Leveraging Standards for Effective Visualization of Early Efficacy in Clinical Trial Oncology Studies

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ABSTRACT

Solid tumor oncology studies have become a major therapeutic focus area and present unique challenges in both quantifying and categorizing efficacy. The related domains (TR/TU/RS) implemented by CDISC SDTM provide a rich, sophisticated data structure to accommodate the complexities of multiple lesion response analysis. The published rules by Response Evaluation Criteria in Solid Tumors (RECIST) to define patient overall response further enable standard programming and analysis in such clinical trials. In this presentation we will demonstrate how these industry standards can be leveraged to create report dashboards for progression-free survival analysis (PFS) and target lesion response analysis using effective visualization to target early efficacy endpoints. In performing lesion response analyses, we will focus on application of graphical techniques common to this therapeutic area; including Swimmer Plots, Waterfall Plots, Forest Plots and Spider Plots. Such visualization techniques provide unique insight and interpretation to multiple-lesion response measurements across trial visits both quantitatively and in the application of RECIST criteria for qualitative overall patient response to oncology therapeutics.

INTRODUCTION

Clinical trials for evaluating cancer therapies offer unique challenges in data capture and analysis, and yet oncology has become one of the largest therapeutic areas in current clinical research. One of the largest challenges is in creating deterministic, consistent endpoints from the clinical evaluation of multiple lesion tumor response studies. For this reason, global standardized response criteria (RECIST) guidelines have been developed and accepted as the recommended evaluation tool by regulatory agencies for categorizing tumor response. Likewise dedicated findings domains available in the Study Data Tabulation Model Implementation Guide (SDTMIG) V3.2 (introduced in V3.1.3 in 2012) tumor package (TU, TR, RS) allow for accurate data representation to handle both the complexities of the data structure as well as the representation of the RECIST guidelines.

These data and evaluation standards allow streamlined clinical programs to implement tumor response analyses and accompanying common visualization techniques that have become common in extensive clinical research. The purpose of this paper is not to summarize or educate on the data standards, but to discuss how interactive visualization reports can leverage data standards and analysis guidelines to more effectively interrogate early efficacy and safety signals in oncology therapeutic studies. The analysis components discussed here are available using JMP® Clinical, a software solution that integrates SAS® programming and JMP® visual exploration tools.

DATA AND RESPONSE EVALUATION STANDARDS

Standardization of both the clinical evaluation of tumor burden and the capture of the data is a critical piece to enabling efficient and effective data analysis review for oncology trials. We briefly summarize these for clarity; refer to the References and Recommended Reading sections for more detailed information for those unfamiliar with these concepts.

RECIST CRITERIA FOR STANDARD RESPONSE EVALUATION

One of the largest sources of inconsistency and data variability arises due to inaccurate measurement of multiple solid tumor lesions. Cancer is uncontrolled cellular growth, and yet to study it, we need to identify and measure reliable lesions for evaluating therapeutic response. RECIST guidelines (proposed in 2000 and updated to RECIST 1.1 in 2008) provide a standard workflow for such data capture and identify standard response criteria. The highlights are:

- **Identify Target or Measureable Lesions:** no more than 2 lesions per organ with a maximum of 5 lesions (generally >10mm in size) that are measured at baseline and selected based on size and suitability. Lesions should be measured as the sum of the longest diameters (uni-dimensional) with short axis consideration for

nodal tumors.

- **Response Identification:** Evaluation should follow four qualitative results for target lesions

    1. Complete Response (CR): All target lesions disappear/shrink.

    2. Partial Response (PR): At least 30% *decrease* in the sum of target lesions with respect to baseline summation.

    3. Progressive Disease (PD): At least 20% *increase* in tumor burden response with reference to the minimum lesion summation on study (including baseline).

    4. Stable Disease (SD): Change in tumor burden response fails to qualify for either PR or PD.

Overall response or best response follows further guidelines around evaluation of the minimum recorded sum of target lesion measurements, confirmation, development of new lesions, and duration.

CDISC SDTM DOMAINS FOR TUMOR RESPONSE

In order to capture the complexity of multiple lesion measurements and support RECIST assessment criteria, CDISC provides three findings domains dedicated to tumor response (details available in SDTMIG V3.2). These three domains include Tumor Identification (TU), Tumor Results (TR), and Disease Response (RS) and are related domains that are linked by Group ID, Reference ID, and Link ID variables provided by SDTM structure.

The TU domain provides an identification map structured as a findings domain to categorize tumors as Target, Non-Target, and New as well as their organ location and other relevant lesion information. The TR domain functions as the main analysis findings domain with records for each lesion assessment and diameter measurements (or even the summed diameter derived result) where each lesion has a Link ID variable to link assessments to identified tumors. The RS domain provides representation of qualitative response evaluation (e.g. RECIST 1.1 criteria for CR, PR, PD, SD) determined from TR for varied evaluators (e.g. Investigator or Independent Assessor) across clinical visits.

These related domains and their structure allow for streamlined workflows, validation and corroboration of qualitative results with quantitative measurements and potential stability analyses in evaluator variability and consistency. In this paper, we rely on these data to provide standard programming flows for visualization of efficacy endpoints in oncology clinical trials.

EFFICACY ENDPOINTS AND VISUALIZATION METHODS IN ONCOLOGY CLINICAL TRIALS

Survival analysis is an essential endpoint for cancer drug approval. As described in the [FDA Industry Guidance for Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics](), overall survival (OS: time from randomization to death) is perhaps the most reliable endpoint. Complexities in oncology therapeutic designs though rarely allow for a trial design and sample size that accommodates OS in early stages. Two key solutions of surrogate endpoints that allow for more flexible design and interpretability are Progression-Free Survival (PFS: time to "disease progression" criteria or death) and Objective Response Rate (ORR). PFS is desirable when the analysis can be performed but often oncology trials in the very early stages evaluate multiple therapeutics with very small sample sizes; giving rise to looking at quantitative and qualitative (RECIST guided) tumor response and duration as the first look to earliest efficacy.

