

PhUSE 2013 DH04

Overcoming difficulties in implementing RECIST criteria

Gerlind Ruhnke (Merck Serono)



About Myself

- Gerlind Ruhnke
Senior principal statistical programmer
Global Biostatistics Oncology Merck KgaA Darmstadt
- Medical technical assistant with 17 years experience in different laboratories
- 13 years statistical programming experience
- 7 years experience in Oncology trials.

Introduction

Tumor shrinkage (response) and time to progression are important endpoints in clinical trials. To get a widely accepted standardized set of guidelines an international working group was formed in 1990.

RECIST criteria 1.0 were published in 2000. They are based on an anatomical unidimensional measurement of the tumor burden.

RECIST1.1 was published in January 2009 to address issues that arose during implementation of RECIST 1.0.

With upcoming new technologies there are ongoing discussions regarding whether it is time to move to a volumetric or functional assessment.

This presentation discusses pitfalls we should be aware of and checks we can implement, how RECIST reacted with the revised version 1.1 and how it is implemented in the new CDISC tumor domains

OVERVIEW OF THE GUIDELINES

- The guidelines discuss
 - When is a measurable lesion regarded as target lesion and how many lesions can be defined as target lesion
 - What is regarded as non-target lesion or as a new lesion
 - Baseline documentation of lesions
 - Assessment methods
 - How progression or response will be calculated (target lesions non-target lesions new lesions overall)
 - Frequency of tumor evaluation
 - Confirmatory measurements

MOST IMPORTANT RULES

- Same imaging methods need to be used for a lesion during the whole study to ensure comparability between the measurements
- Lesions need to be followed during the whole study even if it disappears, splits or merge with other lesions. If a measurement of one lesion is missing the overall assessment is not assessable
- New lesions need to be defined as a new lesion. 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 asses target lesions.

OVERALL RESPONSE (RECIST 1.1)

