

# ‘This Is Not the Date We Need. Let’s Backdate’: An Approach to Derive First Disease Progression Date in Solid Tumor Trials

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## ABSTRACT

A time-to-event analysis, such as duration of response or progression-free survival, is an important component of assessments in oncology clinical trials. Derivation of true response dates is a key feature in developing ADRS and ADTTE ADaM data sets and a solid understanding of how such dates are derived is therefore critical for statistical programmers.

This paper discusses hands-on examples in solid tumor trials based on investigator assessment using RECIST 1.1 and presents SAS® programming techniques that are usually implemented in ADRS.

Response date derivations are categorized as below:

1. Overall response date derivation:
  - a. When an overall response is disease progression (PD): when at least one target, non-target, or new lesion shows PD, the date of PD is derived from the earliest of all scan dates that showed PD
  - b. When an overall response is equivocal progression: when at least one non-target or new lesion shows equivocal progression, the date of PD will be the earliest of all scan dates that showed equivocal progression
  - c. When an overall response is other than PD or equivocal progression: the response date is derived from the latest of all radiologic scan dates for the given response assessments
2. Progression backdating:

If a new lesion progressed to unequivocal right after equivocal assessments, or a non-target lesion progressed to disease progression right after equivocal progression assessments, backdate the progression event to the earliest scan where the new or non-target lesion was assessed as equivocal progression

## INTRODUCTION

In oncology trials, efficacy endpoints are often defined based on the “Response evaluation criteria in solid tumors” (RECIST) criteria, which describe detailed guidelines on the relationship of the tumor measurements to disease status. Assessment of lesions at different locations is obtained via PET, CT, or MRI scans, where measurement error and multiple sources of bias such as evaluation time bias and reader evaluation bias can impact the analysis of images thus obtained. One of the factors contributing to potential bias is the difference in the time between tumor scan date and tumor assessment date (or response date). The impact of this difference is quite pronounced in cancer-focused clinical trials. Therefore, FDA guidance on oncology endpoints recommends additional sensitivity analyses such as actual event and backdating PFS event analyses to assess the impact of such biases and help qualify the conclusions about the performance of investigational drugs. The guidance covers two important considerations around identifying the date of first disease progression (PD), specifically focused on the overall response derivation and backdating. The tumor assessment date in RS and tumor result date in TR enable sponsors to implement this guidance.

Before deriving overall response dates, it is useful to understand response values for target, non-target, and new lesions. All possible response and tumor result values are presented in the **Table 1** below.

**Table 1 - Time point response: patients with target (+/- non-target) disease.**

| 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.

**Table 2 - Time point response: patients with non-target disease only.**

| Non-target lesions | New lesions | Overall response           |
|--------------------|-------------|----------------------------|
| CR                 | No          | CR                         |
| Non-CR/non-PD      | No          | Non-CR/non-PD <sup>a</sup> |
| Not all evaluated  | No          | NE                         |
| Unequivocal PD     | Yes or No   | PD                         |
| Any                | Yes         | PD                         |

CR = complete response, PD = progressive disease, and NE = inevaluable.  
<sup>a</sup> a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

**Table 1. RECIST 1.1 Guidelines for Overall Response based on Target, Non-Target and New Lesions**

**Table 2** and **Table 3** show how this applies to target, non-target, and new lesion measurements for a sample subject, ABC-001. At the target site, lesion diameter values are captured in the SDTM TR data set. The CRF page captures equivocal and unequivocal measurements with corresponding dates under new lesions. The TR data set captures all corresponding scans. In an ideal scenario, both the scan dates and response assessment date correspond to the same date, but unfortunately this is not commonly the case. The date in RSDTC (response date) in the RS data set may or may not be matching with the TRDTC (scan date) in the TR domain. The example in **Table 2** and **Table 3** shows a case where the scan date (TRDTC) and response date (RSDTC) occur on the same day for week 6.

