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Waterfall vis a vis Spider plots: Complex oncology efficacy endpoint made simpler.

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ABSTRACT

Over the past 50 years, cancer diagnosis has transformed medicinal research and advancement. Such changes have only increased the complexity of clinical trials. To analyze such data from oncology studies, scientists measure certain efficacy endpoints such as Best Overall Response (BOR) to evaluate the effect of treatments on tumor response. Among various graphical representations, Waterfall plots and Spider plots have become increasingly efficient in visually depicting tumor shrinkage. However, each of these competing techniques have their share of benefits and drawbacks, causing perplexity within the clinical domain. Waterfall plots, on one hand, display a series of bars, each representing a patient's change in tumor size. While they are clear and concise at allowing scientists to assess differences, they are limited to exhibiting smaller cohorts of patients. On the other hand, Spider plots are a series of web-like projections that represent the change from Baseline for tumors in different groups of individuals. While they provide for simultaneous comparison of multiple variables, they can often oversimplify complex relationships. As there is no comprehensive review comparing the merits of Waterfall and Spider plots, this paper aims to explore appropriate SAS code to generate these figures and to determine the best method of measuring BOR.

INTRODUCTION AND BACKGROUND

As the field of Oncology continues to evolve, statistical analyses of oncology data have become increasingly complex. To assess the effects of experimental medications, these trials use an array of efficacy endpoints. The Best Overall Response (BOR), a composite measure that includes Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD), is one such oncology efficacy endpoint that has become increasingly popular among scientific community.

However, navigating the intricate world of endpoint analysis in cancer is far from simple.

The plethora of methods and resources available for analyzing Best Overall Response is the reason such endpoint analysis is necessary. Among all methods, two visualization techniques—Waterfall plots and Spider plots—have become strong competitors.

These graphical representations offer valuable insights into treatment responses but have not yet undergone a comprehensive comparative analysis in the context of clinical trials for cancer therapy.

Moreover, despite ongoing discussion over the advantages of Spider vs. Waterfall plots, there lacks a comprehensive review that directly compares these two visual aids for BOR efficacy endpoint analysis. Consequently, practitioners and researchers are without a clear understanding about which approach is more informative and successful.

Additionally, within the domain of clinical SAS, these plots can be produced using a wide range of procedures and techniques. The variety of options accessible and the differences in coding techniques further the complexity of the matter.

This research paper aims to bridge this knowledge gap by addressing the critical question: What is the comparative efficacy and utility of Waterfall and Spider plots in the analysis of treatment endpoints within the context of clinical trials for cancer therapy? Moreover, this paper also aims to simplify the process of creating Waterfall and Spider plots in SAS, offering a concise and efficient code that can be easily adopted by programmers/researchers.

HISTORY OF WATERFALL PLOTS AND SPIDER PLOTS

Waterfall plots originated in the field of oncology during the late 20th century (Chia et al., 2016). They were initially used to see changes in tumor size in response to cancer treatments. These early plots typically showed the change in tumor size for each patient. As oncology research advanced, waterfall plots started to incorporate more complex types of data such as changes in

biomarker levels (e.g., blood markers) and genomic alterations. This allowed researchers to assess not only tumor shrinkage but also the impact of treatments on specific molecular targets.

Spider plots have been used in medicine for years to assess the overall health or performance of individuals, including cancer patients. They offer a way to simultaneously display various clinical parameters such as laboratory values and physical exam findings, allowing clinicians to quickly assess a patient's status (Chia et al., 2016). In the context of oncology, as research increased our understanding of the complexity of cancer, spider plots gained much more traction. Spider plots have been used to profile cancer patients based on multiple biomarkers, including gene expression profiles, protein levels, and mutation status. This helps researchers form subgroups of patients with similar molecular characteristics and allows them to explore potential treatment strategies together.

USE OF WATERFALL PLOTS AND SPIDER PLOTS IN ONCOLOGY

Waterfall plots are often used to gauge the response of tumors to cancer treatments. They offer an explicit visual representation of changes in tumor size or relevant parameters within individual patients. These plots enable oncologists and researchers to rapidly show the spectrum of treatment responses, ranging from significant tumor shrinkage to disease stabilization or progression (Gillespie, 2012b). This is essential for determining the effectiveness of specific therapeutic interventions. For example, for new drug trials, waterfall plots can vividly illustrate how different patients' tumors respond, helping to find those individuals who may benefit most from the treatment. Moreover, waterfall plots are crucial for comparing the efficacy of distinct treatment regimens within clinical trials. By displaying the responses of patients in each treatment arm, researchers can compare the outcomes and pinpoint the respective therapy yields that are most favorable for tumor reduction.

Waterfall plots are also frequently used to monitor the progress of clinical trials. They plot the cumulative results of multiple patients over time, to provide a real-time evaluation of the treatment's impact, influencing decisions regarding the continuation or modification of the trial. If a good proportion of patients get positive responses, it may justify continuing the trial, while a lack of efficacy may prompt researchers to explore alternative treatment strategies or endpoints.