In support of these endpoints, key clinical visualizations now dominate clinical oncology research results. The graphical components include the following:

- **Survival Curves and Forest Plots:** summary analysis (PFS) survival Kaplan-Meier (KM) curves and hazard ratio forest plots for patient subgroups.

- **Swimmer Plots:** horizontal bar charts of patients (or "lanes" of a swimming pool) annotated with duration and change in qualitative tumor response evaluation (RECIST) taken from the RS domain.

- **Waterfall Plots:** Ordered vertical bar charts of patients' overall quantitative "Best" response in tumor shrinkage derived from tumor results (TR/TU).

- **Spider or Spaghetti Plots:** Line trend plots across study duration showing patient trends in tumor results and new lesion occurrence across study visits/time.

This paper will highlight the utility of these plots for early efficacy review, with examples and details of implementation to maximize effective communication of tumor response.

PROGRESSION FREE SURVIVAL

PFS is a preferred regulatory endpoint (per the aforementioned guidance) over other survival methods such as time to progression (TTP) as it still incorporates death and correlates more closely with OS, but gains power and interpretability by incorporating tumor assessment for survival benefit determination. In addition to survival curve plots (not pictured here, shown further in Display 2), forest plots provide a very effective means of communication of the differences in hazard ratios and associated confidence intervals in various demographic patient groups. An example on simulated data of such a forest plot is shown below in Figure 1.

Hazard Ratio Forest Plots

Treatment A vs. Treatment B
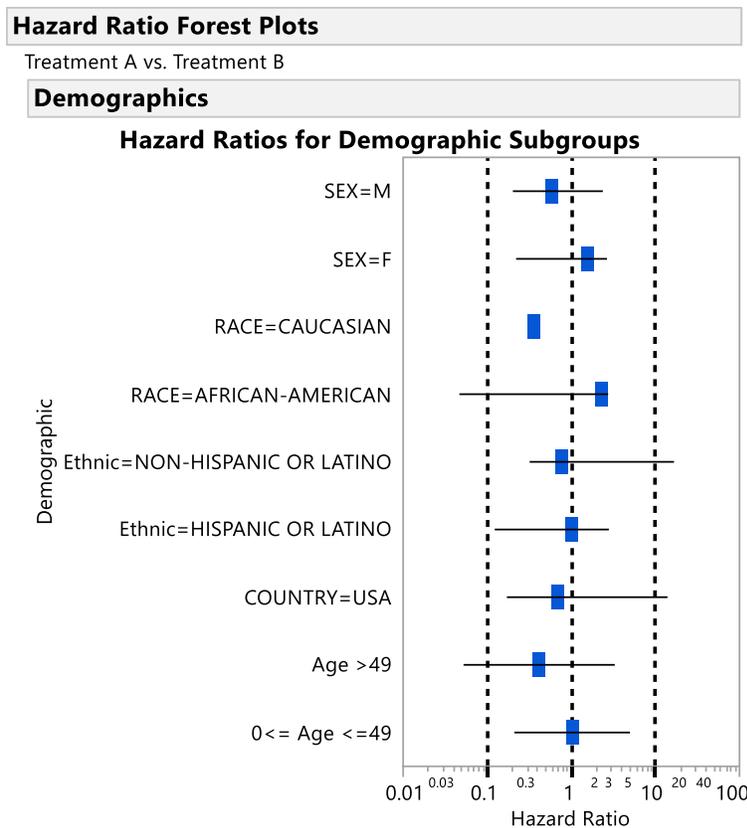
Demographics

Figure 1. A Forest Plot is Useful to Display Hazard Ratios for Different Demographic Subgroups in Survival Analyses.

