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Handling CRS/NT Data in CAR-T Studies and Submission

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ABSTRACT

In most CAR-T (Chimeric antigen receptor T) studies, Cytokine Release Syndrome (CRS) and Neurotoxicity (NT) are the most common types of toxicity caused by CAR-T cells. Thus, the data of CRS and NT becomes essential, and during regulatory submissions, agencies have required special or extra data and analysis beyond regular AE data reporting.

This paper shares our experience from past two CAR-T compounds submissions, on CRS/NT data handling, specifically from the following two topics:

1. How we organized CRS/NT data in SDTM/ADaM package to support Clinical Study Report (CSR).

2. How we supported Health Authority (HA) review by providing supplemental CRS and NT data which were requested by FDA review team.

INTRODUCTION

CAR-T cell therapy has been a popular therapy in recent years, and many pharmaceutical / biotech companies are developing their pipelines using this new technology. In most CAR-T studies, CRS and NT are the most common types of toxicity caused by CAR-T cells. As a result, the management of CRS and NT data becomes important. During regulatory submissions, agencies have required special or extra data and analysis beyond regular AE data reporting. In order to facilitate the analysis, we have applied special data handling for CRS and NT information, and also produced supplemental CRS/NT datasets per FDA requests.

As a team from Juno/Celgene/BMS, we have worked on the filing of both Breyanzi and Abecma consecutively and accumulated some experience on how to handle the data for CRS/NT. In this paper, we hope to share our experience on the following aspects, about how CRS/NT data were organized in submission package:

CRS/NT DATA IN SDTM/ADAM TO SUPPORT CSR

In this chapter, we hope to share our experience from multiple studies on how CRS/NT related data were collected from CRF and organized in following level (SDTM and ADaM) to support CSR purpose. The contents are split into below 4 categories:

HOW CRS/NT DATA ARE COLLECTED IN CRF PAGE

Below is an example of case report form (CRF) pages from one of our Abecma studies, where CRS event and its related signs/symptoms are collected.

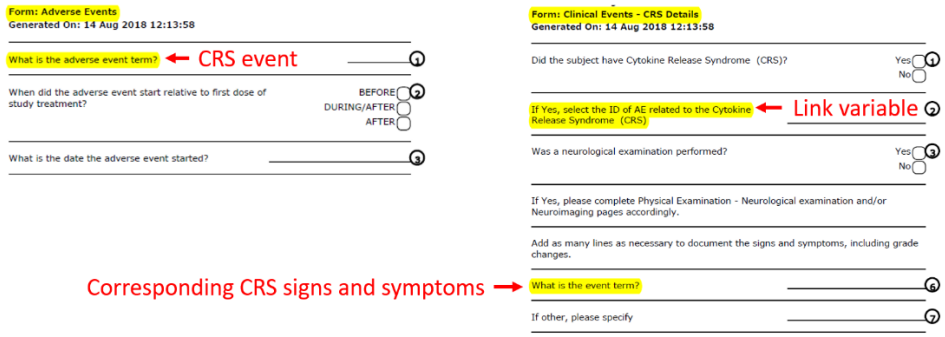

Figure 1. Sample CRF page for CRS/NT event and related signs and symptoms

NT CRF pages are bearing similar structure. As one can see from the page information, any signs or symptoms decided by investigator to be related to either CRS or NT are recorded separately on special CRF page (signs and symptoms page). At the same time, the CRS or NT event itself is recorded in AE CRF page as an event. The AE ID of CRS/NT event from AE page is documented in signs/symptoms page too, and to be used as a link.

