Paper AS01

Computerized Algorithm for Multiple Myeloma Response Assessments

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ABSTRACT

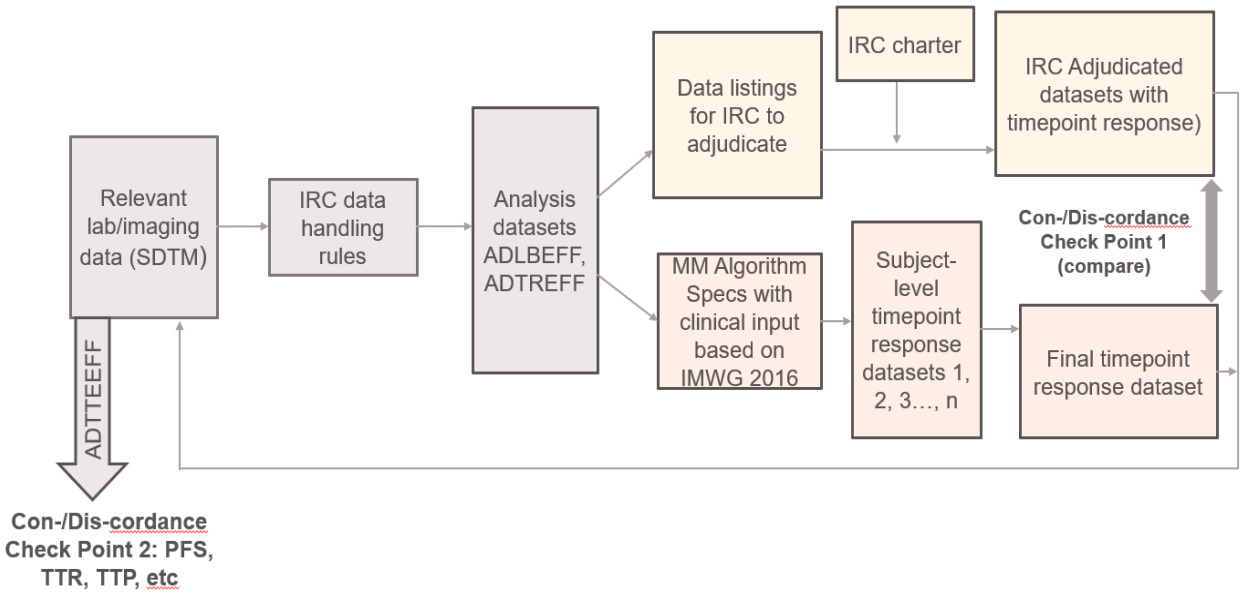
In multiple myeloma (MM) clinical trials, an independent review committee (IRC) is commonly employed to review efficacy data and adjudicate response to therapy for each subject based on the International Myeloma Working Group (IMWG) Response Criteria. However, although IRC lessens potential bias, it is costly and resource-consuming, and often leads to delayed availability of efficacy data. On the other hand, laboratory data collected in MM studies are unequivocal and imaging data collected in the clinical database are directly programmable. To enable broad implementation of algorithms and to ensure regulatory submission readiness, industry data standards were followed while generating the datasets and algorithms. The computerized algorithm was validated retrospectively using multiple studies. Concordance rate between algorithm and IRC assessments of disease response and progression was evaluated. Communication with regulatory agencies is planned to get endorsement of using algorithm in an on-going or new study to prospectively validate and replace IRC assessments.

INTRODUCTION

An Independent Review Committee is commonly employed to review efficacy data and adjudicate response in Multiple Myeloma studies for each subject based on International Myeloma Working Group (IMWG) Response Criteria. Even though IRC lessens potential bias, it is very costly and resource-consuming, and often leads to delayed availability of efficacy data. BMS cross-functional workstream was formed to develop a computerized algorithm for multiple myeloma response assessments following IMWG-2016 response criteria. Using study data and following IMWG-2016 guidance we have developed specification document, a suite of programs to derive MM response. Followed industry data standards to generate the datasets and algorithms, ensuring regulatory submission readiness and easy implementation.

OVERVIEW OF THE ALGORITHM

The goal of creating this Computerized Algorithm for Multiple Myeloma Response Assessments is to provide final response assessment following IMWG-2016 response evaluation criteria. Response derivation needs to be accurate and faster. Study may have Central and Local lab results collected based on study protocol at specified and unspecified time points. Below is a flow chart of the process followed for development, validation, and concordance checks.



