

## SAS Macro to Derive Integrated PET+CT Response in FDG-avid Lymphoma per Lugano 2014

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### ABSTRACT

As it is well known, CT or MRI are traditionally used in clinical practice and clinical trials to assess tumor changes during or at the completion of anti-cancer treatment. With more and more effective therapies in lymphoma and sensitive technologies for disease assessment developed, new response criteria, such as Lugano 2014 [1], emerged and has been increasingly used. Lugano 2014 recommends incorporating positron emission tomography (PET) - computed tomography (CT) to better assess response in fluorodeoxyglucose (FDG)-avid lymphomas. This article aims to introduce a SAS macro to derive the integrated PET+CT timepoint response (hereinafter called “TPR”) according to Lugano 2014.

As in clinical trials for FDG-avid lymphoma patients’ disease status was evaluated periodically using both PET and CT, in order to obtain an accurate integrated PET+CT response, the approach of integrating a PET scan result with CT result at each timepoint must be clearly defined [2]. This article considers two scenarios with different algorithms [2] to derive the integrated PET+CT TPR. The SAS macro proposed in this article can be used to programmably derive the integrated PET+CT TPR and check if it is consistent with the integrated PET+CT TPR assessed by Independent Review Committee (IRC).

### INTRODUCTION

In the past decades, response assessment criteria for lymphoma has achieved great progress. Cheson 1999 [3] and Cheson 2007 [4] criteria mainly rely on CT scan, with the development of more sensitive technologies for disease assessment, such as PET-CT scan, a new criteria Lugano 2014 was proposed and has been increasingly used in setting of clinical practice and clinical trials ever since.

Lugano 2014 incorporates the PET-CT into initial CT-based evaluation, staging and response assessment for FDG-avid lymphomas. PET-CT-based response includes complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), and progressive metabolic disease (PMD), while CT-based response contains complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). If the imaging is missing or not evaluable, the corresponding response will be shown as not evaluable (NE).

In a clinical trial for a FDG-avid lymphoma, the integration of PET into the CT evaluation is not straightforward, meanwhile, in order to mitigate the evaluation bias from investigators, single arm studies oftentimes involve IRC (Independent Review Committee) for independent assessment. Hence, the approach of integrating a PET scan result into a patient’s disease assessment must be clearly defined and the integrated PET+CT result from IRC should be verified programmably using the specific integrating algorithm. This article considers two scenarios as examples and proposes a SAS macro to help derive/verify PET+CT integrated response through certain rules.

### METHODS

In this section, we will discuss two scenarios following the two guiding principles suggested by Cheson et al in 2014 [2] to derive the integrated PET+CT response via our SAS macro. Parameters needed for the SAS macro with detailed notation, example SAS code to generate dummy data and execute the macro, and the related SAS outputs will be covered.

## SCENARIO 1

In scenario 1, we consider a commonly-seen case where PET-based response will generally trump CT-based response except for the case with missing PET, which is the 1<sup>st</sup> guiding principle as mentioned in Cheson et al 2014 [2]. When PET is missing, the integrated response would be non-PD due to unknown status of PET response except when the PD is confirmed by CT.

Figure 1 shows a detailed logic rule that could be considered to use to derive the integrated PET+CT response in this case. In this figure, the PET response is in column 1, the CT response is in column 2, and the integrated PET +CT response is in column 3. For example, when PET response is CMR, as long as the value of CT response falls into CR or PR or SD or NE or PD, the response of the final integrated PET+CT response will be determined as CR.

PET Response	CT Response	Integrated PET+CT Response
CMR	CR/PR/SD/NE/PD	CR
PMR	CR/PR/SD/NE/PD	PR
NMR	CR/PR/SD/NE/PD	SD
NE*	CR/PR/SD/NE	Non-PD
NE*	PD	PD
PMD	CR/PR/SD/NE/PD	PD

**Figure 1: Integrated PET+CT Criteria for Scenario 1**

\*missing PET exam or not evaluable.

We will demonstrate the use of our SAS macro for this scenario in 4 steps as below.

