

Sunburst Plots for Analysing the Impact of Drugs on Cytokine Release Syndrome (CRS) Management



Valentin Legras¹, Justin J. Wilkins², Mahmoud Hallal³, Nicolas Frey¹

¹ Roche Pharma Research and Early Development pRED, Pharmaceutical Sciences PS, Roche Innovation Center Basel, Switzerland

² Occams Coöperatie UA, Amstelveen, The Netherlands

³ Roche Product Development, Data Sciences and Statistics, Roche Innovation Center Basel, Switzerland

Context

Cytokine release syndrome (CRS) is a potentially life-threatening condition that can occur when a substantial and rapid release of cytokines into the circulation, a phenomenon often associated with various types of immunotherapy, including treatment with monoclonal antibodies (mAbs).

One such mAb is glofitamab, a CD20xCD3 T-cell engaging bispecific antibody with a novel 2:1 (CD20:CD3) format. Glofitamab has shown promising results, inducing frequent and durable complete response (CR) in a Phase I/II study (NP30179) with relapsed or refractory diffuse large B-cell lymphoma who had received at least two lines of therapy previously [1]. Like other T-cell engaging therapies, however, its administration can potentially trigger CRS by immune activation.

In this context, tocilizumab, an anti-IL-6 mAb employed to mitigate the risk of severe CRS [2], becomes a crucial part of the treatment protocol. This work aims to apply sunburst plots to describe the effect of tocilizumab on CRS induced by glofitamab over time. This visual representation aims to provide a clearer understanding of how tocilizumab administration, post CRS event, influences the syndrome's progression and aids in patient recovery.

Methods

Sunburst plots are circular, multi-level visualizations used to represent hierarchical data. They were especially chosen in this instance for their ability to exhibit changes within individuals over time.

The process of preparing sunburst plots required substantial data manipulation as the initial datasets (SDTM and ADaM) were not built with the parent-child mindset necessary for these visualizations. The data were initially available in flat CDISC format that needed to be transformed into a hierarchical structure.

In order to prepare the dataset, we rearranged the data using a combination of the data management library dplyr (v1.0.0) and base functions in R. This involved grouping, summarizing, and reordering the data to reflect the hierarchical structure required for the sunburst plots.

With the transformed data, we then proceeded to create sunburst plots in R with the package plotly (v4.10.2), an interface to the external graphing library of the same name (R itself currently lacks native tools for creating sunburst plots). These plots were specifically used to visualize the effect of tocilizumab on glofitamab-induced CRS over time.