Complex trial design, small samples sizes in early trial stages and missing data for adequate visit assessment can make PFS prohibitive or less robust, and is a large reason many oncology therapeutic studies focus more on visualization and data summary of objective response rate (ORR). The graphic in Figure shows an example of a swimmer plot as an alternative way to visualize patient response in oncology studies. It is particularly valuable (over the traditional time-to-event analysis) in small trials to visualize early efficacy by displaying patient level duration and changes in qualitative tumor response using custom graphical annotations to patient bar charts. This plot is useful as a visual representation to accompany ORR (typically counts/proportion of subjects classified as responders (PR + CR)) table summaries.
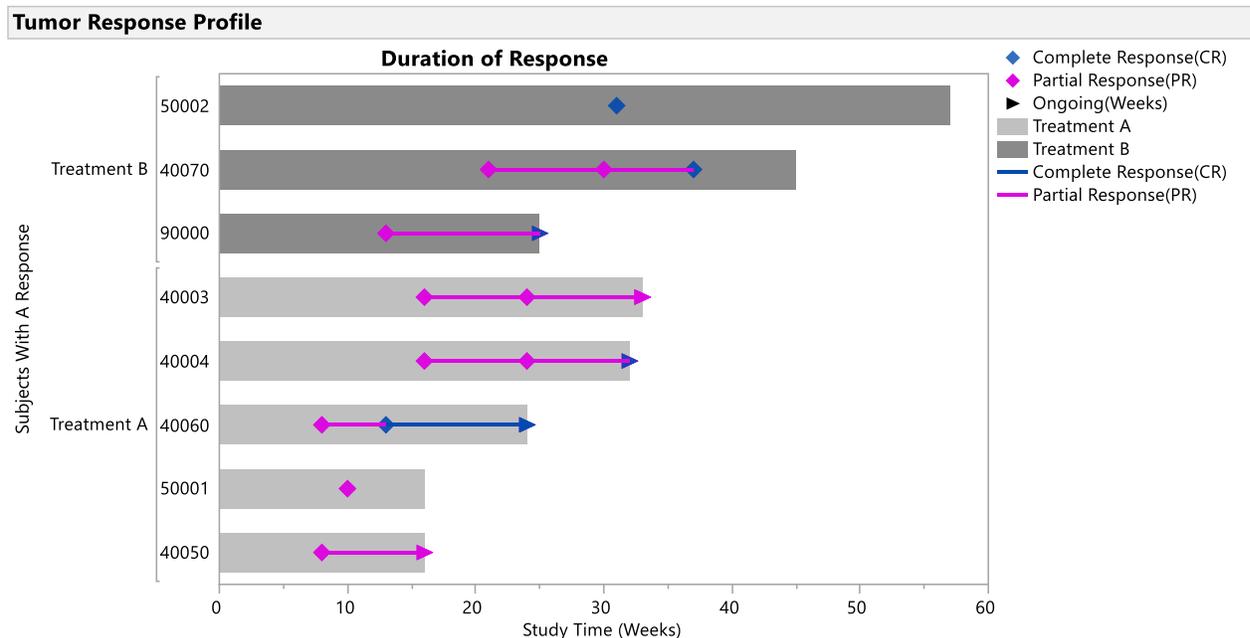
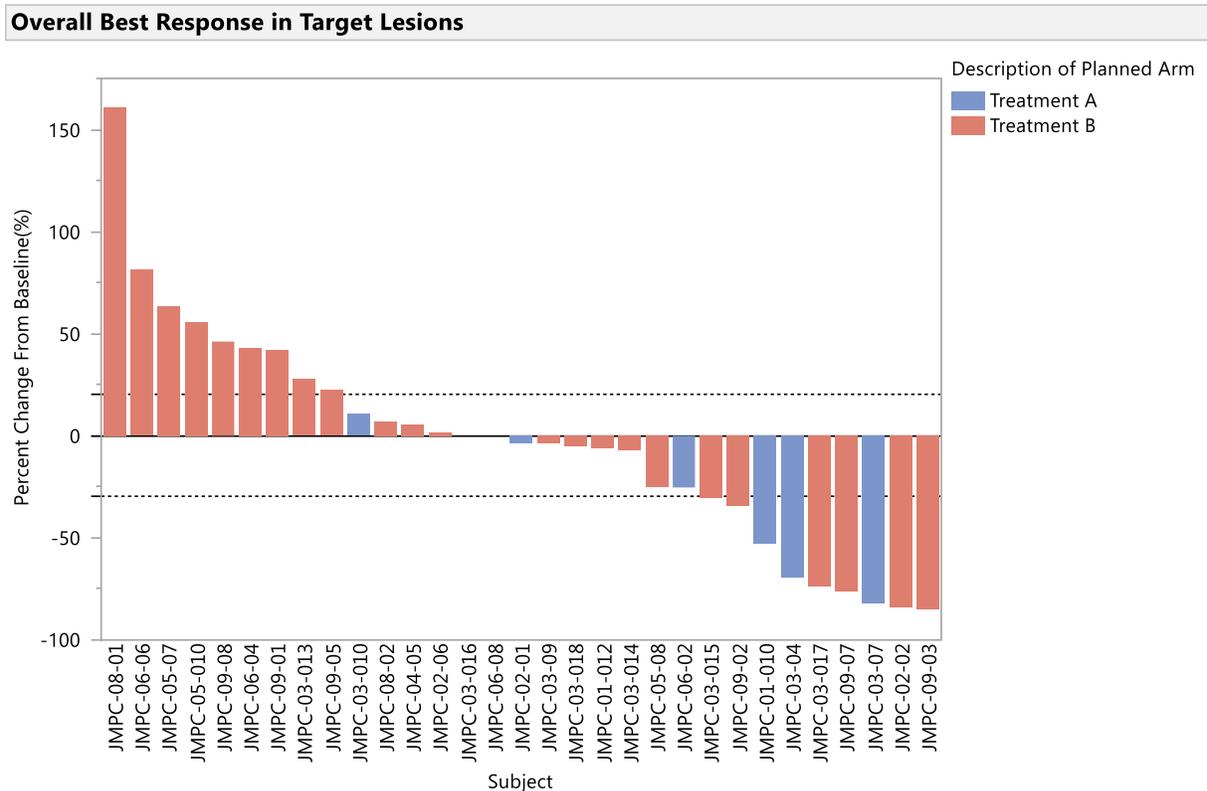**Figure 2. A Swimmer Plot Displays Patient Response for Evaluations Recorded in the RS SDTM Domain.**

BEST RESPONSE AND RESPONSE TRENDS

Both PFS and swimmer plots provide representation or use the qualitative tumor burden results as recorded in the RS domain, following guidelines of RECIST. Another accompanying analysis is to visually interpret the quantitative target lesions by their change from baseline in the summed diameters.

Figure 3. A Waterfall Plot Displays Patients, Ordered by Their Best Response in Tumor Shrinkage, with Y-axis as Percent Change from Baseline of Target Lesions.Figure shows (simulated) patient response data for comparing Best response (height of bars) for patients given two different treatments (color of bars), annotated with reference lines with respect to RECIST criteria for categorizing lesion shrinkage response. This plot is commonly called the waterfall plot due to the behavior of sorting the X-axis by the same value displayed on the Y-axis like a cascade of water. In this case, we sort in descending order so patients on the right (with large negative values in percent change from baseline) represent those responding well to treatment (tumor shrinkage), while those on the left typically represent those with potential disease progression. The bars (each representing a patient) are often colored by therapy treatment, tumor stage, or may also be colored by the qualitative best overall response from RS data entry.

Standard guidelines consider the representative Best (quantitative) response for a given patient as the smallest summed value of tumor burden compared to baseline (representing the maximum lesion shrinkage from baseline in target lesions for negative values or the minimum amount of tumor growth for positive values), where target lesions are identified following RECIST guidelines.

The waterfall plot is an effective way to use color patterns, center/median values and reference lines to communicate tumor endpoint responses in **small sample sizes** as an alternative to PFS analyses. When accompanied by summary tables of objective response rate, this visualization gives better detail of the response distribution.

**Overall Best Response in Target Lesions**

Figure 3. A Waterfall Plot Displays Patients, Ordered by Their Best Response in Tumor Shrinkage, with Y-axis as Percent Change from Baseline of Target Lesions.

