

Split-Coalesce Tumor, Data Handling Woes and Safety-Efficacy Dilemma

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ABSTRACT

For many oncology studies, lesions that split or coalesce on treatment can be difficult to map accurately. Typically, data handling of tumor identification is done once, usually at baseline (e.g. identification of Target and Non-Target tumors). However, a post-baseline record may be included in TU domain when: a new tumor emerges at any time during a study, or if a tumor identified at baseline subsequently splits into distinct tumors or if tumors identified at baseline subsequently merge together. The methodology adopted is to use TUGRPID to group new split tumors or when non-nodal lesions 'fragment', the longest diameters of the fragmented portions are added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each lesion. Often data handling/management of tracking the initial tumor and its subsequent split or coalesce is not easily reconciled.

INTRODUCTION

For oncology studies, it is essential that the same imaging methods are used for a lesion during the whole study to ensure comparability between the measurements. Many CROs, during the life of an oncology study, tend to use different vendors to capture cancer data from sites. Unfortunately, there is no current caveat or ruling to state that lesions need to be followed meticulously by specific imaging methodologies under proper/specific procedures for sites/vendors during the whole study even if it disappears, splits or merges with other lesions. Often, lack of adequate or clear-cut rules or protocol specifications about tumor imaging methods and monitoring, hampers accurate assessment of the tumor and leads to inaccurate results and analyses. There have been cases where if a measurement of one lesion is missing, then the overall assessment is deemed not assessable. Ideally, new lesions should be defined as a new lesion. There have been cases where a split of a lesion is not regarded as new lesion. A lesion that disappeared and reappeared is not regarded as new lesion (according to RECIST 1.1). The sum of longest diameter (1 dimensional) is used to assess target lesions. In theory, if the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

This paper attempts to highlight different use case scenarios where tumors were measured during a sustained period or during the life cycle of a study and measurements were taken to classify whether the tumors were new from a tumor split or coalesced from previous split tumors and the issues facing CROs during data handling/reporting/management and analyses of critical tumor data. Some of the common data handling issues seen during some oncology studies included scenarios where a tumor was not measured using the same method/methodology or tumor progression measurement missing key time points. Vendors and sites are often ill-equipped to handle or assess tumor progression when a tumor may have split or merged. Sometimes, the longest measurable diameter of a lesion can get very small. Progression is defined as 20% increase from the lowest preceding value (NADIR). If the value approaches 0, the increase of 20% is often not measurable. This may cause incorrect interpretation of the result. Sometimes sites report difficulty in identifying from the imaging method if a lesion disappeared and reappeared. Also, the classification and measurement of a lymph node can be challenging. Assessing and measuring affected lymph nodes needs special rules/caveats as lymph nodes are also normal structures that can be measured. Sometimes lesions change shape making it challenging to assess and measure making those lesions non-measurable. Data handling measures need to ensure that if the measurement of one lesion is missing or has been measured with another method, a sum of longest diameter cannot and should not be calculated. If the shape of a lesion changes, the longest diameter (or short axis in case of lymph nodes) will need to be used. Often, there is no easy or correct way to check this data, which may require an independent read of the data point or measure.

If a lesion becomes non-measurable, there have been FAQ suggestions in RECIST 1.1 to reassess the lesion as non-target lesion and drop all measurements from the target lesions if nothing else is possible. This should be avoided to ensure no data manipulation is done. The sites and vendors need to strictly ensure that the investigator assessment is never changed or manipulated to "fit" the data.

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BACKGROUND

Before addressing the key data handling issues facing tumor studies, it is imperative to understand what the word cancer actually means and what is the essential difference between a tumor and cancer. According to Johns Hopkins Medicine, “the term cancer is derived from the Latin word for “crab” because cancers are often very irregularly shaped, and because, like a crab, they “grab on and don’t let go.” The term cancer specifically refers to a new growth which has the ability to invade surrounding tissues, metastasize (spread to other organs) which may eventually lead to the patient's death if untreated”.

So what is the difference between a tumor and cancer?

“The terms tumor and cancer are sometimes used interchangeably which can be misleading. A tumor is not necessarily a cancer. The word tumor simply refers to a mass. A cancer is a particularly threatening type of tumor. It is helpful to keep these distinctions clear when understanding oncology studies.

There are different types of tumor or cancer growth. For example:

neoplasm-	A neoplasm is an abnormal new growth of cells. The cells in a neoplasm usually grow more rapidly than normal cells and will continue to grow if not treated. As they grow, neoplasms can impinge upon and damage adjacent structures. The term neoplasm can refer to benign (usually curable) or malignant (cancerous) growths.
tumor-	A tumor is a commonly used, but non-specific, term for a neoplasm. The word tumor simply refers to a mass. This is a general term that can refer to benign (generally harmless) or malignant (cancerous) growths.
benign tumor-	Benign tumors are non-malignant/non-cancerous tumor. A benign tumor is usually localized, and does not spread to other parts of the body. Most benign tumors respond well to treatment. However, if left untreated, some benign tumors can grow large and lead to serious disease because of their size. Benign tumors can also mimic malignant tumors, and so for this reason are sometimes treated.
malignant tumor-	Malignant tumors are cancerous growths. They are often resistant to treatment, may spread to other parts of the body and they sometimes recur after they were removed.
cancer-	A cancer is another word for a malignant tumor (a malignant neoplasm).”

The cancer statistics can be mind boggling.

- According to the American Cancer Society, in 2018, an estimated 1,735,350 new cases of cancer will be diagnosed in the United States and 609,640 people will die from the disease.
- The most common cancers (listed in descending order according to estimated new cases in 2018) are breast cancer, lung and bronchus cancer, prostate cancer, colon and rectum cancer, melanoma of the skin, bladder cancer, non-Hodgkin lymphoma, kidney and renal pelvis cancer, endometrial cancer, leukemia, pancreatic cancer, thyroid cancer, and liver cancer.
- The number of new cases of cancer (cancer incidence) is 439.2 per 100,000 men and women per year (based on 2011–2015 cases).
- The number of cancer deaths (cancer mortality) is 163.5 per 100,000 men and women per year (based on 2011–2015 deaths).
- Cancer mortality is higher among men than women (196.8 per 100,000 men and 139.6 per 100,000 women). When comparing groups based on race/ethnicity and sex, cancer mortality is highest in African American men (239.9 per 100,000) and lowest in Asian/Pacific Islander women (88.3 per 100,000).
- In 2016, there were an estimated 15.5 million cancer survivors in the United States. The number of cancer survivors is expected to increase to 20.3 million by 2026.
- Approximately 38.4% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2013–2015 data).
- In 2017, an estimated 15,270 children and adolescents ages 0 to 19 were diagnosed with cancer and 1,790 died of the disease

