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Design and Methodological Considerations for Real World Data-Derived Progression-Free Survival in Multiple Myeloma

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Key Takeaway

We present a comprehensive assessment of important design choices for a real-world Progression (rwP) algorithm for patients with newly diagnosed multiple myeloma (MM), including a hierarchy of key assays and the inclusion of confirmatory testing.

Conclusions

The study presents a methodological approach to assessing MM disease progression through development of a rwP algorithm in RWD, which demonstrated how RWD may be analyzed to improve RWE generation and bridge the gap between RWD outcomes and trial-defined endpoints.

Further validation of the algorithm with health care provider assessments and with the inclusion of bone marrow biopsy and imaging data is important for evaluating the performance of the algorithm in RWD.

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- Supplementary material

https://www.congresshub.com/ASH2024/Oncology/ProductAgnostic/Wang

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Introduction

- Progression-free survival (PFS), a common endpoint used in multiple myeloma (MM) trials, is defined as the time to the first occurrence of disease progression or death.
- Disease progression in MM is determined by the International Myeloma Working Group (IMWG) Uniform Response Criteria[1] based on imaging and biomarkers from blood, urine, and bone marrow biopsy testing.
- In clinical trials, IMWG-recommended assessments are protocol-based. However, in routine care, they are often performed and recorded differently based on a multitude of factors.
- Algorithms to ascertain real-world progression events using routinely collected biomarker data are important to classify disease progression and align with trial-defined endpoints.

Objective

The aim of this study was to construct and evaluate a real-world Progression (rwP) algorithm using real-world data (RWD) and demonstrate how biomarker data are captured and used to derive outcomes in routine practice.

Methods

A **rwP** algorithm was developed using key IMWG-recommended biomarkers, including serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), and serum free light chains (FLCs):

- The initial baseline value for each biomarker was identified, if available, during either the pre-treatment period (45 days prior through 7 days after first line treatment (1L) start) or the on-treatment period (8 days after 1L start through 1L end).
- Available biomarkers were followed for disease assessment.
- If any subsequent lab value during 1L treatment was less than the initial baseline value, the subsequent "on-treatment baseline" value was adopted as the new lowest value; otherwise, the initial value was used as the "on-treatment baseline" value for assessing progression events.

Evaluation

Three hierarchies, which describe the order of utilizing key IMWG-recommended biomarkers to define rwP events, were explored, including:

- Strict hierarchy: SPEP > UPEP > FLCs
- Partial hierarchy: SPEP = UPEP > FLCs
- No hierarchy: SPEP = UPEP = FLCs

The strict hierarchy (SH) prioritizes the biomarkers most likely to be available in RWD. The partial hierarchy (PH) option closely resembles the IMWG criteria, with FLCs only used for rwP assessments when no measurable SPEP/UPEP are identified. The no hierarchy (NH) approach considers all available biomarkers equally and resembles how they are utilized in clinical practice.

Confirmatory rwP Testing

The feasibility of requiring confirmatory events following the first suggestion of progression was also explored. Assays following the progression event up to the end of 1L were considered as confirmatory progression events if they met IMWG criteria.

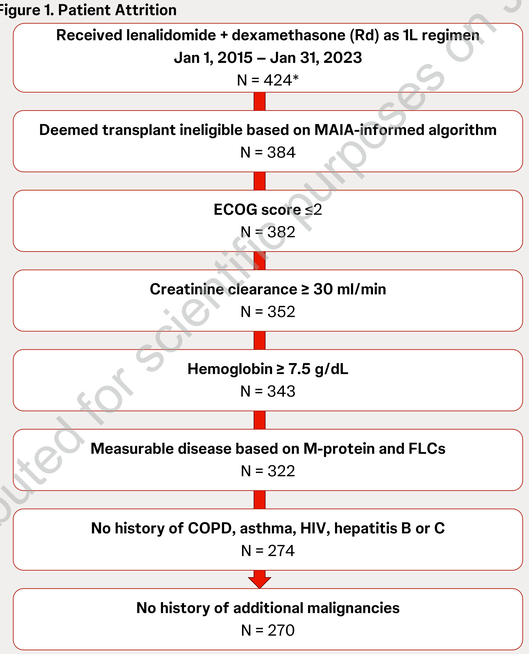
Results

Study Population

A cohort of 270 transplant-ineligible newly diagnosed MM (NDMM) patients starting on lenalidomide and dexamethasone (Rd) and meeting select MAIA (NCT02252172) trial eligibility criteria[2] were included from the nationwide Flatiron Health electronic health record-derived deidentified database[3,4] from 2015 to 2023. Detailed eligibility criteria and patient attrition are shown in *Figure 1.*

