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POSTER ABSTRACTS

801.GENE THERAPIES

Significant Cytokine Release Syndrome Risk Model with T-Cell Engaging Therapies

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Background and Objectives:
Cytokine release syndrome (CRS) is an adverse event associated with T-cell engaging (TCE) therapies and multi-specific antibody therapies, like BiTEs or DARTs. We developed a risk model to predict the pre-infusion risk of significant CRS for patients treated with TCE therapies. A supplementary exploratory analysis evaluated the role of tumor burden and the use of bridging chemotherapy prior to the first dose of TCE infusion on the rate of sCRS.

Methods:
The TCE dataset was sourced from the Medidata Enterprise Data Store, an anonymized repository of data from completed clinical trials.
The outcome of interest was the first sCRS occurring within 10 days of TCE therapy. sCRS was defined as CRS grade ≥ 2 and non-sCRS was defined as CRS grade <2 using the CTCAE 4.0 scale. CTCAE 4.0 was used as these trials gathered data using this version of the scale.
Important risk factors of sCRS were identified from the literature and preliminary data analysis. All the features were measured at the time of, or prior to, the first TCE treatment. Patients were included in the analysis dataset if they had a data element fill rate of >70% in the key features. Features were pruned by assessing the multicollinearity across features to increase the stability of the models. Tumor burden was explored as a potential feature, but was not selected for the final model, as the range of tumor burden in most of the patients selected was narrow (see below). In order to compare different TCE therapies, first treatment doses were normalized by dividing patients' first dose by the mean of the first dose of TCE administered in each study.
Logistic regression and tree-based models were trained. Across 100 iterations with different train-test splits, the average Area Under the Receiver-Operator Characteristic Curve (AUROC) was calculated for each model-type.

Results:
A total of 715 patients were included in the analysis (115 sCRS; 600 non-sCRS); the majority of patients had acute lymphoblastic leukemia (81%) and 19% of patients had solid tumors or Non-Hodgkin's lymphoma. Patients who developed sCRS had a higher incidence of infections prior to first TCE infusion, at 38% vs. 28% ($p = 0.03$). They also received a higher dose of TCE therapy ($p < 0.001$).
The features selected for the model are listed in table 1. The best model to predict sCRS had a mean AUROC of 0.69 (95% CI 0.66-0.72) on the test set. When patients were ranked based on their predicted probability of getting sCRS and divided into quartiles based on predicted sCRS risk (very low, low, high, very high), the very high-risk quartile developed sCRS at 4x the rate (38% (0.347-0.413)) compared to the lowest quartile (5.7% (0.05-0.07); sample average was 16% (0.153-0.167) (figure 1). Compared to patients with very low sCRS risk, patients with very high sCRS risk had mainly ALL as a disease type (99% vs. 67%, $p < 0.001$), received a higher TCE dose (1.00 vs. 0.61, $p < 0.001$) and had a higher rate of infections prior to TCE treatment (49% vs. 12%, $p < 0.001$).
Given the lack of uniform presence of disease burden in the predictive model cohort, a separate cohort of 945 ALL patients was analyzed to evaluate the impact of tumor burden on sCRS. 98% of patients received pre-TCE bridging therapy, resulting in median decline in %blasts from a maximum of 87% (84% vs. 88% for sCRS v/s non-sCRS patients; $p = 0.157$) to 0% (1% vs.

0% for sCRS v/s non-sCRS patients; p = 0.005) prior to TCE infusion. In the setting of these small ranges in tumor burden, neither total burden or most recent value prior to dosing was found to be significantly correlated with sCRS.

Conclusion:

Using the sCRS risk model, it was possible to stratify patients by risk categories. This could allow better selection of patients to receive TCE therapy and tailored pre-treatment and monitoring of CRS, which could in turn allow better resource allocation. As tumor burden can be a critical determinant of sCRS risk in other clinical settings where CRS is a relevant risk, future research is needed to further evaluate the impact of tumor burden on sCRS across different indications.

