

## Key Safety Assessments Following Chimeric Antigen Receptor (CAR) T-Cell Therapy in Early Development Oncology

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### ABSTRACT

In 2017 the U.S. Food and Drug Administration (FDA) approved the first chimeric antigen receptor (CAR) T-cell therapy to treat cancer, and over the past five years there have been six approvals by the FDA.<sup>2</sup> CAR T-cell therapy harnesses a patient's white blood cells and genetically engineered T-cell receptors to target and attack cancerous cells. While the success of CAR T-cell therapy is favorable, the two most common toxicities associated with this treatment, Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), are often severe and periodically life-threatening. The purpose of this paper is to explore key safety assessments associated with CAR T-cell therapy, which are vital to accurately monitor the drug's safety for patients. You will find the analysis of these two Adverse Events of Special Interest (AESI(s)), CRS and ICANS, evaluated within an overall summary of events table and time-to-event analysis utilizing a high-low bar graph.

### INTRODUCTION

Early development clinical trials focus on the safety and tolerability of a new drug, treatment, or procedure. First-in-human (FIH) trials are the essential stepping stones to allow emerging treatments to come to market for patients. It is critical to understand how to clearly represent the trial findings in order to make data-driven decisions. Primarily, FIH trials are conducted to determine a safe dose range for later-phase development. To determine a safe dose and dose escalation scheme, the safety of a patient is often monitored by identifying Adverse Events of Special Interest (AESI). AESI(s) are events or symptoms thought to potentially be associated with the investigational agent or disease under study requiring ongoing monitoring. AESI(s) can be monitored by analyzing the frequency, duration, severity, and time to onset.

CAR T-cell therapy is considered the "living drug" of science as it allows for a targeted, personalized therapy approach to treat certain blood cancers. Presently, marketed CAR T-cell therapies treat patients that fall under the indication of hematology (leukemia, lymphoma, and multiple myeloma).<sup>2</sup> The major concerns to the tolerability and success of CAR T-cell therapy are CRS and ICANS. Within this paper, we will focus on those key safety assessments for CAR T-cell therapy used to observe the pharmacovigilance of a treatment.

### KEY SAFETY ASSESSMENTS

CAR T-cell therapies are relatively new as the first FDA-approved drug was made available for patients in 2017.<sup>2</sup> Through further investigation of these therapies, more data is available and leveraged to better understand what key safety assessments require monitoring. The side effects of CAR T-cell therapy will often vary from person to person. Frequently, ICANS is associated with the occurrence of CRS, however, it could occur without correlation.<sup>4</sup>

Cytokine release syndrome (CRS) is an inflammatory process related to exponential T-cell proliferation and activation. CRS is a clinical diagnosis that is correlated with higher levels of pro-inflammatory cytokines. Symptoms may range from mild flu-like symptoms (such as fever, rigors, fatigue, and headache) to hypotension, hypoxia (which will be used for CRS grading), and even as severe as multi-organ failure.<sup>4</sup>

ICANS is a clinical and neuropsychiatric syndrome that can occur in the days to weeks following the administration of certain types of immunotherapies.<sup>4</sup> CAR T-cell therapies are known to cause specific types of neurotoxicity, which over the years led to the term “Immune effector cell-associated neurotoxicity syndrome” (ICANS). ICANS may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and rarely, cerebral edema. Frequently, ICANS occurs two to four days after onset of CRS, although ICANS is not required to occur in the context of CRS. Symptoms typically begin with a lack of concentration and language deficits. Deterioration can rapidly progress over the course of hours to days.

## **ANALYSIS TECHNIQUE**

### **ADVERSE EVENT EPISODES**

Analyzing CRS and ICANS can be accomplished by reviewing the following specific safety summaries: Duration of AESI, Time to Onset of AESI, and Summary of Events. To support the AESI summary tables a corresponding analysis dataset, ADAE should be created in accordance with ADaM CDISC standards.<sup>1</sup> In addition, it is recommended the derivation of Time to Onset of AESI and Overall Duration of related AESI(s) should be contained within an interim ADaM dataset called ADAESUM following the Basic Data Structure (BDS).<sup>1</sup>

Prior to creating the ADAE and ADAESUM parameters, a strategic approach should be implemented in anticipation of unclean data in order to provide an accurate duration of the event. For example, patients may experience multiple cases of a specific AESI, immediately following infusion. There may be instances when the data has not been reconciled, and AESI events may overlap or occur adjacent to each other (e.g., if the start date of one event is within one day of the end date of an earlier event). To handle this situation, we are introducing episodes of adverse events to represent multiple occurrences of an overlapping adverse event.