In contrast, spider plots are especially valuable in personalized oncology. They allow clinicians to create a visual, multidimensional profile of each individual patient using a wide range of clinical parameters (e.g., tumor markers, side effects, quality of life, and overall health) (Jyothi, 2018). These plots customize treatment plans, tailored to meet the specific needs of individuals, increasing the chances of a positive response to therapy. For example, these plots may reveal a pattern, a different treatment approach could be considered quickly, prioritizing quality of life over aggressive tumor reduction.

Multidimensional assessments can also be benefited using spider plots. Cancer care is rarely limited to a single parameter like tumor size. It often requires researchers to consider many clinical and biological variables. Spider plots provide a comprehensive view of how a patient is responding to treatment across these diverse parameters. Therefore, if a patient’s tumor size does not significantly decrease, doctors can use a more holistic approach to cancer care to better their well-being.

Long-term monitoring is another critical application of spider plots. In the long run, cancer patients may experience fluctuations in their response to treatment or develop new challenges. Spider plots facilitate the tracking of these developments, helping clinicians make informed decisions about treatment modifications, discontinuation, or the introduction of alternative

treatments (Matange, 2023). This is especially relevant for chronic or advanced-stage cancers where treatment needs may change over time.

Furthermore, spider plots are important for combination therapy. Cancer treatment often requires the concurrent administration of several medicines, each of which has an impact on a different component of the patient's health. With the help of spider plots, the combined effects of many medications may be visualized, leading to a more in-depth analysis of how various therapies interact to affect tumor response, side effects, and general health. For instance, plots can show whether a decrease in tumor size is traded off with an increase in adverse effects. This information can help clinicians balance the benefits of treatment with the well-being of their patients.

LIMITATIONS OF WATERFALL PLOTS AND SPIDER PLOTS

Despite their utility in visualizing and assessing treatment responses in various clinical contexts, waterfall plots have their own limitations. One significant limitation is their focus on one single variable, typically tumor size or a related parameter, at a time. This narrow scope can overlook critical information about the bigger clinical picture and miss the effects of treatment on the patient’s well-being, adverse events, or other relevant factors. Additionally, waterfall plots do not account for the heterogeneity of tumor responses within a single patient over time, which is particularly important in cancers with complex dynamics. Furthermore, the definition of what constitutes a meaningful response like a specific percentage reduction in tumor size, depends upon the study, leading to inconsistency in interpretation. Their inability to capture the complexities of multidimensional responses to data highlights the need for complementary tools like spider plots to provide a more comprehensive assessment.

While spider plots offer a unique means of visualizing multidimensional patient data in oncology, they too have limitations. One primary issue is when dealing with numerous parameters,

the interpretation of these plots can become challenging, making patterns less discernible. Moreover, the scales used for different parameters in spider plots can vary, making it difficult to simultaneously compare the impact of many factors on patient outcomes. Additionally, spider plots often rely on subjective interpretation, and the determination of what constitutes a clinically meaningful change in each parameter can vary among practitioners. Furthermore, spider plots may not fully capture the interactions between different clinical parameters, potentially overlooking relationships that can influence treatment decisions. Therefore, while spider plots provide a comprehensive view of patient profiles in oncology, their complexity demands careful interpretation and analysis of the data.

ADVANTAGES OVER ONE ANOTHER

Waterfall plots and spider plots are both valuable visualization tools in clinical research. When it comes to oncology, employing waterfall plots may be more beneficial for treatment analysis. One notable advantage of waterfall plots is their simplicity as these plots' present patient responses as singular bars. This simplicity allows for the quick identification of trends and patterns in tumor size changes among a group of patients. The visual representation of each patient's response in a single bar simplifies the process of assessing treatment outcomes.

Moreover, waterfall plots are especially designed to assess changes in tumor size or specific measurable parameters, which are critical in oncology. The Response Evaluation Criteria in Solid Tumors (RECIST) is a criteria used in tumor response assessment as a fundamental component of clinical trials and treatment evaluation (Frédéric, 2019). Waterfall plots focus on these changes and make them a valuable tool in quantifying the effectiveness of cancer treatments based on tumor size criteria. Additionally, they excel in showing responders and non-responders briefly, streamlining the process of determining treatment efficacy.

However, spider plots offer flexibility in criteria selection. Researchers can customize the response criteria included in the spider plot based on the specific research question and clinical context. Clinicians and researchers can tailor the spider plot to highlight the criteria that are most relevant for their study or patient population, ensuring that the visualization method aligns with the research objectives.

BEST OVERALL RESPONSE AS EFFICACY END POINT ANALYSIS

In the challenging landscape of oncology, the "best overall response" is an essential endpoint, representing a critical milestone in the evaluation of cancer treatments. The term "best overall response" describes the most favorable assessment of a patient's reaction to a particular therapy, considering factors such as tumor size reduction, disease stabilization, and overall well-being. It is the point where the complex interplay between treatment efficacy, clinical parameters, and quality of life converge to form a holistic judgment on the success of any intervention. The best overall response in oncology indicates not only tumor control but also improved patient progress, highlighting the importance of personalized care in tailoring treatments to the unique needs of everyone. Achieving the best overall response is the goal in the fight against cancer, striving for the most positive and sustainable impact on patient’s lives.

