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SUSTAINABLE PATIENT EXPERIENCES



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SYNTHETIC CONTROL ARM®: MEDIDATA'S HISTORICAL TRIAL DATA AND EXPERIENCE IN REGULATORY SETTINGS IS A TRUE DIFFERENTIATOR



4

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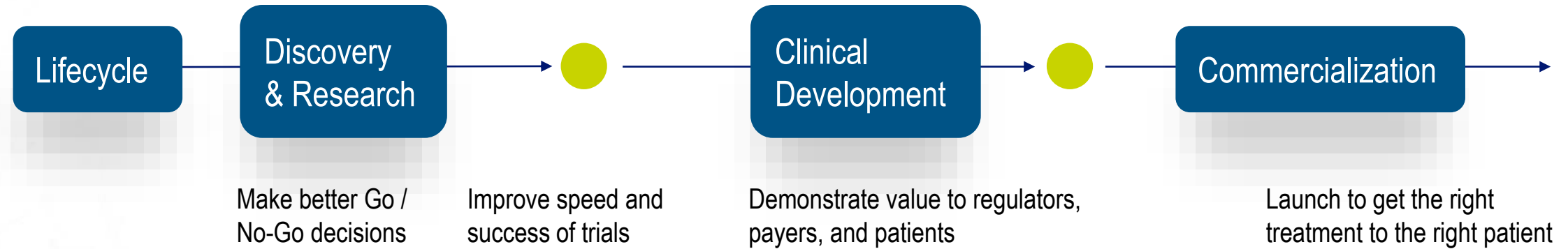
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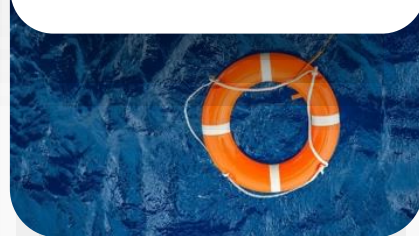
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EXAMPLE: CRS RISK STRATIFICATION MODEL FOR CAR-T

Predictors of severe CRS in longitudinal CAR T-cell clinical trial data

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BACKGROUND

- Cytokine release syndrome (CRS) is a life-threatening toxicity of chimeric antigen receptor (CAR) T-cell therapy and there is a limited understanding of its risk factors.
- Since 2016, no fewer than 15 trials have been put on hold or abandoned due to safety concerns arising out of CRS.
- Known markers of severe CRS lack specificity or require specialized lab facilities, making them impractical for safety surveillance during trials.
- Prior studies on risk factors of CRS following CAR-T treatment are based on small numbers of subjects and findings have not been validated externally.
- Even less is known about the temporal patterns in hematological and chemistry markers collected during CAR-T treatments and their potential use in safety surveillance.

GOALS

- Using the largest pooled dataset from autologous anti-CD19 CAR-T treatments from the Medidata Enterprise Data Store (MEDS) we analyzed laboratory tests with repeated measurements to identify differences in trends that persist across a variety of study designs, sponsors and indications.
- Our aim was to capture the dynamic response to lymphodepletion (LD) and CAR-T infusion events in the time course values of laboratory markers and compare these in the severe CRS (grade 3 and higher) and non-severe CRS groups.

RESULTS

The dataset consisted of anonymized data from 542 patients of which 24.1% are B-ALL and the remainder NHL, comprising DLBCL, High grade BCL, PMBCL, and TFL; average age 54.026 (SE=0.021) years, 67.7% males, 27.3% had CRS 3+ with a median time-to-event of 4.544 days (graded per CTCAE v4.03).

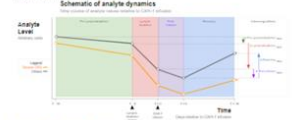


Figure 1. Spline-fitting
The spline segments are constrained to be linear during pre LD (-15d to LD), the LD -infusion, the post-infusion (1d to 5d) and the recovery (5d to 15d) intervals. Knot points placed at -15, -5, 0 and 15 days permit improved fitting to the changes in trends before and after LD -infusion and hematopoietic recovery. The orange spline represents subjects who got severe CRS (grade 3+) whereas the black spline represents subjects who did not (the CRS or CRS grade 1-2).

References

1. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
2. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
3. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
4. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
5. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
6. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
7. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
8. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
9. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.
10. Chimeric Antigen Receptor T-Cell Therapy in Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;381(10):1052-1060.

Table 1. Patient Summary

Age (years)	Overall	B-ALL	NHL
N	542	n = 131	n = 411
Range	18-85	19-84	19-85
Median	50	41	51
Sex (%)			
Female	32.98	41.22	29.93
Race (%)			
White	82.29	82.44	82.24
Black	3.14	0.75	3.89
Asian	2.88	0.34	2.19
Other	10.15	11.45	9.73
Unknown	1.5	0	1.8
Baseline performance (Eastern Cooperative Oncology Group) (%)			
0	41.74	23.85	47.65
1	54.73	72.99	48.21
2	1.4	4.05	2.94
3	0.19	0.78	0
Prior stem cell transplant (%)			
Yes	32.47	38.17	30.85
Prior radiotherapy (%)			
Yes	28.14	25.53	28.28
Time from diagnosis to CAR-T therapy in months (median)			
Overall	19.3	19.55	19.2

Acknowledgements We are thankful to Dr Elizabeth Lambert for her insightful comments on our work.