First, identify the start and end date for prior AESI events using the SAS® LAG function. Then, store the prior dates in temporary variables to be referenced later. Note, the first event identified will generate no prior dates. Next, compare the start date with the prior end date to see if these dates can be combined into one episode. If the prior end date is before or within one day of the start date, then assign a new episode ID.

**Output 1 shows an example of how to demonstrate this technique:**

```
astdt_ = lag(astdt);
aendt_ = lag(aendt);

if first.AEDECOD then do;
  astdt_ = .;
  aendt_ = .;
  aepisode = 1;
end;

else do;
  if . < aendt_ <= astdt <= aendt_ + 1 then do;
    astdt1 = astdt_;
    aendt1 = aendt;
    epifl = 'Y';
  end;

  else if . <= astdt_ <= astdt and . <= aendt <= aendt_ then do;
    astdt1 = astdt_;
    aendt1 = aendt_;
    epifl = 'Y';
  end;

  else do;
    aepisode + 1;
  end;
end;
```

Once completed, sort the data by subject, AESI, episode, start date, and end date. Select the first record per episode for the start date and the last record per episode for the end date based on the episode ID. To consider a missing end date for an ongoing AESI, select the end date from the last record by sorting the start and end date to get the most recent AE, instead of the latest end date available within the same episode. Merge the two dates as the episode's start date and the episode's end date to create a new record as a single episode.

### **DURATION OF AESI/OVERALL DURATION OF AESI PER SUBJECT**

Following the episode identification, the duration of AESI is derived for each episode. If both the episode start date and end date are not missing, then the duration of AESI is (episode end date – episode start date) + 1. Otherwise, if the end date of the episode is missing, then the duration will also be missing. The Overall Duration of an AESI per subject is the cumulative duration of the individual episodes per AESI.

To calculate the Overall Duration of CRS per subject, sum the duration of CRS episodes for each unique subject. Note, parameters for each AESI are created following the criteria above.

**Output 2 shows an example of how to demonstrate this technique:**

```
proc sql;
  create table odurcrs1 as
  select *,sum(aval1) as aval
  from aesum(rename=(aval=aval1) drop=AVALCAT1)
  where AVAL1>. and AEDECOD= "Cytokine release syndrome"
  group by USUBJID
  order by USUBJID;
quit;
```

**Output 3 shows an example of the ADAESUM parameter and analysis value for Overall Duration of CRS per subject:**

USUBJID	PARAM	PARAMCD	PARAMN	AVAL	AVALC
STUDY-001-002	Overall Duration of CRS Events(Days)	ODURCRS	5	6	6
STUDY-001-004	Overall Duration of CRS Events(Days)	ODURCRS	5	4	4
STUDY-001-005	Overall Duration of CRS Events(Days)	ODURCRS	5	3	3
STUDY-001-006	Overall Duration of CRS Events(Days)	ODURCRS	5	4	4
STUDY-001-007	Overall Duration of CRS Events(Days)	ODURCRS	5	1	1
STUDY-001-008	Overall Duration of CRS Events(Days)	ODURCRS	5	2	2
STUDY-001-009	Overall Duration of CRS Events(Days)	ODURCRS	5	4	4
STUDY-001-010	Overall Duration of CRS Events(Days)	ODURCRS	5	1	1

**NUMBER OF PATIENTS WITH CRS, ICANS, and CRS/ICANS**

Ongoing review is key to ensuring a patient’s safety while on treatment, hence creating summary tables to compile evidence-based information is essential. As mentioned previously, FIH trials focus on drug tolerability and governing AESI(s) safeguard patients from experiencing critical or life-threatening outcomes. The following table analyzes the number of patients experiencing CRS and ICANS independently.