WATERFALL PLOTS AND SPIDER PLOTS IN BOR ANALYSIS

Clinical trials, particularly in the Therapeutic Area of Oncology, where assessing the efficacy of cancer treatments is of utmost importance, play a key role in the use of waterfall plots and spider plots for assessing the Best Overall Response (BOR). While both visualization techniques provide insightful information, waterfall plots have some advantages to spider plots particularly when evaluating BOR.

Waterfall plots are commonly used in clinical trials and medical research to assess the BOR of patients undergoing treatment in oncology and related fields (Vasudevan, 2019). These plots offer a clear, concise, and informative way to track the changes in tumor size or other relevant clinical measurements over time for each individual patient and across a group of patients. Waterfall plots have many substantial applications when it comes to measuring the BOR.

First, waterfall plots design individualized assessments of patient responses to treatment. In these plots, each patient is represented as a bar, making it easy to track the progress of their treatment (Vasudevan, 2019). The baseline measurement, typically tumor size, is found at the left end of the bar. Subsequent measurements, taken at specified time intervals, are depicted as changes in tumor size, with positive values indicating tumor growth and negative values indicating tumor shrinkage. Furthermore, we can use distinct color coding or the other symbols to indicate the nature of the response, such as partial response, stable disease, or progressive disease.

One of the significant advantages of using waterfall plots to measure BOR is the ease with which responders can be shown. Clinicians and researchers can swiftly pinpoint patients who are responding positively to the treatment by searching for bars that illustrate a decrease in tumor size beyond a specific threshold, often defined by proven criteria such as RECIST (Response Evaluation Criteria in Solid Tumors).

Waterfall plots also help the assessment of treatment efficacy. These plots offer a comprehensive view of how the treatment affects the entire patient population. By examining the distribution of responses, researchers can measure the overall effectiveness of the treatment, as well as identify the exceptions and outliers, such as patients with exceptional responses or those experiencing disease progression despite the treatment.

In scientific reporting and publication, waterfall plots have set a standard for clinical trial reports. They offer a concise way to link the BOR data to a broader community, making complex data more accessible and understandable.

On the other hand, spider plots, while a valuable tool in oncology for various purposes, are not typically used to measure BOR in clinical trials or patient care. In the context of measuring BOR, standardized criteria like RECIST are more commonly employed to categorize and quantify treatment responses (Manitz et al., 2022). The primary reasons for the limited use of spider plots in assessing BOR include the lack of standardization, complexity, comparability, and the potential for subjectivity.

How to create Waterfall plots and Spider plots in SAS?

Both these plots/figures/graphs can be developed using SAS. The below section will provide the SAS code to generate both waterfall plots and spider plots. The sample data and the outputs from the SAS code will also be shown clearly in the following section.

Creating Waterfall plots in SAS:

The below section will provide 2 most important types of water fall plots used in oncology, sample data and SAS code to develop these figures will be described below.

5 Important figures:

The sample data, SAS code for generating these 5 figures will be discussed below.

1. Waterfall Plot for Best Percent Change from Baseline in Sum of Diameters for Target Lesions.
2. Waterfall Plot for Best Percent Change from Baseline in Target Lesions by subjects.
3. Spider plot of Percent change from Baseline in Target Lesions.
4. Spider plot of Percent change from Baseline in Target Lesions by Tumor cells
5. Spider plot of Percent change from Baseline Target Lesions by IC/TC Responders.

Figure 1: Waterfall Plot for Best Percent Change from Baseline in Sum of Diameters for Target Lesions

