The impact of Regulations on Immuno-Oncology Submissions

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BACKGROUND: IMMUNO-ONCOLOGY

Immuno-Oncology studies add to the complexity of clinical trials. Many of the more recent studies involve multiple study drugs, often combining a monoclonal antibody with a chemotherapeutic agent to elicit improved immunogenicity for tumors.

BACKGROUND: RECIST

The Response Evaluation Criteria In Solid Tumors (RECIST), which provide rules by which cancer patients are determined to be improving, staying the same or worsening, would often fail for immuno-oncology studies whose criteria differ slightly as the action of immunotherapeutic agent is often delayed. These outcomes require different efficacy data.

BACKGROUND: CDISC

Immuno-Oncology outcomes require different efficacy data, typically captured in the relatively new SDTM domains: TU, TR and RS. Reports and analyses are created from these and other domains and included in the Clinical Study Report (CSR). Clinical data scientists rely heavily on changes from baseline of the Tumor Response domain with ancillary data provided primarily by the Demographics and Disposition domains.

BACKGROUND: CSR

The Clinical Study Report must contain evidence of both safety and efficacy of the drug(s). Three visualizations are presented which indicate the progression of diseases with tumors including: Waterfall Plots, Spaghetti Plots and Swimmer Plots. Finally, a mock narrative shows the safety side of the CSR.

