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Double Waterfall Plot Creation for Comparing Target Lesions Data

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ABSTRACT

We use a waterfall plot to present individual patient's best overall percentage change and response to a treatment based on a parameter, such as the tumor burdens at each evaluation time point in Oncology Clinical Trials.

A double waterfall plot accommodates two treatment best overall percentage change for each patient in a single plot for multi-treatment studies and crossover studies. We can also use double waterfall plots for intra-tumor (IT) studies.

In an Intra-tumoral injection study, each patient has multiple target lesions with some lesions injected with treatment. A double waterfall plot presents the best overall change of injected target lesions and noninjected target lesions separately for each patient.

We can use SAS® PROC SGPLOT to create double waterfall plots. The horizontal (X) axis across the plot represents patients in the order of best percentage change which could base on the best response to a specific treatment period or of a type of lesions; VBAR is for vertical bars of each patient's two best percentage changes. The vertical (Y) axis could be for the percent change from baseline, e.g., percent growth or tumor reduction by radiologic measurement. We will include more details on the PROC SGPLOT syntax and plot options in the paper. Furthermore, this paper will also discuss the steps to derive the required variables and dataset pre-processing to categorize tumor response.

KEYWORDS

PROC SGPLOT, VBAR, REFLINE, ADTL, Target Lesions Minimum Sum of Diameters and Best Percent Change from Baseline.

INTRODUCTION

Double Waterfall plots are effective in oncology studies. This paper mainly focuses on Intratumoral and Crossover Studies to demonstrate two best improvements in tumor size related to the responses to a study drug seen in each patient.

This paper will discuss two trial scenarios where double waterfall plots will be useful to represent the data.

1. Injected Target Lesion vs. Target Noninjected Lesions

Intratumoral trials, a few selected target lesions of each patient receive intratumor injects. There is a need to demonstrate the response from both injected target lesions and noninjected target lesions of each patient.

2. Best overall response for two treatment periods

In Crossover trials with two study treatments and periods, it is easy to compare two treatments' lesion responses using double waterfall plots.

SECTION-1: PRESENTING INJECTED LESION VS TARGET NONINJECTED LESIONS

SDTM EXPOSURE DATA (EX) --

The Exposure domain model (EX) records the details of a patient's exposure to protocol specified study treatment. In the below example, Associated Lesion Number(ALSNNUM) information from EX dataset is to identify Injected lesions by selecting unique target lesion numbers with a non-missing dose for each patient.

Figure-1:

	DOMAIN	ID	VISIT	ALSNNUM
1	EX	1	Cycle 1 Day 1	NTEN6
2	EX	1	Cycle 1 Day 8	NTEN7
3	EX	1	Cycle 1 Day 15	NTEN6
4	EX	1	Cycle 2 Day 1	NTEN7
5	EX	1	Cycle 2 Day 1	NTEN6
6	EX	1	Cycle 2 Day 8	NTEN7
7	EX	1	Cycle 2 Day 8	NTEN6
8	EX	1	Cycle 2 Day 15	NTEN7
9	EX	1	Cycle 2 Day 15	NTEN6
10	EX	2	Cycle 1 Day 1	TN3
11	EX	2	Cycle 1 Day 8	TN3
12	EX	2	Cycle 1 Day 15	TN3
13	EX	2	Cycle 2 Day 1	TN3
14	EX	2	Cycle 2 Day 8	TN3
15	EX	2	Cycle 2 Day 15	TN3
16	EX	3	Cycle 1 Day 1	TEN2
17	EX	3	Cycle 1 Day 8	TEN2
18	EX	3	Cycle 1 Day 15	TEN2
19	EX	3	Cycle 2 Day 1	TEN2
20	EX	3	Cycle 2 Day 8	TEN2

SDTM TUMOR RESULTS DATA (TR) --

The Tumor Results (TR) domain contains information about tumors identified in the TU domain in form of quantitative measurements and/or qualitative assessments of the tumors. These measurements are not only taken at baseline but at each subsequent assessment with the purpose of supporting the response evaluations. In contrast to the TU domain the TR domain does not contain information about anatomical locations of the measurements.