Two analysis datasets ADLBEFF (Lab Efficacy dataset) and ADTREFF (Plasmacytoma / Bone Lesion) are generated using study SDTM and ADaM datasets and IRC handling rules. As a next step we re-structured analysis dataset to one record per subject/visit for Lab assessment, Extramedullary Plasmacytoma (EMP) Assessment and Bone Lesion dataset, before deriving the response assessment. Computerized algorithm was validated retrospectively using multiple studies. Performed concordance checks for best overall response, response date and PFS assessments as part of response validation. To ensure traceability and submission compliant CDISC ADaM standards are followed.

Analysis Dataset generation:

Specific lab tests to support IMWG evaluation like Serum M-Protein, Serum Immunofixation, Urine M-Protein, Urine Immunofixation, Serum Free Light Chain, Plasma Cell (%), CD138+/Plasma Cell (%), Conclusion are required to generate Lab analysis dataset (ADLBEFF). Plasmacytoma data points like Measurable, New lesion (to calculate total area) and non-measurable along with bone lesion information are also required for Plasmacytoma analysis dataset (ADTREFF). Change from baseline, percent change from baseline, nadir and percent change from nadir are derived to support the analysis for required parameters.

Relevant lab/imaging data are:

- Serum M-protein (SPEP)
- Urine M-protein (UPEP)
- Serum Free Light Chains (sFLC), κ, λ, κ/λ ratio, |κ-λ|.
- Serum immunofixation
- Urine immunofixation
- Plasmacytoma
- Bone Marrow: Number of PlasmaCells, %PlasmaCells, biopsy/aspirates
- Bone Lesion: Location Laterality, size of bone lesion increased- if present at baseline

Restructuring to Subject level dataset:

Analysis datasets are restructured to one observation per subject per date/visit to enable response derivation by merging lab, plasmacytoma and bone lesion data. Based on study design and data collection we may need to consider local lab results as well as unscheduled visits. For certain lab tests like bone marrow biopsy, which are not performed for every visit, imputation of data may be required. By restructuring and applying imputation we intend to have sufficient data for subject level time point response evaluation.

Depending on how study collects plasmacytoma – measurable, non-measurable may need imputations for both baseline and post-baseline values. Ex: Measurable value available but nothing quantitative – ie, Value is '0' or <= 0.01 cm^2 and non-measurable is absent or missing or NA. We need to carryforward the value and impute measurable value <=0.01 to "0" not non measurable available to "absent". Depending upon baseline and postbaseline plasmacytoma values, subjects may be evaluable for certain response criteria.

MM response baseline categorization:

Baseline value for each lab / imaging parameter needs to be determined to access baseline measurability status. It will help us to determine if the subject qualifies for individual time point response criteria or not. Baseline cases are determined using Serum M-Protein, Urine M-Protein and Serum Free Light Chain. Plasmacytoma measurable and non-measurable baseline values may need imputation based on the study data collection. During baseline evaluation, we need to ensure the measurable values definition aligns with the study inclusion criteria too.

IMWG-2016 response derivation

Response is derived for each subject by visit / date based on hierarchy -PD, sCR, CR, VGPR, PR, MR, SD.
Confirmatory response is derived for each subject based on time point response. Response criteria evaluation can vary based on the baseline categorization as we want to ensure derivation of response assessment is accurate based on given data. From the algorithm development perspective, it will be worth evaluating the practical consideration section from the IMWG reference document*. Please find below IMWG-2016 standard response criteria*.

IMWG 2016 response Criteria*

Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Final Adjudicated results

Final response result and response date are provided as output dataset which will get mapped to SDTM.RS based on IMWG-2016 response category.

Validation and Concordance Checks

Using multiple studies Computerized algorithm was validated retrospectively, and algorithm concordance checks were performed. We were able to achieve a high concordance rate for Best Overall Response, response date, PD/No PD assessment. As computerized algorithm took a conservative approach, team was able to justify the difference in concordance rate, as the results were based on the given data.

CONCLUSION

We were able to successfully implement IMWG-2016 response criteria programmatically which will enable BMS team to use for future clinical trials. It will enable us to have efficacy data in a shorter duration compared to IRC process. We have developed MM adjudication specification, a suite of programs to generate timepoint response and confirmatory response. Following industry data standards to generate the datasets and algorithms, it ensures regulatory submission readiness and easy implementation.

REFERENCES

*Kumar et al. *Lancet Oncol* 2016; 17: e328-46: International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma.

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