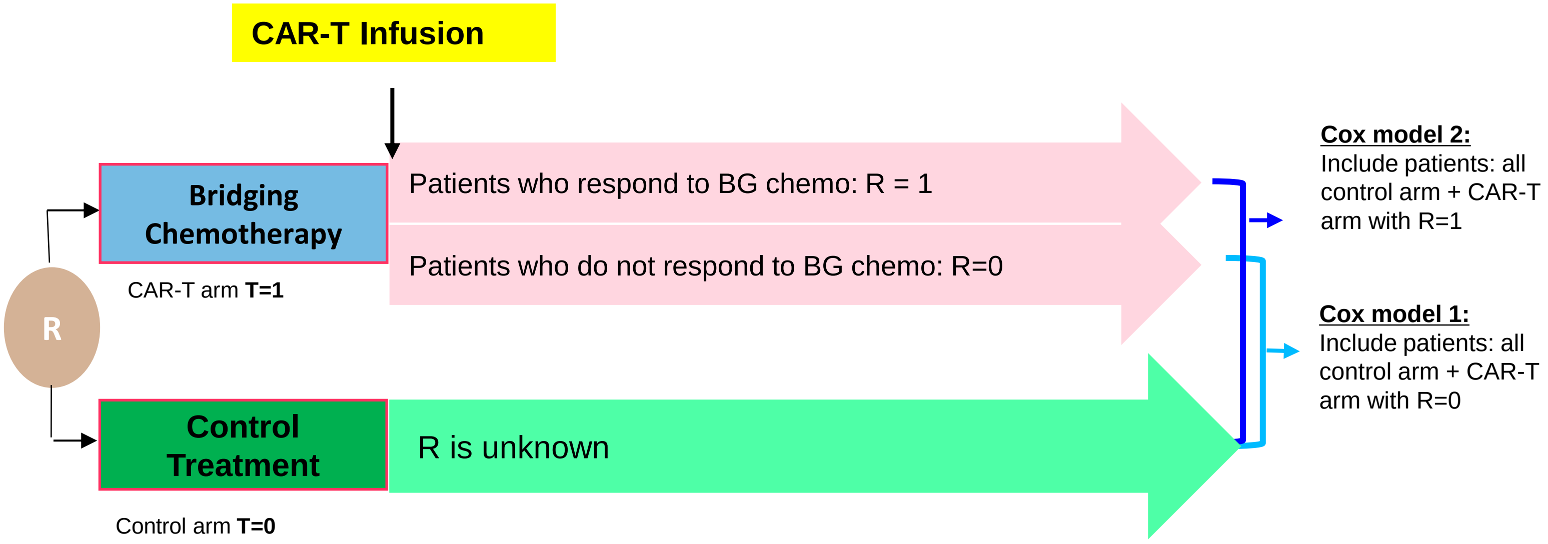
KM curve for stratum of pts responded or not responded to BG chemotherapy in CAR-T arm vs. KM for the control arm



Comparison 1:
Bridging responders from CAR-T arm vs. Control arm (red curve vs. black curve)

Comparison 2:
Bridging non-responders from CAR-T arm vs. Control arm (yellow curve vs. black curve)