In below example Figure 2, the tumor lesion TRSPID was measured in Longest Diameter or Longest Perpendicular dimensions reported per VISIT in TR data. The Lesion measurement is reflected in TRTESTCD, Lesion ID is captured in TRSPID and the standard result is captured in TRSTRESN.

Figure-2:

	DOMAIN	ID	TRTESTCD	TRLNKID	TRSPID	VISIT	TRSTRESN
1	TR	1	LDIAM	TEN1	1	Screening	22
2	TR	1	LDIAM	TEN2	2	Screening	13.3
3	TR	1	LDIAM	TEN3	3	Screening	18.2
4	TR	1	LDIAM	TEN1	1	Cycle 3 Day 15	20.2
5	TR	1	LDIAM	TEN2	2	Cycle 3 Day 15	13.3
6	TR	1	LDIAM	TEN3	3	Cycle 3 Day 15	20.8
7	TR	1	LDIAM	TEN1	1	Cycle 6 Day 1	18.2
8	TR	1	LDIAM	TEN2	2	Cycle 6 Day 1	13.4
9	TR	1	LDIAM	TEN3	3	Cycle 6 Day 1	22.8
10	TR	2	LDIAM	TEN1	1	Screening	15.4
11	TR	2	LPERP	TN2	2	Screening	14.3
12	TR	2	LPERP	TN3	3	Screening	12.9
13	TR	2	LDIAM	TEN4	4	Screening	11.3
14	TR	2	LDIAM	TEN1	1	Cycle 3 Day 1	17.2
15	TR	2	LPERP	TN2	2	Cycle 3 Day 1	14.4
16	TR	2	LPERP	TN3	3	Cycle 3 Day 1	13.1
17	TR	2	LDIAM	TEN4	4	Cycle 3 Day 1	11.6
18	TR	3	LDIAM	TEN1	1	Screening	17.8
19	TR	3	LDIAM	TEN2	2	Screening	14.7
20	TR	3	LDIAM	TEN1	1	Cycle 2 Day 15	18.4
21	TR	3	LDIAM	TEN2	2	Cycle 2 Day 15	14.7
22	TR	3	LDIAM	TEN1	1	Cycle 5 Day 1	20
23	TR	3	LDIAM	TEN2	2	Cycle 5 Day 1	16.1

By merging EX and TR data using injected target lesion information(ALSNNUM) from EX domain and TRSPID or TRLNKID from TR data, we can derive a flag variable INJCTFL to differentiate Injected and Noninjected lesions in the example below

Figure-3:

	ID	TRSPID	VISIT	TRSTRESN	INJCTFL
1	1	1	Screening	22	N
2	1	2	Screening	13.3	N
3	1	3	Screening	18.2	N
4	1	1	Cycle 3 Day 15	20.2	N
5	1	2	Cycle 3 Day 15	13.3	N
6	1	3	Cycle 3 Day 15	20.8	N
7	1	1	Cycle 6 Day 1	18.2	N
8	1	2	Cycle 6 Day 1	13.4	N
9	1	3	Cycle 6 Day 1	22.8	N
10	2	1	Screening	15.4	N
11	2	2	Screening	14.3	N
12	2	3	Screening	12.9	Y
13	2	4	Screening	11.3	N
14	2	1	Cycle 3 Day 1	17.2	N
15	2	2	Cycle 3 Day 1	14.4	N
16	2	3	Cycle 3 Day 1	13.1	Y
17	2	4	Cycle 3 Day 1	11.6	N
18	3	1	Screening	17.8	N
19	3	2	Screening	14.7	Y
20	3	1	Cycle 2 Day 15	18.4	N
21	3	2	Cycle 2 Day 15	14.7	Y

CREATING ADaM ADTL DATASET

Since a double waterfall plot is reporting at the patient-level, we need to generate an analysis dataset of Target Lesions (ADTL) that contains necessary patient-level information for the plot.

ADTL dataset must have the best percent change from the baseline of each treatment or treatment period based on the Sum of Diameters (SOD) at each evaluation time point in multi-treatment studies.