**Table 1 shows an example of a Summary of Key Safety Assessments: CRS:**

*Table 1: Summary of CRS*

	<i>Treatment N=91 Total</i>
Number of Subjects with at Least One CRS Event n(%)	22 (24.2)
<b>Maximum Toxicity Grade</b>	
Grade 1	14 (15.4)
Grade 2	6 (6.6)
Grade 3	1 (1.1)
Grade 4	1 (1.1)
<b>Time to First Onset of CRS (days)</b>	
n	22
Mean	4.1
SD	1.80
Median	4.0
Q1, Q3	3.0, 6.0
Min, Max	1, 8
<b>Number of Episodes by Length of Duration n(%)</b>	
Length 1-5 Days	21 ( 87.5)
Length 6-10 Days	3 ( 12.5)
Length >10 Days	0
<b>Duration of CRS (per Episode) Descriptive Statistics (days)</b>	
n	24
Mean	3.2
SD	1.66
Median	3.0
Q1, Q3	2.0, 4.5
Min, Max	1, 6
<b>Overall Duration of CRS Events Descriptive Statistics (days)</b>	
n	20
Mean	3.8
SD	1.79
Median	4.0
Q1, Q3	2.5, 5.0
Min, Max	1, 8

**Table 2 shows an example of a Summary of Key Safety Assessments: ICANS:**

*Table 2: Summary of ICANS*

	<i>Treatment N=91 Total</i>
Number of Subjects with at Least One ICANS Event n(%)	6 (6.6)
<b>Maximum Toxicity Grade</b>	
Grade 1	5 (5.5)
Grade 2	0
Grade 3	0
Grade 4	1 (1.1)
<b>Time to First Onset of ICANS (days)</b>	
n	6
Mean	6.7
SD	1.86
Median	6.5
Q1, Q3	5.0, 8.0
Min, Max	5, 9
<b>Number of Episodes by Length of Duration n(%)</b>	
Length 1-5 Days	6 ( 85.7)
Length 6-10 Days	0
Length >10 Days	1 ( 14.3)
<b>Duration of ICANS (per Episode) Descriptive Statistics (days)</b>	
n	7
Mean	3.9
SD	3.39
Median	3.0
Q1, Q3	2.0, 5.0
Min, Max	1, 11
<b>Overall Duration of ICANS Events Descriptive Statistics (days)</b>	
n	6
Mean	4.5
SD	3.83
Median	3.0
Q1, Q3	2.0, 5.0
Min, Max	2, 12

**TIME TO ONSET OF AESI**

The Time to Onset of AESI is defined as the time from the first dose of the study drug until the first occurrence of the AESI. Note, this parameter is derived for each AESI per subject. The first occurrence date for each AESI can be derived by sorting the AE data then selecting the earliest start date per subject for the event. Following this procedure, we use the treatment start date for each subject and calculate the time between these two dates. If both the episode’s start date and treatment’s start date are not missing, then the Time to Onset of AESI is (episode start date – treatment start date) + 1.

Output 4 shows an example of the ADAESUM parameter and analysis value for Time to Onset of CRS in ADAESUM data:

USUBJID	PARAM	PARAMCD	PARAMN	AVAL	AVALC
STUDY-001-001	Time to Onset of CRS Events(Days)	ONSETCRS	3	1	1
STUDY-001-002	Time to Onset of CRS Events(Days)	ONSETCRS	3	6	6
STUDY-001-004	Time to Onset of CRS Events(Days)	ONSETCRS	3	3	3
STUDY-001-005	Time to Onset of CRS Events(Days)	ONSETCRS	3	4	4
STUDY-001-006	Time to Onset of CRS Events(Days)	ONSETCRS	3	3	3
STUDY-001-007	Time to Onset of CRS Events(Days)	ONSETCRS	3	6	6
STUDY-001-008	Time to Onset of CRS Events(Days)	ONSETCRS	3	8	8
STUDY-001-009	Time to Onset of CRS Events(Days)	ONSETCRS	3	4	4

The aim of time-to-onset analysis is to investigate a trend used for early intervention to potentially lower toxicity grades.<sup>4</sup> The high-low bar graph provides comprehensive yet straightforward information for each subject, including the duration of episodes, the grade of each episode, and whether the event is ongoing.