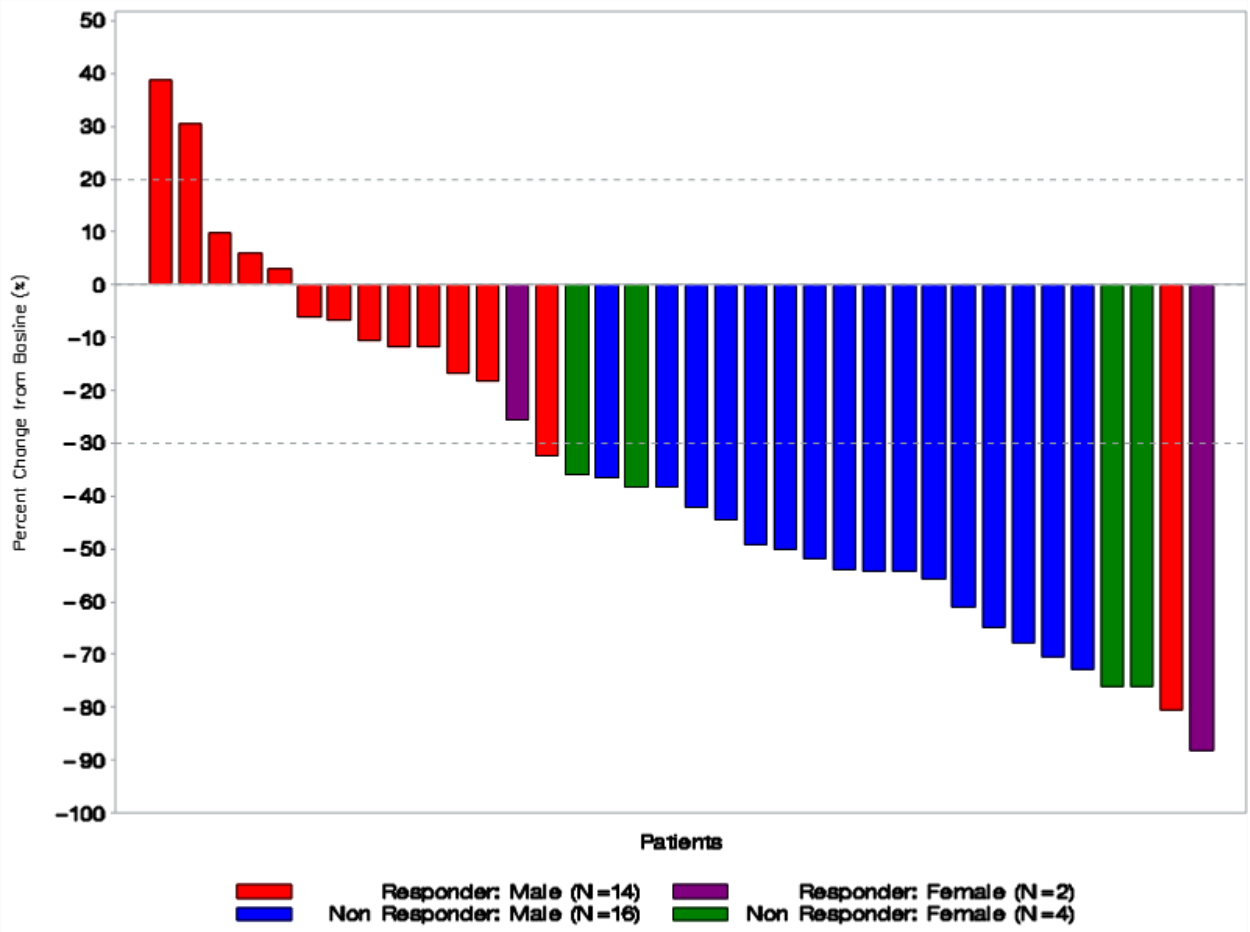


Figure 1. Sample data:

Subjid	bestpchg	trtsort	page	subjnum
A0041003	38.71	1.1	9	1
A0201009	30.56	1.1	9	2
A0191003	9.89	1.1	9	3
A0011017	6.12	1.1	9	4
A0151004	2.94	1.1	9	5
A0112005	-6.12	1.1	9	6
A0011005	-6.60	1.1	9	7
A0021007	-10.42	1.1	9	8

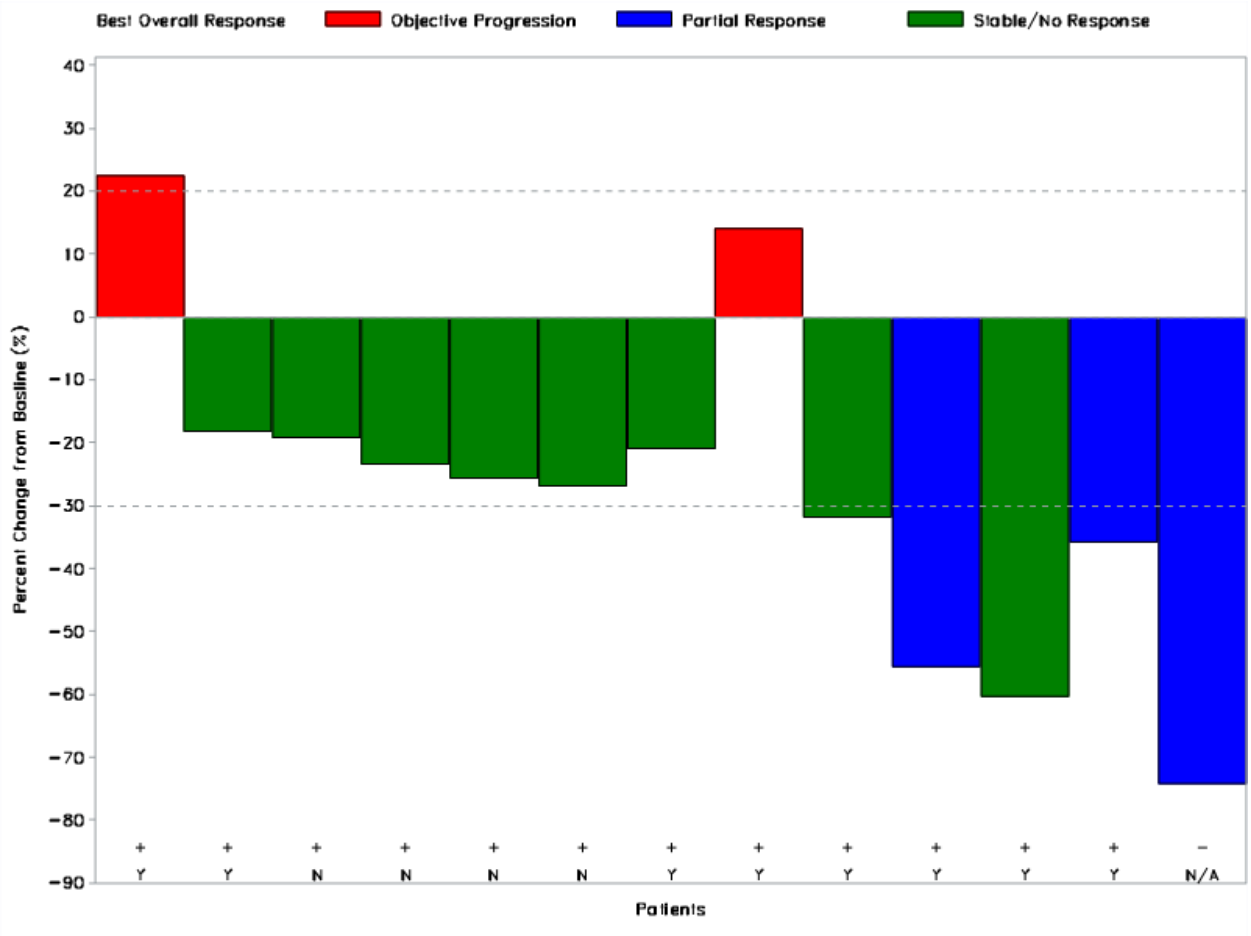
A0011009	-11.76	1.1	9	9
A0201001	-11.76	1.1	9	10