**SCAN DATES**

| DOMAIN | USBJID  | TRGRPID    | TRTEST                | TRORES      | TRSTRESC    | VISIT  | TRDTC      |
|--------|---------|------------|-----------------------|-------------|-------------|--------|------------|
| TR     | ABC-001 | TARGET     | Longest Diameter      | 10          | 10          | WEEK6  | 2020-01-01 |
| TR     | ABC-001 | TARGET     | Longest Perpendicular | 20          | 20          | WEEK7  | 2020-01-07 |
| TR     | ABC-001 | NON-TARGET | Tumor State           | PRESENT     | PRESENT     | WEEK6  | 2020-01-01 |
| TR     | ABC-001 | NEW        | Tumor State           | EQUIVOCAL   | EQUIVOCAL   | WEEK6  | 2020-01-01 |
| TR     | ABC-001 | NEW        | Tumor State           | UNEQUIVOCAL | UNEQUIVOCAL | WEEK12 | 2020-02-15 |

**Table 2. Sample TR SDTM Data Set with Tumor Measurements**

**RESPONSE ASSESSMENT DATES**

| DOMAIN | USBJID  | RSTEST   | RSTESTCD               | RSORRES       | RSEVAL       | VISIT  | RSDTC      |
|--------|---------|----------|------------------------|---------------|--------------|--------|------------|
| RS     | ABC-001 | TRGRESP  | Target Response        | SD            | INVESTIGATOR | WEEK6  | 2020-01-01 |
| RS     | ABC-001 | NTRGRESP | Non-target Response    | NON-CR/NON-PD | INVESTIGATOR | WEEK6  | 2020-01-01 |
| RS     | ABC-001 | NEWLPROG | New Lesion Progression | NO            | INVESTIGATOR | WEEK6  | 2020-01-01 |
| RS     | ABC-001 | OVRLRESP | Overall Response       | SD            | INVESTIGATOR | WEEK6  | 2020-01-01 |
| RS     | ABC-001 | TRGRESP  | Target Response        | PD            | INVESTIGATOR | WEEK12 | 2020-02-15 |
| RS     | ABC-001 | NTRGRESP | Non-target Response    | NON-CR/NON-PD | INVESTIGATOR | WEEK12 | 2020-02-15 |
| RS     | ABC-001 | NEWLPROG | New Lesion Progression | NO            | INVESTIGATOR | WEEK12 | 2020-02-15 |
| RS     | ABC-001 | OVRLRESP | Overall Response       | PD            | INVESTIGATOR | WEEK12 | 2020-02-15 |
| RS     | ABC-001 | TRGRESP  | Target Response        | SD            | INVESTIGATOR | WEEK18 | 2020-03-31 |
| RS     | ABC-001 | NTRGRESP | Non-target Response    | NON-CR/NON-PD | INVESTIGATOR | WEEK18 | 2020-03-31 |
| RS     | ABC-001 | NEWLPROG | New Lesion Progression | YES           | INVESTIGATOR | WEEK18 | 2020-03-31 |
| RS     | ABC-001 | OVRLRESP | Overall Response       | PD            | INVESTIGATOR | WEEK18 | 2020-03-31 |

**Table 3. Sample RS SDTM Data Set with Response Assessments**

## OVERALL RESPONSE DATE DERIVATION

The overall response date is derived (rather than observed) in the ADaM ADRS (response) data set when the scan and response assessment dates are collected on different dates using different imaging techniques. Below are the situations where we need to consider scan dates for the derivation of ADT (ADaM analysis date; here, response date) for overall response.

### WHEN OVERALL RESPONSE IS PD...

#### Scenario 1 (Ideal Situation):

If any target, non-target, or new lesion shows evidence of progression, the date of progression will be the earliest date of all scan dates that showed evidence of progression.

If an overall progression is due to a target lesion, then the earliest scan date among all target lesions (let it be  $PD_{\text{target}}$ ) should be used. If progression is due to a non-target lesion, then we should use the earliest scan date among the non-target lesions with Tumor State (RS.RSORRES) = "PD" ( $PD_{\text{non-target}}$ ). If progression is due to a new lesion, then we should use the earliest scan date among the new lesions with New Lesion Determination = "UNEQUIVOCAL" ( $PD_{\text{new}}$ ). If an overall progression is caused by two or more types of lesions, we should use the earliest date among  $PD_{\text{target}}$ ,  $PD_{\text{non-target}}$ , and  $PD_{\text{new}}$  as the PD date.