HOW CRS/NT EVENT AND THEIR RELATED SYMPTOMS DATA ARE MAPPING TO SDTM

The SDTM mapping of both CRS/NT event and their related signs/symptoms is following the same concept of CRF design. To be more specific:

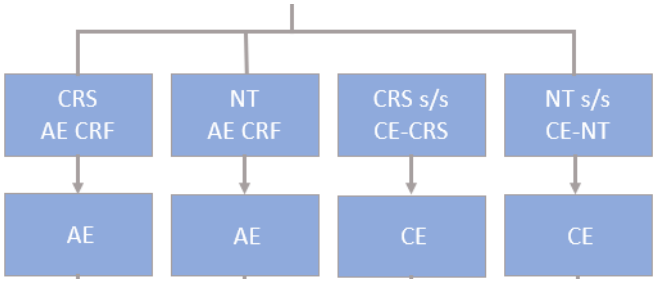

Figure 2. SDTM mapping flow chart for CRS/NT data

The information about CRS and NT event is stored in SDTM.AE/SUPPAE, such as:

USUBJID	AESEQ	AESPID	AETERM	AEDECOD	AEBODSYS	AESER	AEACN	AEREL	AEOUT	AESTDTC	AEENDTC	AETOXGR
101	13	10	CYTOKINE RELEASE SYNDROME	Cytokine release syndrome	Immune system disorders	N	MULTIPLE	MULTIPLE	OVERED/RESOLVED WITH SEQUE	2018-03-13	2018-03-14	1
101	14	16	CYTOKINE RELEASE SYNDROME	Cytokine release syndrome	Immune system disorders	N	MULTIPLE	MULTIPLE	OVERED/RESOLVED WITH SEQUE	2018-03-14	2018-03-15	2
101	15	23	CYTOKINE RELEASE SYNDROME	Cytokine release syndrome	Immune system disorders	N	MULTIPLE	MULTIPLE	RECOVERED/RESOLVED	2018-03-15	2018-03-17	1
102	19	5	NEUROTOXICITY	Neurotoxicity	Nervous system disorders	N	MULTIPLE	MULTIPLE	RECOVERED/RESOLVED	2018-05-29	2018-05-31	1
103	10	10	INTERMITTENT CYTOKINE RELEASE SY	Cytokine release syndrome	Immune system disorders	N	MULTIPLE	MULTIPLE	RECOVERED/RESOLVED	2018-07-11	2018-07-17	1
104	29	23	NEUROTOXICITY	Neurotoxicity	Nervous system disorders	N	MULTIPLE	MULTIPLE	RECOVERED/RESOLVED	2018-07-15	2018-07-17	1

Figure 3. sample of SDTM.AE containing CRS or NT events

At the same time, all the data/information collected by CRS/NT signs/symptoms page are stored in SDTM.CE/SUPPCE, such as:

USUBJID	CESEQ	CESPID	CETERM	CEDECOD	CESOC	CETOXGR	CESTDTC	CEENDTC
101	1	3	CRP ELEVATED	C-reactive protein increased	Investigations	3	2018-03-14	2018-03-15
101	2	7	ELEVATED C-REACTIVE PROTEIN	C-reactive protein increased	Investigations	3	2018-03-15	2018-03-16
102	1	2	BLURRED VISION	Vision blurred	Eye disorders	1	2018-05-29	2018-05-30
102	2	2	CHILLS	Chills	General disorders and administration site conditions	2	2018-05-29	2018-05-30

Figure 4. sample of SDTM.CE containing CRS or NT signs/symptoms

CE/SUPPCE has the same structure as AE, but bears different variable names based on CDISC specification. MedDRA coding has been applied to both AE and CE at SDTM level. The link ID identified in CRF page is mapped to SUPPCE such as:

USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG	QEVAL
101	CESEQ	1	AESPID1	AE Identifier for Clinical Event 1	CYTOKINE RELEASE SYNDROME --16 --14/MAR/2018--GR :2--SAE:NO	CRF	
101	CESEQ	1	CENUER	Neurological Examination	Y	CRF	
101	CESEQ	1	CEPROC	Concomitant Procedures	N	CRF	
101	CESEQ	1	CETERMOT	Other Event	CRP ELEVATED	CRF	

Figure 5. sample of SDTM.SUPPCE containing link information between AE and CE

HOW CRS/NT DATA ARE ORGANIZED AT ADAM LEVEL;

Based on the actual requirement or analysis needed, CRS/NT related data from both AE and CE are linked and reorganized into different ADaM domains including:

ADAE: contains all records from SDTM dataset AE (events as collected by CRF) with all necessary derivation/calculation for analysis purpose. Customized AE categories (CQxxNAM: for AE of special interest purpose) are also added to ADAE. The customized mapping (including CRS and NT) is provided by safety group per team review.