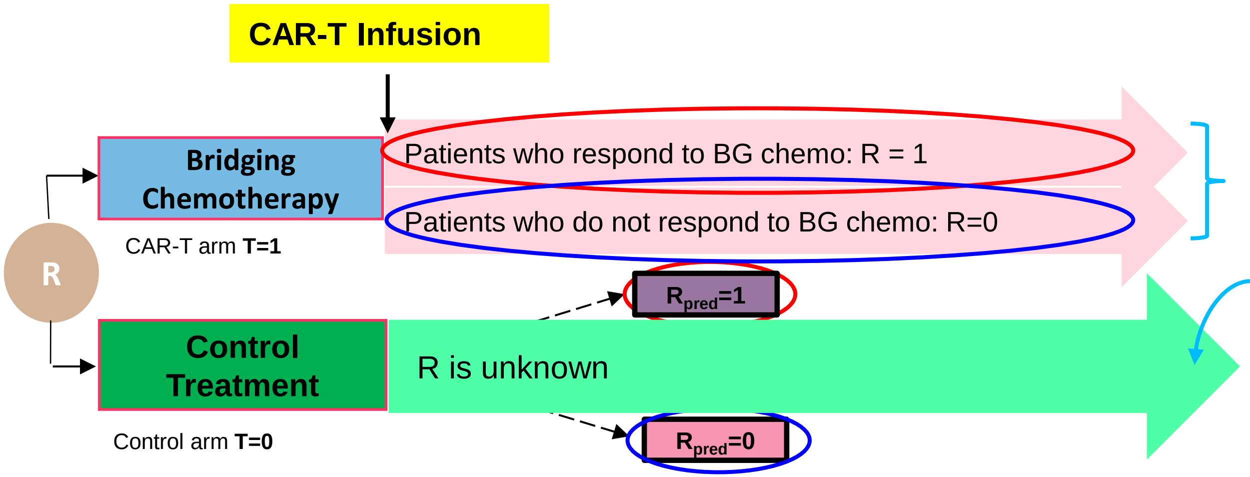
Principal stratum 1: the “Independent” approach



- The naive comparisons provide unbiased estimate of treatment effect if **S(T=0) and R are independent**.
  - All patients in control arm share the same survival distribution regardless of their response status

Principal stratum 2: the "Multiple imputation (MI)" approach

The idea of the MI approach is to **predict a patient's response to bridging** for those randomized to the control arm (as it's not observable)



1. Fit logistic regression model using data from CAR-T arm: R ~ covariates

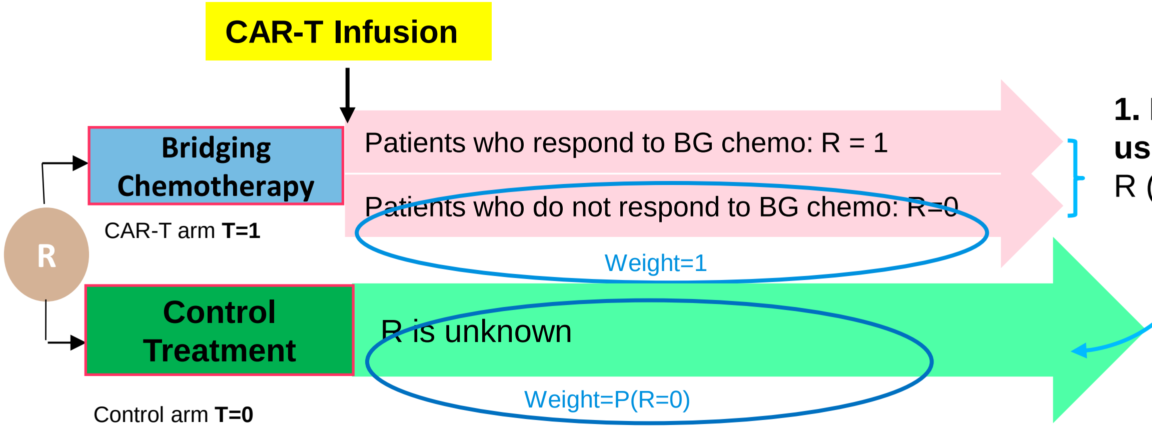
2. Apply the fitted model to control arm and obtain P(R=0|covariates) or P(R=1|covariates)

3. Generate R_{pred} from Bernoulli distribution

4. Fit Cox regression models:
Cox model 1: Estimate HR of CAR-T vs. Control for non-BG responders include patients- CAR-T arm (R=0) + control arm (R_{pred}=0)
Cox model 2: Estimate HR of CAR-T vs. Control for BG responders include patients- CAR-T arm (R=1) + control arm (R_{pred}=1)
5. Combine results with Rubin's rule

Principal stratum 3: the “Weighted” approach

Instead of predicting a patient’s response to bridging for those in the control arm, the **probability of being a responder or non-responder to BG** will be used as weight in the **weighted cox regression model**.



