SAS ® ODS Application of Interactive and Informative Clinical Trial Reports

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ABSTRACT

Graphs and charts are used extensively in the clinical-trial efficacy and safety analyses. They transform large amounts of information and statistical results into easy-to-understand formats. Visualization methodologies have been developed in different languages and software. For clinical trials, directly using the analysis datasets in real time without transferring data from one language/system such as SAS to another language/system such as R is desired. It is also desired to enhance data traceability by producing visualization programmatically rather than transfer data to an excel spreadsheet to manually explore the features. Meanwhile, compared with the traditional graphs and charts, more interactive and informative visualization outputs are in demand to enhance the reviewing efficiency. This paper describes SAS ® ODS Graphic data tip techniques to create interactive outputs for the time to event Kaplan-Meier plots and death bar charts to illustrate the efficacy and safety analysis for oncology clinical trials. The technique demonstrates "details-on-demand"; as the cursor hovers over points on the graphs, more detailed information will be displayed. We also provide the dashboard application of SAS ® ODS Layout to arrange the text, graphs, and tables side by side on the same page for efficient reviewing. Both types of SAS ODS code are presented and explained.

INTRODUCTION

A variety of clinical trials are conducted worldwide to study new treatments and therapies and evaluate the safety and efficacy on human health outcomes. Today, global-multi-center enrollment and advanced technical measurements are the norm for the increasing complexity of study design. Large amounts of data are collected in the clinical trials to ensure the quality and accuracy of the outcomes. When exploring the large amounts of clinical data, there is an explosion in the numbers of conventional statistical analysis outputs. Hundreds or even thousands of statistical Tables, Figures and Listings (TFLs) are generated, which is a major challenge for statistical programmers, biostatisticians, clinical scientists, and other reviewers to analyze the data and communicate the findings.

Compared to tabular outputs, graphics are a great alternative to convey a large amount of information using a single visual. There are many classic and commendable methodologies available to generate the visualized outputs. As an example, for oncology clinical trials, the Kaplan-Meier survival plots created by SAS ® PROC LIFETEST are among the most frequently adopted graphics to estimate the survivor function and compare survival curves between groups (Warren & Ying, 2013). However, when reviewing the conventional Kaplan-Meier plots, biostatisticians and clinical scientists always need the additional efficacy analysis tables and subject-level information listings to manually trace back the individual specific event or censoring type, summary results, and other influencing factors which is time-consuming and error-prone. The traditional SAS graphics have limitations in incorporating and delivering comprehensive information and multiple data elements in one single output. A more holistic and insightful visualized tool is desired to enhance the reviewing efficiency and interactivity.

SAS ® ODS Graphics provides the data tip technique to convert a static plot to an interact one. It allows the user to create custom data tips and review the additional information by simply placing the cursor over the data points on the graphs. In addition, SAS ® ODS Layout is a powerful and user-friendly tool that enables the user to arrange and display the description text, titles, and multiple SAS outputs side by side on the same page. This paper will focus on the ODS applications in clinical trial efficacy and safety analysis to produce interactive and informative reports.

DATA PREPARATION

The input analysis dataset used for Kaplan-Meier progression free survival analysis (example shown in Figure 1) includes the key variables TIME (Event or Censored Time in Month), SURV (Survival Probability), TRT01P (Treatment Group), D_SURV (Survival Rate in Percentage), DATA_INFO (Event/Censor Type), and the additional subject-level information such as USUBJID (Subject ID).

The efficacy outcome variables summarized by the selected timepoints are also part of the input dataset (example shown in Figure 2). They include SUM_CENSOR1 (Count of Censored Subjects in ABC treatment), SUM_CENSOR2 (Count of Censored Subjects in Standard of Care (SOC) treatment), SUM_CNSR_D1_1 (Count of Censored Subjects in ABC Treatment at Day1), SUM_CNSR_D1_2 (Count of Censored Subjects in SOC at Day1), SUM_CNSR_ID1 (Censored Subject IDs in ABC Treatment at Day1), SUM_CNSR_ID2 (Censored Subject IDs in SOC at Day1), SUM_DEATH1 (Count of Event (Death) in ABC Treatment), SUM_DEATH2 (Count of Event (Death) in SOC), SUM_PD1 (Count of Event of Progression Disease (PD) in ABC Treatment) and SUM_PD2 (Count of Event (PD) in SOC).