#### TR

| DOMAIN | USBJID  | TRGRPID    | TRTEST           | TRLNKID | TORRES  | TRSTRESC | TRMETHOD | VISIT | TRDTC      |
|--------|---------|------------|------------------|---------|---------|----------|----------|-------|------------|
| TR     | ABC-001 | TARGET     | Longest Diameter | T01     | 31      | 31       | MRI      | WEEK6 | 2019-12-20 |
| TR     | ABC-001 | NON-TARGET | Tumor State      | NT01    | PRESENT | PRESENT  | CT SCAN  | WEEK6 | 2019-12-20 |
| TR     | ABC-001 | NON-TARGET | Tumor State      | NT02    | ABSENT  | ABSENT   | CT SCAN  | WEEK6 | 2019-12-20 |
| TR     | ABC-001 | NON-TARGET | Tumor State      | NT03    | PRESENT | PRESENT  | CT SCAN  | WEEK6 | 2019-12-20 |
| TR     | ABC-001 | NON-TARGET | Tumor State      | NT04    | PRESENT | PRESENT  | CT SCAN  | WEEK6 | 2019-12-20 |

#### RS

| DOMAIN | USUBJID | RSTEST   | RSTESTCD               | RSORRES       | RSEVAL       | VISIT | RSOTC      |
|--------|---------|----------|------------------------|---------------|--------------|-------|------------|
| RS     | ABC-001 | TRGRESP  | Target Response        | PD            | INVESTIGATOR | WEEK6 | 2020-01-01 |
| RS     | ABC-001 | NTRGRESP | Non-target Response    | NON-CR/NON-PD | INVESTIGATOR | WEEK6 | 2020-01-01 |
| RS     | ABC-001 | NEWLPROG | New Lesion Progression | NO            | INVESTIGATOR | WEEK6 | 2020-01-01 |
| RS     | ABC-001 | OVRLRESP | Overall Response       | PD            | INVESTIGATOR | WEEK6 | 2020-01-01 |

SCAN DATE For Target=2019-12-20

#### ADRS

| USUBJID | PARCAT    | PARQUAL | PARAM                  | PARAMCD   | DTYPE | AVALC         | ADT        | AVISIT |
|---------|-----------|---------|------------------------|-----------|-------|---------------|------------|--------|
| ABC-001 | RECIST1.1 | INV     | Target Response        | TRGRESP   |       | PD            | 2020-01-01 | WEEK6  |
| ABC-001 | RECIST1.1 | INV     | Non-Target Response    | NTRGRESP  |       | NON-CR/NON-PD | 2020-01-01 | WEEK6  |
| ABC-001 | RECIST1.1 | INV     | New Lesion Progression | NEWLPROG  |       | NO            | 2020-01-01 | WEEK6  |
| ABC-001 | RECIST1.1 | INV     | Overall Response       | OVERLRESP |       | PD            | 2019-12-20 | WEEK6  |

RESPONSE ASSESSMENT DATE=2020-01-01



Target Lesion Scan date

Example 1: Suppose a patient had an overall response, target response, and non-target response = PD on the RECIST Response Assessment page at week x with response assessment date = 2019-07-10, and this subject had the following lesions at this week:

- Two target lesions dated 2019-07-08 and 2019-07-10

- Three non-target lesions:
  - NT lesion # 1 had state = “PD” dated 2019-07-09
  - NT lesion # 2 had state = “Present” dated 2019-07-08
  - NT lesion # 3 had state = “PD” dated 2019-07-10
- One “equivocal” new lesion dated 2019-07-05

Then, this patient should have 2019-07-08 as her PD date because in this case, PD should be a min of ( $PD_{\text{target}}$ ,  $PD_{\text{non-target}}$ ), where  $PD_{\text{target}}$  is 2019-07-08, the earliest scan date among all target lesions; and  $PD_{\text{non-target}}$  is 2019-07-09, the earliest scan date among all non-target lesions with tumor state=“PD”. Note that this example is for an ideal scenario. In contrast, Example # 2 below shows a subject with PD caused by a new and target lesion – there, the earliest date gets picked.