If Analysis End Date (AENDT) is missing for an ongoing adverse event, set AENDT to the Last Known Alive Date (LSTALVDT). Create a new variable to visualize the patients with an ongoing event referenced as ACAP in the code below and assign the value to "FilledArrow" to depict the patient's LSTALVDT. This value will be used in the HIGHLOW option statement and allows you to draw a filled arrow at the end of the bar for ongoing AE. Then, create a macro variable called "maxday" to find the longest duration across all AE(s). This date determines the maximum value on the X-axis. In the code below, the SGLOT option: dattrmap=myattrmap defines the filled colors and line colors in the high-low graph. Note a high-low graph of AESI episodes over time can be created by repeating the code below by replacing the macro variable from "par=CRS" with "par=ICANS".

**Output 5 shows an example of how to present the high-low bar graph below:**

```
data myattrmap;
  retain ID "ID";
  input VALUE $1.  fillcolor  : $6.  linecolor  : $6.;
  cards;
    1   green   green
    2   blue   blue
    3   purple  purple
    4   brown  brown;
run;

%macro fcrsnt(par=, );
  data ae;
    set adam.adaesum;
    if paramcd = "&par";
      astdy = astdt - trtsdt + 1;
      aendy = aendt - trtsdt + 1;

      if AEONGO eq "ONGOING" then do;
        acap= "FilledArrow";
        aendt = LSTALVDT;
        aendy = aendt-trtsdt+1;
      end;

    grp=input(aetoxgr,3.);
  run;

  proc sql noprint;
    select max(aendy) into : maxdy from ae;
  quit;

  title1 height=10pt j=center  "&par Episodes Over Time";
  ods listing close;
  ods graphics on / reset=all width=7in height=6in;
  ods pdf file = "c:/PharmaSUG/f_&par..pdf" dpi=300 nogtitle;

  proc sgplot data=ae dattrmap=myattrmap;
    highlow y = usubjid low=astdy high=aendy/type=bar
    attrid=ID group=aetoxgr highcap=acap barwidth=0.8;
    yaxis label = "Subject ID" valueattrs=(size = 5);
    xaxis label = "Study Day" grid values=(0 to %eval(&maxdy+2));
    keylegend;
  run;

  ods graphics off;
  ods pdf close;
%mend;

%fcrsnt(par = CRS);
```



Figure 1 shows an example of a High-Low Graph of Time to Onset of CRS Events:

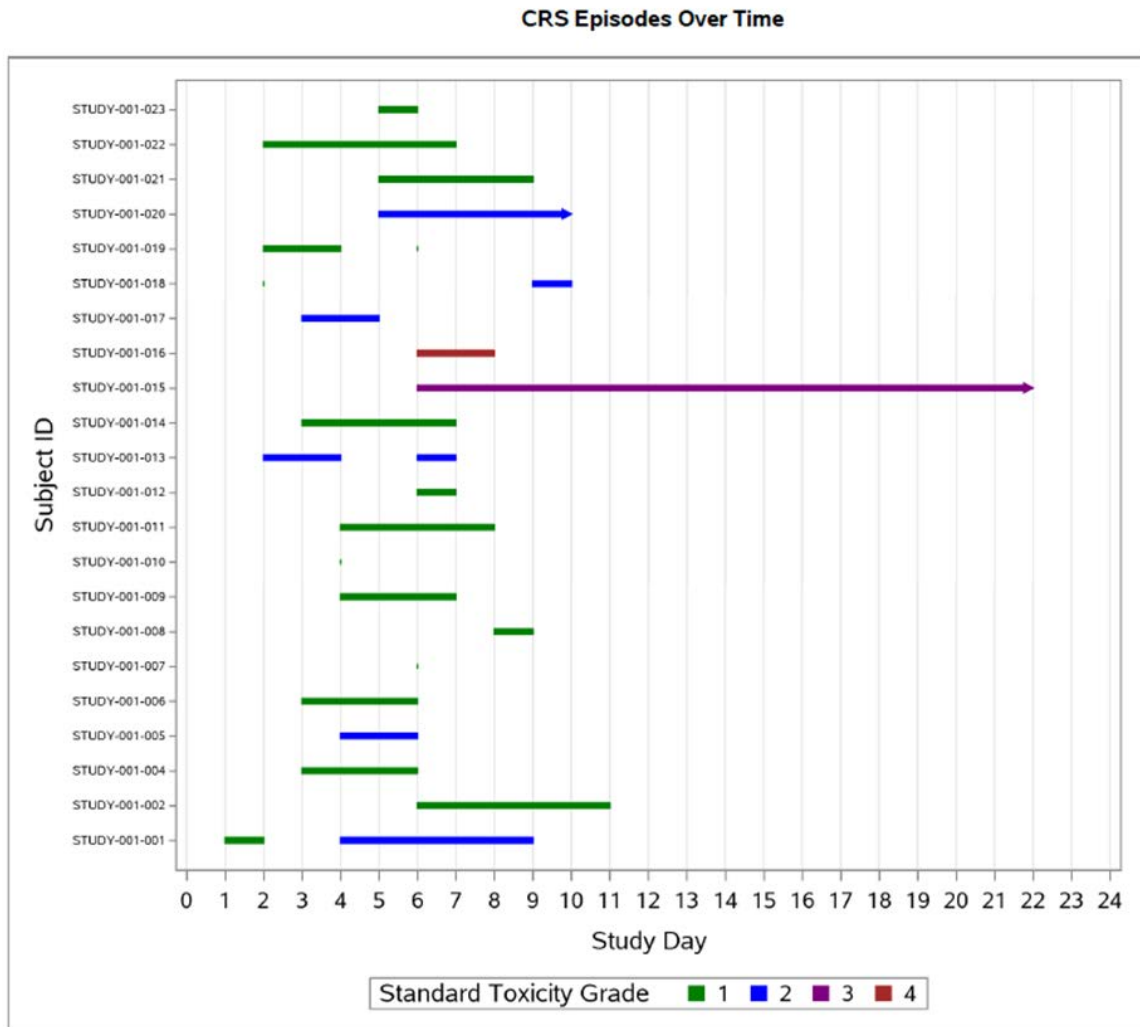
