

## Enhanced Swimmer Plots: Tell More Sophisticated Graphic Stories in Oncology Studies

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### ABSTRACT

In oncology studies, investigators are often interested in the relationship among a subject's various evaluations, including treatment exposure, response timepoint, start and end of adverse events, etc. One of the ways to achieve it is a swimmer plot showing multiple pieces of a subject's response "story" in one glance (Stacey 2014). A traditional swimmer plot providing single cell graphs might be over-simplified because it can't provide sufficient information to the investigators. However, oncology studies often have more complicated scenarios, such as multi-therapies and dosing titration during the study. This paper proposes enhanced swimmer plots which extended the use of swimmer plots to more sophisticated cases with two examples. One example is to investigate the adverse events occurrence during the course of a clinical trial, and the other is to show subject's tumor response status during multi-therapy treatment phase of the study. The paper provides detailed SAS® code and statistical/clinical explanation at each step when creating plots, so readers could understand the "story" behind the study more thoroughly.

### KEY WORDS

Enhanced swimmer plot, Oncology studies, Adverse Events, SAS GTL.

### INTRODUCTION AND BACKGROUND

The swimmer plot was traditionally used in oncology studies to represent the tumor assessment at each timepoint during the course of the study. Per our experience, we realized that the "swimmer" plots could also represent other endpoints, such as adverse events. That is, the addition of onset day and end day of adverse events to the treatment exposure period could be of interest to the investigator. Additionally, a study might have dose adjustment for single treatment. Sometimes it is necessary to plot several of treatment parameters in one figure. Some other enhancements are also possible (like combinational treatment of oral and intravenous drugs). Therefore, we would treat the "swimming pool" as a pooled enhanced treatment exposure site, with which the reviewer can visually monitor the study status.

Unlike the traditional swimmer plot, the enhanced swimmer plot utilizes the function of SAS Graph Template Language (GTL) more thoroughly than before. The HIGHLOWPLOT statement creates a plot that draws horizontal bars from a start day to an end day for each dosage. This statement plays a vital role by providing a possibility to distinguish the treatment doses. The further enhancing of the plot can be done using other GTL statements, such as VECTORPLOT or SCATTERPLOT.

### PRELIMINARY PART: DOSING.

The study has several subjects; these subjects started treatment with oral daily dose of 20 mg, however during the treatment physician may take a decision to reduce patient's dose (up to 3 consecutive reductions: 15 mg, 10 mg, 5 mg). The subject may also skip several days of dosing (in this case the daily dose will be 0 mg). Usually, in Oncology Clinical Trials subjects stay on treatment different time (till progression, or death, or discontinuation for any other reasons).

The output has a requirement that subjects data should be sorted not by subject id, but in order of descending duration of treatment (on the top will be the subject with longest treatment duration, and on the bottom will be the subject with shortest treatment duration). The subject ID should be displayed left from the corresponding dosing bar.

The input data set contains information about 5 subjects. As we can see, the subject 1001 changed dose level several times during the study, while subject 1009 stayed the whole study on the same dose.

| obs | subjid | category | dose  | dose_st_day | dose_en_day |
|-----|--------|----------|-------|-------------|-------------|
| 1   | 1001   | Dosing   | 20 mg | 1           | 49          |
| 2   | 1001   | Dosing   | 15 mg | 50          | 87          |
| 3   | 1001   | Dosing   | 0 mg  | 88          | 107         |
| 4   | 1001   | Dosing   | 10 mg | 108         | 114         |
| 5   | 1001   | Dosing   | 5 mg  | 115         | 143         |
| 6   | 1001   | Dosing   | 0 mg  | 144         | 149         |
| 7   | 1001   | Dosing   | 5 mg  | 150         | 169         |
| 8   | 1001   | Dosing   | 5 mg  | 170         | 207         |
| 9   | 1005   | Dosing   | 20 mg | 1           | 36          |
| 10  | 1005   | Dosing   | 0 mg  | 37          | 57          |
| 11  | 1005   | Dosing   | 20 mg | 58          | 99          |
| 12  | 1005   | Dosing   | 15 mg | 100         | 134         |
| 13  | 1007   | Dosing   | 20 mg | 1           | 155         |
| 14  | 1008   | Dosing   | 20 mg | 1           | 31          |
| 15  | 1008   | Dosing   | 15 mg | 32          | 52          |
| 16  | 1009   | Dosing   | 20 mg | 1           | 19          |