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

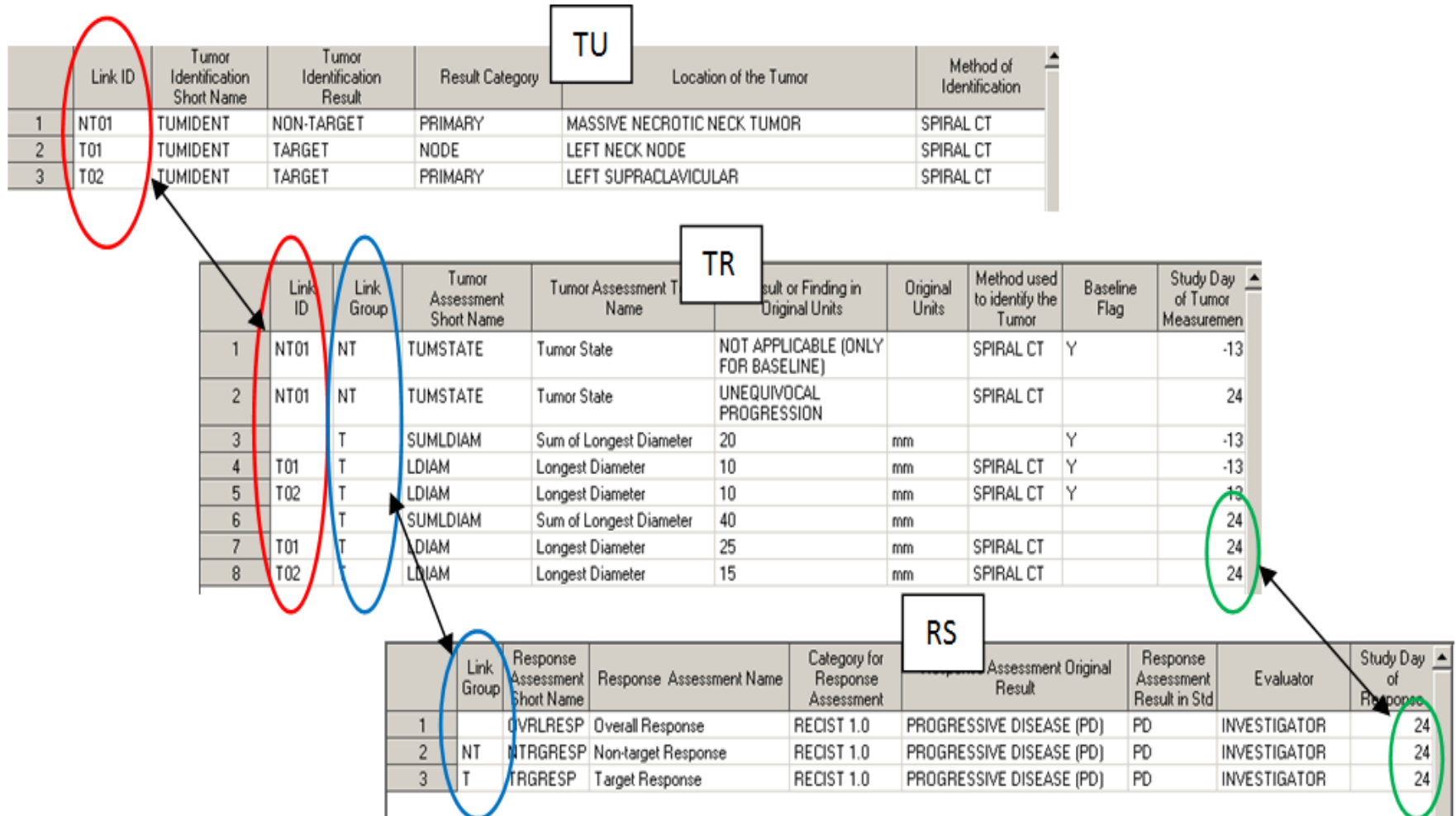
COMMON ISSUES WHILE IMPLEMENTING RECIST

- A Tumor might not have been measured with the same method or measurements might be missing
- A Tumor might have split or merged.
- The longest diameter 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 not really measurable. This causes incorrect interpretation of the result.
- A lesion might disappear and reappear.
- Assessing affected lymphnodes needs some special attention as lymphnodes are also normal structures that can be measured.
- Lesions might change the shape
- Lesions might become inevaluable.

IMPLEMENTAION IN THE CDISC TUMOR DOMAINS

- TU – Tumor identification: In this domain every lesion is captured once with a unique ID. Here all lesion specific details are described, such as description of the lesion, location of the lesion, imaging method to be used.
- TR – Tumor Results. Here all measurements of the lesions are captured by timepoint including the method that has been used in a visit. The longest diameter for target lesions, the assessment for non-target lesions, the sum of longest diameter for target lesions if it is captured in the CRF. It does not include derived parameter.
- RS – Response. Here we find all response assessments as captured in the CRF: Target response, non-target response, overall response, best overall response, but also assessments that are not coming from the tumor domains like symptomatic deterioration or non-radiological progression. It does not include derived parameter.

LINK BETWEEN THE TUMOR DOMAINS



RELREC

RDOMAIN	IDVAR	IDVARVAL	RELTYPE	RELID
RS	RSLNKGRP		ONE	RS-TR
TR	TRLNKGRP		MANY	RS-TR
TR	TRLNKID		MANY	TU-TR
TU	TULNKID		ONE	TU-TR



HANDLING THE ISSUES

- Check if all measurements are available and if the method has been used
 - Merge TU, TR and RS domains. Make sure that all lesions in TU are in every visit of TR and vice versa. Check that the RS entries are matching as well. Make sure that TUMETHOD = TRMETHOD
 - A measurement that has been measured with another method cannot be used, it is not comparable.

Important: If the measurement of one lesion is missing or has been measured with another method, a sum of longest diameter can not be calculated!

EXAMPLE

```
proc sql;
  create table tumortest as select
    coalesce(a.usubjid, b.usubjid, c.usubjid) as usubjid,
    tulnkid, trlnkid, trlnkgrp, rslnkgrp, tumethod, trmethod,
    tudy, trdy, rsdy, b.visitnum as trvisitnum, c.visitnum as rsvisitnum
  from sdtm.tu as a
  full join sdtm.tr(where=(trtestcd ne "SUMLDIAM")) as b
    on a.usubjid = b.usubjid and
       tulnkid = trlnkid
  full join sdtm.rs(where=(rtestcd ne "OVLRESP")) as c
    on a.usubjid = c.usubjid and
       trlnkgrp = rslnkgrp and
       b.visitnum = c.visitnum
  order by usubjid, tulnkid;
quit;
```