SAS Code for Figure 1:

```
%macro figwf1;
%do i=1 %to &maxpg;
 axis1 order= (0 to 15 by 1) label=('Patients');
 axis2 order= (-110 to 20 by 10) label=(position=center a=90 font=simplex"Percent Change from Basline (%)");
 legend1 label=(" ") value=("Responder: Male (N=&A)" "Responder: Female (N=&B)" "Non Responder: Male (N=&C)" "Non Responder: Female (N=&D)");
 pattern1 color=red value=solid;
 pattern2 color=purple value=solid;
 pattern3 color=blue value=solid;
 pattern4 color=green value=solid;

 proc gchart data=final anno=anno1(where=(page=1)) gout=water;
   where page=1;
   vbar subjnum / subgroup=trtsort sumvar=bestpchg maxis=axis1 raxis=axis2 type=sum discrete legend=legend1 vref=0 lref=1 vref=20,-30 lref=2 name="water1";
run;
quit;
%end;
%mend figwf1;
%figwf1;
```

Figure 2: Waterfall Plot for Best Percent Change from Baseline in Target Lesions by subjects



+=evaluated, - = not evaluated Y=detected, N= not detected

Figure 2. Sample data:

Subjid	Comments	DNAFL	BESTOR	BESTPCH		SN
B0021161	Sample Reported	Y	Objective Progression	22.4	YES	1
B0111020	Sample Reported	Y	Stable/No Response	-18.3	YES	2
B0031071	Sample Reported	Y	Stable/No Response	-19.2	NO	3
B0051043	Sample Reported	Y	Stable/No Response	-23.3	NO	4
B0111021	Sample Reported	Y	Stable/No Response	-25.7	NO	5
B0051042	Sample Reported	Y	Stable/No Response	-26.9	NO	6
B0111023	Sample Reported	Y	Stable/No Response	-27	YES	7
B0051044	Sample Reported	Y	Objective Progression	-30.2	YES	8

B0021172	Sample Reported	Y	Stable/No Response	-31.7	YES	9
B0051043	Sample Reported	Y	Partial Response	-55.6	YES	10
B0051045	Sample Reported	Y	Stable/No Response	-60.3	YES	11
B0021168	Sample Reported	Y	Partial Response	-65.7	YES	12
B0031079	QC fail	N	Partial Response	-74.1	NO	13

SAS Code for Figure 2:

```
GOPTIONS DEVICE=SVG FTEXT=duplex GUNIT=PCT HTEXT=2
     CBACK=WHITE COLORS=(BLACK)
     ROTATE=LANDSCAPE
     NOPROMPT;

axis1 order=(1 to &mason by 1) minor=none major=none value=none label=('Patients');

axis2 order=(&minval to &maxval by 10) label=(position=center a=90 "Percent Change from
Basline (%)") minor=none;

legend1 position=(top center) label=('Best Overall Response');

pattern1 color=red value=solid;

pattern2 color=blue value=solid;

pattern3 color=green value=solid;


proc gchart data=final1 anno=anno gout=water;

 vbar patid / subgroup=bestor legend=legend1 sumvar=bestpch maxis=axis1 raxis=axis2
width=8 type=sum vref=0 discrete vref=0 lref=1 vref=20,-30 lref=2 name="water2";

 format bestpchg 4.;

run;
```

Creating Spider plots in SAS:

The below section will provide 3 most important types of spider plots used in oncology, sample data and SAS code to develop these figures will be described below.