ADCE: contains all records from SDTM dataset CE (CRS/NT signs and symptoms as collected by CRF) with all necessary derivation/calculation for analysis purpose.

ADAE2: Per FDA's special request, this is a dataset containing all AE events except all NT events replaced by their related signs/symptoms.

ADAESUM or ADSAFSUM: analysis dataset with BDS structure. It contains derived parameters for CRS/NT summary analysis at subject level in each period. If 2 or more events are occurring close to each other (e.g. the gap between 2 events is within 7 days), they are "Clustered" and analyzed as one event. This clustering algorithm is applied in this dataset.

Below is a full flow chart about how data are organized up to ADaM level:

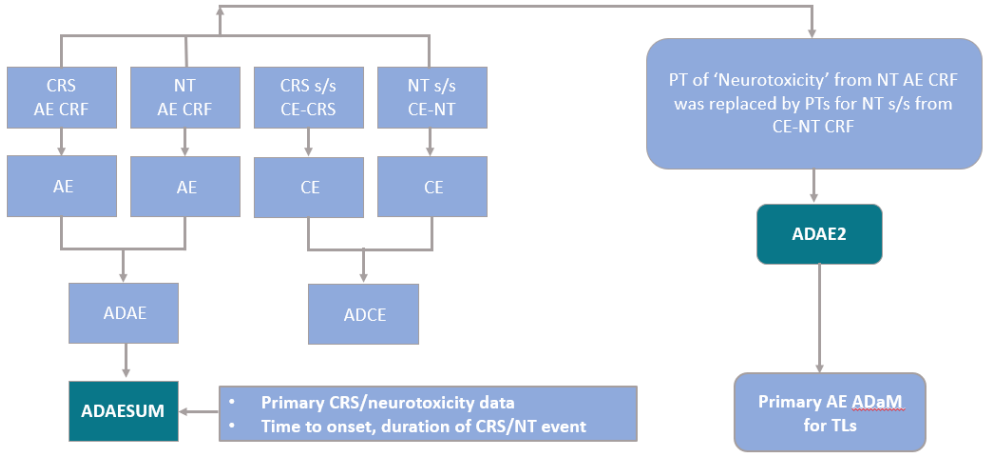

Figure 6. SDTM and ADaM flow chart for CRS/NT data

HOW CRS/NT DATA ARE SUMMARIZED IN CSR TABLES

Analysis on CRS/NT is presented in several general forms:

By event: Since health authority required to conduct analysis replacing NT with its related signs or symptoms, AE tables using this data (ADAE2) were generated for CSR:

Table 14.3.x.x
Adverse Events (AEs) by System Organ Class and Preferred Term
(Including Neurotoxicity Signs or Symptoms)
Treated Population

System Organ Class Preferred Term [a]	Treated Population (N=xxx) Before Infusion n (%)	 On or After Infusion n (%)
Subjects with at least one AE	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS #1		
PREFERRED TERM #1	xx (xx.x)	xx (xx.x)
PREFERRED TERM #2	xx (xx.x)	xx (xx.x)
.....	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS #2		
PREFERRED TERM #1	xx (xx.x)	xx (xx.x)
PREFERRED TERM #2	xx (xx.x)	xx (xx.x)
.....	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)

[a]Coded using MedDRA version xx.x. A subject is counted only once for multiple events within preferred term/system organ class.