The waterfall plot still presents a summary of data values, namely the overall response (e.g. best/minimum tumor burden) taken from all of the trial visits across time. An accompanying trend (spider or spaghetti) plot helps to show the more encompassing quantitative trends for each subject across time.

Figure shows a trend plot for the same simulated data that supplied the waterfall plot, displaying tumor lesion shrinkage (or growth in some cases) across time on study. These data points are the tumor results that are summarized to display the Best response as shown in the waterfall plot. This plot is very useful to see the "path" of changes and duration of quantitative tumor response to treatment and can include more in-depth annotation (as shown using the asterisk to indicate occurrences of a new lesion…which is not incorporated in the target lesion summation).

These plots, when used together, offer powerful communication of complex oncology endpoints in early-stage trial designs.

Target Lesion Response Across Time
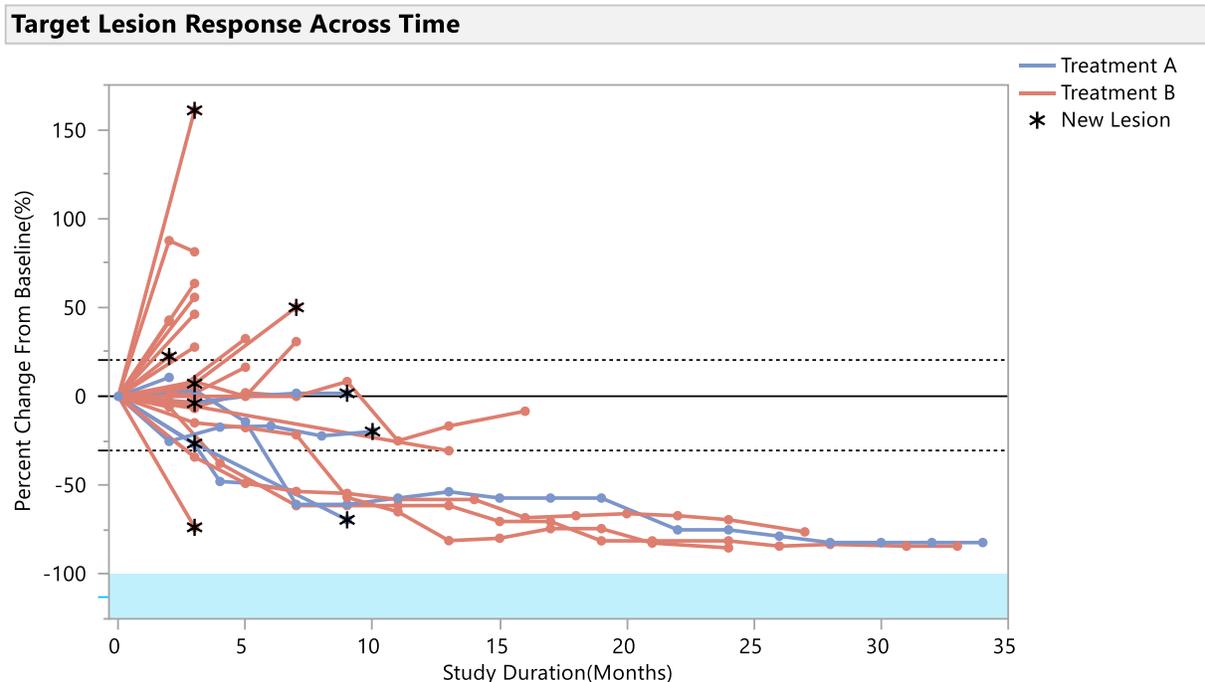
Figure 4. Visualization of Patient Response Trends Across Time is Commonly Called a Spider or Spaghetti Plot.

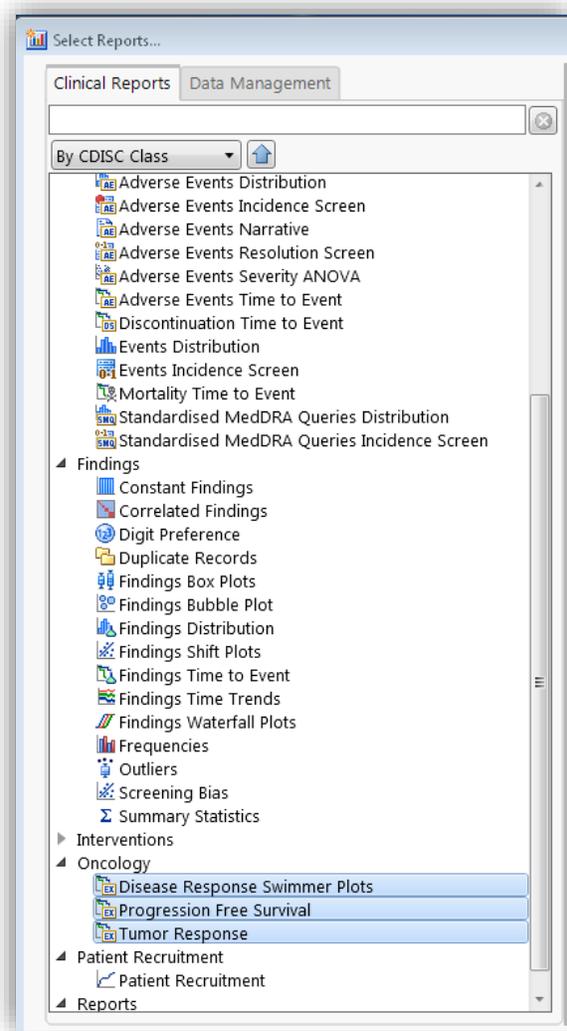## ONCOLOGY DASHBOARDS IN JMP CLINICAL REVIEWS

The concepts around SDTM standards, RECIST evaluation guidelines, and common visualizations and endpoint analyses described above provide the components to create standard clinical research reviews for oncology therapeutic trials. Because the analyses are heavily dependent on patient-level summaries and visualization, using interactive software to filter subjects dramatically enhances the effectiveness of these views. These therapeutic-specific concepts have been implemented in JMP Clinical for standard medical and biometric data review.