Figure 3: Spider plot of Percent change from Baseline in Target Lesions

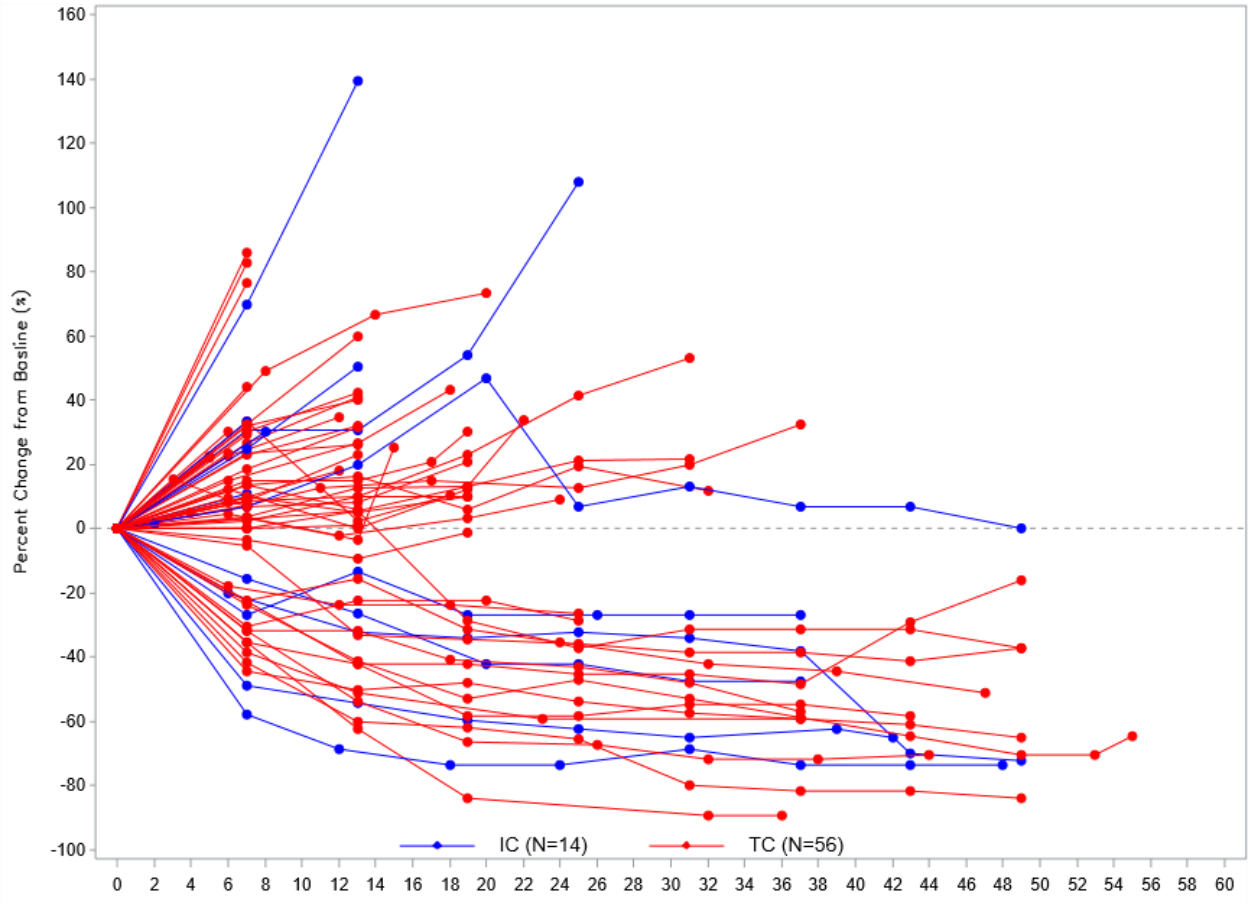


Figure 3. Sample data:

Subjid	ICTC	PCHG	week	trtsort	page
B120021	1	7.45	7	2	1
B120019	1	12.59	11	2	1
B120022	1	14.98	17	2	1
B120023	2	12.99	25	2	1
B120024	2	29.98	31	2	1

B120025	2	31.45	37	2	1
B170026	2	22.99	7	2	1
B170027	2	25.97	13	2	1

SAS Code for Figure 3:

```
%macro figsp1;


proc gplot data=final anno=anno1(where=(page=1)) gout=spider1;
 where page=1;
 plot pchg*week=subjid / haxis=axis1 vaxis=axis2  vref=0 lvref=2 name="spider1";
 format pchg 4. week 4.;
run;
quit;
%end;
%mend figsp1;
%figsp1;
```

Figure 4: Spider plot of Percent change from Baseline in Target Lesions by Tumor cells