Figure 1. Input analysis dataset (1)

TIME	SURV	TRT01P	D_SURV	USUBJID	DATA_INFO
0.0000	1	ABC Treatment	100.0%		
0.0329	1	ABC Treatment	100.0%	ABC00223; ABC00427; ABC00748	Randomization; Randomization; Randomization
0.0329	1	ABC Treatment	100.0%	ABC00223; ABC00427; ABC00748	Randomization; Randomization; Randomization
0.0329	1	ABC Treatment	100.0%	ABC00223; ABC00427; ABC00748	Randomization; Randomization; Randomization
0.0657	1	ABC Treatment	100.0%	ABC00279	Last Radiologic Assessment Showing No Progression
0.0986	1	ABC Treatment	100.0%	ABC00036	Last Radiologic Assessment Showing No Progression
0.1314	1	ABC Treatment	100.0%	ABC00690	Last Radiologic Assessment Showing No Progression
0.1971	1	ABC Treatment	100.0%	ABC00003; ABC00452	Last Radiologic Assessment Showing No Progression; Last Radiologic Assessment Showing No Progression
0.1971	1	ABC Treatment	100.0%	ABC00003; ABC00452	Last Radiologic Assessment Showing No Progression; Last Radiologic Assessment Showing No Progression
0.2300	1	ABC Treatment	100.0%	ABC00438	Last Radiologic Assessment Showing No Progression
0.2628	1	ABC Treatment	100.0%	ABC00282	Last Radiologic Assessment Showing No Progression
0.3286	0.9948717949	ABC Treatment	99.5%	ABC00093; ABC00715	Last Radiologic Assessment Showing No Progression; Documented Progression
0.3286	0.9948717949	ABC Treatment	99.5%	ABC00093; ABC00715	Last Radiologic Assessment Showing No Progression; Documented Progression

Figure 2. Input analysis dataset (2)

TIMEPOINT_LIST1	TIMEPOINT_LIST2	SUM_CENSOR1	SUM_CENSOR2	SUM_CNSR_D1_1	SUM_CNSR_D1_2	SUM_CNSR_ID1	SUM_CNSR_ID2	SUM_DEATH1	SUM_DEATH2	SUM_PD1	SUM_PD2
0	.	3	6	3	6	ABC00223; ABC00427; ABC00748	ABC00008; ABC00015; ABC00037; ABC00755; ABC00756; ABC00842	0	0	0	0
2	2	43	15	3	6			3	5	20	10
4	4	49	18	3	6			5	7	26	11
6	6	56	20	3	6			6	8	27	12
8	8	77	22	3	6			8	10	28	23
10	10	88	24	3	6			8	10	28	32
12	12	93	24	3	6			8	10	29	34
14	14	97	24	3	6			8	11	30	34
16	16	98	24	3	6			8	11	30	35
18	18	105	25	3	6			8	12	30	38
20	20	107	26	3	6			9	12	32	39
22	22	108	27	3	6			10	12	32	39
24	24	112	27	3	6			12	12	32	39
26	26	117	29	3	6			12	13	32	41
28	28	129	30	3	6			12	13	33	42
30	30	137	30	3	6			13	15	33	44
32	32	145	31	3	6			13	16	33	45
34	34	154	32	3	6			13	16	33	45
36	36	155	34	3	6			13	17	33	45
38	38	156	35	3	6			13	17	33	45
40	40	157	36	3	6			13	18	33	45
42	42	158	36	3	6			13	18	33	46
44	44	159	37	3	6			13	18	33	47
48	48	159	37	3	6			13	18	33	47

DATA TIPS APPLICATIONS

Nearly all the plot statements in SAS Graph Template Language (GTL) automatically save the data values as the default data tips. When setting the option IMAGEMAP=ON in the ODS GRAPHICS statement, the HTML file displays the data tip text balloons which are associated with the point where the cursor is positioned in the plot. GTL also enables the user to customize the data tip through the ROLENAME=, TIP=, TIPLABEL= and TIPFORMAT= options in the plot statements. The ROLENAME= option sets up the data tip name/value pairs as *role-name=column-name*. The *role-name* is the user-defined data tip name that can be subsequently quoted in the TIP=, TIPLABEL= and TIPFORMAT= options. The *column-name* is the selected input data variable that contains the additional data information associated with the points in the plot. The TIP= option defines a list of role names and determines the order of data tips to be displayed in the text balloons. The default tip label is the data label or the variable

name. In order to provide a precise description, the user can re-define the label in the TIPLABEL= option and assign the data tip format in the TIPFORMAT=option.