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ONCOLOGY STUDIES DATA AND ANALYSIS

So where does all this lead to in terms of oncology studies for pharmaceutical and CROs. Are there effective data safeguard mechanisms to audit data for oncology studies? According to PhRMA, there are currently more than 800 new anticancer drugs in the development pipeline. It is estimated that the global oncology sales and growth will hit the \$100+ billion mark by 2020. At the same time, the participation rate in trials among adult cancer patients is extremely low. Questions arise, then, as to who will study all these drugs, who will prioritize their study, and how enough patients will be identified to study them, especially given the limitations in infrastructure necessary to conduct clinical trials, including investigators and patients and limited data safeguards, handling and audit mechanisms for oncology data.



According to an FDA document on *Guidance for Industry: Cancer Drug and Biological Products*: "The schedule for collection of baseline and follow-up data for full evaluation of efficacy should be specified in the protocol. In addition to the investigator's evaluation of efficacy, all raw data collected for evaluating efficacy should be recorded on the CRF and submitted to FDA. (Usually, actual tumor images need not be submitted, although tumor images should always be available at the investigative site for FDA audit. If there is a need for such images, the sponsor and the reviewing division should discuss this at end-of-phase-2 or pre-submission meetings.) These data allow FDA to examine the basis for efficacy assessments. When tumor response or progressions are important regulatory endpoints, submission of tumor measurement data is critical. On the other hand, when the primary endpoint is survival and the sponsor anticipates demonstrating a survival advantage in two trials, evaluation of tumor response may not be critical for a determination of efficacy, and recording tumor measurements for the database may not always be important. When response and progression are evaluated, criteria for these endpoints should be detailed in the protocol, and data should be carefully collected at intervals specified in the protocol. The following are important considerations for tumor measurement data:

- The protocol and the corresponding CRF should make clear which tumor evaluations are intended to be used to evaluate response and progression. Missing data has been a chronic problem for FDA in evaluating these endpoints.
- The CRF should document the target lesions identified during the baseline visit, or at least prior to treatment. Retrospective identification of such lesions would rarely be considered reliable.
- Tumor lesions should be assigned a unique identifying letter or number. This allows differentiating among multiple tumors occurring at one anatomic site and matching of tumors measured at baseline and tumors measured during follow-up.

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• It is desirable to have a mechanism that ensures complete collection of data at critical times during follow-up. The CRF should ensure that all target lesions are assessed at each follow-up visit, and especially at the visits when response and progression are noted. For documenting tumor response, one approach is to add an evaluation form to display data from three time points: the baseline visit, the visit first demonstrating tumor response, and the visit verifying that response”.

Typically, for tumor related evaluations in clinical studies, any change in tumor is one of the most important factors for clinical assessment. Tumors can be assessed based on whether a tumor has shrunk or whether a tumor has actually progressed. Tumor progression can be subjective in that, either a tumor can split and has made “progression” in clinical assessment terms, or it has “coalesced” and progressed to a measurable tumor.

Most oncology clinical trials follow a life cycle of tumor identification and repeated measurement (assessments) at periodic timepoints. Any change measured over the timepoints typically forms the basis of tumor disease assessment, progression and evaluation of response.

Currently, the Oncology therapeutic area is mapped under three SDTM domains which are based on the SDTM Findings Observation Class and are related to one another with a specific purpose. According to the SDTM Implementation Guide v3.2, “assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials.

1. **TU (Tumor Identification)** domain represents data that uniquely identifies tumors (i.e. malignant tumors and other sites of disease, e.g. lymph nodes). The tumors are identified by an investigator and/or independent assessor and classified according to the disease assessment criteria. In RECIST (Response Evaluation Criteria in Solid Tumors) terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information. The TU domain represents data that uniquely identifies tumors (i.e. malignant tumors and other sites of disease, e.g. lymph nodes).

STUDYID	DOMAIN	USUBJID	TUSEQ	TULNKID	TUDESCD	TUDESC	TUORRES	TUSTRESC	TUNAM	TULOC	TULAT	TUDIR	TUMETHOD	TUEVAL	TUEVALID	EPOCH	VISITNUM	VISIT	TUOTC	TUDY
Example 1: Simple use case to show both investigator and independent assessor tumor identification (TU) data using RECIST 1.0. This example shows a case where Target and Non-Target tumors are identified at screening (or baseline) and then assessed at subsequent visits. It also shows the identification of a new tumor during study conduct. In this example --EVALID is used in conjunction with --EVAL to provide an additional level of detail when multiple assessors play the role defined by --EVAL.																				
XYZ	TU	11111	1	T01	TUMIDENT	Tumor Identification	TARGET	TARGET		OCCIPITAL LOBE	LEFT	ANTERIOR	IMRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	2	T02	TUMIDENT	Tumor Identification	TARGET	TARGET		OCCIPITAL LOBE	RIGHT		IMRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	3	T03	TUMIDENT	Tumor Identification	TARGET	TARGET		TEMPORAL LOBE	LEFT		IMRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	4	NT01	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET		FRONTAL LOBE	RIGHT		IMRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	5	NT02	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET		CEREBELLUM	LEFT		IMRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	6	R-T01	TUMIDENT	Tumor Identification	TARGET	TARGET	ABCD VENDOR	OCCIPITAL LOBE	RIGHT	ANTERIOR	IMRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	7	R-T02	TUMIDENT	Tumor Identification	TARGET	TARGET	ABCD VENDOR	TEMPORAL LOBE	LEFT		IMRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	8	R-T03	TUMIDENT	Tumor Identification	TARGET	TARGET	ABCD VENDOR	OCCIPITAL LOBE	LEFT		IMRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	9	R-T04	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	ABCD VENDOR	PARIENTAL LOBE	LEFT		IMRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	10	R-T02	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	ABCD VENDOR	FRONTAL LOBE	RIGHT		IMRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	11	R-NT03	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	ABCD VENDOR	OCCIPITAL LOBE	RIGHT		IMRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	
XYZ	TU	11111	12	NEW01	TUMIDENT	Tumor Identification	NEW	NEW		FRONTAL LOBE	RIGHT		IMRI	INVESTIGATOR		TREATMENT	5	Cycle 4 Week 4	112	
XYZ	TU	11111	13	R-NEW01	TUMIDENT	Tumor Identification	NEW	NEW		FRONTAL LOBE	RIGHT		IMRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	Cycle 4 Week 4	2010-04-22	112

The above screenshot is a use case example to show investigator and independent assessor tumor identification (TU), data using RECIST 1.0. This example shows a case where Target and Non-Target tumors are identified at screening (or baseline) and then assessed at subsequent visits. It also shows the identification of a new tumor during study conduct. In this example --EVALID is used in conjunction with --EVAL to provide an additional level of detail when multiple assessors play the role defined by --EVAL.

