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EVIDENCE meta-analysis: evaluating minimal residual disease as an intermediate clinical endpoint for multiple myeloma

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Abstract:
Estimating progression-free survival (PFS) and overall survival (OS) superiority during clinical trials of multiple myeloma (MM) has become increasingly challenging as novel therapeutics have improved patient outcomes. Thus, it is imperative to identify earlier endpoint surrogates that are predictive of long-term clinical benefit to expedite development of more effective therapies. Minimal residual disease (MRD)-negativity is a common intermediate endpoint that has shown prognostic value for clinical benefit in trials of patients with multiple myeloma (MM). This meta-analysis was based on the FDA guidance for considerations for a meta-analysis of MRD as a clinical endpoint and evaluates MRD-negativity as an early endpoint reasonably likely to predict long-term clinical benefit. Eligible studies were phase 2 or 3 randomized controlled clinical trials measuring MRD negativity as an endpoint in patients with MM, with follow-up of {greater than or equal to}6 months following an a priori defined time point of 12{plus minus}3 months post-randomization. Eight newly diagnosed MM-(NDMM)-studies evaluating 4,907 patients were included. Trial-level associations between MRD-negativity and PFS were R2WLSiv (95% CI) 0.67 (0.43-0.91) and R2copula 0.84 (0.64->0.99) at the 12-month timepoint. The individual-level association between 12-month MRD negativity and PFS resulted in a global odds ratio of 4.02 (95% CI: 2.57-5.46). For relapse/refractory MM-(RRMM), there were four studies included, and the individual-level association between 12-month MRD negativity and PFS resulted in a global odds ratio of 7.67 (4.24-11.10). A clinical trial demonstrating a treatment effect on MRD is reasonably likely to eventually demonstrate a treatment effect on PFS, suggesting that MRD may be an early clinical endpoint reasonably likely to predict clinical benefit in MM, that may be used to support accelerated approval and thereby expedite the availability of new drugs to patients with MM.

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Key Points

MRD-negativity at 12 months reduced the risk of progression; the treatment effect on MRD was correlated with the treatment effect on PFS

MRD negativity is reasonably likely to eventually demonstrate a treatment effect on PFS

ABSTRACT

Estimating progression-free survival (PFS) and overall survival (OS) superiority during clinical trials of multiple myeloma (MM) has become increasingly challenging as novel therapeutics have improved patient outcomes. Thus, it is imperative to identify earlier endpoint surrogates that are predictive of long-term clinical benefit to expedite development of more effective therapies. Minimal residual disease (MRD)-negativity is a common intermediate endpoint that has shown prognostic value for clinical benefit in trials of patients with multiple myeloma (MM). This meta-analysis was based on the FDA guidance for considerations for a meta-analysis of MRD as a clinical endpoint and evaluates MRD-negativity as an early endpoint reasonably likely to predict long-term clinical benefit. Eligible studies were phase 2 or 3 randomized controlled clinical trials measuring MRD negativity as an endpoint in patients with MM, with follow-up of ≥6 months following an *a priori* defined time point of 12±3 months post-randomization. Eight newly diagnosed MM-(NDMM)-studies evaluating 4,907 patients were included. Trial-level associations between MRD-negativity and PFS were R^2_{WLSiv} (95% CI) 0.67 (0.43-0.91) and R^2_{copula} 0.84 (0.64->0.99) at the 12-month timepoint. The individual-level association between 12-month MRD negativity and PFS resulted in a global odds ratio of 4.02 (95% CI: 2.57-5.46). For relapse/refractory MM-(RRMM), there were four studies included, and the individual-level association between 12-month MRD negativity and PFS resulted in a global odds ratio of 7.67 (4.24-11.10). A clinical trial demonstrating a treatment effect on MRD is reasonably likely to eventually demonstrate a treatment effect on PFS, suggesting that MRD may be an early clinical endpoint reasonably likely to predict clinical benefit in MM, that may be used to support accelerated approval and thereby expedite the availability of new drugs to patients with MM.