Figure 7. table shell of AE summary table

Similarly, AE of special interest (by customized AE category) is also summarized at event level:

Table 14.3.x.x
Adverse Events of Special Interest (AESI)/Selected Adverse Events by AESI/Selected AEsCategory and Preferred Term

Treated Population

AESI/Selected AEs Category [a] Preferred term [b]	Treated Population (N=xxx) before Infusion n (%)	 On or After Infusion n (%)
Number of subjects with at least one AESI/Selected AEs	xx (xx.x)	xx (xx.x)
Cytokine Release Syndrome (CRS)	xx (xx.x)	xx (xx.x)
Neurologic Toxicity	xx (xx.x)	xx (xx.x)
New malignancies	xx (xx.x)	xx (xx.x)
PREFERRED TERM #1	xx (xx.x)	xx (xx.x)
PREFERRED TERM #2	xx (xx.x)	xx (xx.x)
Hematologic disorders	xx (xx.x)	xx (xx.x)
PREFERRED TERM #1	xx (xx.x)	xx (xx.x)
PREFERRED TERM #2	xx (xx.x)	xx (xx.x)
Rheumatic and autoimmune disorders	xx (xx.x)	xx (xx.x)
PREFERRED TERM #1	xx (xx.x)	xx (xx.x)
PREFERRED TERM #2	xx (xx.x)	xx (xx.x)
Infections	xx (xx.x)	xx (xx.x)
PREFERRED TERM #1	xx (xx.x)	xx (xx.x)
PREFERRED TERM #2	xx (xx.x)	xx (xx.x)
…		

A preferred term may be seen in multiple AESI/Selected AE categories.
[a] AESI/Selected AEs categories used either MedDRA vxx.x SMQ or sub-SMQ or SOC or HLT or list of preferred terms. A subject is counted only once for multiple events within each AESI/Selected AE category.
The preferred terms under AE categories are selected using the protocol specified AESIs, Standardized MedDRA Query (SMQ) definitions or MedDRA SOC and PT definitions, and medical judgment.
[b] Coded using MedDRA version xx.x. A subject is counted only once for multiple events within preferred term.

Figure 8. table shell of AE of special interest summary table

Other than conventional by-event analysis, the CRS/NT related summarized info (from ADAESUM /ADSAFSUM) are presented in table such as:

Table 14.3.x.x
Summary of Cytokine Release Syndrome
Treated Population

	On or After Infusion Arm 1 n=XX	 Arm 2 n=XX	 Arm 3 n=XX	 Total N=XX
Number of Subjects with at Least One CRS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Reported CRS Grade (Lee Criteria), n (%) (from AE data with PT=CRS)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
x	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
x	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to First Onset of CRS (days)[a]from AE data with PT=CRS)				
N	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
Sd	xx.xx	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
max	xx	xx	xx	xx
Total Number of CRS Event, n	Xx	Xx	Xx	Xx
Number of Events by Length of Duration n (%)	Xx (xx.x)	Xx (xx.x)	Xx (xx.x)	Xx (xx.x)
Length 1 days	Xx (xx.x)	Xx (xx.x)	Xx (xx.x)	Xx (xx.x)
Length 2 days	Xx (xx.x)	Xx (xx.x)	Xx (xx.x)	Xx (xx.x)
Length 3 days	Xx (xx.x)	Xx (xx.x)	Xx (xx.x)	Xx (xx.x)
Ongoing[b] (programming note, if ongoing is 0, please also present 0)				
Duration of CRS (per Event) Descriptive Statistics (days)[c] (sum of each event duration)				
N	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
Sd	xx.xx	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
Max	xx	xx	xx	xx
Number of Subjects Received Tocilizumab for CRS n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 Dose Tocilizumab	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>1 Dose Tocilizumab	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Subjects Received Siltuximab for CRS n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 Dose Siltuximab	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>1 Dose Siltuximab	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Figure 9. table shell of CRS summary table

The actual content of this table can be varied based on study specific or team's decision, but it is a place holder for all summarized/derived information related to CRS/NT analysis (e.g. max grade, time from infusion to event, etc.):

SUPPLEMENTAL CRS/NT ANALYSIS DATASETS TO HA REVIEW

Besides above approaches to organize and present CRS/NT related data to support final CSR and submission, FDA requested extra data presentation/analysis to support their review. In following chapter, we will introduce two types of datasets we submitted to FDA before or during their review.