Step 1: We prepare a dummy data set as an example to illustrate the macro usage. This data set contains the values of three variables as shown in Figure 1 above, and it is assumed to be provided by IRC. The program to generate the dummy data and the output are in figure 2.

### DUMMY DATA PROGRAM

```

/*The dataset must contain USUBJID/VISITNUM/VISIT;
  USUBJID: Unique Subject Identifier;
  VISITNUM: Visit Number;
  VISIT: Visit Name*/

data xs;
infile datalines;
input USUBJID $8. VISITNUM $6. VISIT $8. XSCAT $20. XSSCAT $35.
XSSSTRESC $8.;
datalines;
01-001 20300 CYCLE03 LUGANO (CHESON 2014) PET LUGANO ASSESSMENT
PMR
01-001 20300 CYCLE03 LUGANO (CHESON 2014) CT LUGANO ASSESSMENT
PR
01-001 20300 CYCLE03 LUGANO (CHESON 2014) INTEGRATED PET-CT/CT
ASSESSMENT PR
01-001 20600 CYCLE06 LUGANO (CHESON 2014) PET LUGANO ASSESSMENT
CMR
01-001 20600 CYCLE06 LUGANO (CHESON 2014) CT LUGANO ASSESSMENT
CR

```

```

01-001 20600 CYCLE06 LUGANO (CHESON 2014) INTEGRATED PET-CT/CT
ASSESSMENT CR
01-002 20300 CYCLE03 LUGANO (CHESON 2014) PET LUGANO ASSESSMENT
NMR
01-002 20300 CYCLE03 LUGANO (CHESON 2014) CT LUGANO ASSESSMENT
PR
01-002 20300 CYCLE03 LUGANO (CHESON 2014) INTEGRATED PET-CT/CT
ASSESSMENT SD
01-002 20600 CYCLE06 LUGANO (CHESON 2014) PET LUGANO ASSESSMENT
PMR
01-002 20600 CYCLE06 LUGANO (CHESON 2014) CT LUGANO ASSESSMENT
SD
01-002 20600 CYCLE06 LUGANO (CHESON 2014) INTEGRATED PET-CT/CT
ASSESSMENT PR
01-003 20300 CYCLE03 LUGANO (CHESON 2014) PET LUGANO ASSESSMENT
PMD
01-003 20300 CYCLE03 LUGANO (CHESON 2014) CT LUGANO ASSESSMENT
SD
01-003 20300 CYCLE03 LUGANO (CHESON 2014) INTEGRATED PET-CT/CT
ASSESSMENT PD
01-003 20600 CYCLE06 LUGANO (CHESON 2014) PET LUGANO ASSESSMENT
PMR
01-003 20600 CYCLE06 LUGANO (CHESON 2014) CT LUGANO ASSESSMENT
SD
01-003 20600 CYCLE06 LUGANO (CHESON 2014) INTEGRATED PET-CT/CT
ASSESSMENT PR
;
run;

```

USUBJID	VISITNUM	VISIT	XSCAT	XSSCAT	XSSTRESC
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	CMR
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	CR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMD
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PD
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR

**Figure 2: Example of Dummy Dataset**

Step 2: Set each parameter values in macro %resp\_drv, with each required parameter defined as below:

```

%macro resp_drv(
    inds=,
    catvar=,
    cat=,
    pet_crit=,
    ct_crit=,

```

```
int_crit=,  
outds=);
```

#### Definition

##### inds:

name of input dataset, such as XS. The input dataset must contain three standard variables: USUBJID, VISITNUM and VISIT

##### catvar:

category variable in the input dataset that must contain three categories: PET and CT and Integrated PET+CT. For example, the dummy dataset XS uses XSSCAT to store the three categories so we can set catvar to XSSCAT.

##### cat:

put the specific category name that stored in catvar in the dataset, that is, the value of XSSCAT. In the dummy data set, the values of XSSCAT are "PET LUGANO ASSESSMENT", "CT LUGANO ASSESSMENT" and "INTEGRATED PET-CT/CT ASSESSMENT". We only need to put the three values in a fixed sequence of PET/CT/Integrated, separated by "|".