JMP CLINICAL OVERVIEW

JMP Clinical is an integrated solution of JMP and SAS BASE/STAT software that creates clinical reviews for medical reviews, safety and efficacy biometric analyses, and centralized statistical data monitoring. Reviews are built using SAS macro programs that perform data load, manipulation and analysis along with JSL (JMP Scripting Language) scripts to create a custom user interface for clinical trial data analysis. The most powerful capabilities of the solution stem from interactive, highly visual JMP platforms and dashboard displays to create intuitive, comprehensive clinical reviews of analysis results.

The solution leverages CDISC data standard formats to streamline clinical analysis across adverse events, interventions and findings to create custom reviews for a given user role. The analysis data from each domain are virtually joined and linked to the patient demography to enable intuitive global filtering and subject exploration across all of the collected data for a clinical data science review. JMP visualizations are dynamically linked to the data to allow drill down into relevant patient selections for full patient profiles or automated patient adverse event narratives.

Display 1 shows a sample of the reports available in JMP Clinical reviews, including three dedicated oncology reports that utilize the TR, TU, and RS domains.

Display 1. Oncology Reports for Tumor Response Available in JMP Clinical Reviews

INTERACTIVE VISUALIZATION REPORTS FOR TUMOR RESPONSE

For these examples, we have used the TU/TR/RS examples provided on the CDISC Wiki to review the respective analysis reports. Large portions of these data have been fabricated and results should not be interpreted in any other way than as a highlighting example of how to create and use interactive visualization reports for oncology analysis. The following reports available in JMP Clinical are summarized.

- **Progression Free Survival:** Summary analysis of PFS with KM curves and estimates along with hazard ratios for demographic subgroups displayed in a forest plot, using the RS and DS domains for analysis.

- **Disease Response Swimmer Plot:** Displays duration and changes for patient disease response entries for qualitative assessment to lesion shrinkage per RECIST guidelines (CR:Complete Response, PR:Partial Response, or PD:Progressive Disease) as recorded in SDTM RS domain.

- **Tumor Response:** Displays a waterfall plot of best response and a linked line plot showing the trends in target lesion results across study duration using the TR and TU domains for analysis.

Display 2 shows the results of the PFS analysis. As shown in this screenshot, this becomes a tabbed report section of a JMP Clinical review, which contains other relevant domain analysis for a comprehensive data review.

This report provides an essential component to endpoint analysis and regulatory submission for oncology trials, but because it is a summary analysis, does not benefit greatly from interactive capabilities of JMP. The analysis presented in this report combines the JMP survival platform analysis as well as SAS/STAT PHREG and LIFETEST procedures for computation.
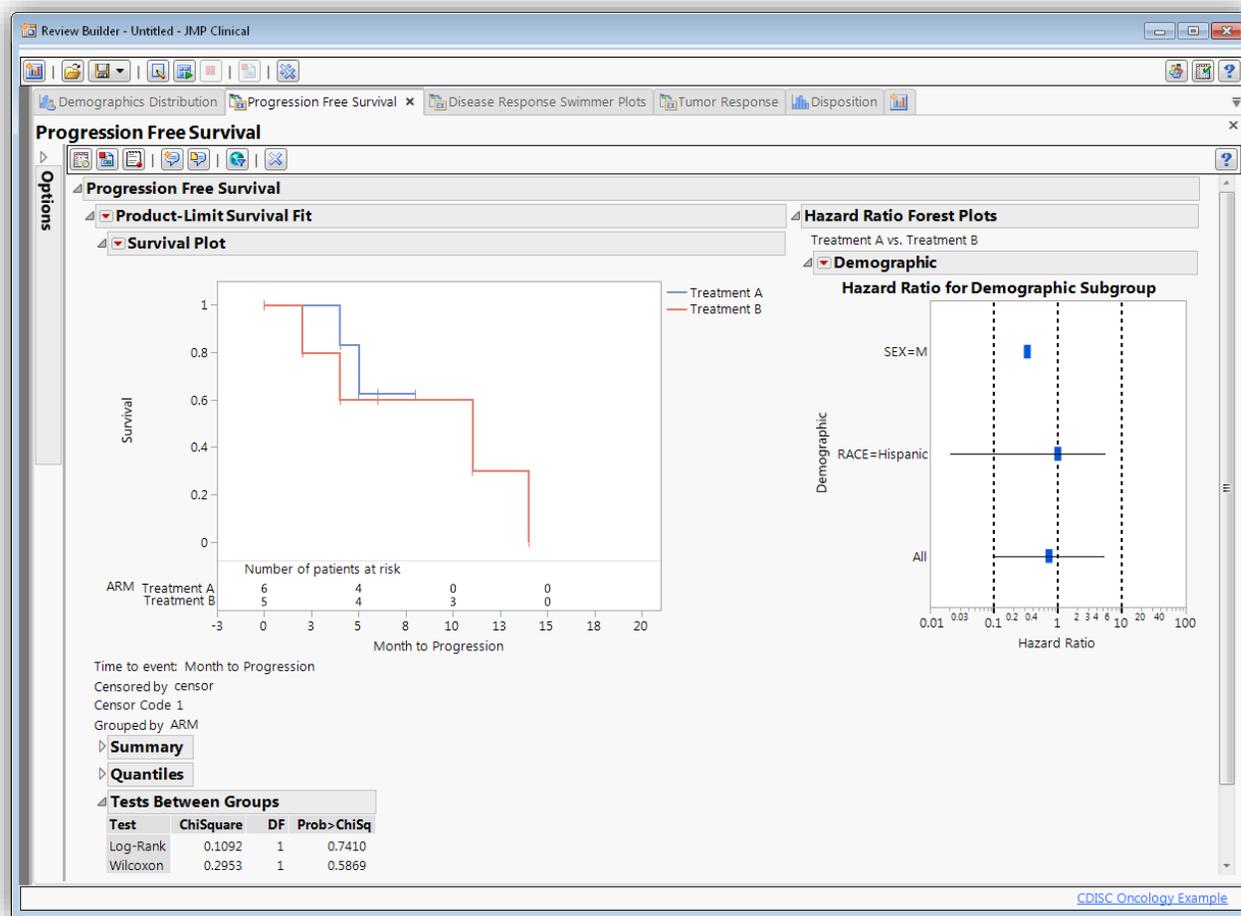