STUDYID	DOMAIN	USUBJID	TUSEQ	TUGRPID	TUREFID	TUSPID	TULNKID	TUDESCD	TUDESC	TUORRES	TUSTRESC	TUNAM	TULOC	TULAT	TUMETHD	TUEVAL	TUEVALID	EPOCH	VISITNUM	VISIT	TUOTC	TUDY	QNAM	PREVAL	QNAM	PREVSP
Example 2: Example to show independent assessor tumor identification, tumor results and response data using RECIST 1.0. This example shows the preferred approach to representing split (fragmented) and merged (coalesced) tumors.																										
A2D03	TU	10001	1		IMG-0001	TRG-SCP-01	T01	TUMIDENT	Tumor Identification	TARGET	TARGET	BBB IMAGING	LUNG, RIGHT MIDDLE LOBE	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-04-01	1N					
A2D03	TU	10001	2		IMG-0001	TRG-SCP-02	T02	TUMIDENT	Tumor Identification	TARGET	TARGET	BBB IMAGING	LUNG, RIGHT MIDDLE LOBE	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-04-01	1N				Y	
A2D03	TU	10001	3		IMG-0001	TRG-SCP-03	T03	TUMIDENT	Tumor Identification	TARGET	TARGET	BBB IMAGING	LUNG, LEFT LOWER LOBE	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-04-01	1N					
A2D03	TU	10001	4		IMG-0001	TRG-SCP-04	T04	TUMIDENT	Tumor Identification	TARGET	TARGET	BBB IMAGING	LUNG, LEFT LOWER LOBE	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-04-01	1N					
A2D03	TU	10001	5		IMG-0001	NTG-SCP-01	NT01	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	BBB IMAGING	LIVER	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-04-01	1					
A2D03	TU	10001	6		IMG-0001	NTG-SCP-02	NT02	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	BBB IMAGING	LIVER	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-04-01	1					
A2D03	TU	10001	7	T04	IMG-0002	TRG-W-01	T04.1	TUSPLIT	Tumor Split	TARGET	TARGET	BBB IMAGING	LUNG, RIGHT MIDDLE LOBE	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	WEEK 16	2010-04-24	12					
A2D03	TU	10001	8	T04	IMG-0002	TRG-W-02	T04.2	TUSPLIT	Tumor Split	TARGET	TARGET	BBB IMAGING	LUNG, LEFT LOWER LOBE	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	WEEK 16	2010-04-24	12					
A2D03	TU	10001	9	T02/T03	IMG-0003	TRG-W-04	T02/T03	TUMERGE	Tumor Merged	TARGET	TARGET	BBB IMAGING	LUNG, LEFT LOWER LOBE	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	7	WEEK 24	2010-06-16	88					
A2D03	TU	10001	10		IMG-0004	NTG-T-01	NEW01	TUMIDENT	Tumor Identification	NEW	NEW	BBB IMAGING	LUNG, LEFT LOWER LOBE	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	9	WEEK 32	2010-08-31	224					

The above screenshot is another use case example to show independent assessor tumor identification using RECIST 1.0. This example shows the preferred approach to representing split (fragmented) and merged (coalesced) tumors. In this example, the tumor with TULNKID=T04 splits and the split tumors are represented with TULNKID T04.1 and T04.2 and TUGRPID T04 to link them together. In the example, the tumors with TULNKID=T02 and T03 merge and the merged tumor is represented with TULNKID T02 and T03, and TUGRPID T02/T03 to link them together. This example also shows the 3 SDTM ID variables (--GRPID, --REFID, --SPID) in use. In this case, --GRPID is used to identify the 'parent' tumor of split tumors and the 'parents' of merged tumors, --REFID is used to represent the image identifier, and --SPID is used to represent the sponsors internal tracking identifier. This example shows the data on

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whether a tumor was previously irradiated (QNAM.PREVIR) and whether that tumor was shown to be progressing since it was irradiated (QNAM.PREVIRP).

STUDYID	DOMAIN	USUBID	TUSEC	TULNKID	TTESTCD	TTEST	TUDRES	TUSTRES	TULOC	TULAT	TUMETHOD	TUEVAL	EPOCH	VISITNUM	VISIT	TUDTC	TUDY	QNAM/PRE	QNAM/PRE
Example 3: Example to show investigator tumor identification using RECIST 1.0. This example shows the alternative approach to representing split (fragmented) and merged (coalesced) tumors. This example also shows a case where progressive disease due to symptomatic deterioration was determined based on a clinical assessment by the investigator.																			
AZD03	TU	10008	1	R1T01	TUMIDENT	Tumor Identification	TARGET	TARGET	LUNG, RIGHT MIDDLE LOBE		CT SCAN	INVESTIGATOR	SCREEN	1	SCREEN	2010-01-01	1	Y	Y
AZD03	TU	10008	2	R1T02	TUMIDENT	Tumor Identification	TARGET	TARGET	LIVER		CT SCAN	INVESTIGATOR	SCREEN	1	SCREEN	2010-01-01	1	Y	Y
AZD03	TU	10008	3	R1T03	TUMIDENT	Tumor Identification	TARGET	TARGET	LIVER		CT SCAN	INVESTIGATOR	SCREEN	1	SCREEN	2010-01-01	1	Y	Y
AZD03	TU	10008	4	R1T04	TUMIDENT	Tumor Identification	TARGET	TARGET	KIDNEY, UPPER LOBE	RIGHT	CT SCAN	INVESTIGATOR	SCREEN	1	SCREEN	2010-01-01	1	N	N
AZD03	TU	10008	5	R1NT01	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	LUNG		CT SCAN	INVESTIGATOR	SCREEN	1	SCREEN	2010-01-01	1		
AZD03	TU	10008	6	R1NT02	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	ABDOMINAL CAVITY		CT SCAN	INVESTIGATOR	SCREEN	1	SCREEN	2010-01-01	1		
AZD03	TU	10008	7	R1NT03	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	CLAVICLE	RIGHT	SCINTIGRAPHY	INVESTIGATOR	SCREEN	1	SCREEN	2010-01-01	1		
AZD03	TU	10008	8	T04	TUMIDENT	Tumor Identification	TARGET	TARGET	LUNG, LEFT LOWER LOBE		CT SCAN	INVESTIGATOR	TREATMENT	5	WEEK 16	2010-04-24	12		
AZD03	TU	10008	9	T02	TUMIDENT	Tumor Identification	TARGET	TARGET	LUNG, RIGHT MIDDLE LOBE		CT SCAN	INVESTIGATOR	TREATMENT	7	WEEK 24	2011-06-19	68		
AZD03	TU	10008	10	T03	TUMIDENT	Tumor Identification	TARGET	TARGET	LUNG, LEFT LOWER LOBE		CT SCAN	INVESTIGATOR	TREATMENT	7	WEEK 24	2011-06-19	68		