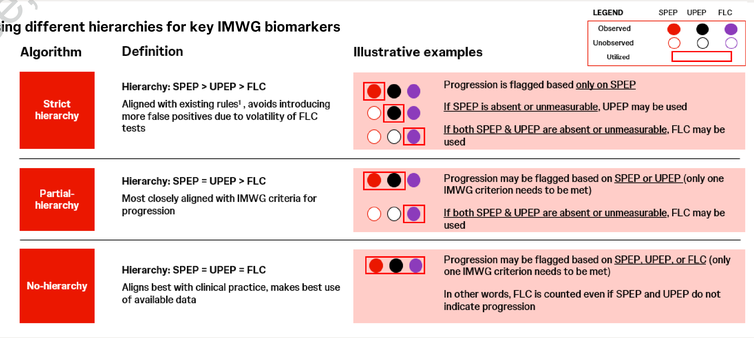
*Flatiron Health MM Database is a nationwide, longitudinal, electronic health record-derived, deidentified database, comprising patient-level data originated from ~280 US cancer clinics (~800 sites of care; primarily community oncology settings) and curated via technology-enabled abstraction.

Figure 1. Patient Attrition



*Additional inclusion and exclusion criteria were applied to the EHR database prior to patient selection, including having qualifying MM diagnose and documented visits, age over 18, no evidence of prior MM treatments, and having necessary structured documents for abstraction needs.

Illustration: rwP algorithm using different hierarchies for key IMWG biomarkers

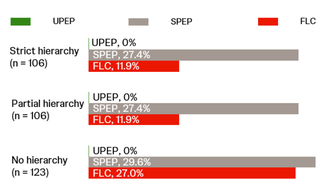


Evaluation

We applied the rwP algorithm with each hierarchy (*Illustration*) to all eligible NDMM patients (N = 270). The SH, PH, and NH approaches respectively identified 106 (39.3%), 106 (39.3%), and 123 (45.6%) patients with progression events. Details on patients with a progression event captured by algorithm and biomarker are shown in *Figure 2*.

Results from the SH and PH approach are consistent likely due to the rarity of UPEP usage in clinical practice. The NH approach captured more progression events because FLCs are used in the presence of measurable SPEP or UPEP, resulting in 73 progression events captured by FLCs in comparison to 32 from other approaches, potentially increasing false-positive capture due to the volatility of FLC results.

Figure 2. Patients with progression events, by algorithm & biomarker, n (%)*



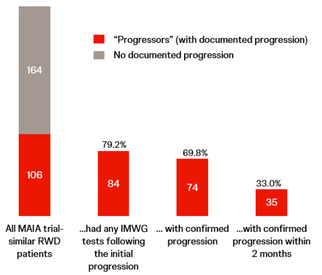
*Percentages of progression events captured by algorithm & biomarkers were calculated using the number of patients in the total study population (N = 270) as the denominator. Patients can have multiple progression events qualified through different IMWG biomarkers when using the PH and NH approaches.

Confirmatory rwP Testing

Among the 106 PH-identified patients who progressed, 84 (79.2%) had IMWG-recommended tests following their progression event, and 74 (69.8%) had their progression confirmed before the end of 1L, with 35 (33.0%) receiving their confirmatory reading within 2 months after progression (*Figure 3*).

These results suggest that requiring confirmatory testing as part of the rwP is feasible, though it may introduce false negatives, considering that some patients may receive clinical progression confirmation directly instead of getting confirmatory labs in routine clinical practice.

Figure 3. Progression documentation among real-world MAIA trial-similar patients, n (%)*



* Percentages of progression documentations captured following the first progression event were calculated using the patients with any progression event (N = 106) as the denominator.

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