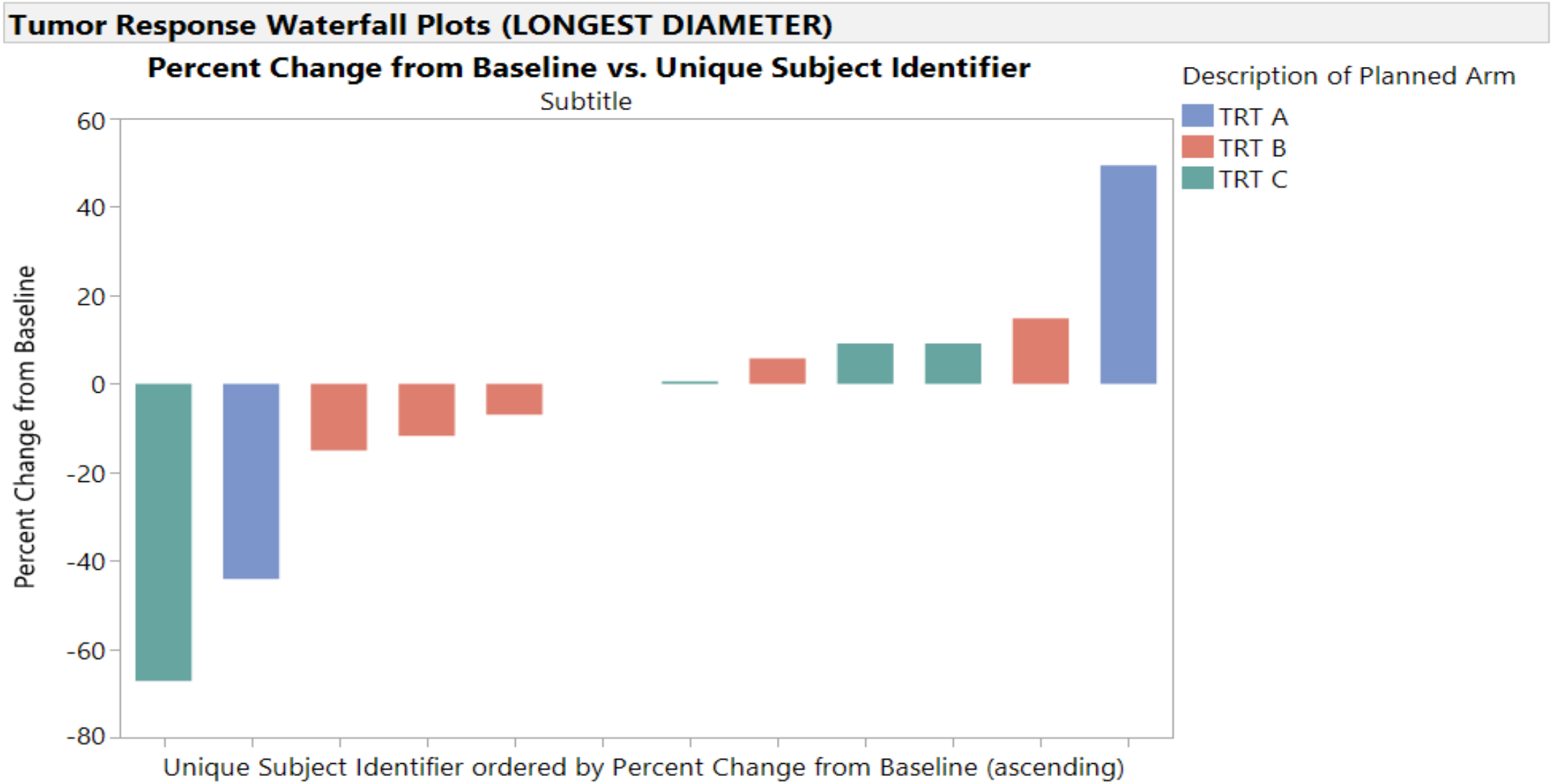
WATERFALL PLOTS

Waterfall Plots are very useful for indicating Percent Change from Baseline calculations on the individual level. This view allows each subject to be evaluated based on the treatment they receive to determine if their tumors are growing, shrinking or staying the same. The Waterfall Plot in this example is relatively simple in that it combines information from fewer domains than the others in this paper. Whether the values increase, decrease or stay the same indicate progressive disease (PD), complete or partial response (CR/PR) or no change respectively.

WATERFALL PLOTS

- Category of Question
- Name of Measurement, Test or Examination
- Unique Subject Identifier
- Percent Change from Baseline (derived)
- Visit Number
- Visit Name
- Date/Time of Collection
- Study Day of Collection
- Subject Identifier for the Study
- Study Identifier
- Age
- Age Units
- Sex
- Race
- Ethnicity
- Planned Arm Code
- Description of Planned Arm
- Country
- Subject Reference Start Date/Time
- Subject Reference End Date/Time
- Study Site Identifier
- Date/Time of Birth