The above use case example shows investigator tumor identification data. This example shows the alternative approach to representing split (fragmented) and merged (coalesced) tumors. This example also shows a case where progressive disease due to symptomatic deterioration was determined based on a clinical assessment by the investigator. In the example, the split and merged tumor are not represented in the TU domain. The split and merged tumors use the TULNKID value originally assigned at initial identification, i.e. the continued assessments are attributed back to the originally identified tumor.

However, there are data collection and data handling issues that are often seen with tumor imaging data collected at different timepoints. For example, there have been data collection/handling issues seen when there was (1) inappropriate selection of a target lesion when it was not unequivocally a metastasis (*development of secondary malignant growths at a distance from a primary site of cancer*), (2) selection of too many target lesions at baseline, (3) inappropriate selection of a small lesion as a target lesion, and (4) inappropriate selection of a target lesion from within a radiation field. There is often no clear-cut data collection/handling guideline or proper training to sites and investigators and radiologists to identify correct tumors and tag the tumors as either a new, split or coalesced tumor. There are often gaps seen in correctly identifying such tumor data which could likely affect tumor analysis.

2. Tumor Response (TR) domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. The TR domain represents quantitative measurements and/or qualitative assessments of the tumors i.e. malignant tumors and other sites of disease, e.g. lymph nodes) identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information. Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data. The TR domain represents quantitative measurements and/or qualitative assessments of the tumors (i.e. malignant tumors and other sites of disease, e.g. lymph nodes) identified in the TU domain. Since these measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations.

- TRLNKID is used to relate records in the TR domain to an identification record in TU domain.
- TRLNKGRP is used to relate records in the TR domain to a response assessment record in RS domain. The organization of data across the TR and RS domains requires a RELREC relationship to link the related data rows.
- TRTESTCD / TRTEST values for this domain are published as Controlled Terminology. The sponsor should not derive results for any test (e.g. "Percent Change from Nadir in Sum of Diameter") if the result was not collected.
- When a tumor has split or merged, assessments will be recorded for the new records created in the TU domain.

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DOMAIN	USUBJID	TRSEQ	TRGRPID	TRLNKGRP	TRLNKID	TRTESTCD	TRTEST	TORRES	TORRESU	TRSTRESC	TRSTRESN	TRSTRESU	TRNAM	TRMETHOD	TREVAL	TREVALD	EPOCH	VISITNUM	VISIT	TRDTC	TRDY
1. Example to show both investigator and independent assessor tumor identification tumor results using RECIST 1.0. This example shows a case where Target and Non-Target tumors are identified at screening (or baseline) and then assessed at ent visits. It also shows the identification of a new tumor during study conduct. In this example –EVALD is used in conjunction with –EVAL to provide an additional level of detail when multiple assessors play the role defined by –EVAL.																					
TR	11111	1	TARGET	A1	T01	LDIAM	Longest Diameter	10	mm	10	10	mm		MRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	1
TR	11111	2	TARGET	A1	T02	LDIAM	Longest Diameter	10	mm	10	10	mm		MRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	1
TR	11111	3	TARGET	A1	T03	LDIAM	Longest Diameter	5	mm	5	5	mm		MRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	1
TR	11111	4	NON-TARGET	A1	N101	TUMSTATE	Tumor State	PRESENT		PRESENT				MRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	1
TR	11111	5	NON-TARGET	A1	N102	TUMSTATE	Tumor State	PRESENT		PRESENT				MRI	INVESTIGATOR		SCREEN	1	SCREEN	2010-01-01	1
TR	11111	6	TARGET	RA1	R101	LDIAM	Longest Diameter	10	mm	10	10	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	1
TR	11111	7	TARGET	RA1	R102	LDIAM	Longest Diameter	5	mm	5	5	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	1
TR	11111	8	TARGET	RA1	R103	LDIAM	Longest Diameter	10	mm	10	10	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	1
TR	11111	9	NON-TARGET	RA1	R101	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	1
TR	11111	10	NON-TARGET	RA1	R102	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	1
TR	11111	11	NON-TARGET	RA1	R103	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	SCREEN	1	SCREEN	2010-01-01	1
TR	11111	12	TARGET	A2	T01	LDIAM	Longest Diameter	10	mm	10	10	mm		MRI	INVESTIGATOR		TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	13	TARGET	A2	T02	LDIAM	Longest Diameter	10	mm	10	10	mm		MRI	INVESTIGATOR		TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	14	TARGET	A2	T03	LDIAM	Longest Diameter	5	mm	5	5	mm		MRI	INVESTIGATOR		TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	15	NON-TARGET	A2	N101	TUMSTATE	Tumor State	PRESENT		PRESENT				MRI	INVESTIGATOR		TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	16	NON-TARGET	A2	N102	TUMSTATE	Tumor State	PRESENT		PRESENT				MRI	INVESTIGATOR		TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	17	TARGET	RA2	R101	LDIAM	Longest Diameter	10	mm	10	10	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	18	TARGET	RA2	R102	LDIAM	Longest Diameter	5	mm	5	5	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	19	TARGET	RA2	R103	LDIAM	Longest Diameter	10	mm	10	10	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	20	NON-TARGET	RA2	R101	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	21	NON-TARGET	RA2	R102	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	22	NON-TARGET	RA2	R103	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	3	Cycle 2 Week 4	2010-02-25	56
TR	11111	23	TARGET	A3	T01	LDIAM	Longest Diameter	10	mm	10	10	mm		MRI	INVESTIGATOR		TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	24	TARGET	A3	T02	LDIAM	Longest Diameter	10	mm	10	10	mm		MRI	INVESTIGATOR		TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	25	TARGET	A3	T03	LDIAM	Longest Diameter	5	mm	5	5	mm		MRI	INVESTIGATOR		TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	26	NON-TARGET	A3	N101	TUMSTATE	Tumor State	PRESENT		PRESENT				MRI	INVESTIGATOR		TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	27	NON-TARGET	A3	N102	TUMSTATE	Tumor State	PRESENT		PRESENT				MRI	INVESTIGATOR		TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	28	NEW	A3	NEW01	TUMSTATE	Tumor State	PRESENT		PRESENT				MRI	INVESTIGATOR		TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	29	TARGET	RA3	R101	LDIAM	Longest Diameter	10	mm	10	10	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	30	TARGET	RA3	R102	LDIAM	Longest Diameter	5	mm	5	5	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	31	TARGET	RA3	R103	LDIAM	Longest Diameter	10	mm	10	10	mm	ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	32	NON-TARGET	RA3	R101	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	33	NON-TARGET	RA3	R102	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	34	NON-TARGET	RA3	R103	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	Cycle 4 Week 4	2010-04-22	112
TR	11111	35	NEW	RA3	RNEW01	TUMSTATE	Tumor State	PRESENT		PRESENT			ABCD VENDOR	MRI	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT	5	Cycle 4 Week 4	2010-04-22	112