VIEWTABLE: Work.Tumortest									
	TULNKID	TRLNKID	TRLNKGRP	RSLNKGRP	TUMETHOD	TRMETHOD	TUDY	TRDY	RSDY
647				NEW					45
648	NEW01				SPIRAL CT		45		
649	NEW02				SPIRAL CT		45		
650	NT01	NT01	NT		SPIRAL CT	SPIRAL CT	-27	-27	
651	NT01	NT01	NT	NT	SPIRAL CT	SPIRAL CT	-27	45	45
652	T01	T01	T		SPIRAL CT	SPIRAL CT	-27	-27	
653	T01	T01	T	T	SPIRAL CT	SPIRAL CT	-27	45	45
654	T02	T02	T		SPIRAL CT	SPIRAL CT	-27	-27	
655	T02	T02	T	T	SPIRAL CT	SPIRAL CT	-27	45	45

SPLITTED OR MERGERD LESIONS

TULINKID	TUTESTCD	TUTEST	TUORRES	VISIT
T01	TUMIDENT	Tumor Identification	TARGET	SCREEN
T02	TUMIDENT	Tumor Identification	TARGET	SCREEN
T03	TUMIDENT	Tumor Identification	TARGET	SCREEN
T04	TUMIDENT	Tumor Identification	TARGET	SCREEN
NT01	TUMIDENT	Tumor Identification	NON-TARGET	SCREEN
NT02	TUMIDENT	Tumor Identification	NON-TARGET	SCREEN
T04.1	TUSPLIT	Tumor Split	TARGET	WEEK 16
T04.2	TUSPLIT	Tumor Split	TARGET	WEEK 16
T02/T03	TUMERGE	Tumor Merged	TARGET	WEEK 24
NEW01	TUMIDENT	Tumor Identification	NEW	WEEK 32

A split of a lesion is not a new Lesion!

A split lesion will be counted within the sum of longest diameter and might in fact be a shrinkage of the tumor.

SMALL VALUES OF THE LONGEST DIAMETER

According to RECIST 1.1 a value of 5 mm has to be used in these cases.

Implementaion in the Tumor domains:

TRLINKID	TRTESTCD	TRTEST	TORRES	TORRESU	TRSTRESC	TRSTRESN	TRSTRESU
T01	LDIAM	Longest Diameter	TOO SMALL TO MEASURE	mm	5	5	mm

DISAPPEARING AND REAPPEARING LESIONS

If a lesion disappears and reappears later it is not regarded as a new lesion. According to RECIST 1.1 it should be handled as if it did not disappear and added to the sum of longest diameter. A value of 0 will be used for the disappeared lesion.

➡ Check if the new lesions are in fact not new lesions but reappearing lesions.

LYMPHNODES

Lymphnodes should not be used as target lesions if there is another choice. In RECIST 1.1 lymphnodes are discussed separately. If lymphnodes are used as target lesion the short axis has to be taken for measurement. A Lymphnode < 1 cm is regarded as normal.

➡ Check all lesions that are classified as lymphnodes.

CHANGING SHAPE

If the shape of a lesion changes still the longest diameter (or short axis in case of lymphnodes) has to be used.

This is something we cannot check in the data. Therefore an independent read is favorable

INEVALUABLE LESIONS

If lesions become inevaluable the sum of longest diameter cannot be derived for that visit. There might be other visits with evaluable measurements. Otherwise the subject is not evaluable.

In the FAQ section about RECIST 1.1 it was suggested to reassess the lesion as non target lesion and drop all measurements from the target lesions if nothing else is possible. Make sure not to manipulate data. The investigator assessment needs to be unchanged.

➡ Check the data for inevaluable measurements.

OTHER CHECKS

- Check the overall response for new lesions: Is it PD?
- Recalculate the percentage change from NADIR. >20 % increase from NADIR is regarded as PD (if ≥ 5 mm).
- Recalculate the percentage change from baseline. 30 % decrease from baseline is regarded as partial response. A confirmation in the following visit is needed.

Caveat: Do not change investigator assessments!

CONCLUSION

The assessment of tumor burden is challenging and there might be a lot of issues and patient specific special cases in the data.

The new RECIST1.1 guidelines and the CDISC tumor domains help a lot regarding data handling and evaluation. But nothing replaces the special human attention to these special data.

**Thanks for your
Attention!**