RESULTS, CONT.

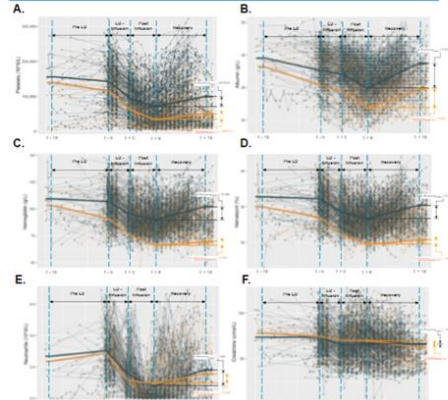


Figure 2. Example lab marker measurements across the trial
Analytic values during pre LD (-15d to LD), the LD -infusion, post-infusion (1d to 5d) and recovery (5d to 15d) intervals. Each line represents values for a given subject over time. Bold lines represent the fitted mean values for the severe CRS (orange) and other (dark grey) subjects respectively. A. Platelets, B. Albumin, C. Hemoglobin, D. Hematocrit, E. Neutrophils, F. Creatinine.

Table 2. Lab parameter measurements across the trial
Average rates of change (units per day) for the severe CRS subjects in the pre LD, LD-infusion, post-infusion, and recovery intervals relative to the other subjects.

Interval	Pre lymphodepletion (-15 to 0)	LYMPHO-depletion (0 to 15)	Post-infusion (1 to 5)	Recovery (5 to 15)
Platelets	0.00	-0.01	-0.02	-0.02
Albumin	0.00	-0.01	-0.02	-0.02
Hemoglobin	0.00	-0.01	-0.02	-0.02
Hematocrit	0.00	-0.01	-0.02	-0.02
E. Neutrophils	0.00	-0.01	-0.02	-0.02
Creatinine	0.00	-0.01	-0.02	-0.02

DISCUSSION

- Delayed hematopoietic recovery correlates with severe CRS. A lower rate of rise in platelets and total leukocytes post-infusion in the severe CRS subjects (relative to all other subjects) suggests delayed hematopoietic recovery, also reported earlier[4].
- Progressive hypoalbuminemia correlates with severe CRS. The changes in serum Albumin, Hemoglobin and Hematocrit concentrations during the LD-1d and >1d interval in the severe CRS patients versus others have been described earlier[3]. Our approach recapitulates these trends both in sign and magnitude, in a larger yet similar study population. In particular a stable renal function as indicated by the Creatinine trajectory in the study population lends credence to the hypothesis that severe CRS in the study population may be driven by endothelial dysfunction and merits further investigation.
- Neutropenia does not correlate specifically with severe population become neutropenic after LD. However, the nadir neutrophil levels accompanied by a fall in albumin levels, a that follow neutropenia such as infections.

CONCLUSIONS & FUTURE DI

- Lab markers collected in phase 1/2 trials of anti CD19 CAR hematopoietic recovery as characteristic clinical feature of be indicative of a pathophysiology driven by endothelial dysfunction.
- Impact: A potential use case related to anti CD19 CAR.
- Impact: State-space modeling based on the joint Neutrophils and CRS onset.
- The association between CRS severity and delayed hematopoietic recovery simultaneously result in earlier recovery.
- Impact: Early detection of distinguishing trends in data.

METHODS

- The pooled CT data was sourced from Medidata Enterprise with 6.3 million patients from approximately 1,400 customer companies. 6,013 patients in the CAR-T cell or other T-cell (over 20 trials) were exposed to the CAR-T cell or other T-cell.
- This database included phase I-III trials on several indications on patients with early and advanced stage as well as doses were captured in the data with extremely high fidelity.

- Subjects on anti-CD19 CAR T-cell therapy obtained from Medidata Enterprise were included: B-Cell Lymphoblastic Leukemia (B-ALL), Diffuse Large B-cell Lymphoma (DLBCL).
- Inclusion criterion across studies included ECOG 0-2, solid disease as well as morphological evidence. Subjects below prior treatment with cell therapies, HIV were excluded in an effort to reduce confounding. Laboratory markers with repeated measurements were included.

Analysis

- Response to LD, CAR-T infusion and the onset of hematopoietic recovery were modeled as a piecewise linear spline at the boundaries of the pre LD (-15d to LD), LD -infusion, post-infusion, and recovery intervals relative to the other subjects.
- Model:
$$Y(t) = \sum_{k=1}^K \text{spline}_{k, \text{severe}}(t) + b(t) + c(t) + \epsilon(t)$$
 - $Y(t)$: Observed marker value at time t
 - $\sum_{k=1}^K \text{spline}_{k, \text{severe}}(t)$: an indicator variable whose value is 1 if subject experiences a severe CRS event following CAR-T treatment and 0 otherwise.
 - $b(t)$: Vector of spline coefficients (fixed)
 - $c(t)$: Vector of spline coefficients (random)
 - $\epsilon(t)$: Random noise with mean and variance σ^2
 - K was set to 1 in order to fit piecewise linear splines to the time course lab marker values.



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By Annalee Armstrong • Jun 6, 2022 07:10am

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