In an Intra-tumoral injection study, we need to generate the best percent change from baseline of both Injected and Noninjected lesions for each patient. If a target lesion is injected at least once throughout the study period, we consider it in the injected lesion category; otherwise, we consider it in the target noninjected lesion category. We can select the minimum PCHG value per each patient and lesion type as the best percentage change of that type of lesion.

Figure-4:

	ID	PARAM	PARAMCD	PCHG	PARAMN
1	1	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	13.404255319	41
2	2	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	16.896551724	31
3	2	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	30	41
4	3	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	10	31
5	3	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	17.692307692	41
6	6	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	43.333333333	31
7	6	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	60	41
8	8	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	60	31
9	8	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	65.555555556	41
10	11	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	39.166666667	31
11	12	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	-30.22988506	41
12	13	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	46.842105263	31
13	13	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	-1.475409836	41
14	18	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	32.058823529	31
15	18	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	17.792207792	41
16	19	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	24.285714286	31
17	19	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	31.245421245	41
18	20	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	-59.64285714	31
19	20	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	12.097902098	41

HOW TO DEVELOP THE PLOT

Like a regular waterfall plot, a double waterfall plot has a horizontal(x) axis across the plot that may serve as a baseline measurement. In this example, zero percentage change is the baseline. One or multiple PCHG (best percentage change) vertical bars for each patient, either above or below the baseline. Each patient's vertical bars are grouped together. Patients are displayed in the order of percentage change, from highest change to the lowest change.

This example uses the minimum sum of diameters for the Target Lesions variable (PARAMCD=MSDTLINV) as an order variable. MSDTLINV Parameter is the sum of Target Lesion measurements.

Figure-5:

	ID	PARAM	PARAMCD	PCHG	ORDER	PARAMN
1	8	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	63.246753247	63.246753247	21
2	6	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	56.376811594	56.376811594	21
3	11	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	39.166666667	39.166666667	21
4	19	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	30.186335404	30.186335404	21
5	2	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	27.26618705	27.26618705	21
6	18	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	26.901408451	26.901408451	21
7	3	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	14.8	14.8	21
8	1	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	13.404255319	13.404255319	21
9	13	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	10	10	21
10	20	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	-3.065326633	-3.065326633	21
11	12	Min of Sum of Diam for Target Lesions Per INV	MSDTLINV	-30.22988506	-30.22988506	21

Create final input dataset with ORDER variable for Plot.

Figure-6:

	ID	PARAM	PARAMCD	PCHG	ORDER	TLINJFL
1	1	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	13.404255319	13.404255319	N
2	2	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	16.896551724	27.26618705	Y
3	2	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	30	27.26618705	N
4	3	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	10	14.8	Y
5	3	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	17.692307692	14.8	N
6	6	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	43.333333333	56.376811594	Y
7	6	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	60	56.376811594	N
8	8	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	60	63.246753247	Y
9	8	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	65.555555556	63.246753247	N
10	11	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	39.166666667	39.166666667	Y
11	12	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	-30.22988506	-30.22988506	N
12	13	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	46.842105263	10	Y
13	13	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	-1.475409836	10	N
14	18	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	32.058823529	26.901408451	Y
15	18	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	17.792207792	26.901408451	N
16	19	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	24.285714286	30.186335404	Y
17	19	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	31.245421245	30.186335404	N
18	20	Min of Sum of Diam for Target Injected Lesions Per INV	MSDTILIN	-59.64285714	-3.065326633	Y
19	20	Min of Sum of Diam for Target Non-Injected Lesions Per INV	MSDTNLIN	12.097902098	-3.065326633	N

SAMPLE CODE TO CREATE PLOT

Example-1 with Colors:

Below ATTRMAP1 dataset in Figure-7 assigns colors to Target Injected Lesions Parameter and Target Noninjected Lesions bars in the plot. SGPLOT procedure DATTRMAP and ATTRID options highlighted in Pink will use this dataset.

```
data attrmap1;

    input ID $ VALUE $ FILLCOLOR $;
    datalines;

    myid Y Teal

    myid N Maroon
    ;
run;
```

Figure-7:

	ID	VALUE	FILLCOLOR
1	myid	Y	Teal
2	myid	N	Maroon

The value of the ID variable, MYID, is referenced in one or more plot statements within the procedure.