DATA TIP APPLICATION 1: EFFICACY ANALYSIS, INTERACTIVE KAPLAN-MEIER PLOT, THE USAGE OF INTERACTIVE TECHNIC

When the cursor hovers over the points on the Kaplan-Meier curves, data tips display the subjects' time to event/censor, overall survival probability, subject's treatment group, subject ID, and event/censor type (examples shown in Figure 3 and Figure 4). The additional data tip information facilitates easier trace back to the subject information by subject ID while directly exploring the individual efficacy endpoints in the Kaplan-Meier plot for the reviewer. The example in Figure 3 below shows a subject with a death event, while Figure 4 displays the specific censoring types of censored subjects.

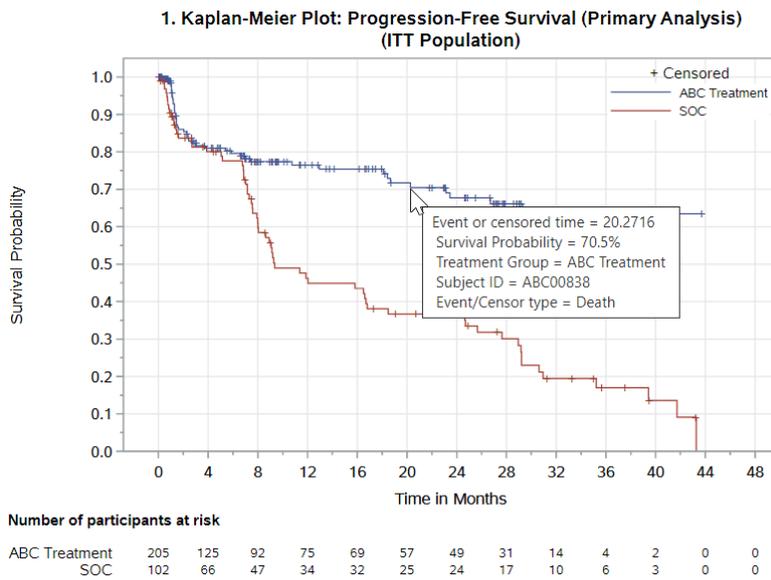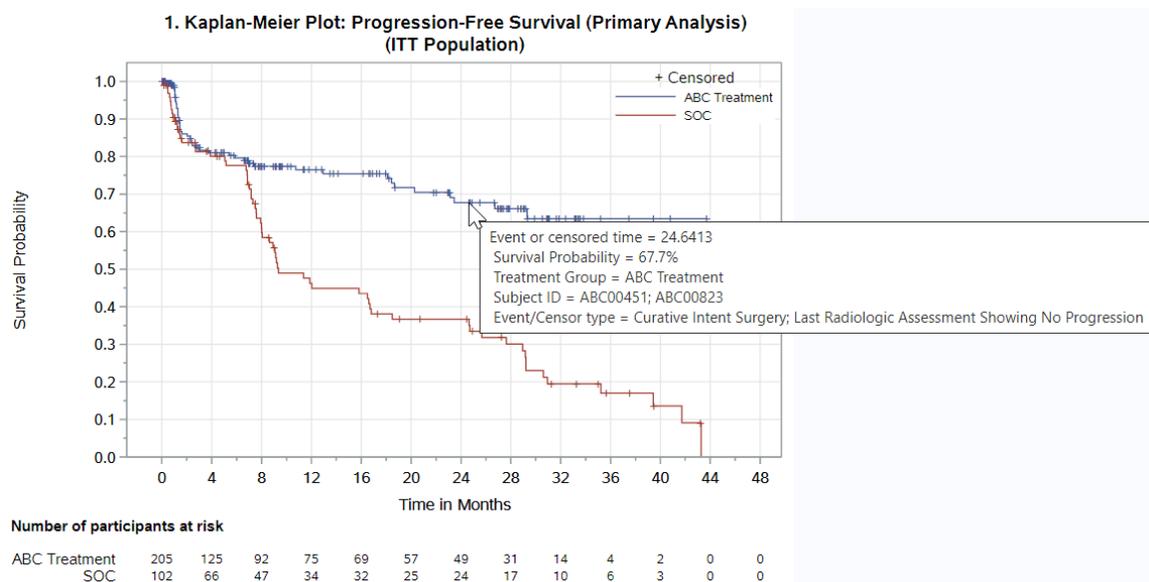**Figure 3. Kaplan-Meier Progression Free Survival Plot (1)**

