



MRC
Biostatistics
Unit



UNIVERSITY OF
CAMBRIDGE



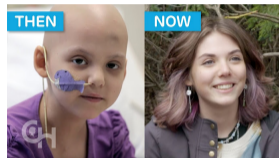
Early Phase Dose-Finding Designs for CAR-T cell Therapies

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Dr M.A. has a research question

Dr M.A. works on Peripheral T-cell lymphomas (brain Lymphomas).

- Poor prognosis after relapse: overall survival (OS) 6 to 12 mths
- Breakthrough in ALCL and then in B-cell Lymphoma: CD19-chimeric antigen receptor (CAR)-T cells



ZUMA-1 phase II trial, 101 patients:

- Response rate = 82%
- Duration of response: median 11 mths
- Frequent adverse events: 93% of cytokine release syndrome (CRS), 13% at grade ≥ 3

JULIET phase II trial, 111 patients:

- Response rate = 52%
- OS: median 40 months
- 58% of CRS, 23% at grade ≥ 3

Dr M.A. has a research question

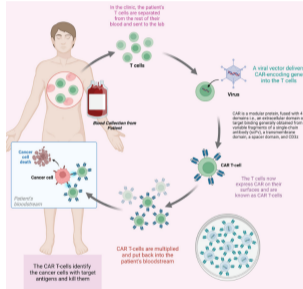
A new Anti-CD7 PEEL-CAR-T cells therapy

- Compassionate use in T-cell acute lymphoblastic leukemia (T-ALL)
- Good candidate against brain lymphomas

How does it work?

How does CAR-T cells work?

- A sophisticated manufacturing



- Dose: in number of (million) cells
3 doses: $d_1 = 35 \times 10^6$, $d_2 = 70 \times 10^6$ and $d_3 = 105 \times 10^6$
but no clear rationale

How does CAR-T cells work?

- 1 injection: A living agent
Cells multiplies (or die out ...) in the body

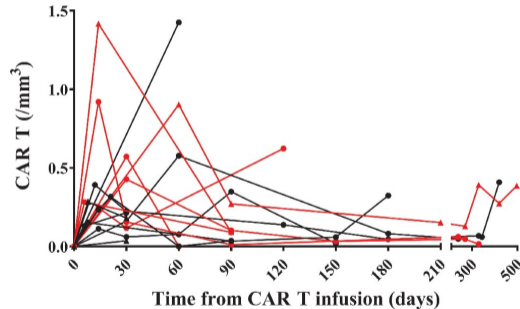
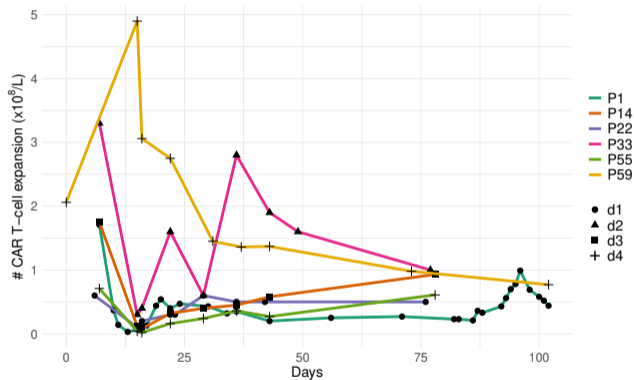


Figure: red = clinical response; black= no response

Why not existing designs?

- Designs with **only toxicity** endpoint?
No clear dose-toxicity relationship, lack of DLT
- Existing designs using **toxicity+efficacy** endpoints?
Too complicated / Not applicable for CAR-T efficacy endpoint
- Designs using **PK/PD** information?
Living compounds with initial expansion

Observed CAR-T cells expansion



3 types of trajectories:

1. Increases initially but quickly decays to zero.
2. Increases initially and maintained high for some times.
3. Decreases straight to zero without increasing.

Pre-planned common measurement times to all patients with potential missing measurements.

Efficacy model

- Pre-planned measurement times t_1, \dots, t_K for all patients
- Dose levels d_1, \dots, d_J
- $d_{[i]}$: dose received by patient i
- $Z_{i,k}$: CAR-T expansion of patient i at the k th measurement time t_k
- Bi-exponential model:

$$Z_{i,k} = d_{[i]} \left\{ \underbrace{\exp(b_1 d_{[i]} t_k + \log 2)}_{\text{expansion}} - \underbrace{\exp(b_2 d_{[i]} t_k)}_{\text{decay}} \right\} + \varepsilon_{i,k},$$

where $b_2 \leq b_1 < 0$, $\varepsilon_i = (\varepsilon_{i,1}, \dots, \varepsilon_{i,K})^T \sim \mathcal{N}(0, \Sigma)$

Toxicity model

- CRM (O'Quigley, 1990)