Example2:

TR

SCAN DATE is TRDTC

| DOMAIN | USBJID  | TRGRPID    | TRTEST           | TRLNKID | TRORES      | TRSTRESC    | TRMETHOD | VISIT  | TRDTC      |
|--------|---------|------------|------------------|---------|-------------|-------------|----------|--------|------------|
| TR     | ABC-001 | TARGET     | Longest Diameter | T01     | 13          | 13          | MRI      | WEEK18 | 2020-03-31 |
| TR     | ABC-001 | NON-TARGET | Tumor State      | NT01    | PRESENT     | PRESENT     | CT SCAN  | WEEK18 | 2020-03-28 |
| TR     | ABC-001 | NON-TARGET | Tumor State      | NT02    | ABSENT      | ABSENT      | CT SCAN  | WEEK18 | 2020-03-28 |
| TR     | ABC-001 | NEW        | Tumor State      | NEW01   | UNEQUIVOCAL | UNEQUIVOCAL | CT SCAN  | WEEK18 | 2020-03-28 |

RS

RESPONSE ASSESSMENT DATES FOR PD

| DOMAIN | USBJID  | RSTEST   | RSTESTCD               | RSORRES | RSEVAL       | VISIT  | RSBTC      |
|--------|---------|----------|------------------------|---------|--------------|--------|------------|
| RS     | ABC-001 | TRGRESP  | Target Response        | PD      | INVESTIGATOR | WEEK18 | 2020-04-30 |
| RS     | ABC-001 | NTRGRESP | Non-target Response    | PD      | INVESTIGATOR | WEEK18 | 2020-04-30 |
| RS     | ABC-001 | NEWLPROG | New Lesion Progression | YES     | INVESTIGATOR | WEEK18 | 2020-04-30 |
| RS     | ABC-001 | OVRLRESP | Overall Response       | PD      | INVESTIGATOR | WEEK18 | 2020-04-30 |

ADRS

| USBJID  | PARCAT    | PARQUAL | PARAM                  | PARAMCD   | DTYPE | AVALC | ADT        | AVISIT |
|---------|-----------|---------|------------------------|-----------|-------|-------|------------|--------|
| ABC-001 | RECIST1.1 | INV     | Target Response        | TRGRESP   |       | PD    | 2020-02-01 | WEEK18 |
| ABC-001 | RECIST1.1 | INV     | Non-Target Response    | NTRGRESP  |       | PD    | 2020-02-01 | WEEK18 |
| ABC-001 | RECIST1.1 | INV     | New Lesion Progression | NEWLPROG  |       | YES   | 2020-02-01 | WEEK18 |
| ABC-001 | RECIST1.1 | INV     | Overall Response       | OVERLRESP |       | PD    | 2020-03-28 | WEEK18 |



Earliest Scan date

**Scenario 2:**

If no lesion shows evidence of progression, but overall response is PD, then the date of the progression will be the earliest date of all scan lesion dates.

**WHEN OVERALL RESPONSE IS EQUIVOCAL PROGRESSION...**

**Scenario 1 (Ideal Situation):**

If at least one non-target or new lesion shows evidence of equivocal progression, then the date of progression will be the earliest date of all scan dates that showed evidence of equivocal progression.

If equivocal progression is due to a non-target lesion, we should use the earliest scan date among non-target lesions with Tumor State = “Equivocal Progression” ( $EP_{\text{non-target}}$ ). If equivocal progression is due to a new lesion, then we should use the earliest scan date among new lesions with New Lesion Determination = “Equivocal” ( $EP_{\text{new}}$ ). If overall progression is caused by both types of lesions, we should use the earlier date between  $EP_{\text{non-target}}$  and  $EP_{\text{new}}$  as a response date.