INTRODUCTION

Recent therapeutic advancements from clinical trials have resulted in substantial improvements in the survival of patients with newly diagnosed multiple myeloma (NDMM) (1), a malignant plasma cell disorder affecting almost 180,000 individuals annually worldwide.(2, 3) This improved survival has correspondingly increased the prevalence of patients with MM, reflected in over 450,000 patients living with the disease globally.(2-5) However, no curative therapy has yet been defined. Indeed, according to the NCI-SEER database, patients diagnosed with MM are confronted with a 5-year relative survival rate (measured from 2013 to 2019) of 59.8%,(6) highlighting the strong need for more effective and less toxic treatments. Importantly, improved survival rates have also complicated the development of such therapeutics because demonstrating clinical benefit (i.e. the application of current regulatory endpoints) through improved life expectancy now requires lengthier clinical trials with larger sample sizes and longer follow-up periods.(7)

Improving overall survival (OS) remains the ultimate goal for therapeutic agents. However, the extended time periods required to measure OS in clinical trials necessitated the adoption of progression-free survival (PFS) as a clinical endpoint that may be predictive of OS, can be obtained in a shorter time period, and which provides direct clinical benefit to patients (e.g., allowing patients to forego changes to therapy and limiting the anxiety caused by progressive disease).(7) The endorsement of PFS as a regulatory endpoint has allowed more rapid drug development, facilitating the approval of 13 new drugs for the treatment of MM in the United States over the last decade, resulting in the improvement of survival rates and quality of life for patients.(8) Yet, advancements in the clinical efficacy of these therapeutic agents have once again created a demand for increasingly lengthy trials, thereby delaying the availability of

improved therapeutic options to patients with great unmet medical needs.(7) Thus, it is prudent to identify and make use of intermediate clinical endpoints as surrogates to predict direct clinical benefit (i.e., PFS and OS), which can be measured earlier than progression or death, and will expedite access to advantageous therapeutics for patients with MM.

Minimal residual disease (MRD) negativity has been found to correlate well with improved survival in patients with NDMM, which motivates the investigation of whether a treatment's effect on MRD negativity may potentially be correlated with the treatment's effect on both PFS and OS.(9-15)

The use of MRD negativity (determined by a validated bone marrow-based assay able to rule out at least 1 myeloma cell in 100,000 tested cells; assay sensitivity of 10^{-5}) as a response category and as early evidence of clinical activity is supported by The International Myeloma Working Group (IMWG)(16) and the National Comprehensive Cancer Network (NCCN)(17) clinical guidelines. Additionally, MRD has been established by the United States Food and Drug Administration (FDA) as a key prognostic indicator and endpoint in several other hematologic malignancies, including acute lymphocytic leukemia, chronic lymphocytic leukemia, acute promyelocytic leukemia, and chronic myeloid leukemia.(18)

Over the past decade, numerous published meta-analyses have evaluated the prognostic value of MRD for PFS or OS in clinical studies of treatments for multiple myeloma, and these meta-analyses have indicated that MRD negativity has strong prognostic value for clinical benefit as measured by PFS or OS. (9, 15, 19-21)

Here, we were motivated to perform a comprehensive meta-analysis designed to EValuate mInimal residual DiseasE as an iNtermediate Clinical Endpoint for Multiple Myeloma (the EVIDENCE meta-analysis). Specifically, we wanted to examine the potential role of MRD negativity as an intermediate clinical endpoint reasonably likely to predict long-term clinical benefit in patients with MM. Sponsors for published, eligible randomized controlled trials (RCTs) reporting on MRD negativity (based on an assay with a sensitivity of 10^{-5} or better) as an endpoint in assessment of MM were invited to participate in this analysis. The analysis incorporates the FDA guidance for considerations for a meta-analysis to be used for validation of MRD as a clinical endpoint and potential basis for accelerated approval. (22) As part of this study, we first developed a formal Statistical Analysis Plan (SAP) together with the FDA. Once the SAP was approved by the FDA, we performed the statistical analysis, The results from this analysis are supportive of the regulatory consideration of MRD as an early clinical endpoint reasonably likely to predict clinical benefit in multiple myeloma that may be used to support accelerated approval and thereby expedite the availability of new drugs to patients with multiple myeloma.

METHODS

Data Sources

A systematic literature review was conducted to identify RCTs reporting MRD negativity as an endpoint in assessment of NDMM. Relevant studies were identified by searching PubMed, clinical trial registries (including ClinicalTrials.gov, the ISRCTN registry, European Union Clinical Trial Register, and Australian New Zealand Clinical Trials Registry), cooperative groups' websites, research organization meeting websites, and other sources such as personal

communications. Identified studies were restricted to RCTs with human subjects in which relevant documentation was written in English. Full text or title and abstract review was performed to determine adherence to eligibility criteria, and bibliographies of eligible articles were examined for identification of additional studies. The final list of studies was reviewed and approved by the study principal investigator. This systematic literature review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for meta-analyses.