After some simple data manipulations, this data set became ready to be converted into the graph. These manipulations include:

- Creating a new character variable id\_subject, value of which will be displayed at the graph
- Deriving duration of treatment for each subject
- Creating a new variable needed\_order with values 1, 2, 3, 4 ... (which will have values of variable id\_subject after formatting) to control appearance of the bars in the needed order (by descending duration of treatment)
- Combining several consecutive records with the same dose for the same subject into one record (records 7 and 8 from above will be combined together into one record with dose\_st\_day = 150 and dose\_en\_day = 207)
- Subtracting 0.5 from dose\_st\_day and adding 0.5 to dose\_en\_day to make dosing information consecutive.
- Adding variable dose\_num\_equivalent will allow to sort legend in the needed order
- The value of newly added variable id\_subject\_left indicates the left edge of displaying subject ID

After sorting by the final data set **by descending dose\_num\_equivalent dose\_en\_day**, the final data set will look like:

| obs | subjid | category | dose  | id_subject | dose_st_day | dose_en_day | trtdurd | needed_order | dose_num_equivalent | id_subject_left |
|-----|--------|----------|-------|------------|-------------|-------------|---------|--------------|---------------------|-----------------|
| 1   | 1009   | Dosing   | 20 mg | ID = 1009  | 0.5         | 19.5        | 19.5    | ID = 1009    | 20                  | 0               |
| 2   | 1008   | Dosing   | 20 mg | ID = 1008  | 0.5         | 31.5        | 52.5    | ID = 1008    | 20                  | 0               |

| obs | subjid | category | dose  | id_subject | dose_<br>st_day | dose_<br>en_day | trtdurd | needed_order | dose_num_<br>equivalent | id_subject_left |
|-----|--------|----------|-------|------------|-----------------|-----------------|---------|--------------|-------------------------|-----------------|
| 3   | 1005   | Dosing   | 20 mg | ID = 1005  | 0.5             | 36.5            | 134.5   | ID = 1005    | 20                      | 0               |
| 4   | 1001   | Dosing   | 20 mg | ID = 1001  | 0.5             | 49.5            | 207.5   | ID = 1001    | 20                      | 0               |
| 5   | 1005   | Dosing   | 20 mg | ID = 1005  | 57.5            | 99.5            | 134.5   | ID = 1005    | 20                      |                 |
| 6   | 1007   | Dosing   | 20 mg | ID = 1007  | 0.5             | 155.5           | 155.5   | ID = 1007    | 20                      | 0               |
| 7   | 1008   | Dosing   | 15 mg | ID = 1008  | 31.5            | 52.5            | 52.5    | ID = 1008    | 15                      |                 |
| 8   | 1001   | Dosing   | 15 mg | ID = 1001  | 49.5            | 87.5            | 207.5   | ID = 1001    | 15                      |                 |
| 9   | 1005   | Dosing   | 15 mg | ID = 1005  | 99.5            | 134.5           | 134.5   | ID = 1005    | 15                      |                 |
| 10  | 1001   | Dosing   | 10 mg | ID = 1001  | 107.5           | 114.5           | 207.5   | ID = 1001    | 10                      |                 |
| 11  | 1001   | Dosing   | 5 mg  | ID = 1001  | 114.5           | 143.5           | 207.5   | ID = 1001    | 5                       |                 |
| 12  | 1001   | Dosing   | 5 mg  | ID = 1001  | 149.5           | 207.5           | 207.5   | ID = 1001    | 5                       |                 |
| 13  | 1005   | Dosing   | 0 mg  | ID = 1005  | 36.5            | 57.5            | 134.5   | ID = 1005    | 0                       |                 |
| 14  | 1001   | Dosing   | 0 mg  | ID = 1001  | 87.5            | 107.5           | 207.5   | ID = 1001    | 0                       |                 |
| 15  | 1001   | Dosing   | 0 mg  | ID = 1001  | 143.5           | 149.5           | 207.5   | ID = 1001    | 0                       |                 |