Sunburst plot

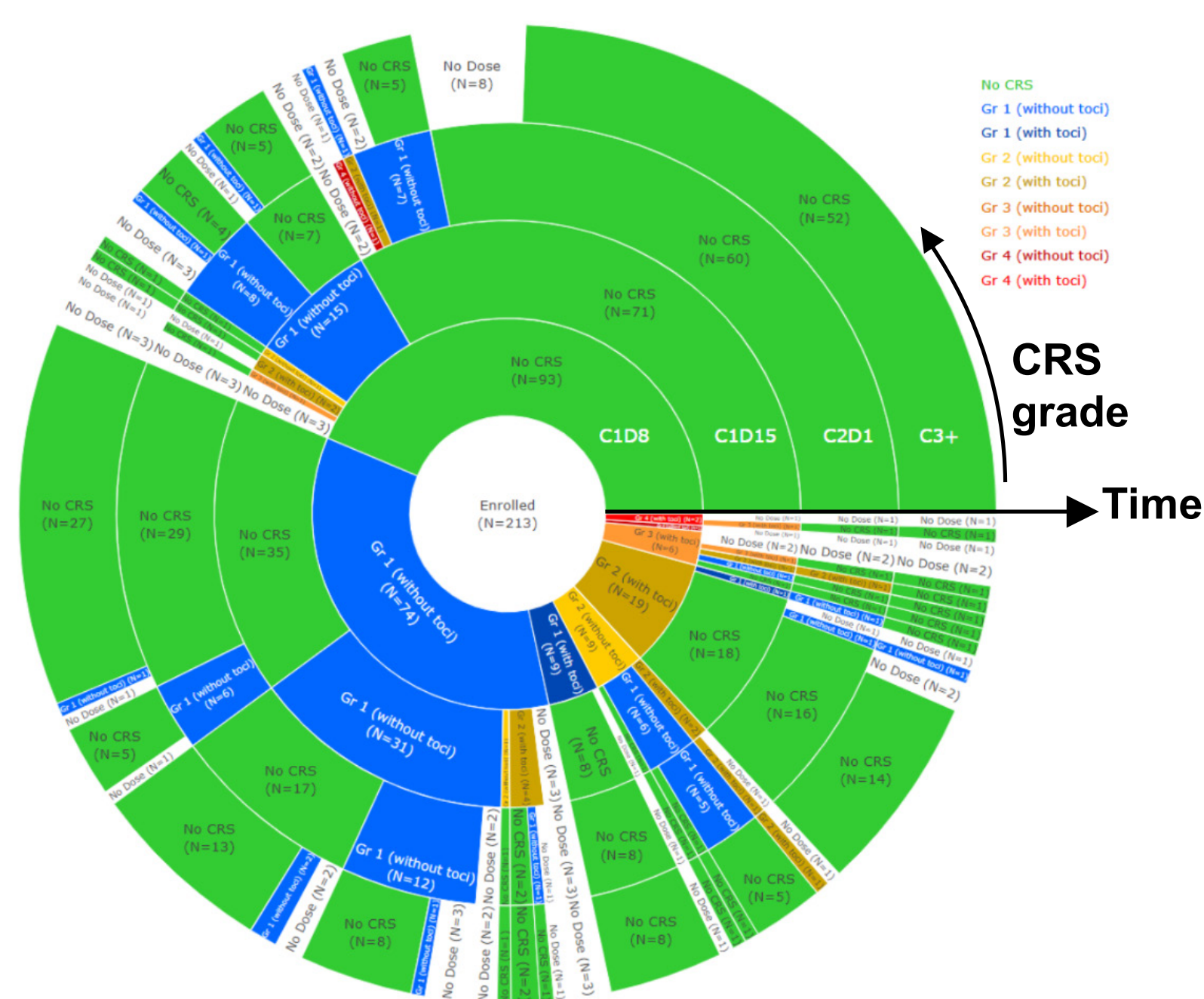
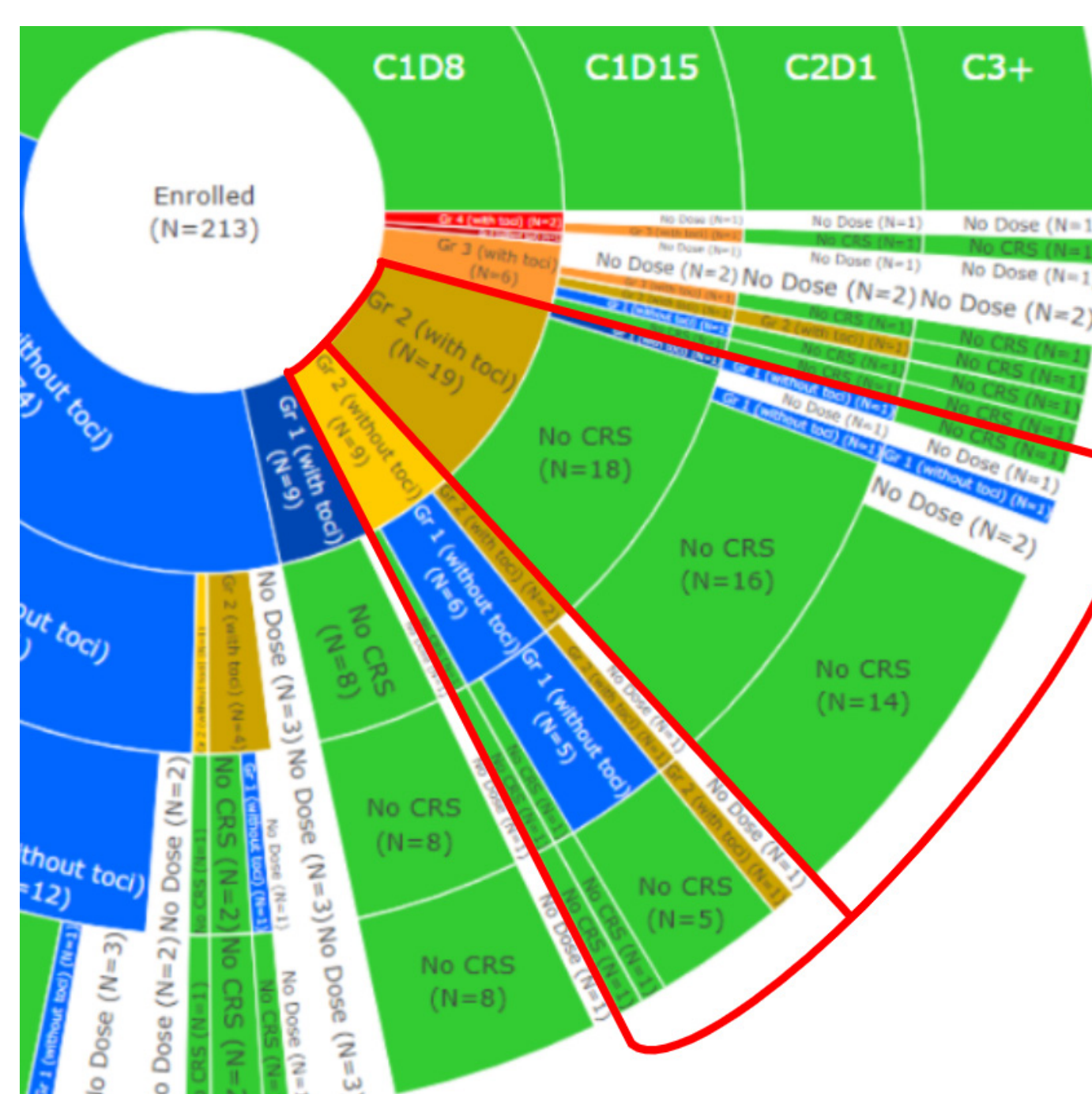