Figure 4. Kaplan-Meier Progression Free Survival Plot (2)

The code shown below demonstrates the process to add subject-level data tips in the Kaplan-Meier curves. The original Kaplan-Meier curves are created by STEPPLOT and the subject-level data tips are added by SERIESPLOT in GLT statements. The TIP1, TIP2, and TIP3 are role names assigned for the selected variables D_SURV, USUBJID, and DATA_INFO besides the default role names X, Y, and GROUP in the SERIESPLOT statement. The display order and labels for data tips are defined in the TIP= and TIPLABEL= options.

```
proc template;
   define statgraph KM;
   begingraph;
   …
   /*create Kaplan-Meier curves by stepplot*/
   stepplot x=TIME y=SURV / group=TRT01P name='s' primary=true;
   /*add Kaplan-Meier curves subject-level data tips by seriesplot*/
   seriesplot x=TIME y=SURV /datatransparency=1 group=TRT01P
       lineattrs=(thickness=8px)
       rolename=(tip1=D_SURV tip2=USUBJID tip3=DATA_INFO)
       tip=(X tip1 GROUP tip2 tip3)
       tiplabel=(tip1="Survival Probability" GROUP="Treatment Group"
             tip2="Subject ID" tip3="Event/Censor type");
   …
   endgraph;
   end;
run;
```
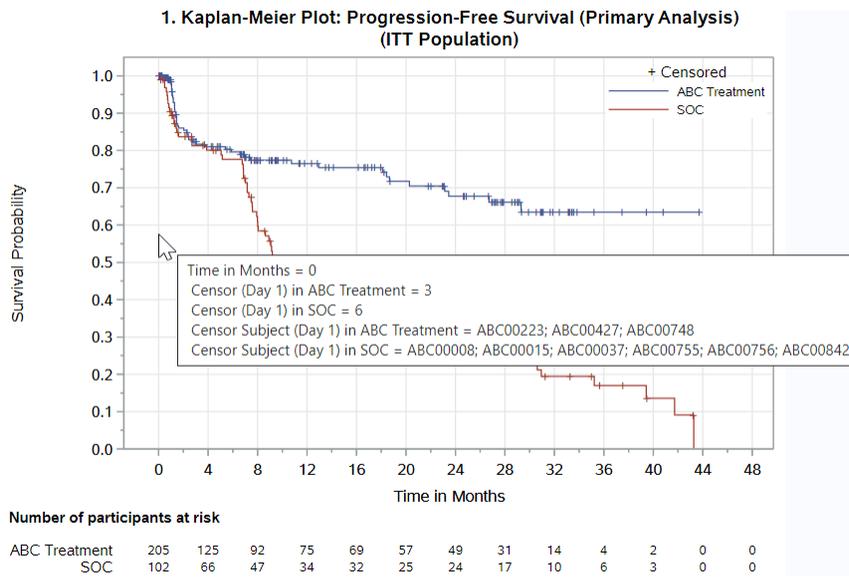
The advantages of defining the data tips in a separated series plot are:
  (1) The data tips are displayed continuously, and evenly distributed between two consecutive data points, which allows the user to rest the cursor on and around the data points to review the data tips.
  (2) The display area for data tips can be enlarged using the thickness option, which enhances control when the user rests the cursor on the curves.