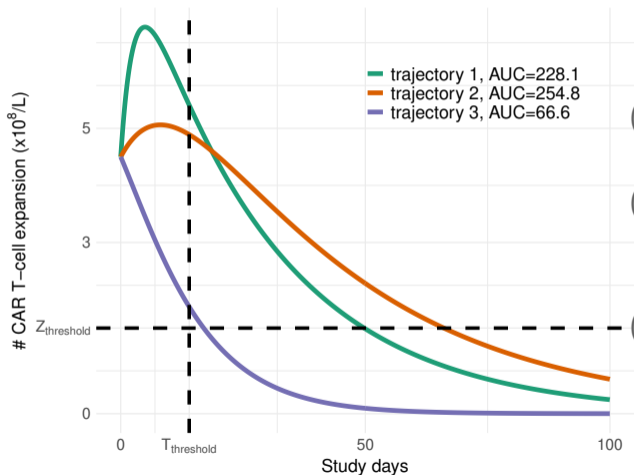
$$p_j = \alpha_j^{\exp(a)}$$

Assume monotonic dose-toxicity relationship

- Safe doses

$$\mathcal{A} := \{d_j; \mathbb{P}(p_j \geq \theta + 2\delta) < \mathbf{c}_{\text{overdose}}, j = 1 \dots, J\}$$

Escalation criteria



(C_1) Maximise the expansion at $t = T_{\text{threshold}}$.

(C_2) Maximise the duration with expansion above $Z_{\text{threshold}}$.

(C_3) Maximise the area under the curve (AUC).

Early phase design for CAR-T cells

1. Enrol the first cohort to d_1
2. Fit the toxicity model to find the set of safe doses \mathcal{A}
3. Fit efficacy model to safe doses $d \in \mathcal{A}$
4. Assign the next cohort to $d^* \in \mathcal{A}$ that maximises the 3 escalation criteria
5. Repeat steps 2-4 until all patients are enrolled.

Simulations

- Dose levels: 25, 75, 225, 450×10^6 cells per kg of bodyweight
- Target toxicity level 20%, acceptable if $\leq 30\%$
- 5 cohorts of 2 patients
- One measurement per week for 14 weeks upon infusion
- $T_{\text{threshold}} = 14$, $Z_{\text{threshold}} = 25 \times 10^6$ cells per kg
- Benchmark: an upper bound on the model performance under a given scenario
- Metric for accuracy: PCS ratio. **P**roportion of **C**orrect **S**election of the optimal dose under the proposed model to the benchmark

Scenarios

- Toxicity scenarios

T_1 : all safe;

T_2 : d_4 not safe

- Efficacy scenarios:

- E_1 : CAR-T cells expansion simulated from the bi-exponential model
- E_2 : correlation between repeated measurements
- E_3 : two **subpopulation** among patients
- E_4 : from **observed** data (Cwynarski, 2024)
- E_5 : **correlated** toxicity and efficacy endpoints

Scenarios

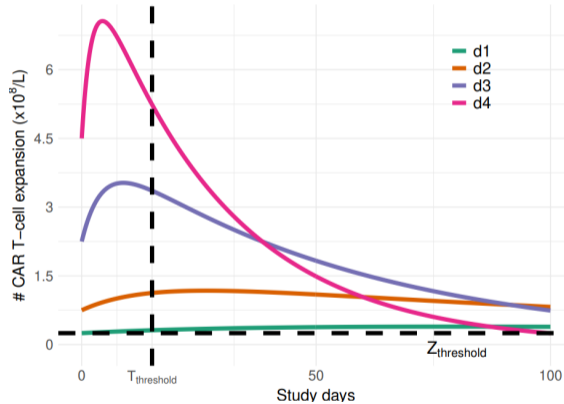


Figure: Scenario E_1, E_2, E_5 .

Scenarios

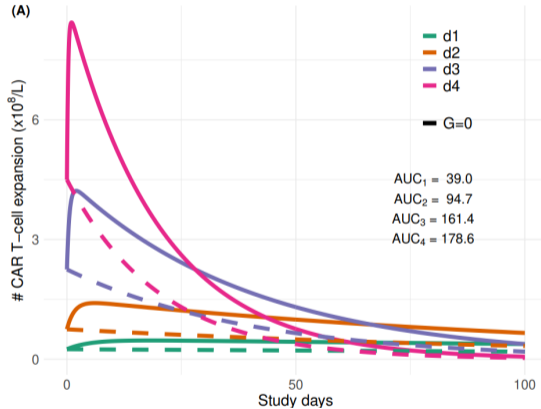


Figure: Scenario E_3 . Solid: subpopulation with expansion; Dashed: subpopulation without expansion.