##### pet\_crit:

values of PET response. That is, the value of PET response in the first column in Figure 1, separated by "|". For example, "CMR|PMR|NMR|NE|NE|PMD"

##### ct\_crit:

values of CT response. That is, the value of CT response in the second column in Figure 1, separated by "|" for each criterion. For example, "CR PR SD NE PD|CR PR SD NE PD |CR PR SD NE PD|CR PR SD NE|PD|CR PR SD NE PD". In each criterion, if there are multiple CT response values, different CT responses should be separated by blank.

##### int\_crit:

values of integrated PET+CT response. That is, the value of integrated PET+CT response in the third column in Figure 1, separated by "|" for each criterion. For example, set as "CR|PR|SD|PD".

##### outds:

name of output dataset. we can name the output dataset as FINAL in this example.

An example of parameter setting could be:

```
%resp_drv(  
  inds=xs,  
  catvar=xsscat,  
  cat= PET LUGANO ASSESSMENT|CT LUGANO ASSESSMENT|INTEGRATED  
      PET-CT/CT ASSESSMENT,  
  pet_crit=CMR|PMR|NMR|NE|NE|PMD,  
  ct_crit =CR PR SD NE PD|CR PR SD NE PD|CR PR SD NE PD|CR PR SD  
          NE|PD|CR PR SD NE PD,  
  int_crit=CR|PR|SD|Non-PD|PD|PD,  
  outds=final);
```

Step 3: After executing the macro, three extra variables will be added into the FINAL dataset and the three variables are "INT", "MISSING" and "MISMATCH".

- INT—The integrated PET+CT TPR. This variable will be filled only for category of integrated PET-CT/CT Assessment. For PET response or CT response, the value in INT will all be blank.

- MISSING—Indicate if the derived integrated PET+CT TPR is missing. If the integrated PET+CT TPR is not generated by the macro, the value will be “Y” to indicate this situation. There will also be a WARNING message shows in the log when “Y” in this variable. SAS code of WARNING message shown as below:

```

%if %index(&missing,Y) %then %do;
  %put WARNING: &sysmacroname: Missing Integrated derived response, please check!!!;
%end;

```

- MISMATCH—If ‘Y’ then it means that our derived integrated PET+CT response is inconsistent with the integrated PET+CT response provided by IRC. Figure 3 is an example of the output data set FINAL. It can be seen from Figure 3 that for 01-001, the integrated PET+CT responses of CYCLE 03 and CYCLE06 are PR and CR, respectively, and are consistent with the results provided by IRC in the input dataset. Hence the IRC-assessed integrated PET+CT Response is verified.

USUBJID	VISITNUM	VISIT	XSCAT	XSSCAT	XSSTRESC	INT	MISSING	MISMATCH
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR			
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR			
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	PR		
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	CMR			
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR			
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	CR	CR		
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR			
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR			
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD	SD		
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR			
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD			
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	PR		
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMD			
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD			
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PD	PD		
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR			
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD			
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	PR		

Figure 3: Example of Output FINAL dataset for Scenario 1

Step 4: If the algorithm of integrated PET+CT response is changed, our SAS macro is flexible enough to allow us to adjust the parameters in pet\_crit/ct\_crit/int\_crit to accommodate such a change. For example, in the figure below, we could change the integrated PET+CT response to SD when PET is PMR, then the value of INT variable in FINAL dataset will also be changed to SD accordingly, and the MISMATCH variable will be marked with Y to remind us the integrated response that does not match with IRC data.

```

%resp_drv(
  inds=xs,
  catvar=xsscscat,
  cat=PET LUGANO ASSESSMENT|CT LUGANO ASSESSMENT|INTEGRATED
    PET-CT/CT ASSESSMENT,
  pet_crit=CMR|PMR|NMR|NE|NE|PMD,
  ct_crit =CR PR SD NE PD|CR PR SD NE PD|CR PR SD NE PD|CR PR
    SD NE|PD|CR PR SD NE PD,
  int_crit=CR|SD|SD|Non-PD|PD|PD,
  outds=final);