Example: Suppose a patient had an overall response of equivocal progression. The following week, we see:

- three non-target lesions:
  - NT lesion # 1 had state = “Present” dated 2019-07-08
  - NT lesion # 2 had state = “Equivocal Progression” dated 2019-07-09
  - NT lesion # 3 had state = “Equivocal Progression” dated 2019-07-10
- one “equivocal” new lesion dated 2019-07-10

This patient should have 2019-07-09 as the response date for “Equivocal Progression,” because in this case, EP should be a min of (EP<sub>non-target</sub>, EP<sub>new</sub>), where EP<sub>non-target</sub> is 2019-07-09, the earliest scan date among all “equivocal progression” new lesions; and EP<sub>new</sub> is 2019-07-10, the earliest scan date among all “equivocal” new lesions.

**Scenario 2:**

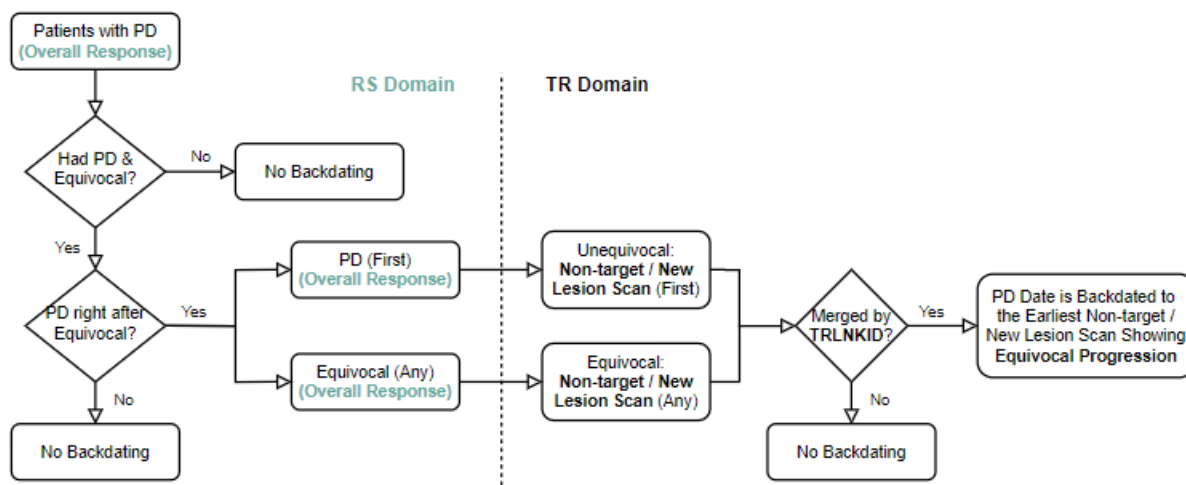
If no lesion shows evidence of equivocal progression, the date of equivocal progression will be the earliest date of all scan lesion dates.

**WHEN OVERALL RESPONSE IS SOMETHING OTHER THAN PD OR EQUIVOCAL PROGRESSION...**

If overall response is neither PD nor equivocal progression, the response date will be the latest of all radiological scan dates for the given response assessment.

**THE KICKER: PD BACKDATING**

If a new lesion progressed to “unequivocal” (with an overall response (OR)=PD) right after (a series of consecutive) “equivocal” assessments (with OR=equivocal progression), or a non-target lesion progressed to “PD” (with OR=PD) right after (a series of consecutive) “equivocal progression” assessments (with OR=equivocal progression), we need to reset, or backdate, the PD date to the earliest scan date when the new lesion or the non-target lesion was assessed as “equivocal”/“equivocal progression”. If any new anti-cancer therapy was given or there was a missed scheduled assessment between the earliest equivocal and unequivocal lesion scan date, we still should implement PD backdating. Figure 1 presents how a backdated PD is identified and how the rule is applied.