This data set is ready to be used with SAS code below:

```
/* assigning system options */
```

```
option
```

```
  nonumber
```

```
  orientation = landscape
```

```
  papersize = letter
```

```
  leftmargin = 1 in
```

```
  rightmargin = 1 in
```

```
  topmargin = 1 in
```

```
  bottommargin = 1 in
```

```
  nobyline
```

```
;
```

```
title;
```

```
footnote;
```

```
/* to remove border around wall area we need to make minor changes in default style.
```

```
See web-site http://support.sas.com/kb/48/138.html with the sample how to do it.
```

```
For RTF output - the default (parent) style is RTF. The newly created style should be  
named rtf_swimmer_gtl.
```

```
For PDF output - the default (parent) style is printer. The newly created style should  
be named pdf_swimmer_gtl. */
```

```
ods path show;
```

```

ods path(prepend) work.templat(update);

proc template;
  define style rtf_swimmer_doses_gtl;
    parent = styles.rtf;
    class graphwalls / frameborder = off;
  end;
  define style pdf_swimmer_doses_gtl;
    parent = styles.Printer;
    class graphwalls / frameborder = off;
  end;
run;

/* code for graphic */
ods _all_ close;

ods graphics
  /
  noborder
  height = 6.5 in
  width = 9 in
  ;

ods
  pdf file = 'R:\...\presentation\swimmer_only_doses_gtl_color.pdf'
  notoc style = pdf_swimmer_doses_gtl
  ;

proc template;

  define statgraph swimmer_doses_gtl;

    begingraph / ;

    /* creating an attribute map for future swimmer bars */
    discreteattrmap name = 'bar_gtl';
      value '20 mg' / fillattrs = (color = lightgreen) lineattrs = (color = black);
      value '15 mg' / fillattrs = (color = cyan) lineattrs = (color = black);
      value '10 mg' / fillattrs = (color = violet) lineattrs = (color = black);
      value '5 mg' / fillattrs = (color = gold) lineattrs = (color = black);
      value '0 mg' / fillattrs = (color = white) lineattrs = (color = black);
    enddiscreteattrmap;

    discreteattrvar attrvar = swimmer_doses_bar var = dose attrmap = 'bar_gtl';

    entrytitle halign = center textattrs = (family = 'SAS Monospace' color = black size =
10 pt) 'Figure x.y.main: Dosages of Treatment';

```

```

entrytitle halign = center textattrs = (family = 'SAS Monospace' color = black size =
9 pt) 'Full Analysis Set';
entryfootnote halign = left textattrs = (family = 'SAS Monospace' color = black size
= 9 pt) 'Source: ADEX';
layout overlay
/

xaxisopts = (
  type = linear
  offsetmin = 0.2 offsetmax = 0.05
  label = 'Treatment Duration (days)'
  labelattrs = (family = 'SAS Monospace' size = 10 pt)
  linearopts = (tickvaluesequence = (start = &min_hor_scale end = &max_hor_scale
increment = &hor_interval))
  tickvalueattrs = (family = 'SAS Monospace' size = 10 pt)
)
yaxisopts = (
  type = discrete
  display = none
  reverse = true
  offsetmin = 0.125 offsetmax = 0.05
)
/* second horizontal axis is needed for displaying patient ID */
x2axisopts = (
  display = none
  offsetmin = 0 offsetmax = 0
  linearopts = (viewmin = 0 viewmax = 100)
)
;

/* drawing bars for duration of different dosages */
highlowplot
  y = needed_order
  low = dose_st_day
  high = dose_en_day
/
  type = bar
  group = swimmer_doses_bar
  outlineattrs = (pattern=solid)
  barwidth = 0.75
  name = 'dosages'
;

/* drawing text information about subject ID */
scatterplot
  x = id_subject_left
  y = needed_order
/
  xaxis = x2
  datalabel = id_subject