WATERFALL PLOTS



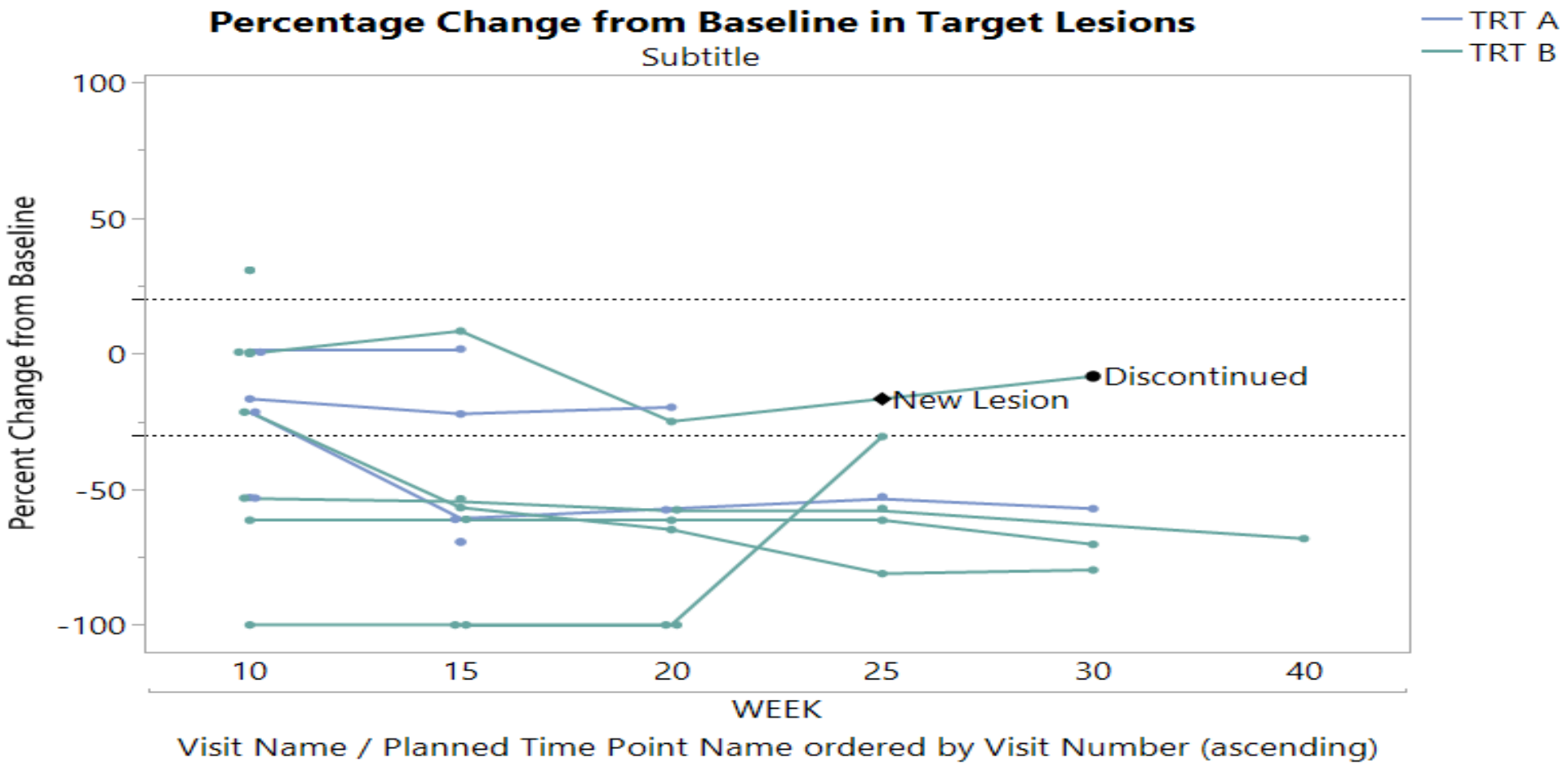
SPAGHETTI PLOTS

Spaghetti Plots raise the level of sophistication as the changes from baseline can be measured over time. By combining the tumor domains TR and RS merged with Disposition and Demographics Domains. In order to more completely understand the disease progression it is useful to highlight discontinuation from study drug as well as the occurrence of new lesions.

SPAGHETTI PLOTS

- Unique Subject Identifier
- Visit Number
- Visit Name
- Planned Time Point Number
- Planned Time Point Name
- LONGDIA_1 (derived)
- PERLODIA_1 (derived)
- Study Identifier
- Domain Abbreviation
- Subject Identifier for the Study
- Subject Reference Start Date/ Time
- Subject Reference End Date/ Time
- Study Site Identifier
- Date/Time of Birth
- Age
- Age Units
- Sex
- Race
- Ethnicity
- Planned Arm Code
- Description of Planned Arm
- Country
- Date/Time of Collection
- Study Day of Collection
- Study Day of Start of Disposition Event
- Category for Disposition Event
- Subcategory for Disposition Event
- DSWK (derived)
- DSSTWK (derived)