Scenarios

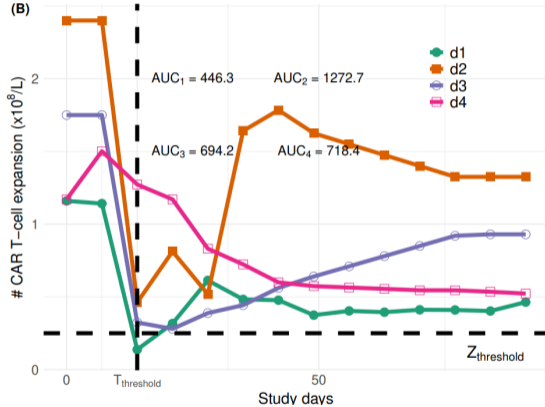
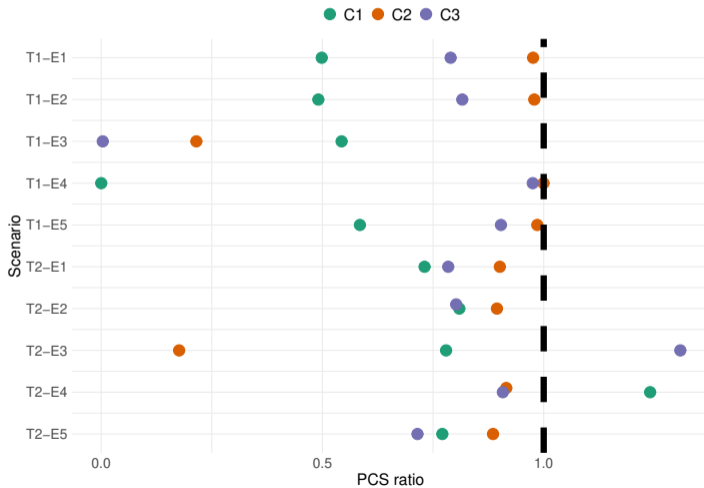


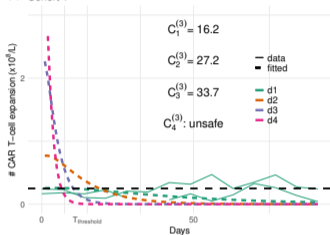
Figure: Scenario E_4 . Observed data from Cwynarski (2024).

Results

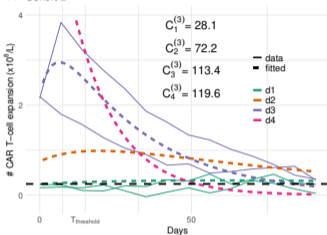


Scenario T1-E3 under (C_3)

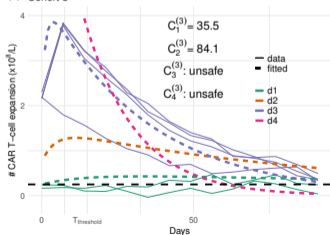
(A) Cohort 1



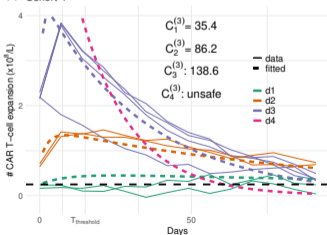
(B) Cohort 2



(C) Cohort 3

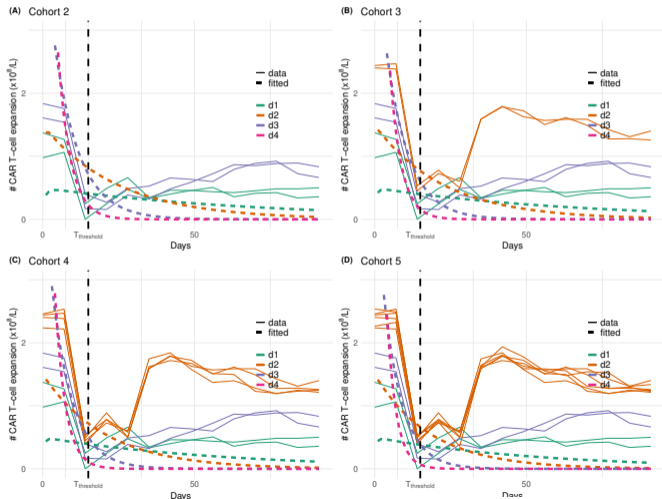


(D) Cohort 4



d_4 deemed unsafe \Rightarrow CRM does not work well when patients are not allocated to the MTD.

Scenario T1-E4 under (C_1)



Bi-exponential
model cannot
handle double
expansion.

Discussion

- Need early phase designs specifically for CAR-T cells
- Use CAR-T cell expansions in serial blood as indicators for activity.
- The bi-exponential model assumes a **single expansion**, might not be flexible enough
- The **thresholds** and **escalation criteria** need to be chosen carefully
- The **CRM** is not well-adapted when patients are not allocated to the best estimate of the MTD

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