The values of the VALUE variable are valid data group values. The data group is associated with the GROUP= optionin the plot statement.

The values for FILLCOLOR= is valid SAS colors. You can specify colors using a number of different color-naming schemes.

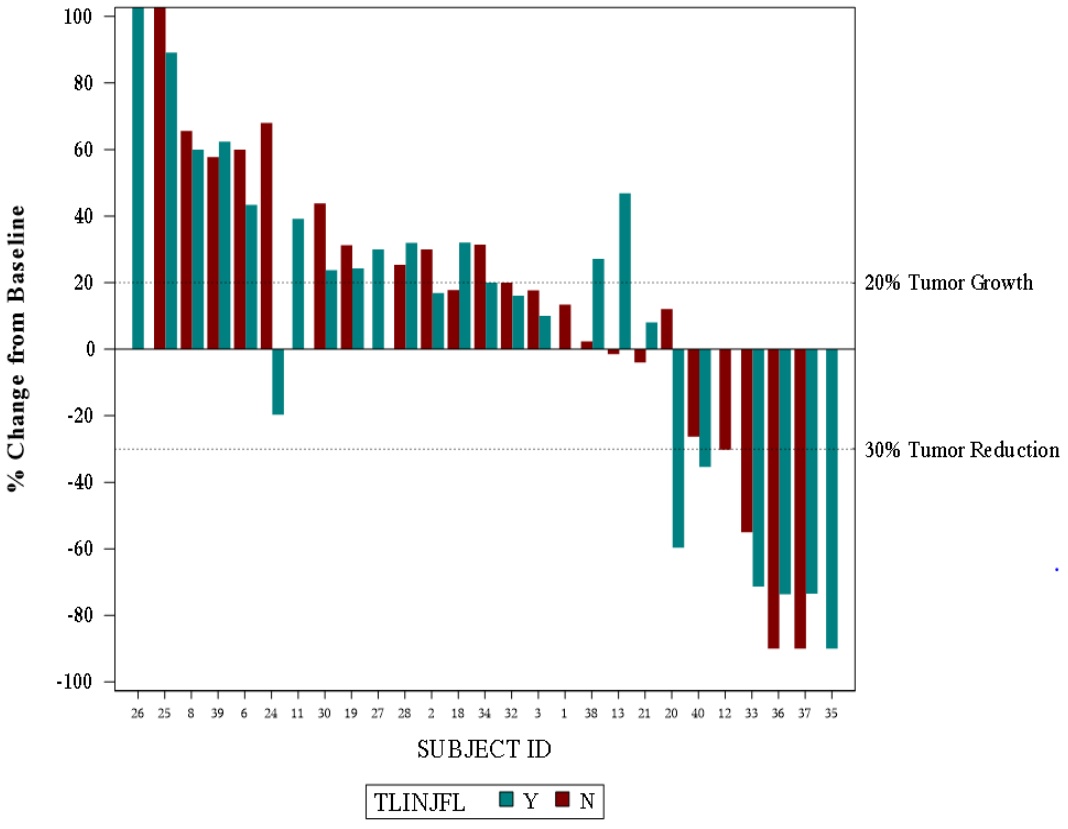
```
ods listing close;

ods graphics / reset=all noborder imagename="Double Waterfall" width= 7.0in height= 5.0in;

ods rtf file="%sysfunc(pathname(fptog,f))/og0db0waterfall0plot.rtf" bodytitle nogtitle
nogfootnote;

goptions cback=gray;

proc sgplot data=og0db0waterfall0plot dattrmap=attrmap1;

    vbar id / response=PCHG
              name="vol"
              fill group=TLINJFL
              groupdisplay=cluster
    attrid=myid;

    refline -30 / axis=y
              labelloc=outside
              labelpos=auto
              lineattrs=(pattern=dot color=black)
```

```
            label="30% Tumor Reduction";

    refline  20 / axis=y
            labelloc=outside
            labelpos=auto
            lineattrs=(pattern=dot color=black)
            label="20% Tumor Growth";

    xaxis label = "SUBJECT ID"
            valueattrs=(size=6pt color=black)
            discreteorder=data;

    yaxis label="% Change from Baseline"
            labelattrs=(weight=bold)
            min=-100 max=200
            values= (-100 to 200 by 20);
run;

ods graphics off;

ods rtf close;

ods listing;
```

The above code uses TLINJFL variable as a group variable and the PCHG variable for RESPONSE option in the VBAR statement to produce the vertical bars shown below Figure-8.