STUDYID	DOMAIN	USUBJID	TRSEQ	TRGRPID	TRLNKGRP	TRLNKID	TRTESTCD	TRTEST	TORRES	TORRESU	TRSTRESC	TRSTRESN	TRSTRESU	TRNAM	TRMETHOD	TREVAL	TREVALD	EPOCH	VISITNUM	VISIT	TRDTC	TRDY
Example 2: Example to show independent assessor tumor results using RECIST 1.0. This example shows the preferred approach to representing split (fragmented) and merged (coalesced) tumors.																						
ASD02	TR	10001	1	TARGET	RA1	T01	LDIAM	Longest Diameter	10	mm	10	10	mm		CT SCAN	INDEPENDENT RADIOLOGIST	SCREEN	1	SCREEN	2010-02-11	1	
ASD02	TR	10001	2	TARGET	RA1	T02	LDIAM	Longest Diameter	20	mm	20	20	mm		CT SCAN	INDEPENDENT RADIOLOGIST	SCREEN	1	SCREEN	2010-02-11	1	
ASD02	TR	10001	3	TARGET	RA1	T03	LDIAM	Longest Diameter	41	mm	41	41	mm		CT SCAN	INDEPENDENT RADIOLOGIST	SCREEN	1	SCREEN	2010-02-11	1	
ASD02	TR	10001	4	TARGET	RA1	T04	LDIAM	Longest Diameter	30	mm	30	30	mm		CT SCAN	INDEPENDENT RADIOLOGIST	SCREEN	1	SCREEN	2010-02-11	1	
ASD02	TR	10001	5	TARGET	RA1	SUM4	LDIAM	Sum of Longest Diameter	80	mm	80	80	mm		CT SCAN	INDEPENDENT RADIOLOGIST	SCREEN	1	SCREEN	2010-02-11	1	
ASD02	TR	10001	6	NON-TARGET	RA1	N101	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	SCREEN	1	SCREEN	2010-02-11	1	
ASD02	TR	10001	7	NON-TARGET	RA1	N102	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	SCREEN	1	SCREEN	2010-02-11	1	
ASD02	TR	10001	8	TARGET	RA2	T01	LDIAM	Longest Diameter	10	mm	10	10	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	3	WEEK 8	2010-02-29	56	
ASD02	TR	10001	9	TARGET	RA2	T02	LDIAM	Longest Diameter	20	mm	20	20	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	3	WEEK 8	2010-02-29	56	
ASD02	TR	10001	10	TARGET	RA2	T03	LDIAM	Longest Diameter	30	mm	30	30	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	3	WEEK 8	2010-02-29	56	
ASD02	TR	10001	11	TARGET	RA2	T04	LDIAM	Longest Diameter	45	mm	45	45	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	3	WEEK 8	2010-02-29	56	
ASD02	TR	10001	12	NON-TARGET	RA2	N101	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	3	WEEK 8	2010-02-29	56	
ASD02	TR	10001	13	NON-TARGET	RA2	N102	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	3	WEEK 8	2010-02-29	56	
ASD02	TR	10001	14	NON-TARGET	RA2	N102	TUMSTATE	Tumor State	ABSENT		ABSENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	3	WEEK 8	2010-02-29	56	
ASD02	TR	10001	15	TARGET	RA3	T01	LDIAM	Longest Diameter	100 SMALL TO MEASURE	5	5	5	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102	
ASD02	TR	10001	16	TARGET	RA3	T02	LDIAM	Longest Diameter	12	mm	12	12	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102	
ASD02	TR	10001	17	TARGET	RA3	T03	LDIAM	Longest Diameter	10	mm	10	10	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102	
ASD02	TR	10001	18	TARGET	RA3	T04	LDIAM	Longest Diameter	30	mm	30	30	mm	NOT	TUMOR SPLIT ORIGINATED	CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102
ASD02	TR	10001	19	TARGET	RA3	T05	LDIAM	Longest Diameter	10	mm	10	10	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102	
ASD02	TR	10001	20	TARGET	RA3	T06	LDIAM	Longest Diameter	10	mm	10	10	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102	
ASD02	TR	10001	21	NON-TARGET	RA3	N101	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102	
ASD02	TR	10001	22	NON-TARGET	RA3	N102	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102	
ASD02	TR	10001	23	NON-TARGET	RA3	N102	TUMSTATE	Tumor State	ABSENT		ABSENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	5	WEEK 9	2010-04-24	102	
ASD02	TR	10001	24	TARGET	RA4	T01	LDIAM	Longest Diameter	0	mm	0	0	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88	
ASD02	TR	10001	25	TARGET	RA4	T02	LDIAM	Longest Diameter	0	mm	0	0	mm	NOT	TUMOR MERGED OR COALESCE	CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88
ASD02	TR	10001	26	TARGET	RA4	T03	LDIAM	Longest Diameter	20	mm	20	20	mm	NOT	TUMOR MERGED OR COALESCE	CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88
ASD02	TR	10001	27	TARGET	RA4	T04	LDIAM	Longest Diameter	30	mm	30	30	mm	NOT	TUMOR SPLIT ORIGINATED	CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88
ASD02	TR	10001	28	TARGET	RA4	T05	LDIAM	Longest Diameter	5	mm	5	5	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88	
ASD02	TR	10001	29	TARGET	RA4	T06	LDIAM	Longest Diameter	30	mm	30	30	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88	
ASD02	TR	10001	30	NON-TARGET	RA4	N101	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88	
ASD02	TR	10001	31	NON-TARGET	RA4	N102	TUMSTATE	Tumor State	ABSENT		ABSENT			NOT	NOT ASSASSABLE Image	CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88
ASD02	TR	10001	32	NON-TARGET	RA4	N102	TUMSTATE	Tumor State	ABSENT		ABSENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	7	WEEK 10	2010-06-09	88	
ASD02	TR	10001	33	TARGET	RA5	T01	LDIAM	Longest Diameter	0	mm	0	0	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	
ASD02	TR	10001	34	TARGET	RA5	T02	LDIAM	Longest Diameter	0	mm	0	0	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	
ASD02	TR	10001	35	TARGET	RA5	T03	LDIAM	Longest Diameter	30	mm	30	30	mm	NOT	TUMOR MERGED OR COALESCE	CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104
ASD02	TR	10001	36	TARGET	RA5	T04	LDIAM	Longest Diameter	30	mm	30	30	mm	NOT	TUMOR MERGED OR COALESCE	CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104
ASD02	TR	10001	37	TARGET	RA5	T05	LDIAM	Longest Diameter	50	mm	50	50	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	
ASD02	TR	10001	38	TARGET	RA5	T06	LDIAM	Longest Diameter	50	mm	50	50	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	
ASD02	TR	10001	39	TARGET	RA5	T07	LDIAM	Longest Diameter	48	mm	48	48	mm	NOT	TUMOR SPLIT ORIGINATED	CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104
ASD02	TR	10001	40	TARGET	RA5	T08	LDIAM	Longest Diameter	6	mm	6	6	mm		CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	
ASD02	TR	10001	41	NON-TARGET	RA5	N101	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	
ASD02	TR	10001	42	NON-TARGET	RA5	N101	TUMSTATE	Tumor State	UNRECOGNIZED PROLIFERATION		UNRECOGNIZED PROLIFERATION				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	
ASD02	TR	10001	43	NON-TARGET	RA5	N102	TUMSTATE	Tumor State	ABSENT		ABSENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	
ASD02	TR	10001	44	NON-TARGET	RA5	N102	TUMSTATE	Tumor State	PRESENT		PRESENT				CT SCAN	INDEPENDENT RADIOLOGIST	TREATMENT	9	WEEK 11	2010-08-04	104	