Display 2. JMP Clinical Progression-Free Survival Analysis Report

The screenshot shown in Display 3 depicts the disease response swimmer plot, a visual representation of data records in the RS domain. Report options (not shown) allow customization for plot annotation, for example to connect responses across records, only show when response changes, include (or not) Progressive Disease results, etc. This report also provides a table of overall response counts. Using this CDISC wiki data with only a few subjects, this is a powerful visualization. In larger studies, this plot can become very condensed and lose interpretability. Using the JMP data filter shown to the left of the plot to subset down to specific patient subgroups increases usability. The bars of the plot can also be selected, and when done so, patient selection filter actions become available along the toolbar at the top of the report.
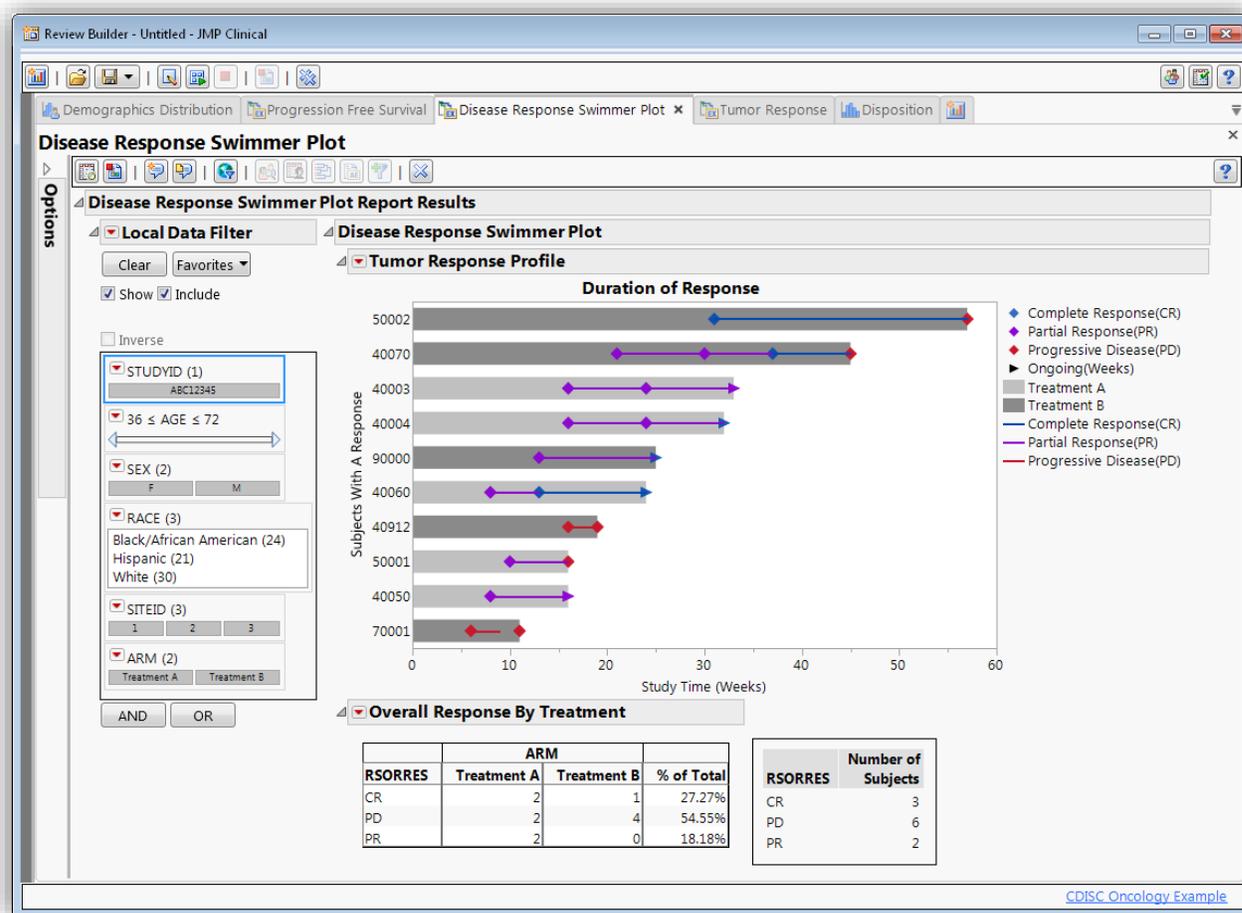
Display 3. JMP Clinical Disease Response Swimmer Plot Report