REFLINE statement on the Y-axis generates reference dotted lines for Tumor Growth and Reduction.

Figure-8:



Example-2 with Patterns:

We can create an attribute dataset ATTRMAP2 for patterns as in Figure-9.

Figure-9:

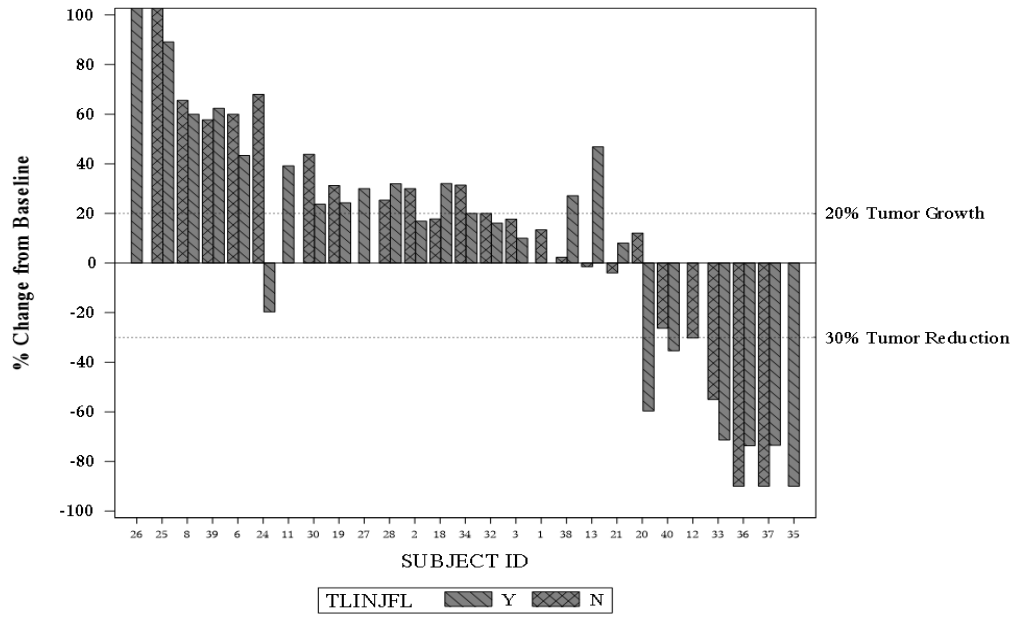
	ID	VALUE	FILLCOLOR	LINECOLOR
1	myid	Y	Grey	Black
2	myid	N	Grey	Black

```
data attrmap2;
    input ID $ VALUE $ FILLCOLOR $ LINECOLOR $;
    datalines;

    myid Y Grey Black
    myid N Grey Black
    ;
run;
```

Add Fill Pattern option highlighted in green in VBAR statement to generate vertical bars with patterns for Injected and Target noninjected lesions as in Figure-10.

```
proc sgplot data=og0db0waterfall0plot dattrmap=attrmap2;

    vbar id / response=PCHG
              name="vol"
              fill group=TLINJFL
              groupdisplay=cluster
attrid=myid
fillpattern;
```

Figure-10:



SECTION-2: PATIENT'S BEST OVERALL RESPONSE OF TWO TREATMENT PERIODS

This example will discuss patient lesion response to two study treatments administered in two different periods.