```

```

        datalabelposition = right
        markerattrs = (size = 0)
        datalabelattrs = (size = 9 pt color = black)
        ;

discretelegend 'dosages'
/
location = inside
exclude = (' ')
halign = right
valign = 0.1
border = false
down = 1
title = "Dosage of Treatment:"
titleattrs = (size = 10 pt weight = bold)
valueattrs = (size = 9 pt)
;

endlayout;

endgraph;

end;

run;

proc sgrender data = final template = swimmer_doses_gtl;
run;

ods pdf close;

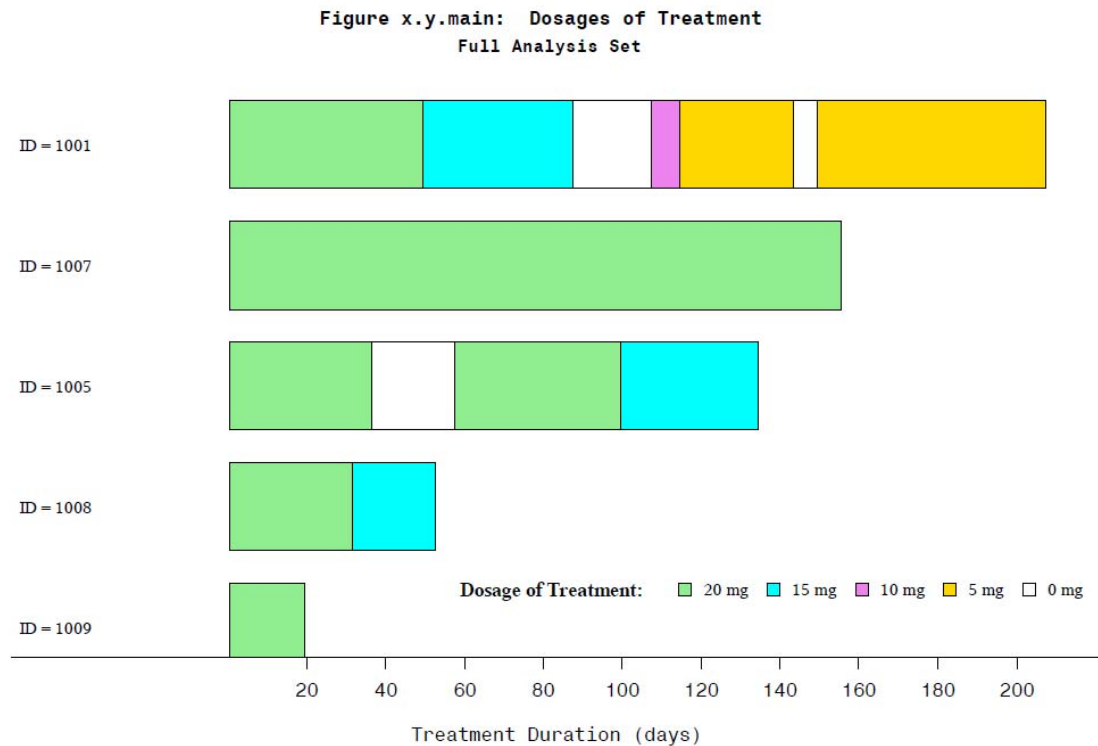
title;
footnote;

ods graphics / reset;

ods listing;

to produce a figure:

```



Source: ADEX

## PART 1: DOSING WITH ADVERSE EVENTS OF SPECIAL INTEREST.

The figure shown in the preliminary part of this article, is suitable for different types of enhancements. One of the most useful enhancements is to display Adverse Events of Special Interest (these events are usually identified by medical staff and provided to statistical programmer as selected Preferred Terms). In our example we will show the duration of Adverse Events. Some subjects may experience such adverse events more than once during the treatment and in 30 days after the last dose; some subjects may not have such adverse events at all.

Let's return to the subjects above. During the study, the Adverse Events of Special Interest were recorded as below:

| obs | category | subjid | ae_st_day | ae_en_day |
|-----|----------|--------|-----------|-----------|
| 1   | AE       | 1001   | 85        | 111       |
| 2   | AE       | 1001   | 137       | 178       |
| 3   | AE       | 1005   | 30        | 56        |
| 4   | AE       | 1008   | 35        | 68        |
| 5   | AE       | 1009   | 25        | 33        |

To be used with SAS code, this data set needs adjustment similar to already described adjustments for dosing information. After this adjustment, this data set will be concatenated with data set about dosing and resulting SAS data set will be used for graphic production.