Disclosures Lafeuille: *Medidata, a Dassault Systèmes company:* Current Employment. **Blumentals:** *Sanofi:* Current Employment. **Brulle Wohlhueter:** *Sanofi:* Current Employment. **Chen:** *Medidata, a Dassault Systèmes company:* Current Employment. **Sang:** *Medidata, a Dassault Systèmes company:* Current Employment. **Manning:** *Medidata, a Dassault Systèmes company:* Current Employment. **Saltzman:** *Medidata, a Dassault Systèmes company:* Current Employment. **Canvin:** *Sanofi:* Current Employment. **Richard:** *Sanofi:* Current Employment. **Kamperschroer:** *Sanofi:* Current Employment. **Abbadessa:** *Sanofi:* Current Employment, Current holder of *stock options* in a privately-held company. **Talwai:** *Medidata, a Dassault Systèmes company:* Current Employment. **Der-Nigoghossian:** *Medidata, a Dassault Systèmes company:* Current Employment. **Itzkovich:** *Medidata, a Dassault Systèmes company:* Current Employment. **Agarwal:** *Medidata, a Dassault Systèmes company:* Ended employment in the past 24 months. **Jain:** *Medidata, a Dassault Systemes company:* Current Employment. **Jain:** *Medidata, a Dassault Systèmes company:* Current Employment. **Aptekar:** *Medidata, a Dassault Systemes company:* Current Employment. **Grupp:** *Novartis:* Consultancy, Research Funding; *Allogene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Juno:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Cellectis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Adaptimmune:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *CBMG:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Jazz:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Kite:* Research Funding; *Servier:* Research Funding; *Cabaletta:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Vertex:* Consultancy, Research Funding.

Feature / Test	Very Low CRS risk quartile	Very High CRS risk quartile	p value
First Dose (normalized by study)	0.61 (0.50-0.87)	1.00 (1.00-1.00)	<0.001
Bilirubin mg/dL	0.35 (0.24-0.50)	0.51 (0.42-0.71)	<0.001
White Blood Cells 10^9/L	4.20 (2.42-6.39)	3.40 (1.84-6.88)	0.182
Hemoglobin g/dL	10.50 (9.59-12.0)	10.20 (8.70-11.6)	0.074
Serum Creatinine mg/dL	0.38 (0.27-0.73)	0.66 (0.52-0.81)	<0.001
Lactate Dehydrogenase U/L	446 (290-666)	197 (155-425)	<0.001
Alanine Aminotransferase U/L	39 (24-73)	25 (14-45)	<0.001
Time Since Diagnosis years	2.00 (1.42-2.92)	0.92 (0.42-2.25)	<0.001
Baseline ECOG Score			0.150
0	25%	46%	
1	80%	41%	
2	4%	13%	
Infections	12%	49%	<0.001
Disease Type (ALL)	67%	99%	<0.001
Categorical data presented as %, numerical data presented as median (IQR) Chi-square test for categorical variables, Kruskal-Wallis for continuous variables. Mann-Whitney test for ordinal variables.			

Table 1: Predictive Model Features between Very Low and Very High in the Model

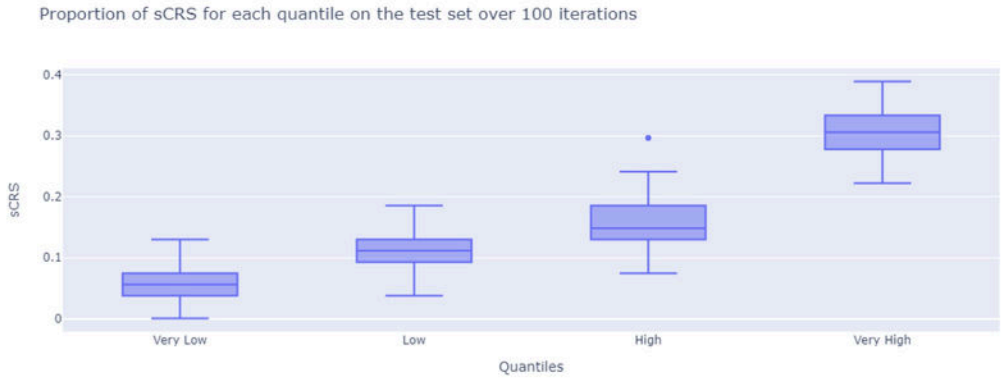

Figure 1: Proportion of sCRS for each risk quantile

Figure 1

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