SPAGHETTI PLOTS



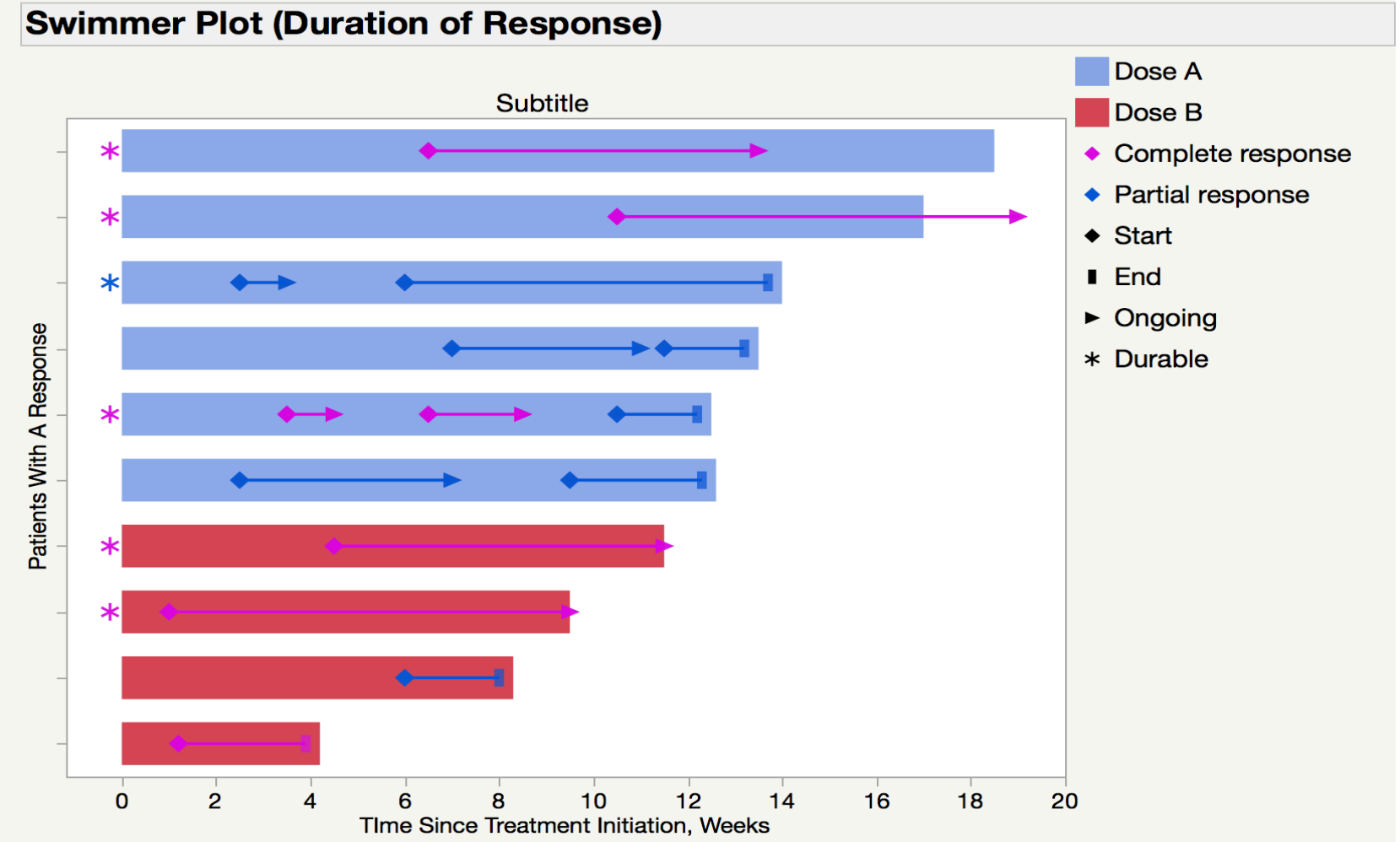
SWIMMER PLOTS

Swimmer Plots are used to indicate the duration of patient response time on different treatment regimes. There are numerous variables in SDTM used to create the Swimmer Plots as they are are merged from TR, RS, DS and DM.

SWIMMER PLOTS

- Unique Subject Identifier
- Subject Reference Start Date/Time
- Subject Reference End Date/Time
- Study Identifier
- Domain Abbreviation
- Sequence Number
- Sponsor-Defined Identifier
- Short Name of Measurement, Test or Exam
- Response Assessment/Test
- Category of Question
- Subcategory for Question
- Result or Finding in Original Units
- Character Result/Finding in Std Format
- Completion Status
- Reason Not Performed
- Method of Test or Examination
- Vendor Name
- Radiologist or Reader
- Visit Number
- Visit Name
- Date/Time of Assessment
- Study Day
- Planned Time Point Name
- Planned Time Point Number
- STDY
- errdtSTDY (derived)
- partial_RSDTC (derived)
- ENDY
- RSENDY
- errdtENDY (derived)
- RSENDTC
- partial_RSENDTC (derived)
- RSDUR
- LOG2_RSDUR (derived)
- RSWK (derived)
- Category for Disposition Event
- Subcategory for Disposition Event
- Date/Time of Collection
- Start Date/Time of Disposition Event
- Study Day of Visit/Collection/Exam
- Study Day of Start of Disposition Event
- DSWK (derived)
- DSSTWK (derived)
- Subject Identifier for the Study
- Study Site Identifier
- Date/Time of Birth
- Age
- Age Units
- Sex
- Race
- Ethnicity
- Planned Arm Code
- Description of Planned Arm
- Country
- Date/Time of Collection 2
- Study Day of Collection
- errdtRFDY (derived)
- partial_rfendtc (derived)
- RFDY (derived)
- RFWK (derived)
- Epoch
- Start Date/Time of Visit
- End Date/Time of Visit
- Study Day of Start of Visit
- Study Day of End of Visit
- Description of Unplanned Visit
- partial_SVSTDTC (derived)
- partial_SVENDTC (derived)
- SVDUR
- LOG2_SVDUR (derived)
- SVENWK (derived)
- end
- start
- ResponseWK
- Complete
- Ongoing
-

SWIMMER PLOTS



SERIOUS ADVERSE EVENT NARRATIVES

Serious adverse event narratives provide a key part of the safety story for subjects on immuno-oncology trials. They are more complex than the typical trial as the patients are often on multiple drugs for which outcomes, causality and actions must be accounted for each treatment. Added complexity exists in the medications as well as current medications received and prior cancer therapies are included. The data populating these narratives resides throughout the SDTM data model and creates a comprehensive overview of each patient. Medical Writers can augment these as they see fit.