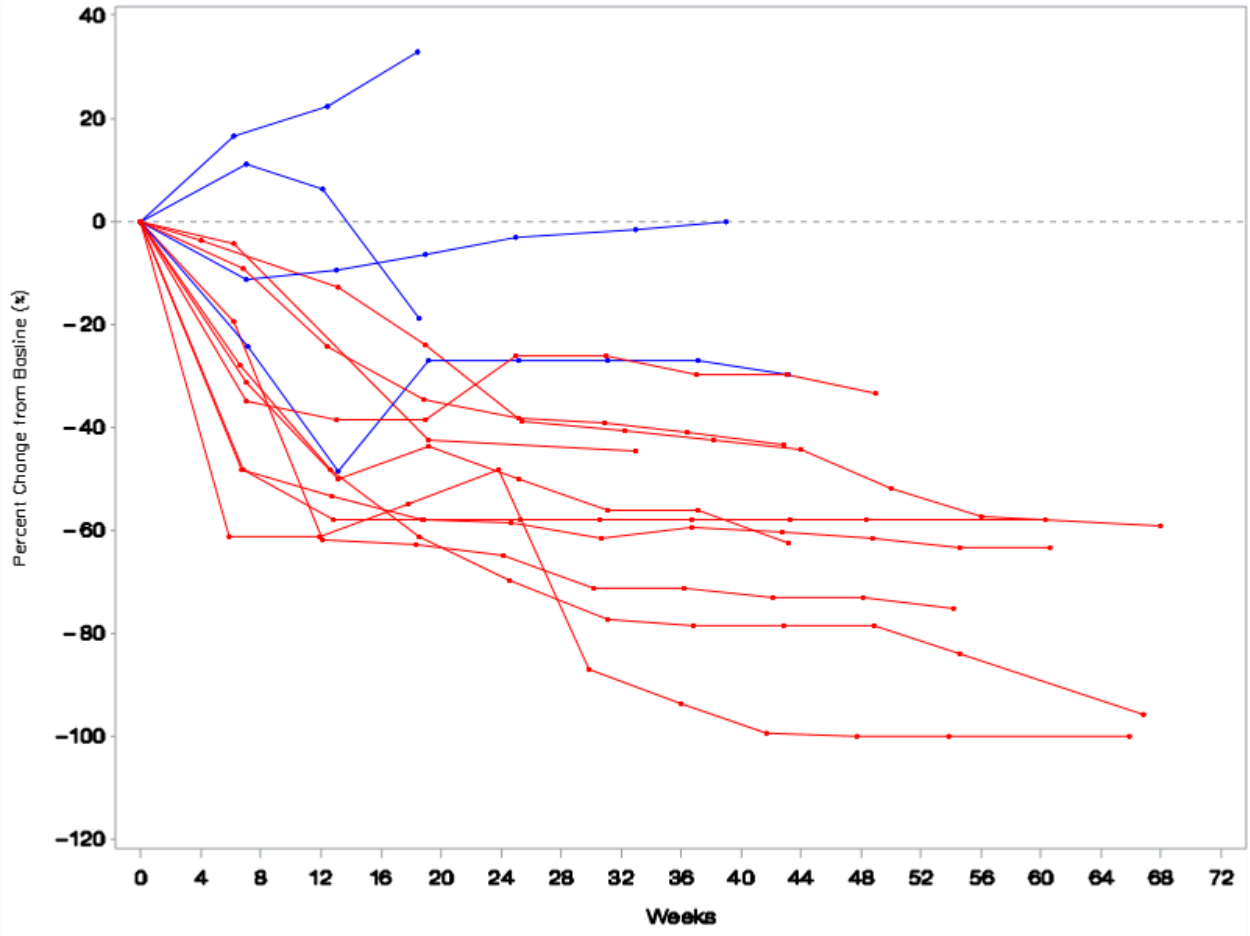


Figure 4. Sample data:

Subjid	Pctchg	Week	ord	trt	type
B0041004	-70.99	30.0	5	2	IC
B1004105	-72.03	35.99	5	2	IC
B0041006	-72.99	42.09	5	2	IC
B0041007	-74.01	47.99	5	2	IC
B0041008	-74.95	55.01	5	2	IC
B0041009	0	0	0	2	TC
B0041001	-20.15	5.99	0	2	TC
B0041002	-62.08	12.4	0	2	TC
B0041003	-63.01	17.99	0	2	TC

B0041004	-65.14	25.01	0	2	TC
B0041005	-72.01	31.04	0	2	TC
B0041006	-70.10	35.94	0	2	TC
B0041007	-72.99	41.98	0	2	TC
B0041008	-72.98	47.94	0	2	TC
B0041009	-74.95	53.97	0	2	TC

SAS Code for Figure 4:

```
axis1 order=(0 to 72 by 4) minor=none offset=(2) label=('Weeks');

axis2 order=(-120 to 140 by 20) label=(position=center a=90 font=simplex"Percent Change from Basline (%)") minor=none;

%do j=1 %to &&maxsub&i;

 symbol&j i=join value=dot color=&&color&j;

%end;

proc gplot data=final gout=spider2;

where page=2;

plot pct_chg*week=subjid / haxis=axis1 vaxis=axis2 nolegend vref=0 lvref=2 name="spider2";

format pct_chg 4. week 4.;

run;
```

Figure 5: Spider plot of Percent change from Baseline Target Lesions by IC/TC Responders