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[illegible]

The above example shows investigator tumor results. This example shows the alternative approach to representing split (fragmented) and merged (coalesced) tumors. This example also shows a case where progressive disease due to symptomatic deterioration was determined based on a clinical assessment by the investigator. The split tumors are represented with TRTEST='Tumor State' and TRORES='TUMOR SPLIT OR DIVIDED'. The tumor measurement for the split tumor is the sum of the split tumors. The merge tumors are represented with TRTEST='Tumor State' and TRORES='TUMOR MERGED OR COALESCED'. The tumor measurement of the merged tumors are represented by recording the sum of the merged tumor under one of the 'parent' tumor TRLNKID and a '0' is recorded as the measurement of the other 'parent' tumor TRLNKID. This example includes a visit where not all target tumors were measured.

3. **Disease Response (RS)** domain represents the response evaluation(s) determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response". According to the SDTM IG v 3.2 The RS domain represents the response evaluation(s) determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response.

STUDY	DOMAIN	USUBJID	RS	CS	INMGAP	RSTSTCSD	TEST	RSCAT	RSORSE	RSRSTR	RSNAM	RSEVAL	RSEVALID	EPOCH	VISITNUM	VISIT	RSDTC	RSDY
Example 2: Domain to show independent assessor response data using RECIST 1.0. This example shows the preferred approach to representing split (fragmented) and merged (coalesced) tumors.																		
AZD123	RS	10001	1			TRGRSP	Target Response	RECIST 1.0	SD	SD	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 1	WEEK 8	2010-02-27		
AZD123	RS	10001	2			NTRGRSP	Non-Target Response	RECIST 1.0	SD	SD	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 1	WEEK 8	2010-02-27	56	
AZD123	RS	10001	3	R A2		OVRLRSP	Overall Response	RECIST 1.0	SD	SD	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 1	WEEK 8	2010-02-27	56	
AZD123	RS	10001	4			TRGRSP	Target Response	RECIST 1.0	PR	PR	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 5	WEEK 16	2010-04-11		
AZD123	RS	10001	5			NTRGRSP	Non-Target Response	RECIST 1.0	PR	PR	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 5	WEEK 16	2010-04-11	112	
AZD123	RS	10001	6	R A3		OVRLRSP	Overall Response	RECIST 1.0	PR	PR	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 5	WEEK 16	2010-04-11	112	
AZD123	RS	10001	7			TRGRSP	Target Response	RECIST 1.0	SD	SD	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 7	WEEK 24	2010-06-19		
AZD123	RS	10001	8			NTRGRSP	Non-Target Response	RECIST 1.0	SD	SD	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 7	WEEK 24	2010-06-19	144	
AZD123	RS	10001	9	R A4		OVRLRSP	Overall Response	RECIST 1.0	PR	PR	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 7	WEEK 24	2010-06-19	144	
AZD123	RS	10001	10			TRGRSP	Target Response	RECIST 1.0	PD	PD	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 9	WEEK 32	2010-08-14	224	
AZD123	RS	10001	11			NTRGRSP	Non-Target Response	RECIST 1.0	PD	PD	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 9	WEEK 32	2010-08-14	224	
AZD123	RS	10001	12			OVRLRSP	Overall Response	RECIST 1.0	PD	PD	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 9	WEEK 32	2010-08-14	224	
AZD123	RS	10001	13	R A5		OVRLRSP	Overall Response	RECIST 1.0	Increased shortness of breath	Increased shortness of breath	BBB IMAGING	INDEPENDENT ASSESSOR	RADIOLOGIST	TREATMENT 9	WEEK 32	2010-08-14	224	

The above is an example to show both investigator and independent assessor response (RS) data using RECIST 1.0. This example shows a case where Target and Non-Target tumors are identified at screening (or baseline) and then assessed at subsequent visits. It also shows the identification of a new tumor during study conduct. In this example --EVALID is used in conjunction with --EVAL to provide an additional level of detail when multiple assessors play the role defined by --EVAL. This example also shows a case where the target response and non-target response indicate progression radiologically. The investigator also indicated that there was symptomatic deterioration indicating progression based on a clinical assessment (RSCAT='PHYSICIAN DECISION'). The actual symptomatic deterioration is represented in the RSORRES value and the standardize representation (RSSTRESC) is PD.