Eligibility Criteria

For this study, in accord with the SAP approved by the FDA, we included phase 2 or 3 RCTs that enrolled patients with transplant eligible or transplant ineligible NDMM (TE NDMM and TIE NDMM, respectively) or RRMM and specified MRD negativity as a primary, secondary, or exploratory endpoint. Maintenance studies and those in which the primary endpoint was safety, toxicity, quality of life, or feasibility were excluded from consideration. Eligible studies must have performed MRD assays with a sensitivity of 10^{-5} or better (i.e. $<10^{-5}$) by multiparameter-flow cytometry (MFC) and/or next-generation sequencing (NGS) in accordance with guidelines from IMWG, NCCN, the FDA, and National Cancer Institute, as well as institutional standards of care for the treatment of patients with MM. To allow proper evaluation between MRD testing and clinical outcomes, eligible trials must have had a median follow-up of at least 6 months following an *a priori* defined time point of 12±3 months after randomization for the assessment of MRD negativity (Figure 1).

Data Sources

Studies meeting eligibility criteria and included in this study's analyses are described in Table 1. Secure transfer of information was requested from clinical trial sponsors for eligible studies, with data provided for MRD evaluation technique, and follow-up data on disease and outcomes.

Outcomes for Analysis

The primary objective of this study was to evaluate whether MRD negativity while in at least a complete response (CR; as defined by IMWG criteria)(23) at the *a priori* defined time point is a reasonably likely endpoint to predict clinical benefit as measured by PFS in patients with TE NDMM, in patients with TIE NDMM, in a combined "all-NDMM" population, and in the RRMM population. The primary endpoint of MRD negativity at 12±3 months was defined as follows: if a patient achieved at least a complete response (CR) at or before the time window, the MRD assessment closest to 12 months within the window was selected for the primary endpoint (if the patient had multiple assessments); if the patient did not have an MRD assessment during the window but progressed or died during the window, the patient was considered MRD-positive; lastly, if the patient did not have an MRD assessment and remained alive and in remission during the window, the primary endpoint was considered missing. Only trials in which the MRD endpoint could be ascertained in ≥80% of patients were included in the primary analysis. For all trials fulfilling the >80% criterion, patients with missing MRD information were considered MRD-positive, and the intent-to-treatment principle was followed.

Key secondary objectives of this study were to evaluate MRD negativity as an endpoint reasonably likely to predict clinical benefit in NDMM and RRMM for overall survival (OS), in addition to the attainment of MRD negativity at least once was also considered as endpoints reasonably likely to predict PFS. For all analyses, overall survival was defined as the time from

randomization to death from any cause, and progression-free survival was defined as the time randomization to progression of disease or death. Censoring rules for all trials followed the censoring rules outlined in each study's protocol.

Data Analysis

To evaluate MRD negativity as a reasonably likely endpoint for the prediction of clinical benefit (PFS or OS) in clinical trials of treatments for MM, a correlation approach was undertaken at both the individual- and trial-level. This approach evaluated the veracity of the following statements:

- MRD negativity is prognostic for clinical benefit.
- A treatment effect on MRD negativity in a clinical trial is predictive of a treatment effect on PFS or OS in the same clinical trial.

Within-trial treatment effects for MRD negativity and survival were estimated using logistic regression and the Cox proportional hazard regression model, respectively. Trial-level correlation was estimated using either a Plackett copula model(24) or weighted least squares (WLS), in which the weights were derived from either the sample size of each trial or the estimated inverse variance (WLSiv) of the log odds ratios of the treatment effect on MRD for each trial. The WLS approach estimates the treatment effect on the two outcomes using two marginal models, while the copula approach accounts for patient-level correlation. For the individual-level association, the Placket copula estimated the global odds ratio for comparing OS and PFS for patients with and without MRD. In addition to the copula, the association between MRD at 12 months and PFS and OS was assessed using a 12-month landmark. A random effects meta-analysis estimated the average effect of MRD on the two long-term outcomes. Various

sensitivity analyses were conducted, including leave-one-trial out re-estimation of the trial-level correlation. Analyses were conducted using R (v4.2.2) and SAS.