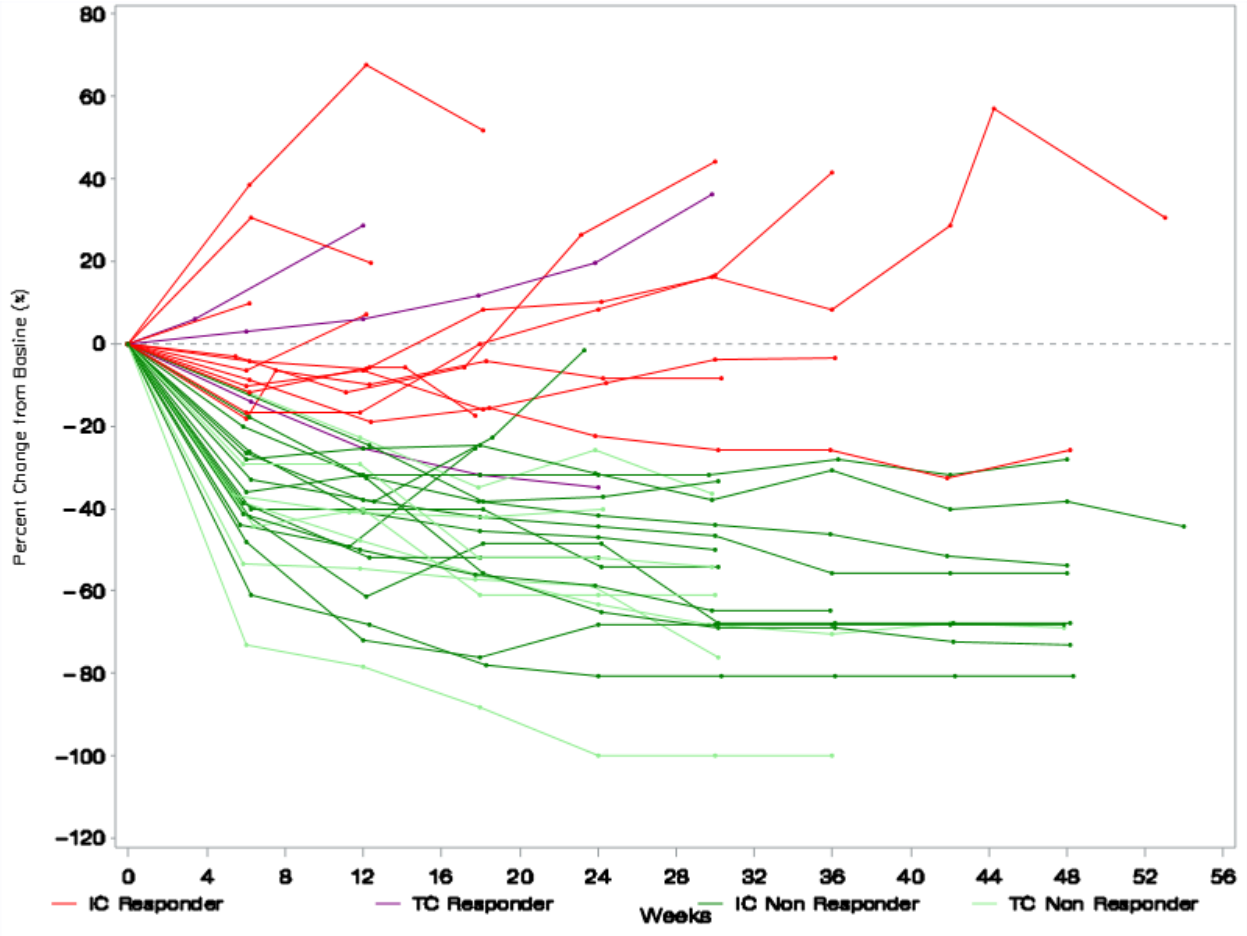


Figure 5. Sample data:

Subjid	week	pchg	resp	ord	trtsrt	rttsrt2	page
A0011001	0	0	1	5	1.1	1D1	11
A0011002	6	-6.45	1	5	1.1	1D1	11
A0011003	12.1	6.98	1	5	1.1	1D1	11
A0011004	0	0	2	5	2.1	2D1	11
A0011005	6.2	-39.90	2	5	2.1	2D1	11
A0011006	12	-41	2	5	2.1	2D1	11
A0011007	18.1	-39.98	2	5	2.1	2D1	11
A0011008	24.1	-54.02	2	5	2.1	2D1	11

A0011009	30.1	-53.99	2	5	2.1	2D1	11
A0011000	0	0	2	5	2.1	2D1	11

SAS Code for Figure 5:

```
 axis1 order=(0 to 72 by 4) minor=none offset=(1) label=('Weeks');

 axis2 order=(-120 to 40 by 20) label=(position=center a=90 font=simplex"Percent Change from Basline (%)") ;

 %do j=1 %to &&maxsub;

  symbol&j i=join value=dot color=&&color&j;

 %end;

proc gplot data=final anno2=anno(where=(page=&i)) gout=spider3;

  where page=3;

  plot pchg*week=subjid / haxis=axis1 vaxis=axis2 nolegend vref=0 lvref=2 name="spider3";

  format pchg 4. week 4.;

run;
```

CONCLUSION

To conclude, waterfall plots play a vital role in measuring the best overall response in oncology, spider plots on the other hand are a valuable visualization tool in oncology trials data analysis for comparing the performance of different treatments or variables across multiple dimensions. In both cases, determining the best overall response involves a subjective assessment based on clinical judgment and predefined response criteria. Researchers and clinicians need to consider several factors, including the specific disease being treated, the treatment goals, and the importance of individual response criteria in the context of the study.

The decision between a waterfall plot, a spider plot, or a combination of both, relies on the goals of research and how complicated the data being studied is. Making educated decisions about the effectiveness of treatment and choosing the best overall response as a measure of oncology efficacy endpoint in clinical research can be made easier with the help of these visualization tools.

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