NON-CDISC DATASETS CONTAINED IN BLA SUBMISSION

Based on the agreement with FDA from pre-BLA meeting, we submitted four CRS/NT related datasets which were not part of ADaM/SDTM package, and not in CDISC format. These datasets include:

CRSPRIM: subject level overview of CRS events, including info such as subject level CRS/NT start and end date, max grade as well as usage of any specific treatment of interest.

CRSINVD: containing individual CRS treatments identified by investigator with related information (e.g. standard term, dose, route, start/end date, etc.)

CRSNT: integrated dataset containing all CRS/NT events and symptoms

NT: containing all details about NT events

These datasets were generated from final ADaM datasets, and submitted along with BLA submission package. The purpose for generating these datasets is to give health authority reviewer an initial look at CRS/NT profile of the CAR-T product, but their necessity or detailed format/algorithm is upon the discussion and decision between regulatory team and health authority before submission. Samples of key variables specification of CRSPRIM and CRSNT have been attached in appendix 1 for reference.

INTRODUCE ADCRSNT REQUESTED BY FDA REVIEW

Besides above datasets submitted for CSR and submission purpose, another key dataset requested by FDA during their final review stage is ADCRSNT. The metadata of this dataset is being standardized by PHUSE Working Group, and its details can be found at https://advance.phuse.global/display/WEL/ADCRSNT.

In general, it organizes all AE or CRS/NT related signs and symptoms into one dataset and has more derived variables for CRS/NT analysis purpose. Samples of key CRS/NT related variables are listed in below table:

Variable	Label	Type	Definition
USUBJID	Unique Subject Identifier	text	
AEDECOD	Dictionary-Derived Term	text	AEDECOD from original AE data
FDAGT	FDA Grouped Term	text	Recode AEDECOD based on FDAGT (provided by FDA)
CRSFLR	Record level CRS flag	text	Set 'Y' if this is CRS record; Otherwise 'N'
NTFLR	Record level NT flag	text	Set 'Y' if this is NT record; Otherwise 'N'
CRSFLS	Subject level CRS flag	text	Set 'Y' at subject level, if subject has at least one CRS; Otherwise 'N'
NTFLS	Subject level NT flag by Period	text	Set 'Y' at subject level, if subject has at least one NT; Otherwise 'N'
CRSONFL	Ongoing CRS flag	text	If AENDT is missing and record is CRS; Otherwise 'N'
NTONFL	Ongoing NT flag	text	If AENDT is missing and record is NT Otherwise 'N'
CRSSTDY	Start day of CRS by subject	integer	AESTDY of first CRS for each subject
CRSENDY	End day of CRS by subject	integer	AEENDY of last CRS event for each subject; Set missing if any event ongoing.

NTSTDY	Start day of NT by subject	integer	AESTDY of first NT event for each subject
NTENDY	End day of NT by subject	integer	AEENDY of last NT event for each subject; Set missing if any event ongoing.
CRSMAXTX	CRS max tox grade by subject	integer	Max CRS toxicity grade for each subject
NTMAXTX	NT max tox grade by subject	integer	Max NT toxicity grade for each subject
CRSMXSDY	Time to CRS max tox grade by subject	integer	AESTDY of first CRS event with max toxicity grade (CRSMAXTX) for each subject
NTMXSDY	Time to NT max tox grade by subject	integer	AESTDY of first NT event with max toxicity grade (NTMAXTX) for each subject
CRSDUR	Time to CRS resolution by subject	integer	CRSENDY – CRSSTDY + 1; NTENDY – NTSTDY + 1; the duration is not calculated for ongoing CRS
NTDUR	Time to NT resolution by subject	integer	NTENDY – NTSTDY + 1; the duration is not calculated for ongoing NT
CRS0xFL	CRS Definition Flag 0x	text	Set 'Y' if any customized CRS is involved
NT0xFL	NT Definition Flag 0x	text	Set 'Y' if any customized NT is involved