**Figure 1. PD Backdating Flowchart**

To help understand the workflow, the source code is presented below to explain these details:

```
/*FIND THE PATIENTS WHO HAD ANY DISEASE PROGRESSION*/
proc sort data=adrs(where=(param='Overall Response' and
                        avalc in ('PD')))
    out=pd_subj nodupkey;
    by usubjid parqual;
run;

/*FIND THE PATIENTS WHO HAD ANY EQUIVOCAL PROGRESSION*/
proc sort data=adrs(where=(param='Overall Response' and
                        avalc in ('EQUIVOCAL' 'EQUIVOCAL PROGRESSION')))
    out=equ_subj nodupkey;
    by usubjid parqual;
run;

/*IDENTIFY THE PATIENTS WHO HAD BOTH PD & EQUIVOCAL PROGRESSION*/
proc sql;
    create table equ_pd_subj as
    select distinct adrs.usubjid, adrs.parqual
    from adrs, pd_subj, equ_subj
    where adrs.usubjid=pd_subj.usubjid and adrs.usubjid=equ_subj.usubjid and
          adrs.parqual=pd_subj.parqual and adrs.parqual=equ_subj.parqual;

    create table backdating as
    select a.*
    from adrs(where=(param='Overall Response' and ^missing(avalc))) a,
         equ_pd_subj b
    where a.usubjid=b.usubjid and a.parqual=b.parqual
    order by a.usubjid, a.parqual, a.adt desc;
quit;

data backdating_x;
    set backdating;
    by usubjid parqual;
    retain x;
    if first.parqual then x='';
    else if avalc not in ('PD', 'EQUIVOCAL', 'EQUIVOCAL PROGRESSION'
                        'NOT EVALUABLE')
    then x='x';
run;

proc sql;
    create table backdating_pd as
    select usubjid, parqual, avisit, adt, avalc
    from backdating_x
    where x='' and avalc in ('PD')
    order by usubjid, parqual, avisit;

    create table backdating_eq as
    select usubjid, parqual, avisit, adt, avalc
    from backdating_x
    where x='' and avalc in ('EQUIVOCAL', 'EQUIVOCAL PROGRESSION');
quit;
```

```

*-----+
| CONDITION 1: NEW LESION FROM EQUIVOCAL TO UNEQUIVOCAL |
+-----+;
proc sort data=tr out=unequivocal_byvisit_newlesion(rename=(visit=avisit));
  by usubjid parqual visit;
  where trtestcd='TUMSTATE' and trgrpid='NEW' and
        trstresc='UNEQUIVOCAL PROGRESSION';
run;

proc sort data=tr out=equivocal_byvisit_newlesion(rename=(visit=avisit));
  by usubjid parqual visit;
  where trtestcd='TUMSTATE' and trgrpid='NEW' and trstresc='EQUIVOCAL';
run;

data pd_newlesion_byvisit;
  merge unequivocal_byvisit_newlesion
        backdating_pd(in=a);
  by usubjid parqual avisit;
  if a and ^missing(trlnkid);
  keep usubjid parqual avisit trlnkid trdt trstresc;
run;

proc sql;
  create table eq_newlesion_byvisit as
  select a.usubjid, a.parqual, a.avisit, a.trlnkid, a.trdt,
        a.trstresc
  from equivocal_byvisit_newlesion a,
        backdating_eq b
  where a.usubjid=b.usubjid and a.avisit=b.avisit and
        a.parqual=b.parqual
  order by a.usubjid, a.parqual, a.trlnkid, trdt;
quit;

data eq_newlesion_1st;
  set eq_newlesion_byvisit;
  by usubjid parqual trlnkid trdt;
  if first.trlnkid;
  rename trdt=trdt_eq_1st;
run;

proc sql;
  create table pdbackdt_newlesion as
  select a.usubjid, a.parqual, min(trdt_eq_1st) as pdbackdt format=date9.,
        b.avisit
  from eq_newlesion_1st a,
        pd_newlesion_byvisit b
  where a.usubjid=b.usubjid and a.trlnkid=b.trlnkid and a.parqual=b.parqual
  group by a.usubjid, a.parqual;
quit;

*-----+
| CONDITION 2: NON-TARGET LESION FROM EQUIVOCAL PROGRESSION TO PD |
+-----+;
proc sort data=tr out=unequivocal_byvisit_nontarget(rename=(visit=avisit));
  by usubjid parqual visit;
  where trtestcd='TUMSTATE' and trgrpid='NON-TARGET' and