```

USUBJID	VISITNUM	VISIT	XSCAT	XSSCAT	XSSTRESC	INT	MISSING	MISMATCH
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR			
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR			
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	SD		Y
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	CMR			
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR			
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	CR	CR		
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR			
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR			
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD	SD		
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR			
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD			
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	SD		Y
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMD			
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD			
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PD	PD		
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR			
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD			
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	SD		Y

**Figure 4: Updated output dataset FINAL for Scenario 1**

In addition to changes in the data set shown in Figure 4, as mentioned above, a prompt is set in the SAS macro so that there will also be a WARNING message shown in SAS log to indicate the mismatch information. SAS Log Notification:

`WARNING: RESP_DRV: Integrated Response Mismatch, please check!!!`

## SCENARIO 2

Here we consider another scenario, when PET is missing while CT response is available at certain cases. Missing PET scan may be due to radiation consideration, rapid disease progression or patients' compliance during treatment. As discussed by Cheson et al in 2014 [2] that for timepoints with only CT available, following a prior FDG-PET assessment, CT assessments may be affected by the prior PET/CT assessment, a concept of potentially imputing the missing PET scan with previous scan results could be considered to deal with this circumstance. The method of handling missing PET response here in this scenario is a practical case application of the principle. Despite the complexity of the true relationship between PET and CT in real life, to simplify the work, we consider to only use the previous non-missing PET response(s) prior to current visit to impute the current missing PET response. Based on the completed PET responses after imputing, we can then derive the integrated PET + CT response per the logic as in Figure 5.

PET Response	CT Response	Integrated PET+CT Response
CMR	CR/PR/SD/NE/PD	CR
PMR	CR/PR/SD/NE/PD	PR
NMR	CR/PR/SD/NE/PD	SD
CMR <sup>1</sup>	CR/PR/SD	CR
PMR <sup>2</sup>	CR/PR/SD	PR
NMR <sup>3</sup>	CR/PR/SD	SD
NE <sup>4</sup>	CR <sup>5</sup> /PR	PR
NE <sup>4</sup>	SD	SD
NA/NE	PD	PD
PMD	CR/PR/SD/NE/PD	PD
NA/NE	NE	NE

**Figure 5: Integrated PET+CT Criteria for Scenario 2**

- CMR<sup>1</sup>: CMR is carried forward from previous PET responses.
- PMR<sup>2</sup>: PMR is carried forward from previous PET responses.
- NMR<sup>3</sup>: NMR is carried forward from previous PET responses.
- NE<sup>4</sup>: This PET response is missing and there is no PET response from previous visits.
- CR<sup>5</sup>: If the PET response is missing and there is no PET response from previous visits, although the current CT response is CR, the integrated PET+CT response will be downgraded to PR.

The PET responses without superscript in the first column in Figure 5 have the following meaning:

- CMR: The current PET response is not missing and result is CMR.
- PMR: The current PET response is not missing and result is PMR.
- NMR: The current PET response is not missing and result is NMR.
- NA/NE: The current PET response is either not evaluable or missing.

Regarding the specific rule of imputing the PET response, we consider to use the conservative but simple LOCF (Last Observation Carry Forward) single-imputation method to assign the last available PET response to the current missing PET response, and then derive the integrated PET+CT response based on the algorithm in above Figure 5, although we admit there are more advanced imputation methods that consider the inner relationship of PET and CT responses and the nature of the missingness in this scenario and might better fit this case.

Figure 6 is a dummy dataset with missing PET response at certain visits. Dummy data program is similar to scenario 1.