DATA TIP APPLICATION 2: EFFICACY ANALYSIS, INTERACTIVE KAPLAN-MEIER PLOT, SUBJECT CENSORED AT DAY 1

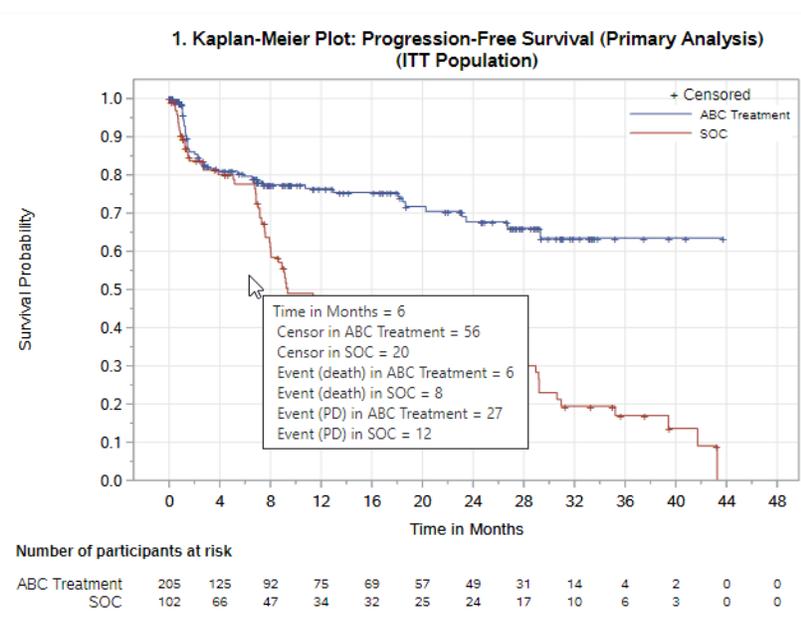When the cursor hovers over the vertical grid at timepoint=0, data tips display the count and subject IDs who were censored at Day 1 by treatment group (example shown in Figure 5). Patients censored at the early stage of the trial, especially Day 1 where no imaging or other endpoint measurement can be the cause of the cross of the survival curves, may be of particular interest for the analysis investigation.

Figure 5. Kaplan-Meier Progression Free Survival Plot (3)

1. Kaplan-Meier Plot: Progression-Free Survival (Primary Analysis)
(ITT Population)

Time in Months = 0
Censor (Day 1) in ABC Treatment = 3
Censor (Day 1) in SOC = 6
Censor Subject (Day 1) in ABC Treatment = ABC00223; ABC00427; ABC00748
Censor Subject (Day 1) in SOC = ABC00008; ABC00015; ABC00037; ABC00755; ABC00756; ABC00842

Number of participants at risk

ABC Treatment	205	125	92	75	69	57	49	31	14	4	2	0	0
SOC	102	66	47	34	32	25	24	17	10	6	3	0	0

When the cursor hovers over other blank areas in the plot, data tips display the x-axis corresponding summary information including cumulative censor, event (death), and event (progression disease) counts by treatment group (example shown in Figure 6). Different survival patterns between treatment groups can be one critical factor influencing the efficacy analysis.

Figure 6. Kaplan-Meier Progression Free Survival Plot (4)

1. Kaplan-Meier Plot: Progression-Free Survival (Primary Analysis)
(ITT Population)

Time in Months = 6
Censor in ABC Treatment = 56
Censor in SOC = 20
Event (death) in ABC Treatment = 6
Event (death) in SOC = 8
Event (PD) in ABC Treatment = 27
Event (PD) in SOC = 12

Number of participants at risk

ABC Treatment	205	125	92	75	69	57	49	31	14	4	2	0	0
SOC	102	66	47	34	32	25	24	17	10	6	3	0	0

The code shown below demonstrates the process to add early censor and event/censor type summary data tips in the Kaplan-Meier plot. The data tip options defined in the bar chart statement allow the data tips to be displayed when the cursor rests on any datapoint in the vertical bars.

```
proc template;
   define statgraph KM;
   begingraph;
   …
   /*add early censor data tips in the Kaplan-Meier plot*/
   barchart x=timepoint_list1 /datatransparency=1 clusterwidth=1
       rolename=(tip1=sum_cnsr_d1_1 tip2=sum_cnsr_d1_2
             tip3=sum_cnsr_id1 tip4=sum_cnsr_id2)
       tip=(X tip1 tip2 tip3 tip4)
       tiplabel=(tip1="Censor (Day 1) in ABC Treatment"
             tip2="Censor (Day 1) in SOC"
             tip3="Censor Subject (Day 1) in ABC Treatment"
             tip4="Censor Subject (Day 1) in SOC"
             X="Time in Months");

   /*add Event/Censor summary data tips in the Kaplan-Meier plot*/
   barchart x=timepoint_list2 /datatransparency=1 barwidth=1
       rolename=(tip1=sum_censor1 tip2=sum_censor2
       tip3=sum_death1 tip4=sum_death2 tip5=sum_pd1
             tip6=sum_pd2)
       tip=(X tip1 tip2 tip3 tip4 tip5 tip6)
       tiplabel=(tip1="Censor in ABC Treatment"
             tip2="Censor in SOC"
             tip3="Event (death) in ABC Treatment"
             tip4="Event (death) in SOC"
             tip5="Event (PD) in ABC Treatment"
             tip6="Event (PD) in SOC"
             X="Time in Months");
   …
   endgraph;
   end;
run;
```

DATA TIP APPLICATION 3: SAFETY ANALYSIS: INTERACTIVE DEATH ANALYSIS BAR CHART

When the cursor hovers over the bars in the event (death) count comparison chart, the data tips display the subject IDs who died at the corresponding timepoints. When the cursor hovers over the bars in the early death chart, the data tips display the cause of death (example shown in Figure 7). The death information, particularly the early death data in a clinical trial, is a critical outcome for both efficacy and safety analysis.