STUDYID	DOMAIN	SUBJID	RSVQSTG	RSLNKRGR	RSTEST	RSRSC	RSRORSE	RSRSTRESC	RSEVAL	EPOCH	VISITNUM	VISIT	RSQTC	RSQY	SUPPRS	ASRSEANE
Example 3: Example to show investigator tumor identification, tumor results and response data using RECIST 1.0. This example shows the alternative approach to representing split (fragmented) and merged (coalesced) tumors. This example also shows a case where progressive disease due to symptomatic deterioration was determined based on a clinical assessment by the investigator.																
AZD123	RS	10009	1	TRGRRESP	Target Response	RECIST 1.0	SD	SD	INVESTIGATOR	TREATMENT	3	WEEK 8	2010-02-27	56		
AZD123	RS	10009	2	NTRGRRESP	Non-target Response	RECIST 1.0	SD	SD	INVESTIGATOR	TREATMENT	3	WEEK 8	2010-02-27	56		
AZD123	RS	10009	3	OVRLRESP	Overall Response	RECIST 1.0	SD	SD	INVESTIGATOR	TREATMENT	3	WEEK 8	2010-02-27	56		
AZD123	RS	10009	4	TRGRRESP	Target Response	RECIST 1.0	PR	PR	INVESTIGATOR	TREATMENT	5	WEEK 16	2010-04-24	112		
AZD123	RS	10009	5	NTRGRRESP	Non-target Response	RECIST 1.0	SD	SD	INVESTIGATOR	TREATMENT	5	WEEK 16	2010-04-24	112		
AZD123	RS	10009	6	OVRLRESP	Overall Response	RECIST 1.0	PR	PR	INVESTIGATOR	TREATMENT	5	WEEK 16	2010-04-24	112		
AZD123	RS	10009	7	TRGRRESP	Target Response	RECIST 1.0	PR	PR	INVESTIGATOR	TREATMENT	7	WEEK 24	2010-06-19	168		
AZD123	RS	10009	8	NTRGRRESP	Non-target Response	RECIST 1.0	SD	SD	INVESTIGATOR	TREATMENT	7	WEEK 24	2010-06-19	168		
AZD123	RS	10009	9	OVRLRESP	Overall Response	RECIST 1.0	PR	PR	INVESTIGATOR	TREATMENT	7	WEEK 24	2010-06-19	168		
AZD123	RS	10009	10	TRGRRESP	Target Response	RECIST 1.0	NE	NE	INVESTIGATOR	TREATMENT	9	WEEK 32				Insufficient Images/Anatomical Assessment
AZD123	RS	10009	11	NTRGRRESP	Non-target Response	RECIST 1.0	NE	NE	INVESTIGATOR	TREATMENT	9	WEEK 32				
AZD123	RS	10009	12	SYMPTDTR	Symptomatic Deterioration	PHYSICIAN DECISION	PD	PD	INVESTIGATOR	TREATMENT	9	WEEK 32	2011-08-12	226		

The above example shows investigator tumor response data. This example shows the alternative approach to representing split (fragmented) and merged (coalesced) tumors. This example also shows a case where progressive disease due to symptomatic deterioration was determined based on a clinical assessment by the investigator. This

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example includes a visit where not all target tumors were measured and therefore the response is not evaluable at that visit. This example also shows a case where progressive disease due to symptomatic deterioration was determined based on a clinical assessment by the investigator (RSCAT='PHYSICIAN DECISION'). The actual symptomatic deterioration is represented in the RSORRES value and the standardized representation (RSSTRESC) is PD.

With the rapid drug development in oncology, there exist some discrepancies. In terms of tumor burdens, the most significant difference between RECIST and irRECIST is how to handle newly appeared lesions. As is well known, based on RECIST (Eisenhauer, 2009), if a new lesion comes up and is considered unequivocal progressive, patients will be considered to have progressive disease and need to be removed from treatment. However, taking irRECIST for example, if there is a measurable new lesion, the patient might not necessarily be considered as developing progressive disease due to the special "immune-related" mechanism of action. Instead, the new measurable lesions will be measured and incorporated into total measurements of tumor burden (TMTB). Based on the new tumor burden which combines both target lesions and measurable new lesions, a response will be given accordingly. On the other hand if non-measurable new lesions appear, according to irRECIST, the investigators or clinicians will make a judgment based on the size or number of the new lesions and decide whether the new lesions are massive enough to result in a progressive disease.

So how does the above impact safety-efficacy analysis in ADaM? It is generally known that the evaluation of efficacy in oncology studies, in particular for solid tumors, is pretty standard and well defined by several regulatory guidance agencies (e.g. EMA and FDA), including some specific cancer type guidance (e.g. NSCLC from FDA). The solid tumors efficacy endpoints mainly include Overall Survival, Best Overall Response as per RECIST criteria, Progression Free Survival (PFS), Time to Progression (TTP), Best Overall Response Rate are some of the key efficacy indicators. Initially tumor response rate was sufficient for FDA approval of oncologic drugs. However, in early '80s, the FDA started requesting demonstration of improvement in survival. Thereafter, Overall survival (OS) became the key endpoint to measure efficacy for most of the oncology indications as it is the only endpoint which demonstrates a "direct" clinical benefit to patients. Thereafter, surrogate endpoints have been used to speed the market arrival of new agents with the potential to save or extend lives. Thus, the use of Objective Response Rate (ORR), Time to Progression (TTP), Disease Free Survival (DSF), Progression Free Survival (PFS), increased in the application for new oncology drug approval; in particular ORR with or without TTP was used in almost 50% of the application (from Jan 90 to Nov 2002). While the creation of surrogate endpoints may serve the purpose of drug to market for companies investing in cancer research, what is perhaps still missing is the true efficacy endpoint in identifying if the DSF and PFS are truly cases of patients who have survived the cancer or the disease progression has considerably been reduced.