Fig. 1 Sunburst plot of CRS Severity w or w/o Tocilizumab over time

In Figure 1, each concentric circle represents consecutive dosing cycles of glofitamab, progressing outward from the center to the periphery. Within each circle, segments indicate the number of patients experiencing or not CRS events, and treated or not with tocilizumab, sorted by severity from no CRS (green) to grade 4 with tocilizumab (red) in a counterclockwise manner. Group of patients initially recorded in a segment within the first circle are tracked through subsequent circles, enabling the observation of how CRS evolve over time. Segments are colored white when no dose of glofitamab was given. [3]



Deriving Insights from Sunburst Plots



Zoom on Fig. 1

By focusing on the 28 patients who had CRS Grade 2 at Cycle 1, Day 8, it can be observed that 9 did not receive tocilizumab after their CRS diagnosis and 19 did. On Cycle 1, Day 15, 95% (18 out of 19) of the patients who received tocilizumab no longer exhibited CRS symptoms, while only 10% (1 out of 9) of the patients who did not receive tocilizumab had no further CRS symptoms. Overall, most of the patients who did not receive tocilizumab after their CRS diagnosis continued to experience CRS at subsequent glofitamab doses, albeit at a similar or lower grade.

The sunburst plot effectively illustrates the benefit of tocilizumab in managing CRS events induced by glofitamab, by demonstrating its effectiveness in minimizing CRS events compared to scenarios without tocilizumab administration.

ADaM dataset and other visualizations

The production of the sunburst plot required the preparation of a specific and complex structured dataset. To optimize the creation of these plots, an Analysis Data Model (ADaM) dataset (ADCRS) was developed internally. Although it is not yet a standard, it may become a Roche internal standard in the future.

The main advantage of the sunburst plot over other hierarchical plots like Sankey and alluvial plots is its ability to trace CRS event progression over time within patient subgroups. As hierarchical levels increase, however, sunburst plots become more difficult to interpret. In such cases, Sankey plots (as shown below in figure 2) offer a simpler alternative, integrating both time and CRS grade components. While both plotting approaches show a significant decrease in CRS events at C1D15 for patients who received tocilizumab at C1D8, the Sankey plot does not allow for long-term tracking of patient subgroups.