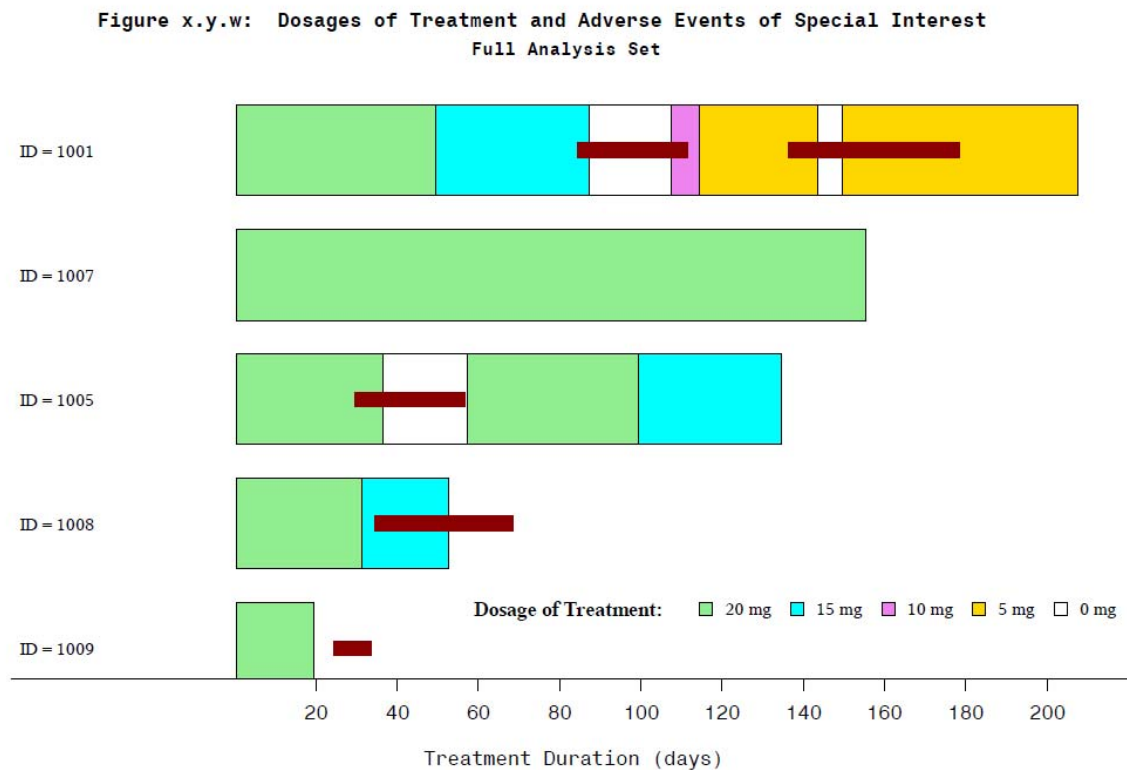
The additional statements were added into SAS code:

```

/* second vertical axis is needed because vectorplot statement does not work with discrete type
of axis */
y2axisopts = (
  display = none
  type = linear
  reverse = true
  offsetmin = 0.125 offsetmax = 0.05
  linearopts = (integer = true thresholdmin = 0 thresholdmax = 0 viewmin = 1 viewmax =
&total_subjects)
)
;
/* drawing lines (as vectors without arrows) to indicate AEs of special Interest */
vectorplot
  x = ae_en_day
  y = needed_order
  xorigin = ae_st_day
  yorigin = needed_order
  /
yaxis = y2
arrowheads = false
includemissinggroup = no
lineattrs = (thickness = 10 color = darkred)
;

```

As a result, we will get a figure below:



This figure clearly displays our ability to show some additional information, collected as a time intervals, on a top of previously created figure.

## PART 2: DOSING WITH BEST OVERALL RESPONSES AND RESULTS OF TIMEPOINT EVALUATIONS.

In the following example, we will show how to enhance swimmer plot with the derived values of Best Overall Response and collected results for Time Point Evaluations. Usually, subjects in Oncology Clinical Trials are evaluated once in several cycles. Let's, for simplicity, assume that subjects are expected to be evaluated once in 50 days. In reality, the time between 2 consecutive evaluations can be slightly more or slightly less than proposed time (50 days in our case).

The input information for this graph contains 3 categories:

- Dosing (similar to data in graph from preliminary part)
- Overall (subject level information about Best Overall Response). The possible values of Best Overall Response are limited to: CR (Complete Response), PR (Partial Response), SD (Stable Disease), PD (Progressive Disease), and NE (Not Evaluable). For this study the confirmation of response was not required:

| obs | subjid | category | bor |
|-----|--------|----------|-----|
| 1   | 1001   | Overall  | PR  |
| 2   | 1005   | Overall  | SD  |
| 3   | 1007   | Overall  | CR  |
| 4   | 1008   | Overall  | PD  |
| 5   | 1009   | Overall  | NE  |