```

```

        trstresc='UNEQUIVOCAL PROGRESSION';
run;

proc sort data=tr out=equivocal_byvisit_nontarget(rename=(visit=avisit));
  by usubjid parqual visit;
  where trtestcd='TUMSTATE' and trgrpid='NON-TARGET' and
        trstresc='EQUIVOCAL PROGRESSION';
run;

data pd_nontarget_byvisit;
  merge unequivocal_byvisit_nontarget
        backdating_pd(in=a);
  by usubjid parqual avisit;
  if a and ^missing(trlnkid);
  keep usubjid parqual avisit trlnkid trdt trstresc parqual;
run;

proc sql;
  create table eq_nontarget_byvisit as
  select a.usubjid, a.parqual, a.avisit, a.trlnkid, a.trdt,
        a.trstresc
  from equivocal_byvisit_nontarget a, backdating_eq b
  where a.usubjid=b.usubjid and a.avisit=b.avisit and a.parqual=b.parqual
  order by a.usubjid, a.parqual, a.trlnkid, trdt;
quit;

data eq_nontarget_1st;
  set eq_nontarget_byvisit;
  by usubjid parqual trlnkid trdt;
  if first.trlnkid;
  rename trdt=trdt_eq_1st;
run;

proc sql;
  create table pdbackdt_nontarget as
  select a.usubjid, min(trdt_eq_1st) as pdbackdt format=date9., a.parqual,
        b.avisit
  from eq_nontarget_1st a,
        pd_nontarget_byvisit b
  where a.usubjid=b.usubjid and a.trlnkid=b.trlnkid and a.parqual=b.parqual
  group by a.usubjid, a.parqual;
quit;

data pdbackdt;
  set pdbackdt_newlesion
        pdbackdt_nontarget;
run;

proc sort data=pdbackdt nodupkey;
  by usubjid parqual pdbackdt avisitn;
run;

data pdbackdt;
  set pdbackdt;
  by usubjid parqual frstpddt avisitn;
  if first.parqual;
run;

```



Comments to the source code above:

1. Patients, with OR=PD, are identified from the ADaM ADRS domain where PARAM is "Overall Response". Those who also had an equivocal OR (avalc="EQUIVOCAL") are classified as the PD backdating group. In ADRS, PARQUAL is defined as the identifier for evaluation. Usually, the evaluator can be "Investigator" or "BICR" (Blinded Independent Central Review).
2. As shown below, the ADRS dataset is sorted by OR assessment dates (ADT) in descending order. A RETAIN statement is used to mark the first response, other than PD or Equivocal, and all the previous visits. It helps to identify those not-wanted responses between an Equivocal and PD response. If there is any other response in between, then backdating is not applicable.

Assessments marked with "x" need to be excluded from PD backdating, as shown in the grayed-out cells. In scenario 1, no equivocal assessments are applicable, because there is an overall response of SD (visit 30) before PD which breaks the association between an equivocal and unequivocal progression. Similarly, in scenario 2, the equivocal progression at visit 12 cannot be counted. In scenario 3, all the Equivocal progressions before PD are applicable for PD backdating.

|          | Scenario 1       |   | Scenario 2       |   | Scenario 3       |   |
|----------|------------------|---|------------------|---|------------------|---|
| Visit    | Overall Response |   | Overall Response |   | Overall Response |   |
| Visit 36 | PD               |   | PD               |   | PD               |   |
| Visit 30 | SD               | x | Equivocal        |   | Equivocal        |   |
| Visit 24 | Equivocal        | x | Equivocal        |   | Equivocal        |   |
| Visit 18 | Equivocal        | x | SD               | x | Equivocal        |   |
| Visit 12 | Equivocal        | x | Equivocal        | x | Equivocal        |   |
| Visit 6  | PR               | x | PR               | x | SD               | x |