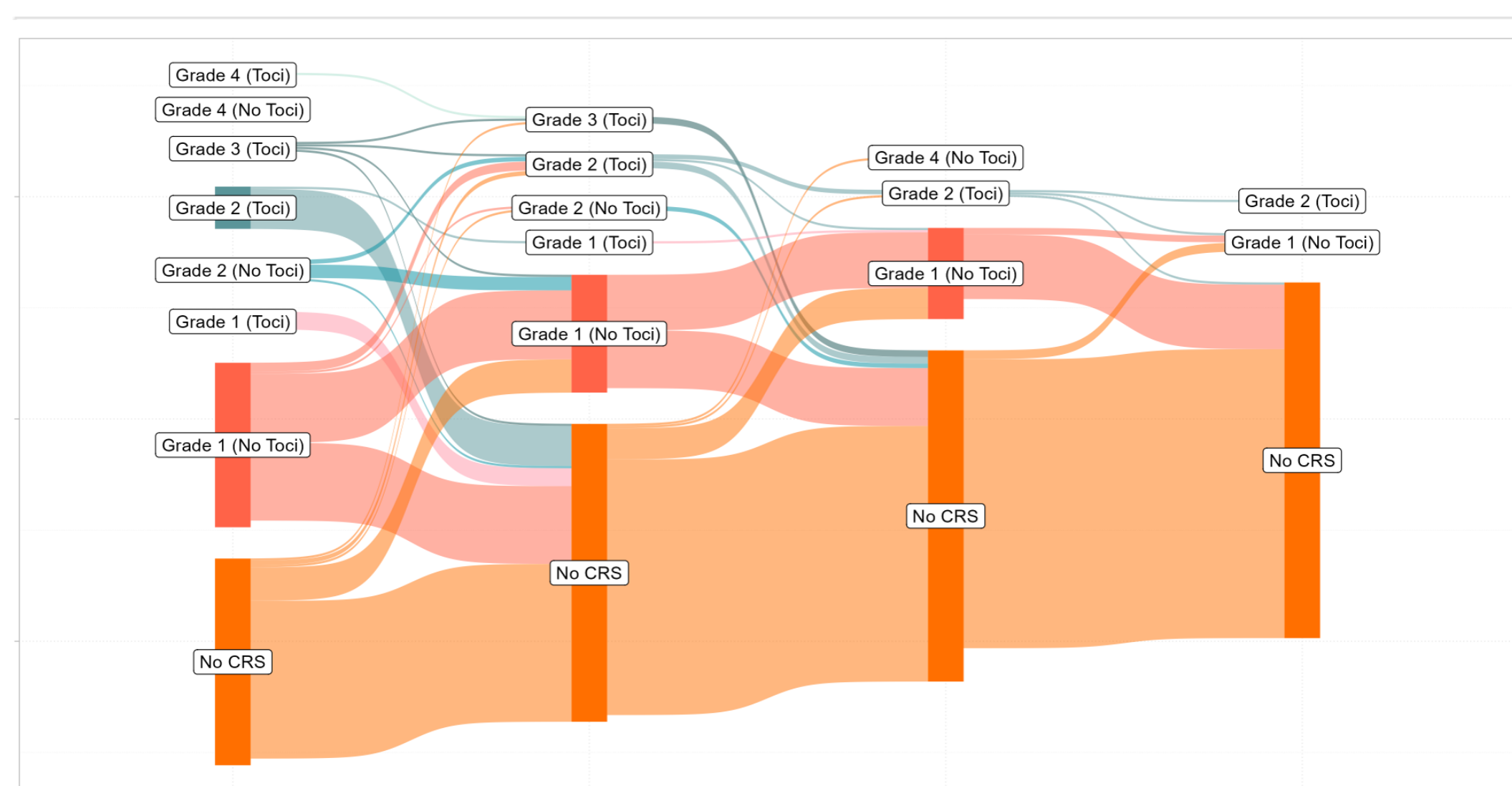


Fig. 2 Sankey plot of CRS Severity w/ or w/o Tocilizumab over time

Conclusions

This work demonstrates the effectiveness of sunburst plots as tools for presenting complex, dynamic longitudinal data visually in a clear and understandable manner. The intuitive display of the reduction in CRS adverse events associated with tocilizumab treatment in this example validates its potential use in supporting dosing strategies.

The labor-intensive process of creating the input dataset was a significant part of our methodology, thus highlighting the potential for establishing a new standard ADaM dataset.

As experience with sunburst plots grows, we anticipate they will find additional applications in other pharmacometric contexts, providing a convenient, accessible and visually attractive way of exploring data over time, identifying trends, and informing model development.

References

- [1] Hutchings et al., JCO 39, 1959-1970 (2021). DOI: 10.1200/JCO.20.03175
- [2] Kotch et al., Expert Rev Clin Immunol. 2019;15(8):813-822. DOI: 10.1080/1744666X.2019.1629904.
- [3] Stasko & Zhang, IEEE INFOVIS 2000, pp. 57-65. DOI: 10.1109/INFOVIS.2000.885091.