SERIOUS ADVERSE EVENT NARRATIVES

- USUBJID
- AGE
- RACE
- SEX
- RFSTDTC
- AESTDTC
- AEENDTC
- AEDECOD
- AETERM
- AESTDY
- CMTRT
- AESER
- MHTERM
- LBTESTCD
- ACTARM
- AEACNOTH
- AECONTRT
- AESCAN
- DSEPOCH
- HODECOD
- HOSTDTC
- MHOCCUR
- CMOCCUR
- DSENDY
- HOSTDY
- HOENDY
- COUNTRY
- STUDYID
- SUBJID
- AEACNXXX
- AEACNYYY
- AEOUTXXX
- AEOUTYYY
- AERELXXX
- AERELYYY
- AEDECOD
- AETOXGR
- AESEQ
- CMTRT
- CMSTDTC
- CMENDTC
- DSDECOD
- DSSTDTC
- DSCAT
- EXDOSE
- EXDOSU
- EXTRT
- EXSTDTC
- EXENDTC
- LBTRTEM
- LBDTC
- LBTESTCD
- LBTEST
- LBSTRESN
- LBBLFL
- LBORRESU
- LBNRIND
- LBSTNRHI

SERIOUS ADVERSE EVENT NARRATIVES

Protocol Identification:	ONCOLOGY STUDY
Subject identification/Country:	09012017 (USA)
Investigation Product/Cohort/Route:	SASIMAB and JMPIMAB/ONE/INTRAVENOUS
Date of first dose:	09APR2001
Date of last dose:	09MAY2002
TESAE (Preferred Term):	headache/09JUN2001
TESAE(Preferred Term):	phlebitis/05JUN2001
TESAE(Preferred Term):	haemorrhage/02JUL2000
TESAE(Preferred Term):	pyrexia/26MAY2000

Narrative

Subject 09012017, a 49-year-old Caucasian male received 300 mg/kg SASIMAB and 10 mg/kg JMPIMAB / 10 mg/kg SASIMAB (S1) - Expansion. The subject's past medical history included abdominal pain(grade 2), fatigue (grade 1), phlebitis (grade 1), nausea (grade 1), hypertension (grade 1), high cholesterol(grade 1), and hypertension(grade 2). The subject is a non-smoker.

SERIOUS ADVERSE EVENT NARRATIVES

The subject was diagnosed with Melanoma on 03NOV2000 with non-metastatic lymph nodes. At study entry, the subject's cancer was stage 2 and ECOG performance status was: 1. Previous anticancer therapy included CHEMOTHERAPY/XXXX from 02MAR1998 through 18APR1998, CHEMOTHERAPY/ BBBB from 19AUG1999 through 07OCT1999, SURGERY/YYY from 24FEB2000 through 24FEB2000.

On 09JUN2000 (Day 42) the subject experienced headache that was (Grade 3) in severity. The last dose of SASIMAB and JMPIMAB prior to the event onset was administered on 27MAY2000. Concurrent with this event that occurred within a +/- 7-day window of the onset of the SAE included phlebitis (Grade 3), pyrexia (Grade 2), … Concomitant medications taken 7 days before the onset of the SAE up to 30 days following onset included: vitamin d3*, vitamin b*, simvastatin*, maxeran*, ...

The subject was discharged on 12JUN2000 and the adverse event was considered recovered/resolved on 12JUN2000. The event was 3 days in duration and SASIMAB was NONE and JMPIMAB was NONE due to this event. The investigator considered the AE to be NOT RELATED to SASIMAB and NOT RELATED to JMPIMAB.

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SERIOUS ADVERSE EVENT NARRATIVES

Relevant laboratory findings included:
…

NOTE TO AUTHOR: …

Re-CHALLENGE/De-CHALLENGE: …

NOTE TO AUTHOR: DEATH: On 16JUL2003, 679 days after starting study drug(s) and 10 days after permanently discontinuing study drug(s), the subject died.