RESULTS

Analysis Sets and Demographic and Baseline Characteristics

In NDMM, a total of 5,130 patients were randomized from 8 studies, 1 of which provided 2 randomized comparisons (Table 1). Median (range) sample size was 306 (220-1085). There were 3 studies assessing patients with TE NDMM and 5 assessing patients with TIE NDMM. Eight of the 9 total comparisons, representing 4,907 patients, fulfilled criteria for the 12-month MRD negative endpoint and were included in the primary individual-level and trial-level analysis for the all-NDMM population. One comparison was excluded from this primary analysis due to >20% of patients being assigned a value of "missing" for the primary endpoint definition based on MRD. The median (IQR) follow-up for PFS was 29 months (19-58), and the median (IQR) follow-up for OS was 37 months (22-59).

In RRMM, four randomized studies fulfilled the study's inclusion criteria, with 1,835 patients in total. The median (IQR) follow-up for the included studies was 37.7 months (22-54.2) for PFS and 38.7 months (26.3-43.8) for OS.

Individual-Level Associations in Newly Diagnosed Multiple Myeloma

The global odds ratio demonstrated strong individual-level associations between 12-month MRD negativity and PFS, as well as between 12-month MRD negativity and OS, for both the all-NDMM population (PFS: 4.72 [95% CI: 3.53-5.90], OS: 4.02 [95% CI: 2.57-5.46]), the TIE

subgroup (PFS: 6.15 [95% CI: 4.27-8.03], OS: 4.08 [95% CI: 2.44-5.72]), and the TE subgroup (PFS: 2.45 [95% CI: 1.40-3.51], OS: 3.78 [95% CI: 0.78-6.78]) These individual-level associations remain strong in sensitivity analyses of other groupings of clinical trial results (Supplementary Tables 1) and indicate that being MRD negative at 12 months is highly prognostic of better long-term outcomes.

An alternative analysis investigated the association between MRD-negativity at 12 months and PFS by creating a 12-month post-randomization landmark. Among patients who were alive, progression-free, and under follow-up at 12 months, those who were MRD-negative at 12 months had reduced risk for progression or death in 1 out of 2 TE studies and 5 out of 5 TIE studies. Using a random effects meta-analysis, the average estimated hazard ratio in the NDMM population was 0.40 (95% CI: 0.24-0.68). For the individual trials included in the analysis, the association with OS was less strong (Supplemental Figures 1 and 2). This further supports the value of MRD negativity as a prognostic marker for better long-term outcomes.

Trial-Level Associations in Newly Diagnosed Multiple Myeloma

Correlations between the treatment effect on MRD negativity and the treatment effect on PFS at the trial level were R^2_{WLSiv} (95%CI) of 0.67 (0.43-0.91) for the all-NDMM population and 0.83 (0.71-0.96) for TIE NDMM subgroups. Using the copula model, R^2_{copula} (95% CI) was 0.84 (0.64->0.99) for the all-NDMM population and 0.85 (0.62->0.99) for the TIE subgroup. The three TE NDMM studies were too limited to estimate trial-level corrections. Sensitivity analyses additionally support a correlation between MRD negativity and PFS across various groupings of included trials (Table 2). Similar results for the weighted least squares R^2 were observed when the weights were derived from the sample size of each trial.

Correlation coefficients were lower in comparison of the treatment effect on MRD negativity and the treatment effect on OS, with R^2_{WLSiv} (95% CI) of 0.21 (<0.01-0.53) for the all-NDMM population and 0.79 (0.63-0.95) for TIE NDMM subgroup (Supplemental Figure 3). Using the copula model, R^2_{copula} (95% CI) was 0.32 (<0.01-0.86) for the all-NDMM population and 0.63 (0.12->0.99) for TIE NDMM subgroup.

Treatment effects on MRD negativity were statistically significant in 4 of the 8 comparisons, among which the treatment effect was also statistically significant on PFS in 4 studies and on OS in 3 studies (Table 3). Of the 4 treatment comparisons that did not have a statistically significant treatment effect on MRD negativity, the treatment effect was also not significant on PFS in 3 out of 4 studies and on OS in 4 studies. Side-by-side Forest plots of the treatment effects on MRD negativity and on PFS showed that studies with a strong treatment effect on MRD (producing MRD-negativity) tended to also have a strong treatment effect on PFS (Figure 2); the association was not clear for OS (Supplemental Figure 4).

Evaluation of Any MRD in Newly Diagnosed Multiple Myeloma

The attainment of MRD negativity at least once was evaluated as alternative measures of clinical benefit, in terms of their correlation with PFS and OS across studies. Data from 9 studies showed that attainment of MRD negativity at any time during the study (at least once) and PFS were R^2_{WLSiv} (95% CI) 0.54 (0.23-0.84) and R^2_{copula} (95% CI) 0.76 (0.49-0.99), and its correlation with OS was R^2_{WLSiv} (95% CI) 0.07 (<0.01-0.28) and R^2_{copula} (95% CI) 0.11 (<0.01-0.49). These data, combined with those of the primary analysis, support MRD as an endpoint reasonably likely to predict clinical benefit in studies of patients with NDMM.