- Point (Results of Time Points Efficacy Evaluations). Usually, subjects are evaluated several times during the treatment or after it, but some subjects may not have any of the evaluations. The possible results of Overall Time Point Evaluations are limited to: CR (Complete Response), PR (Partial Response), SD (Stable Disease), PD (Progressive Disease), NE (Not Evaluable).

| obs | subjid | category | evald | time_point_eval |
|-----|--------|----------|-------|-----------------|
| 1   | 1001   | Point    | 50    | SD              |
| 2   | 1001   | Point    | 100   | SD              |
| 3   | 1001   | Point    | 150   | PR              |
| 4   | 1001   | Point    | 200   | NE              |
| 5   | 1005   | Point    | 48    | SD              |
| 6   | 1005   | Point    | 107   | SD              |
| 7   | 1007   | Point    | 55    | SD              |
| 8   | 1007   | Point    | 100   | CR              |
| 9   | 1007   | Point    | 156   | PD              |
| 10  | 1008   | Point    | 62    | PD              |

To be used with SAS code, these data sets need adjustments, similar to already described adjustments for dosing information. After such adjustment, these 2 data sets will be concatenated with data set about dosing and resulting SAS data set will be used to make graphic. We need to add a new variable `time_point_num_equivalent` to data set for results of Time Point evaluations: this will allow sorting legend information in the needed order.

```
if time_point_eval = 'CR' then time_point_eval_num_equivalent = 1;
if time_point_eval = 'PR' then time_point_eval_num_equivalent = 2;
if time_point_eval = 'SD' then time_point_eval_num_equivalent = 3;
if time_point_eval = 'PD' then time_point_eval_num_equivalent = 4;
if time_point_eval = 'NE' then time_point_eval_num_equivalent = 9;
```

Before using final data set as a source for the graph, it should be sorted as:

```
proc sort data = final;
  by descending dose_num_equivalent dose_en_day time_point_eval_num_equivalent;
run;
```