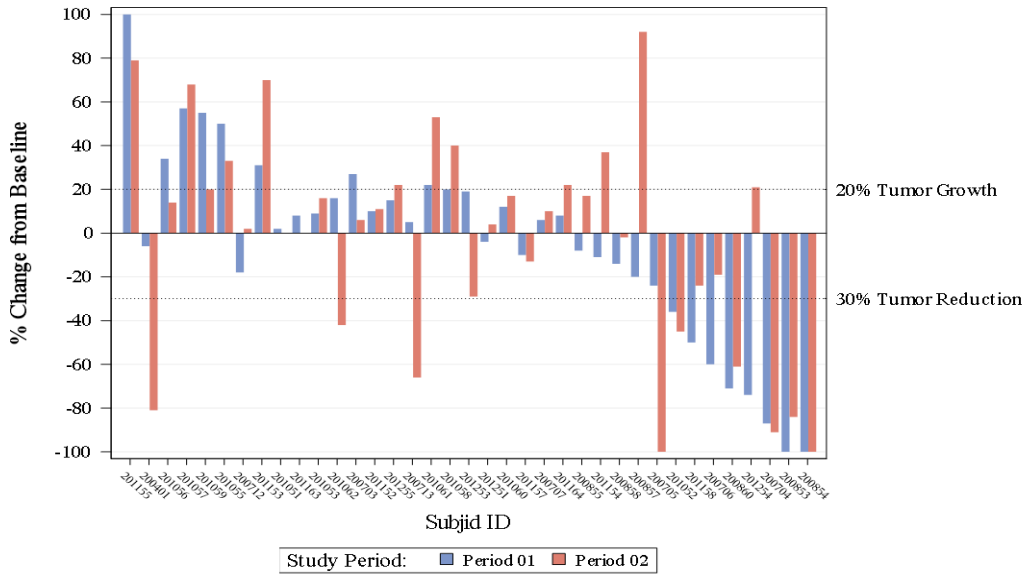
ADLESION DATASET

Like the above ADTL derivations, each patient and visit have one parameter for Period 1 "P1TLINV" and one parameter for Period 2 "P2TLINV" sum of lesions. ANL01FL is a flag variable, with a value "Y" for the best percentage change from baseline. P1TLINV and P12LINV lesion response created using treatment period start dates from ADSL and visit information from TR domain. In the below plot example, the patient has two treatment period lesion responses. Double waterfall plots also represent even if any patient has only one treatment in an ongoing study.

Figure-11:

SUBJID	AVISITN	PARAMCD	PARAM	AVAL	CHG	PCHG	ANL01FL
201155	10100	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	14	.	.	
201155	20251	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	30	16	114.28571	Y
201155	10100	P2TLINV	Sum of Diam for Target Period 2 Lesions Per INV	9.1	.	.	
201155	20251	P2TLINV	Sum of Diam for Target Period 2 Lesions Per INV	16.3	7.2	79.120879	Y
201155	10100	SODTLINV	Sum of Diam for Target Lesions Per INV	23.1	.	.	
201155	20251	SODTLINV	Sum of Diam for Target Lesions Per INV	46.3	23.2	100.4329	Y
201056	10100	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	6.5	.	.	
201056	20165	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	8.7	2.2	33.846154	Y
201056	20265	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	10.7	4.2	64.615385	
201056	10100	P2TLINV	Sum of Diam for Target Period 2 Lesions Per INV	5.1	.	.	
201056	20165	P2TLINV	Sum of Diam for Target Period 2 Lesions Per INV	5.8	0.7	13.72549	Y
201056	20265	P2TLINV	Sum of Diam for Target Period 2 Lesions Per INV	6.9	1.8	35.294118	
201056	10100	SODTLINV	Sum of Diam for Target Lesions Per INV	11.6	.	.	
201056	20165	SODTLINV	Sum of Diam for Target Lesions Per INV	14.5	2.9	25	Y
201056	20265	SODTLINV	Sum of Diam for Target Lesions Per INV	17.6	6	51.724138	
200401	10100	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	3.4	.	.	
200401	20265	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	3.2	-0.2	-5.882353	Y
200401	20265	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	4.2	0.8	23.529412	
200401	20265	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	4	0.6	17.647059	
200401	99943	P1TLINV	Sum of Diam for Target Period 1 Lesions Per INV	5.8	2.4	70.588235	

Figure-12:



CONCLUSION

Double Waterfall Plot is a handy tool for various types of quantitative analysis. It will help to reduce the number of plots created for each treatment or for multiple responses from one treatment and easy to compare multiple responses in one plot. Developing a double waterfall plot is straightforward using PROC SGPLOT procedure.

REFERENCES

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