TUMOR DATA HANDLING ISSUES

While Oncology studies have been using TU, TR and RS domains to display and analyze tumor data, there remain some key data issues in terms of scope of data and loopholes in data handling. Many clinical trials in oncology lack adequate safeguards to ensure accuracy in data collection and data handling. Reconciliation of dynamic oncology data (Splitting/Merging of Tumors) is often inaccurate and lacks audit safeguards to ensure data quality and accuracy. It is imperative to ensure that data is captured and analyzed consistently using RECIST.

RECIST guidelines were introduced in 2000 to provide a standard for evaluating tumor response, with the goal of maintaining consistency at sites and across sites as well as limiting any site bias. An updated Version 1.1 was released in 2008. The guidelines provide Baseline instructions for data collection/reporting. At Baseline, tumors lesions will be categorized into measurable and non-measurable, and target and non-target. The lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement to be recorded). Challenges may occur when it comes to validating lesion measurement and calculating Overall Response, and it's critical to establish a clear process in order to appropriately reconcile the tumor assessment data.

The Clinical Data Manager and statistical teams working on the study should have extensive knowledge of these RECIST guidelines. Where possible, the EDC system should be used for automatic edit checks as prompting the sites at the time of entry is beneficial and leads to a higher quality of data. System edit checks can be used to ensure that the method of assessment is consistent across all follow-up tumor assessments based on the data entered at Baseline. An auto calculation may also be used for the sum of lesions to facilitate cleaning and ensure quality of data from the site end.

It is well known that most tumors within the body grow and regress irregularly and some cancers may display mixed responses. As a result, the sum of all lesions measured may 'disguise' differential tumor responses and may not truly reflect the overall disease status. In such circumstances, the radiologist or the evaluator should provide detailed comments to explain possible response 'discrepancies'. Also, misclassification of response can often be the result of the selection of fewer and smaller target lesions and so interpreters should be encouraged to select the maximum number of target lesions and give preference to large lesions, whenever possible. While there are no specific guidelines on the quantity of target lesion selections, it is often left to the choice of the evaluator or interpreter to select a right mix of lesions for tumor analysis and evaluation. This could affect tumor evaluation results in the long term.

Another issue seen in tumor data is that in early phase oncology studies, patients may continue through various cycles of study treatment until development of disease progression, a dose limiting toxicity or another withdrawal criterion. These multiple cycles imply a high volume of data collection and bring an inherent issue of variability in trial length for the subjects. What is needed is a close collaboration between Data Management and Statistics groups during CRF creation to ensure that no duplicate data is being collected. The Clinical Data Manager must also ensure that eCRFs are designed to facilitate accurate and timely data collection. It's of course critical that data is cleaned consistently throughout the course of the study (through both automatic and manual checks). This means that by the time of an interim or final analysis the data is clean and ready to be analyzed.

Another challenge seen is the use of medical coding in combination therapies. Chemotherapy treatments are often composed of various drug combinations which are not all catered for by the WHO Drug dictionary. The WHO Drug Dictionary should be willing to include new terms on request. The Coding Team should be versed in requesting additions. Planning for up-versioning the study before the lock should be discussed and documented early on in the trial within the Data Management Plan.

Different oncology trials have reported gaps in data handling specifically when progression-free survival (PFS) is used as the primary efficacy endpoint in the evaluation of cancer treatment. In a final statistical outcome analysis, missing or incomplete data issues become more acute with a PFS endpoint (compared with overall survival). In any given clinical trial, it is common to observe incomplete data due to premature treatment discontinuation, missed or flawed assessments, change of treatment, lack of follow-up, and unevaluable data. When incomplete data issues are substantial, interpretation of the data becomes tenuous. Plans to prevent, minimize, or properly analyze incomplete data are critical for generalizability of results from the clinical trial. Variability in progressive disease measurement between radiologists further contributes to data problems with a PFS endpoint. The repercussions of this, for example, on Phase III clinical trials are complex and depend on several factors, including the magnitude of the variability and whether there is a systematic reader evaluation bias favoring one treatment arm particularly in open-label trials. What is perhaps needed is clear-cut guidelines on how to resolve or evaluate cases of missing data or data handling issues if the data gaps are significant in tumor studies. Any occurrence of bias in analyses and evaluation of tumor data can result in significant spiraling effect on pipeline tumor drugs, especially if the tumor data handling issues are not resolved or acknowledge in early phase of the clinical trial.

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TUMOR DOMAIN UPDATES

The next version of the SDTMIG (version 3.3) is expected to add a number of new domains, variables, and concepts that will be included in SDTMIG v3.3. It is interesting to note that among the other new domains, the definitions of the Tumor domains (TU, TR) have been expanded to include non-tumor lesions.

With SDTMIG v3.3, the scope of the TU and TR domains has been broadened to include other types of lesions, rather than being limited to tumors. The domain names have been updated to include "Tumor/Lesion" to reflect the broadened usage. The documentation mentions the very broad definition of "lesion", which "can be almost any abnormal change involving any tissue or organ, usually due to disease or injury." Text and examples have been updated to include examples for Cardiovascular Lesions data and the representation of cysts for the Polycystic Kidney Disease.

CONCLUSION

An important outcome of long years of research and development in oncology is perhaps new research in tumor drug paint, designed to improve surgical outcomes in children with brain tumors – the most common solid tumor cancer in kids. Currently, this phase 1 trial, which is being conducted under an open U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) application, is open to infants through young adults under age 30 who have been diagnosed with a brain tumor.

Complete removal of a brain tumor in surgery is the greatest predictor of survival for patients with brain cancer. However, tumor cells are difficult to distinguish from healthy cells in surgery, and the removal of healthy tissue can lead to serious long-term side effects. Tumor paint aims to enable better detection and surgical resection of solid tumors without injuring surrounding healthy tissue. The drug acts as a molecular flashlight that binds to tumors cells and makes them glow, providing surgeons with real-time, high-resolution visualization of cancer cells.

If successful, tumor paint has the potential to completely revolutionize surgical oncology. This will have large scale impact on how tumor data is collected, handled, analyzed and reported. There is likelihood of better tumor data accuracy if the tumor split or coalesced which can be recorded effectively by paint biomarkers to correctly assess tumor datapoints and predict measurable outcomes with significantly less data collection and handling errors by sites, investigators and radiologists.

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