The additional statements were added into SAS code:

```
/* creating an attribute map for future time-point responses */
discreteattrmap name = 'time_point_response_gtl';
  value 'CR' / markerattrs = (color = black symbol = SquareFilled);
  value 'PR' / markerattrs = (color = black symbol = CircleFilled);
  value 'SD' / markerattrs = (color = black symbol = TriangleFilled);
  value 'PD' / markerattrs = (color = black symbol = TriangleLeftFilled);
  value 'NE' / markerattrs = (color = black symbol = StarFilled);
enddiscreteattrmap;

discreteattrvar attrvar = time_point_responses var = time_point_eval attrmap =
'time_point_response_gtl';

/* creating an attribute map for text information about Best Overall Responses */
discreteattrmap name = 'bor_gtl';
  value 'CR' / markerattrs = (color = darkred);
  value 'PR' / markerattrs = (color = violet);
  value 'SD' / markerattrs = (color = green);
  value 'PD' / markerattrs = (color = darkgray);
  value 'NE' / markerattrs = (color = blue);
enddiscreteattrmap;

discreteattrvar attrvar = bor var = bor attrmap = 'bor_gtl';

/* drawing markers to indicate time-point responses */
scatterplot
  x = evald
  y = needed_order
  /
  group = time_point_responses
  name = 'responses'
  markerattrs = (size = 6 pt)
```

```

;

/* drawing text information about Best Overall Responses */
scatterplot
  x = bor_center
  y = needed_order
  /
  xaxis = x2
  group = bor
  name = 'bor_gtl'
  datalabel = bor
  datalabelposition = center
  markerattrs = (size = 0)
  datalabelattrs = (size = 9 pt)
;

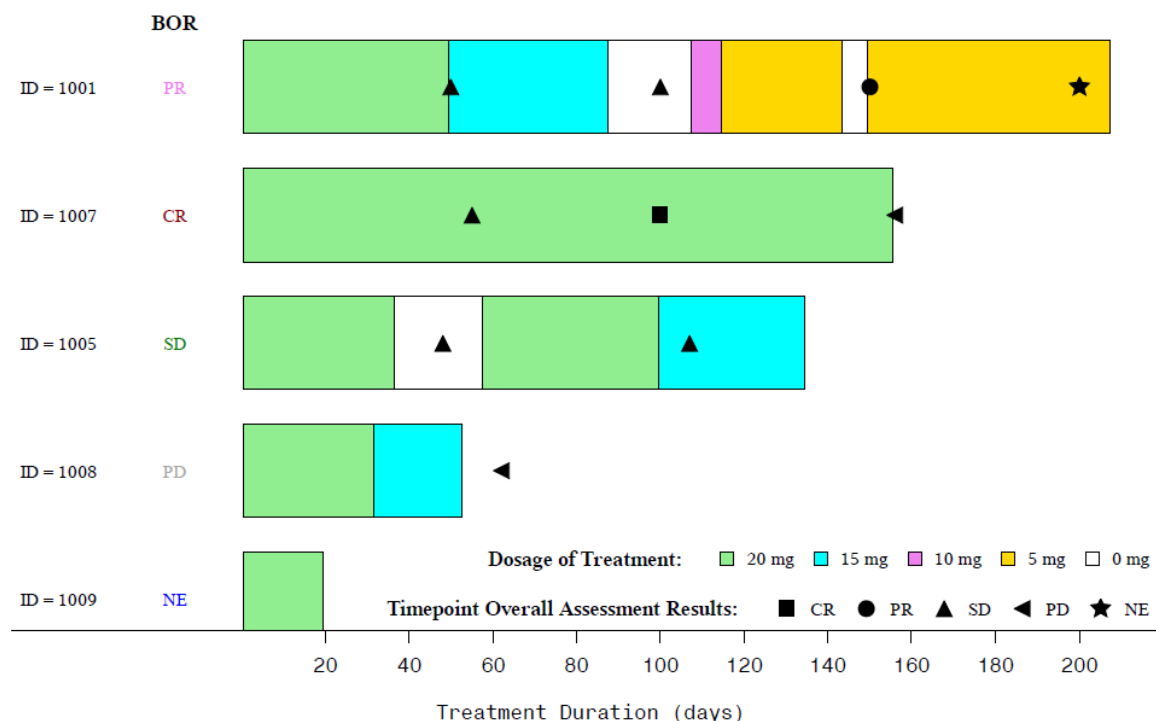
discretelegend 'responses'
/
  location = inside
  exclude = (' ')
  halign = right
  valign = bottom
  border = false
  down = 1
  title = "Timepoint Overall Assessment Results:"
  titleattrs = (size = 10 pt weight = bold)
  valueattrs = (size = 9 pt)
;

drawtext
  textattrs = (weight = bold size = 10 pt color = black)
  "BOR"
  /
  width = 100
  widthunit = percent
  anchor = top
  xspace = wallpercent
  yspace = wallpercent
  x = 14
  y = 100
  justify = center
;

```

As a result, we will get a figure below:.

**Figure x.y.z: Dosages of Treatment and Overall Timepoint Assessments**  
Full Analysis Set



Source: ADEF, ADEX, ADTRS

This figure clearly shows our ability to display additional information, collected as a time point and / or as a treatment overall, on a top of previously created figure.

### PART 3: DOSING WITH FUTURE ENHACMENTS:

The similar technique can be used in many similar figures. For example, we can display

- if the treatment is ongoing; this can be easily displayed using HIGHLOWPLOT statement with the option HIGHCAP to specify the type of cap used at the right end of the bar or line.
- if Best Overall Response, derived as Stable Disease, is a durable Stable Disease
- time points (study days) and planned doses for intravenous injections
- results (scores) of Quality of Life examinations
- casualty (toxicity grades) or seriousness of Adverse Events of Special Interest
- if Adverse Events of Special Interest are ongoing (not resolved) - this can be easily done using VECTORPLOT statement with corresponding ARROWHEADS selection

### CONCLUSIONS:

SAS has provided US with powerful tools to generate graphs using Graph Template Language technique. This paper has shown that telling an enhanced story about our data is flexible and can easily be done using just a few GTL statements. This technique allows for different types of future enhancements, and all of these enhancements can be achieved using Graph Template Language.

## REFERENCES

SAS® 9.3 Graph Template Language: Reference, Third Edition

SAS® 9.3 Graph Template Language: User's Guide

Matange, Sanjay. 2013. Getting Started with the Graph Template Language in SAS®: Examples, Tips, and Techniques for Creating Custom Graphs. Cary, NC: SAS Institute Inc.

Stacey D. Phillips. 2014. Swimmer Plot: Tell a Graphical Story of Your Time to Response Data Using PROC SGPLOT

## CONTACT INFORMATION

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