The screenshots shown in Display 4 and Display 5 show the Tumor Response dashboard in this JMP Clinical review and represents the analysis on the TR/TU domain for tumor results across time and quantitative best response. The waterfall and spider plots are linked to the same underlying data table, where the waterfall plot is created using the MIN summary statistic value from the table supplying the time trend plot. Unique features in the JMP Graph Builder platform makes it very easy to create annotations to the trend plot to display occurrence of new lesions (asterisk) as well as relevant disposition events (Death).
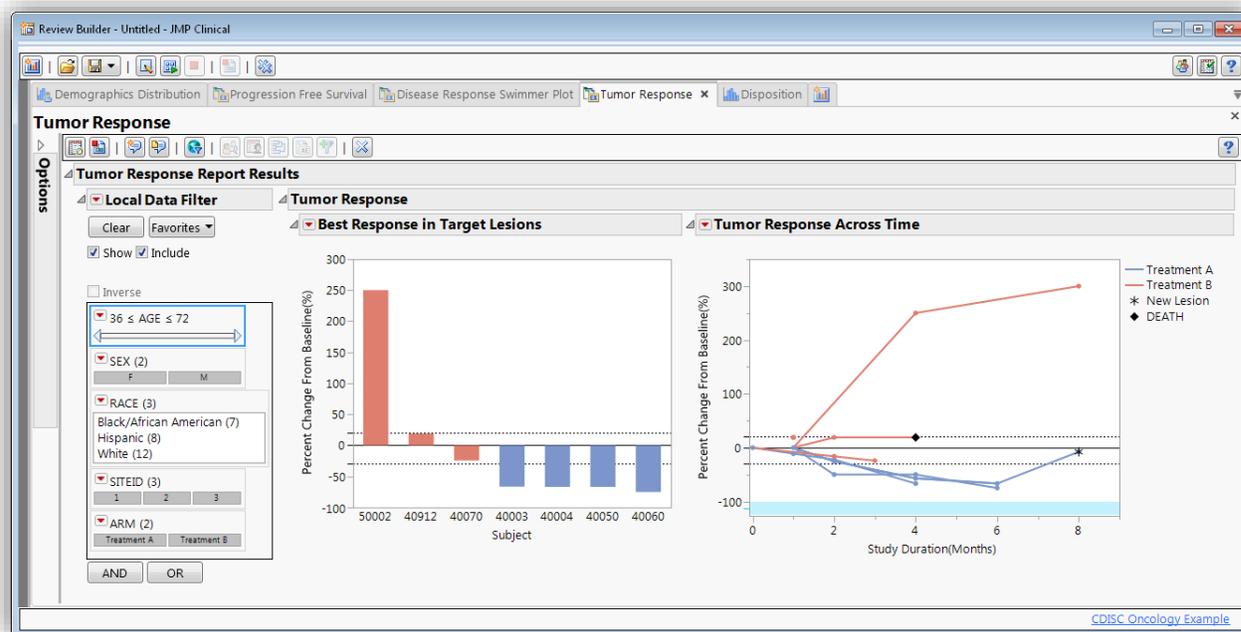
Display 4. JMP Clinical Tumor Results Report

The screenshot in Display 5 shows the results of tumor response when the data filter is used to selectively show females only in the study. By selecting one of the bars (for patient 40004) in the waterfall plot, dynamic linking immediate shows us the trend line associated with that patient.
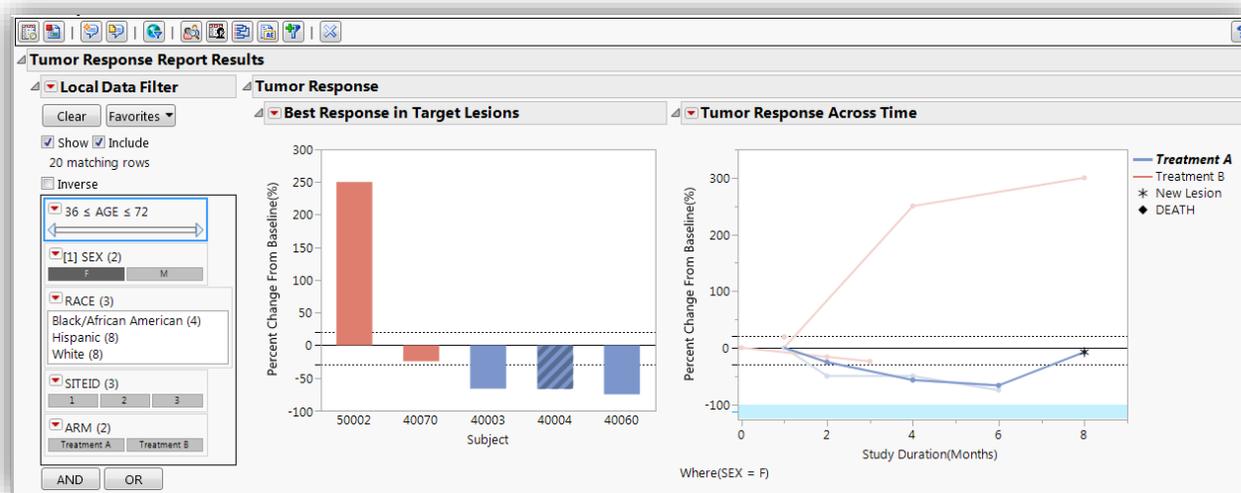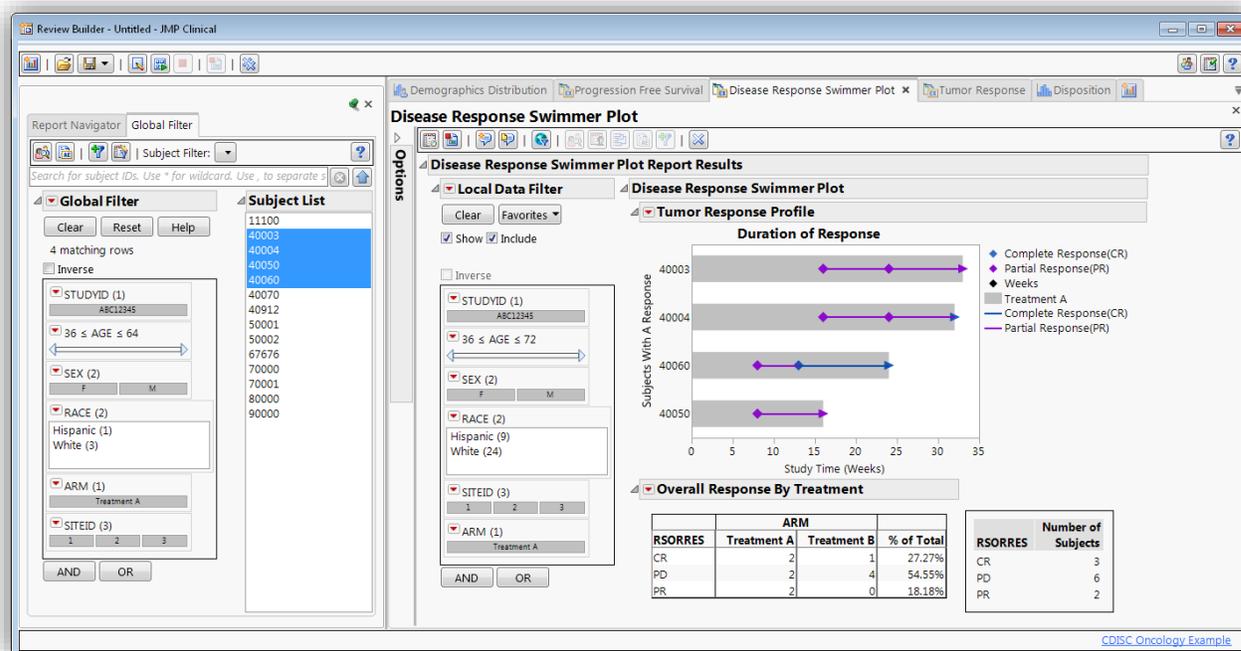