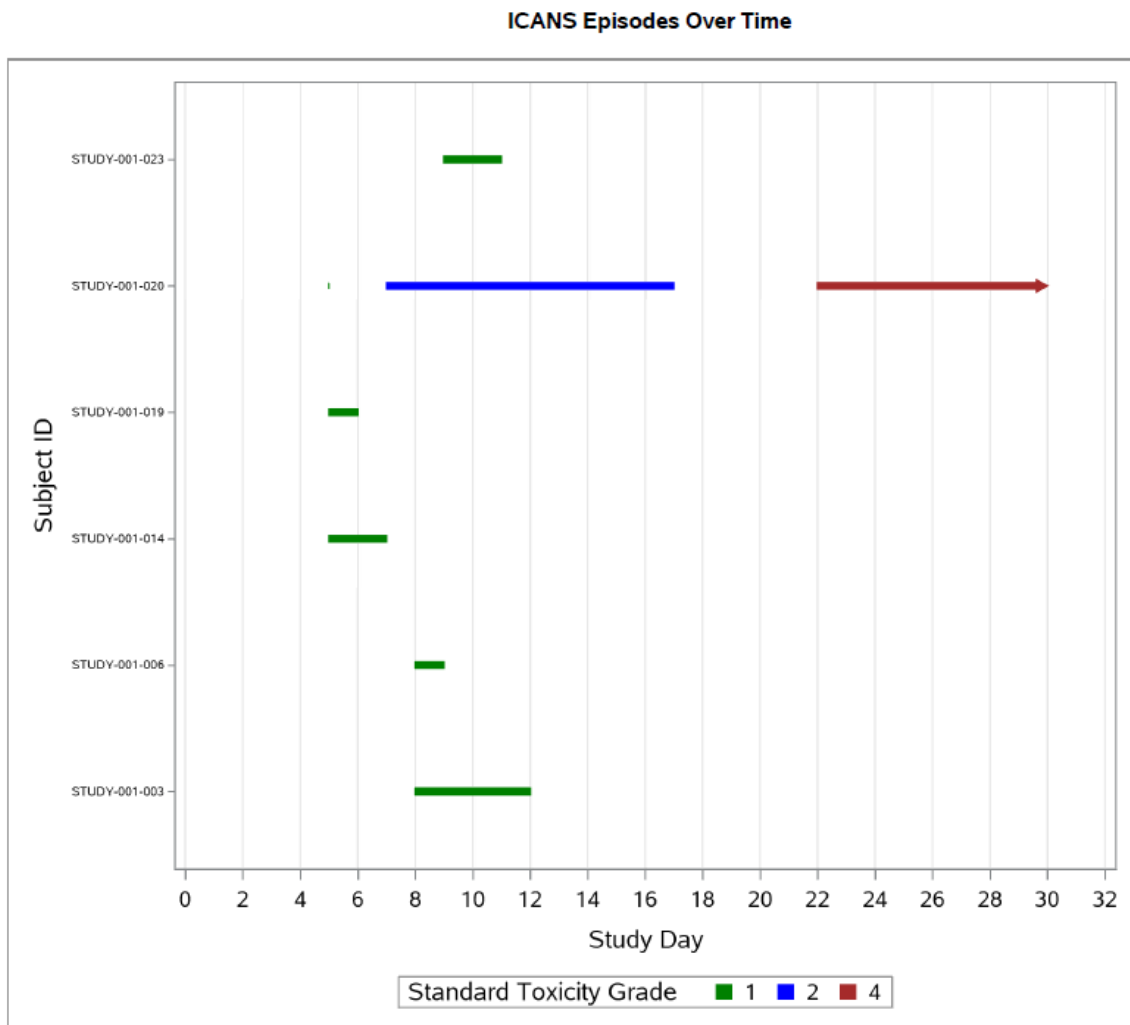