Relapse/Refractory Multiple Myeloma

Among the four studies included in the primary analysis, the global odds ratio between MRD and PFS was 7.67 (95% CI: 4.24-11.10) using the copula model, and the odds ratio between MRD and OS was 6.03 (3.12-6.23). These estimates indicate a strong association between MRD and both PFS and OS. Trial-level correlations could not be estimated with only four studies. Supplemental Figure 5 provides a plot of the treatment estimate on MRD and the treatment estimate on PFS.

DISCUSSION

Initially, this effort was launched in 2009 as an U.S. inter-agency collaboration between investigators at NCI (OL and MS-S), NHLBI (GM), and the FDA (GM) (14); subsequently, additional collaborators were invited to join. The EVIDENCE meta-analysis was designed to further evaluate the prognostic value of bone marrow MRD negativity and assess its use for prediction of long-term clinical benefit, as measured by PFS, in patients with MM. The ultimate goal was to examine the potential role of MRD negativity as an intermediate clinical endpoint reasonably likely to predict long-term clinical benefit in patients with MM. Therefore, the analysis incorporates the FDA guidance for considerations for a meta-analysis to be used for validation of MRD as a clinical endpoint and potential basis for accelerated approval. (22) Data were compiled and analyzed from all available (N=8) studies for NDMM that used MRD negativity (sensitivity 10^{-5} or better) as a measure of efficacy. According to our meta-analysis, the odds ratio relating MRD negativity at 12 months to either prolonged PFS or OS was approximately 4 and was statistically significant. These results indicate a strong association between MRD negativity and PFS and a moderate association between MRD negativity and OS, suggesting that MRD negativity measured using a pre-specified timepoint may be an objective measure of anti-myeloma clinical activity that is highly prognostic of long-term outcomes.

Additionally, clinical trial designs easily allow for extended follow-up of patients assessed for MRD, allowing subsequent intra-trial evaluation of PFS and OS to confirm clinical benefit of investigational therapies. Furthermore, in the primary analysis for RRMM, the global odds ratio between MRD and PFS was 7.67 using the copula model, and the odds ratio between MRD and OS was 6.03, showing there is a strong association between MRD and both PFS and OS. Establishing associations between intermediate endpoints and OS, in general, are difficult in diseases with highly efficacious treatments because of subsequent effective therapies that patients receive after trial-treatment and off-study "crossover" of control arms whereby patients may derive benefit from the experimental agent but not be captured in the shorter-term endpoints (i.e. PFS, ORR, CR, or MRD-negativity) assessment.

Our findings align with those of previous meta-analyses, which have described strong evidence for the prognostic value of MRD negativity in clinical trials of new therapeutic agents in patients with NDMM.(9, 15, 19-21) The methods used to measure MRD have advanced in recent decades, resulting in sensitivity such that several studies have demonstrated MRD-positivity, i.e., disease burden that was not detected by current, conventional evaluation techniques for assessment of complete response.(25-27) This suggests that MRD negativity describes a deeper level of response driven by the availability of new technologies and has led to the IMWG including MRD-negativity as a response criterion for patients with MM.(16) The EVIDENCE meta-analysis is consistent with multiple prior studies that have shown that depth of response correlates with clinical benefit, namely PFS (9, 11-13, 19)

While some patient subgroups (transplant eligible NDMM and RRMM) were limited by the number of available studies, the EVIDENCE meta-analysis shows a moderate-to-high trial-level correlation in the overall NDMM and the transplant ineligible NDMM subgroup. As more

studies incorporate MRD testing into their study protocols, future meta-analyses will be able to better estimate the trial-level correlation across all patient subgroups (transplant ineligible NDMM, transplant eligible NDMM, and RRMM).

Although substantial improvements in the treatment of patients with MM have been made over the last decade, further advancement is limited by the extended time periods currently required to properly estimate and demonstrate clinical benefit as measured by PFS or OS. Extended clinical trial durations may deny patients access to effective subsequent therapeutic options for many years. To speed up the development process and provide access to new therapeutic options for these patients, an objective and reliably measured intermediate endpoint that is well-correlated with an anti-myeloma treatment effect and long-term outcomes is needed. This meta-analysis has provided evidence that MRD negativity (defined as 10^{-5} or better) may well be that surrogate marker that is predictive for long-term outcomes at an earlier timepoint.