Display 5. Best Response Waterfall Plot and Trend Plots are Linked for Dynamic Filtering

In addition to dynamically linked results WITHIN a given analysis report, JMP Clinical also globally links reports across different domain analyses through the patient demography table. This capability extends subject exploration to very quickly select subjects that show tumor shrinkage response in the waterfall plot (e.g. the blue bars pictured in Display 4) and broadcast that selection to all other subject-level reports in the clinical review. Screenshots shown in Display 6 and Display 7 highlight this connection.
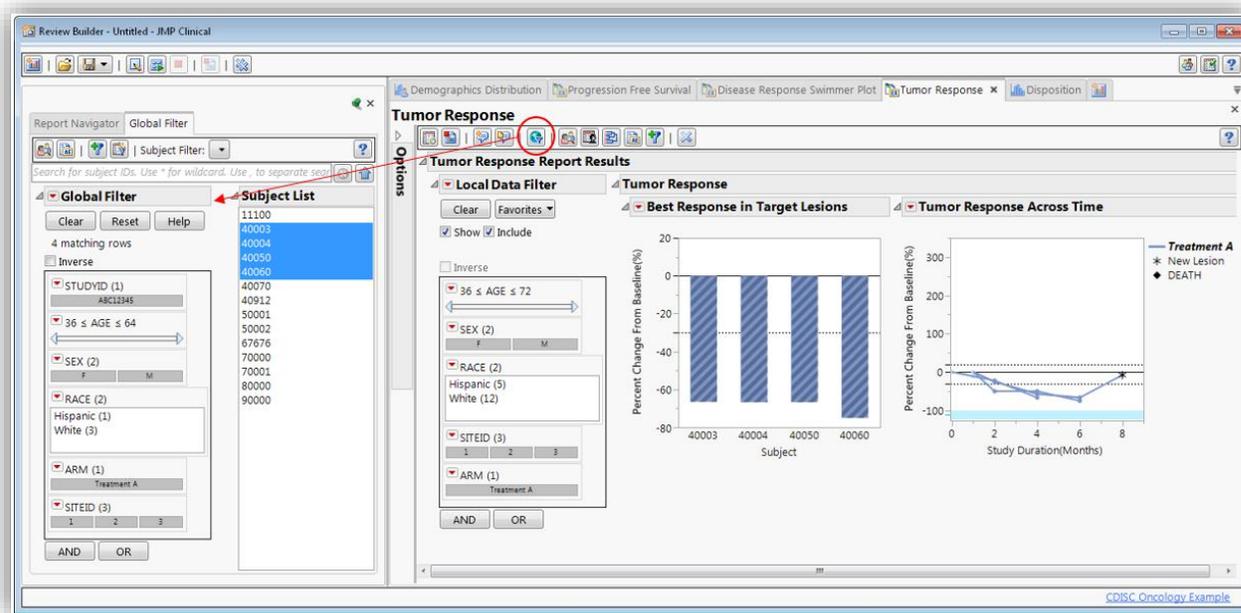
Display 6. Patient Selections in a JMP Clinical Report can be Broadcast to a Global Filter to Reflect that Patient Selection Throughout Other Clinical Analyses.

Once patients have been selected from one analysis and broadcast to the global filter, other patient-level analysis reports such as the Disease Response Swimmer Plot are updated to show that filtered set. Alternatively, the global filter can be used to comprehensively filter reports across a clinical review.

Display 7. Swimmer Plot Results For Patient Selection Made from Tumor Response Waterfall Plot.

The tumor shrinkage response shown in the waterfall plot for selected patients is validated by the qualitative disease response results shown in the swimmer plot.

CONCLUSION

This paper highlights the benefit of interactive visualization software for clinical review in oncology therapeutic studies, where patient-level summary analyses are a critical component to early efficacy endpoint detection. Clinical oncology research studies, which leverage complex but clear data standards (SDTM Tumor Package) and standardized evaluation criteria for endpoint derivation (RECIST guidelines), can be streamlined and effectively analyzed through the use of visual, integrated medical and biometric analysis reviews. New reports in JMP Clinical provide dedicated oncology features for the respective endpoint analysis and visualizations that have also become standard for this therapeutic area and promise to be the beginning of more therapeutic-specific analysis programming and reporting.

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Article in conference proceedings Mann, Geoffrey. 2017. "The impact of Regulations on Immuno-Oncology Submissions" *Proceedings of PhUSE 2017 Paper RG08.* Available at http://www.phusewiki.org/docs/Conference%202017%20RG%20Papers/RG03.pdf

RECOMMENDED READING

- *Study Data Tabulation Model Implementation Guide: Human Clinical Trials, Version 3.2, CDISC Submission Data Standards Team (November 26, 2013)*

- *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)*

- *Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*

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