Table 1. some key variables for ADCRSNT

The detailed algorithm for each variable can be study-specific, or decided based on discussion with health authority, but these general variables required reflect the basic thinking of FDA on how the reviewer hopes to look at the CRS/NT data. One specific variable to be mentioned is FDAGT which allows study team to re-code/re-categorized the event based on FDA preferred coding, which may be different from MedDRA coding or sponsor customized AESI coding. Besides, CRSFLR/NTFLR (flags at record level) and CRSFLS/NTFLS (flags at subject level) can be used for flagging CRS/NT. Other special flags can be added as well per requirement or discussion with FDA.

CONCLUSION

CRS and NT are important to CAR-T related research and safety analysis, so they are usually required to be handled, submitted and reviewed specifically in CAR-T clinical studies. This paper summarizes different formats or approaches for CRS/NT data presentation, that we used within past CAR-T studies/submissions. Each approach has its own purpose for either facilitating CRS/NT analysis and submission or supporting health authority review.

Though the details (including the algorithm, the data format) can vary from compound to compound based on actual situation, we hope this paper can provide some initial insights or guidance to other teams who are working on CAR-T studies, or preparing CAR-T product submission packages, from the perspective of handling CRS/NT data.

REFERENCES

PHUSE Working Groups. “FDA Oncolocgy Full Consolidated Comments - ADCRSNT” Accessed Sep. 21, 2021. https://advance.phuse.global/display/WEL/ADCRSNT.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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APPENDIX 1: SAMPLE OF CRSPRIM AND CRSNT KEY VARIABLES

CRSPRIM:

Variable Name	Variable Label	Type	Study Mapping Instructions
USUBJID	Unique Subject Identifier	text	
TR01SDT	Date of First Exposure	integer	CAR-T infusion date
CRSSTDT	Start Date of CRS	integer	Earliest CRS start date
CRSENDT	End Date of CRS	integer	End date of last CRS
CRSMAX	CRS Max Grade	text	Max CRS Grade
NTMAX	NT Max Grade	text	Max CRS Grade
DIAFL	Analysis Flag for Dialysis	text	Flag if subject was treated with Dialysis during CRS period (CRSSDT to CRSENDT)
TOCIFL	Analysis Flag for Tocilizumab	text	Flag if subject was treated with Tocilizumab for CRS or NT
CSFL	Analysis Flag for Corticosteroid	text	Flag if subject was treated with Corticosteroid for CRS or NT

CRSNT:

Variable Name	Variable Label	Type	Study Mapping Instructions
USUBJID	Unique Subject Identifier	text	
TR01SDT	Date of First Exposure	integer	CAR-T infusion date
SUBCAT	Subcategory for Adverse Event	text	Specify the type of each record as one of categories below: CRS AE CRS Signs/Symptoms NT AE NT Signs/Symptoms
INFECTFL	AE of Infection (Yes/No)	text	If subject had infection during CRS period (CRSSTDT to CRSENDT). This is a subject level flag
BODSYS	Body System or Organ Class	text	Body system class of original record
DECOD	Preferred Term	text	Preferred term of original record
TOXGRN	CTCAE Toxicity Grade	integer	Toxicity grade of original record
STDTC	Start Date (day)	text	Start date of original record
ENDTC	End Date (day)	text	End date of original record
FEVERFL	Fever within 7 days of getting CAR-T and without diagnosis of CRS	text	Subject level flag if subject qualified criteria
WK8FL	Within 8 Weeks Flag (Yes/No)	text	Set to 'Yes' if ASTDT within 8 weeks of CAR-T infusion. Otherwise, set to 'No'