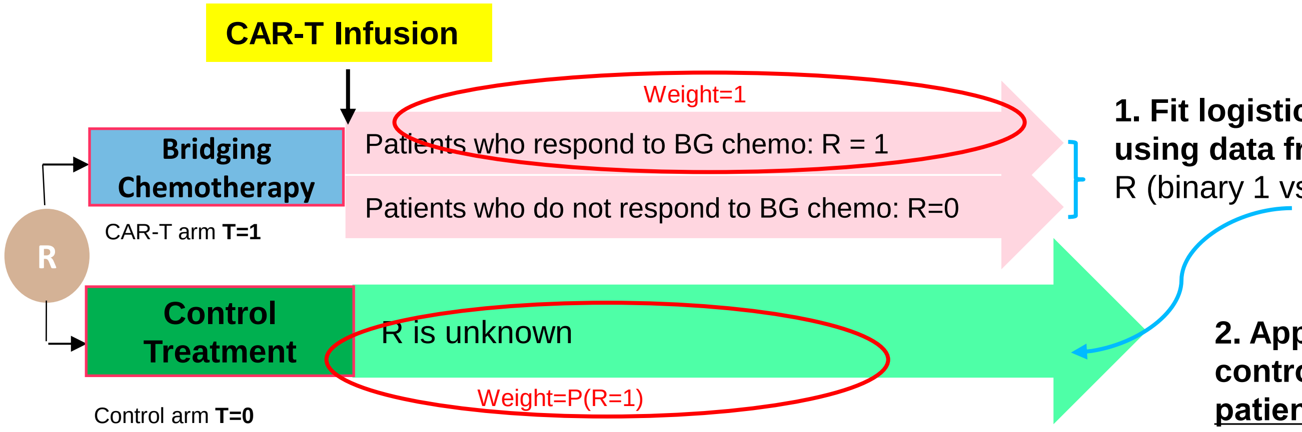
1. Fit logistic regression model using data from CAR-T arm:
R (binary 1 vs. 0) ~ covariates

2. Apply the fitted model to control arm and predict <u>a patient’s probability of responding/not responding to BG: P(R=1) (or P(R=0))</u>

3. Fit <u>weighted</u> Cox regression models:
Cox model 1: Estimate HR of CAR-T vs. Control for non-BG responders include patients- CAR-T arm (R=0, weight=1) + all control arm (weight=P(R=0))

Principal stratum 3: the "Weighted" approach

Instead of predicting a patient's response to bridging for those in the control arm, the **probability of being a responder or non-responder to BG** will be used as weight in the **weighted cox regression model**.



1. Fit logistic regression model using data from CAR-T arm:
R (binary 1 vs. 0) ~ covariates

2. Apply the fitted model to control arm and predict <u>a patient's probability of responding/not responding to BG: P(R=1) (or P(R=0))</u>

3. Fit <u>weighted</u> Cox regression models:
Cox model 1: Estimate HR of CAR-T vs. Control for non-BG responders
include patients- CAR-T arm (R=0, weight=1) + all control arm (weight=P(R=0))
Cox model 2: Estimate HR of CTL vs. SOC for BG responders
include patients- CTL arm (R=1, weight=1) + all control arm (weight=P(R=1))

Summary

- **Patient population selection for analysis and labelling**
  - ITT analysis and extended K-M analysis

- **Utilization of RWD to contextualize single arm trial results**
  - Implementation of the target trial & estimand frameworks would be beneficial

- **Exploration of principal stratum strategy**
  - Not common for primary but useful for secondary or exploratory analysis