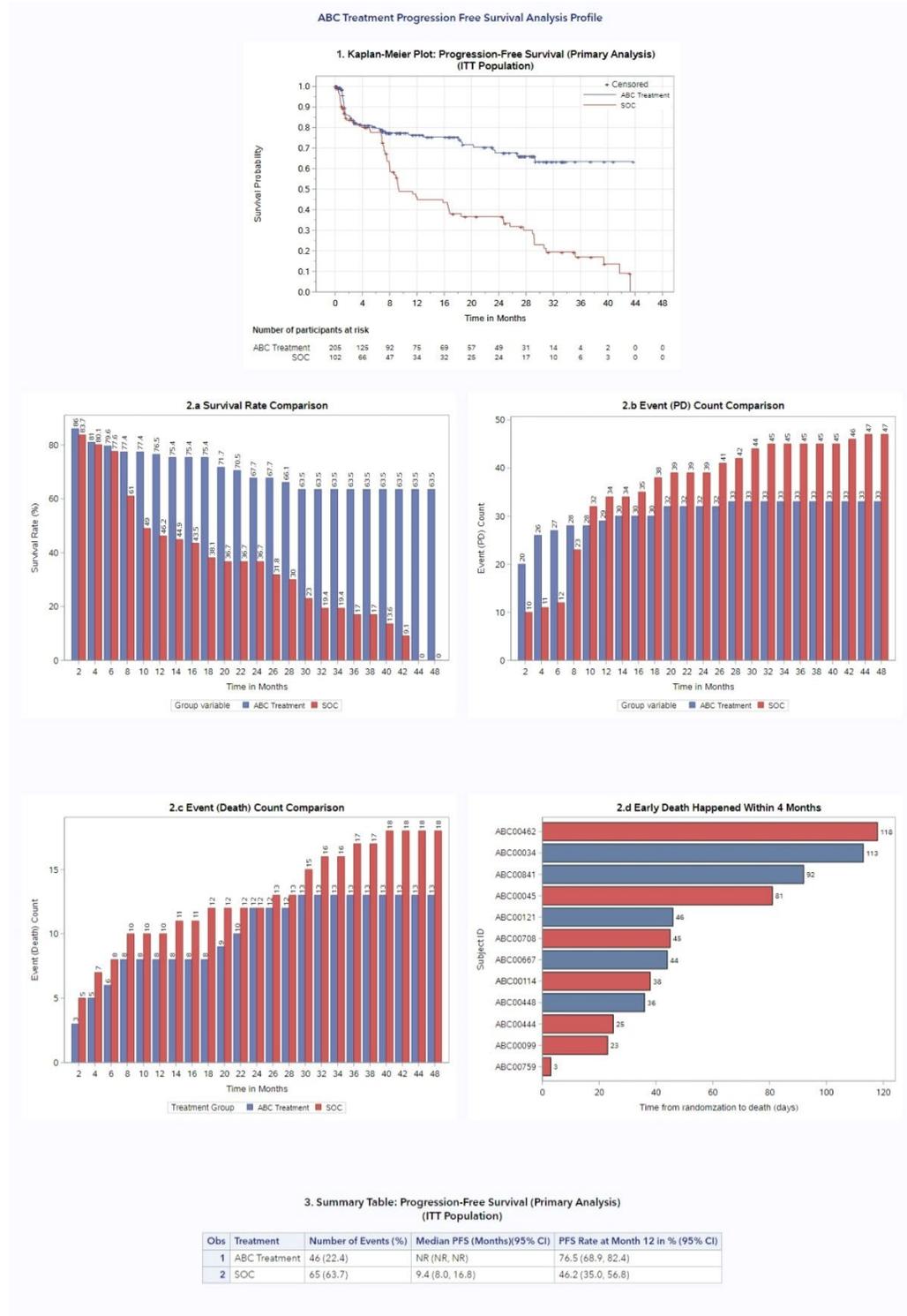**Figure 7. Death Analysis Bar Chart**
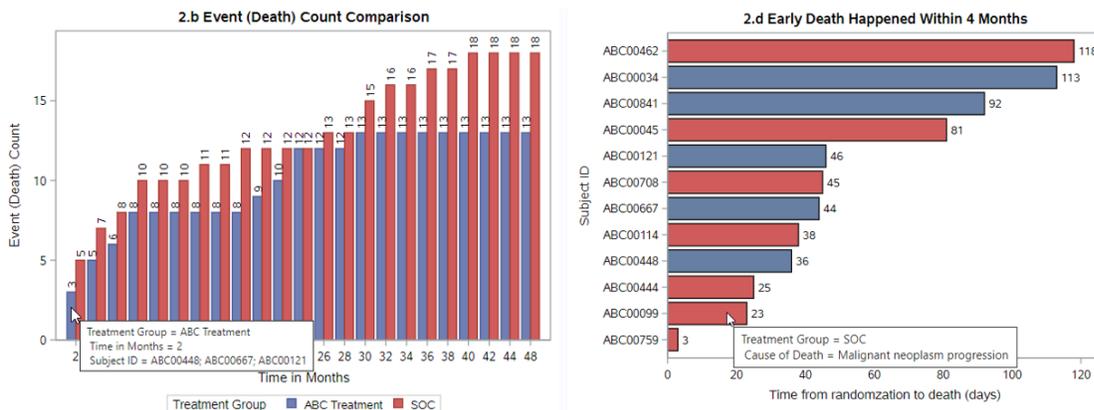
ODS LAYOUT DASHBOARD APPLICATION