USUBJID	VISITNUM	VISIT	XSCAT	XSSCAT	XSSTRESC
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR

**Figure 6: Dummy data with missing PET response at certain timepoints:**

The program to impute missing PET response via LOCF:

```

data LOCF;
  length dtype avallocf retain $15;
  retain retain;
  set xs;
  by usubjid xsscscat visitnum;
  if first.xsscscat then retain="";
  if xsstresc NE "" then retain=xsstresc;
  if xsstresc="" then do;
    avallocf=retain;
    dtype='LOCF';
  end;
  else avallocf=xsstresc;
  /*add * to the response using LOCF*/
  if dtype='LOCF' and not missing(avallocf) then
    xsstresc=strip(avallocf)||"*";
  /*set to NE if no previous PET response*/
  else if dtype='LOCF' and missing(xsstresc) then xsstresc="NE";
run;

```

An example of imputing PET Response using LOCF:

For 01-001, the PET response of CYCLE 06 is missing, but the PET response of CYCLE 03 is available and can be used to impute the PET response of CYCLE 06. Hence, the PET response of CYCLE 06 is imputed with “PMR\*”. The asterisk is added to the PET response derived by the LOCF method in order to distinguish the originally non-missing PET response from the PET response imputed by LOCF.

For 01-003, the PET response of CYCLE03 is missing, since CYCLE 03 is the first assessment visit and there is no other PET response before CYCLE 03, the PET response of CYCLE 03 as shown in Figure 7 is set as “NE”.

USUBJID	VISITNUM	VISIT	XSCAT	XSSCAT	XSSTRESC
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR*
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NE
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR



Figure 7: Example of PET response imputed by LOCF

Our SAS macro is capable of handling Scenario 2 with the “inds” parameter set to be “LOCF” as below:

```

%resp_drv(
  inds=LOCF,
  catvar=xsscscat,
  cat=PET LUGANO ASSESSMENT|CT LUGANO ASSESSMENT|INTEGRATED PET
  CT/CT ASSESSMENT,

```

```

pet_crit=CMR|PMR|NMR|CMR*|PMR*|NMR*|NE|NE|NA NE|PMD|NA NE,
ct_crit =CR PR SD NE PD|CR PR SD NE PD|CR PR SD NE PD|CR PR
SD|CR PR SD|CR PR SD|CR PR|SD|PD|CR PR SD NE PD|NE,
int_crit=CR|PR|SD|CR|PR|SD|PR|SD|PD|PD|NE,
outds=final);

```

USUBJID	VISITNUM	VISIT	XSCAT	XSSCAT	XSSTRESC	INT	MISSING	MISMATCH
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR			
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR			
01-001	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	PR		
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR*			
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR			
01-001	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	PR		
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR			
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	PR			
01-002	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD	SD		
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NMR			
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR			
01-002	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	SD	SD		
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	NE			
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	CR			
01-003	20300	CYCLE03	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	PR		
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	PET LUGANO ASSESSMENT	PMR			
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	CT LUGANO ASSESSMENT	SD			
01-003	20600	CYCLE06	LUGANO (CHESON 2014)	INTEGRATED PET-CT/CT ASSESSMENT	PR	PR		

**Figure 8: Example of Output FINAL dataset for Scenario 2**

For 01-001, the imputed PET response of CYCLE 06 is PMR\*, according to the criteria in Figure 5, when PET response is PMR (imputed), as long as CT response falls in CR/PR/SD, the integrated PET+CT response of CYCLE 06 is consistent with PET response, that is PR, and matches the IRC result.

For 01-003, the PET response of CYCLE03 is missing and there is no previous PET response to be carried forward, so PET response is still "NE". Hence, although the CT response is CR, according to the criteria shown in Figure 5, the integrated PET+CT response should be downgraded to PR and it matches the IRC result.

## CONCLUSION

The SAS macro is based on Linux and created using SAS9.4. The main purpose of this paper is to provide a SAS macro that enables us to programmably derive/verify the final integrated PET+CT response, TPR, based on the response of PET evaluation and the response of CT evaluation according to certain rules efficiently and flexibly. It should be noted that the derivative rules that are mentioned in this paper are proper for patients classified as FDG-avid. For patients classified as FDG-non-avid, there will be no integrated PET+CT response. The derivation rules involved in this article simply are based on two practices that we considered to be commonly seen and might not be sufficient to cover all other cases.

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