Figure 2 shows an example of a High-Low Graph of Time to Onset of ICANS Events:



**Output 6 shows an example of how to present the high-low bar graph below** (Note: Groupdisplay=cluster option will cluster CRS and ICANs bars together for each patient):

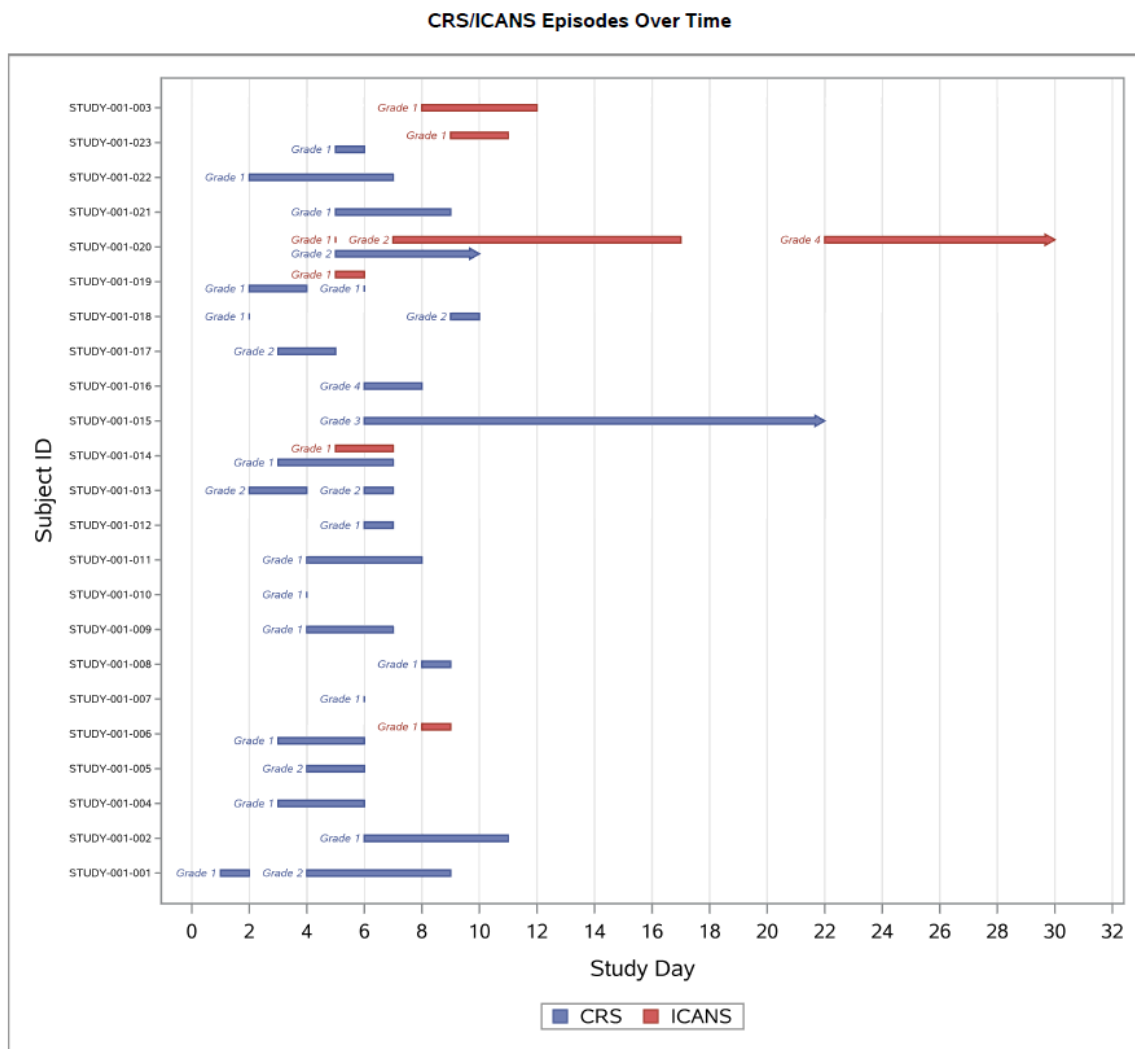
```
data ae;
  set adaesum;
  where paramcd in ("CRS" "ICANS");

  astdy = astdt - trtsdt + 1;
  aendy = aendt - trtsdt + 1;
  aetoxgr_ = "Grade "||strip(aetoxgr);

  if AEONGO eq "ONGOING" then do;
    acap= "FilledArrow";
    aendt = LSTALVDT;
    aendy = aendt-trtsdt+1;
  end;
run;

proc sgplot data=ae;
  highlow y = usubjid low=astdy high=aendy/type=bar attrid=ID group=paramcd
  lowlabel=aetoxgr_ highcap=acap
  barwidth=0.8 clusterwidth=0.8 groupdisplay=cluster
  labelattrs=(Size=5 Style=Italic);
  yaxis label="Subject ID" valueattrs=(size = 5);
  xaxis label="Study Day" grid values=(0 to %eval(&maxdy+2));
  keylegend /title="";
run;
```

Figure 3 shows an example of a High-Low Graph of Time to Onset of CRS and ICANS Events:



## CONCLUSION

The industry is beginning to understand how to potentially optimize the clinical benefits of CAR T-cell therapy. Through this growth, more information emerges allowing the clinical team to identify abnormal lab results sooner which prompts courses of action in preventing severe toxicities.<sup>3</sup> The value of historical data provides the capability to make data-driven decisions leveraging trend analysis.

Additionally, CAR T-cell therapy offers benefits to patients including shorter treatment times due to single infusions, prolonged durability, and fewer side effects; though not without risks.<sup>4</sup> The benefits of CAR T-cell therapy are meaningful, as the therapy can lead to long-lasting remission for patients with advanced cancers. Through active monitoring of key safety assessments, these risks can be minimized, and the success of CAR T-cell therapy can continue to rapidly advance toward revolutionizing the Cell Therapy Therapeutic Area.

## REFERENCES

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