**Table 4. PD with Prior Equivocal Assessments**

3. Once the first PD is identified, the next step is to look for the lesion-level record to show the evidence of this progression from the TR domain, where TRSTRESC="UNEQUIVOCAL PROGRESSION". It can be a new lesion or a non-target lesion. TRLNKID is selected as the merge key in step 5.
4. Similarly, once the overall equivocal progressions are identified, the next step is to look for the lesion level record to find the evidence for this association from the TR domain. Based on the selected overall equivocal progression in step 2, new lesion and non-target lesion are identified in TR where TRSTRESC="EQUIVOCAL". TRLNKID is selected as the merge key in step 5.
5. Based on TRLNKID, the lesion assessments with PD and EQUIVOCAL are associated with either a new lesion or a non-target lesion, or both, across visits. Then select the earliest lesion which shows the equivocal progression among the ones that qualify for PD backdating. Eventually, use the earliest date as the backdated PD date.

Note: the above rule is only applied to the first PD date. If a patient has multiple PDs, PDs after the first one does not need to be backdated. Please see the following examples.

**Example 1: Backdate PD to week 6**

If a timepoint assessment has "No"/"Not Assessed"/"Not Evaluable" or has OR ="Not Evaluable", the timepoint assessment is considered as missing between the earliest equivocal lesion scan date and the unequivocal lesion scan date, and we still should implement PD backdating.

If a patient had new lesion #1 with New Lesion Determination = “Equivocal” at week 6 and week 12, and this new lesion became “Unequivocal” at week 18, we should backdate the PD date to the new lesion #1 scan date at week 6. If there was new anti-cancer therapy between week 6 and week 18, or if the patient didn’t have a week 12 assessment, the PD date should still be backdated to week 6.

| <b>Week 6</b>                                       | <b>Week 12</b>   | <b>Week 18</b>                      |
|---|--|-------------------------------------|
| New lesion #1=Equivocal<br>OR=Equivocal progression | OR= <b>Not Evaluable</b><br>No matter what new lesion #1’s response is | New lesion #1 =Unequivocal<br>OR=PD |

**Table 5. PD Backdating Example 1**

Example 2: No backdating is needed. PD at week 12 will be used as primary endpoint.

The PD at week 12 is caused by New lesion #2 (unequivocal progression). When we look for an equivocal progression at week 6, there is no new lesion for #2. So, we cannot backdate the PD from week 12 to week 6. Based on TRLNKID, there is no evidence showing the same lesion progressed to unequivocal PD. The PD at week 18 is the second PD, so we do not backdate any PD after the first one.

| <b>Week 6</b>                                       | <b>Week 12</b>  | <b>Week 18</b>   |
|---|---|--|
| New lesion #1=Equivocal<br>OR=Equivocal progression | New lesion #1=Equivocal<br>New lesion #2=Unequivocal<br>OR= <b>PD (1<sup>st</sup> PD)</b> | New lesion #1 =Unequivocal<br>OR=PD (2 <sup>nd</sup> PD) |

**Table 6. PD Backdating Example 2**

Example 3: No backdating is needed since OR=SD at week 12.

| <b>Week 6</b>                                       | <b>Week 12</b>                               |
|---|--|
| New lesion #1=Equivocal<br>OR=Equivocal progression | New lesion #1 =Unequivocal<br>OR = <b>SD</b> |

**Table 7. PD Backdating Example 3**

Example 4: No backdating is needed since OR=SD at week 6.

| <b>Week 6</b>                            | <b>Week 12</b>                       |
|--|--------------------------------------|
| New lesion #1=Equivocal<br>OR= <b>SD</b> | New lesion #1 =Unequivocal<br>OR =PD |

**Table 8. PD Backdating Example 4**

## CONCLUSION

The derivation of an overall response of progressive disease is very important to determine the first PD date. In this paper, all the backdating concepts with ideal scenarios and examples were discussed. Implementation of these scenarios will help Biostatisticians and Statistical Programmers to determine the date of first progression in an analysis to accurately calculate hazard ratios, p-values, Kaplan-Meier curves and other oncology efficacy endpoints.

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