The ODS LAYOUT statement enables the user to customize the informative one-page dashboard profile that could contain titles, footnotes, text, images, multiple graphs, and tables. Two types of layouts namely GRIDDED and ABSOLUTE are available in the ODS LAYOUT statement. ODS LAYOUT GRIDDED enables the user to arrange outputs dynamically in a grid structure, while ODS LAYOUT ABSOLUTE allows the user to position the outputs with exact page location using x and y coordinates. Both layout types are supported for PRINTER destinations includes PDF, Postscript (PS), and Printer Control Language (PCL). In addition, ODS LAYOUT GRIDDED is also supported for HTML and PowerPoint. The ODS REGION statement locates each SAS outputs in the profile.

ODS LAYOUT APPLICATION: PROGRESSION FREE SURVIVAL ANALYSIS PROFILE

Here, in Figure 8, an example of "ABC Treatment Progression Free Survival Analysis Profile" presents the interactive Kaplan-Meier plot, survival rate comparison chart, event (death)/(PD) count comparison chart, early death chart, and statistical summary table on the same page. The informative profile allows the user to interact with the individual graphs in HTML format, comprehend the complicated analysis results, and easily interpret the findings.

Figure 8. ABC Treatment Progression Free Survival Analysis Profile

ABC Treatment Progression Free Survival Analysis Profile

1. Kaplan-Meier Plot: Progression-Free Survival (Primary Analysis) (ITT Population)

2.a Survival Rate Comparison

2.b Event (PD) Count Comparison

2.c Event (Death) Count Comparison

2.d Early Death Happened Within 4 Months

3. Summary Table: Progression-Free Survival (Primary Analysis) (ITT Population)

Obs	Treatment	Number of Events (%)	Median PFS (Months)(95% CI)	PFS Rate at Month 12 in % (95% CI)
1	ABC Treatment	46 (22.4)	NR (NR, NR)	76.5 (68.9, 82.4)
2	SOC	65 (63.7)	9.4 (8.0, 16.8)	46.2 (35.0, 56.8)

CONCLUSION

This paper illustrates the flexibility of adding interactivity to SAS Graphics using the ODS data tip technique and customizing an informative one-page dashboard report with ODS Layout tools using examples from Oncology trials. It demonstrates how analysis datasets can be used for interactive interrogation of graphs in real time without transferring data from one language/system such as SAS to another language/system such as R. It also enhances data traceability by creating visualization programmatically rather than transferring data to an excel spreadsheet to manually explore the features. As a result, the employment of powerful ODS applications has the potential to greatly enhance the efficiency of data review and promote better traceability in clinical trials.

REFERENCES

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