As with all studies, additional analyses will provide further insight into and evidence for the prognostic value of this metric across all patients with MM. The fact that this meta-analysis is limited to 8 comparisons of heterogenous patient populations restricts extensive extrapolation, and additional analyses of broader patient populations, such as those with relapsing/refractory MM, will be necessary. It should be noted that measurement of MRD negativity, including that of studies included in this analysis, has previously involved challenges of capture-rate, resulting in an inability to assess MRD status in a subset of patients (up to ~20% using early assays). However, modern technology (such as ClonoSEQ) results in 90-95% capture rate among patients, allowing trial populations to be adequately assessed for this endpoint to achieve statistical significance.(28) It may additionally prove beneficial to analyze potential differences in the correlation of MRD and outcomes of clinical benefit across categories of therapeutic

agents, such as standard therapies versus CAR T-cell therapy. Furthermore, it should be stated that any surrogate marker has the inherent limitation where toxicity can lead to excess deaths despite superior PFS. Therefore, it is important to confirm superior PFS and rule out inferior OS for full regulatory approval. Lastly, as shown in this analysis, there is a strong relationship between clinical outcomes and the attainment of MRD negativity obtained at least once. Over time, an increasing number of studies have started to include repeated MRD testing to confirm sustained MRD negativity (e.g., annually). As expected, sustained MRD negativity has an even stronger correlation with clinical outcomes.

CONCLUSIONS

There exists a strong demand for an early clinical endpoint that is reasonably likely to predict long-term clinical benefit in patients with MM. The EVIDENCE meta-analysis was designed based on the FDA guidance for considerations for a meta-analysis of MRD as a clinical endpoint and potential basis for accelerated approval (22), and it assessed the prognostic value of bone marrow MRD negativity and prediction of the treatment effects for PFS and OS in clinical trials of patients with MM. The results support consideration of MRD as an early clinical endpoint reasonably likely to predict clinical benefit in MM that may be used to support accelerated approval and thereby expedite approval and adoption of novel therapeutic agents and advantageous therapeutic regimens for treatment of patients with MM.

AUTHORSHIP

S.M.D.: statistical analyses, conceptualization, methodology, investigation, visualization, writing.

T.J.P.: conceptualization, data curation, investigation, methodology, supervision, writing.

T.M.: conceptualization, investigation, methodology, visualization, supervision, writing.

C.H.: conceptualization, methodology, investigation, visualization, writing.

O.F.B.: conceptualization, data curation, investigation, writing.

A.B.D.: conceptualization, methodology, investigation, visualization, writing.

H.E.: conceptualization, methodology, investigation, visualization, writing.

S.K.: contributed data, critically revised the manuscript.

C.L.: conceptualization, methodology, investigation, visualization, writing.

U-H.M.: conceptualization, methodology, investigation, visualization, writing.

I.M.: conceptualization, methodology, investigation, visualization, writing.

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G.M.: conceptualization, methodology, investigation, visualization, writing.

D.K.: conceptualization, methodology, investigation, visualization, writing.

O.L.: conceptualization, methodology, validation, data curation, investigation, resources, visualization, writing, supervision, project administration, funding acquisition.

All authors fully reviewed and commented on all previous versions of the manuscript and approved the final manuscript.

CONFLICTS OF INTEREST

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REFERENCES

1. Anderson KC, Auclair D, Adam SJ, Agarwal A, Anderson M, Avet-Loiseau H, et al. Minimal Residual Disease in Myeloma: Application for Clinical Care and New Drug Registration. Clin Cancer Res. 2021;27(19):5195-212.
2. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Pineros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
4. Polsinelli B, Tsigkos S, Naumann-Winter F, Mariz S, Sepodes B. Evolving prevalence of haematological malignancies in orphan designation procedures in the European Union. Orphanet J Rare Dis. 2017;12(1):17.
5. Turesson I, Bjorkholm M, Blimark CH, Kristinsson S, Velez R, Landgren O. Rapidly changing myeloma epidemiology in the general population: Increased incidence, older patients, and longer survival. Eur J Haematol. 2018.
6. SEER. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Myeloma. 2022 [Available from: https://seer.cancer.gov/statfacts/html/mulmy.html.
7. Holstein SA, Suman VJ, McCarthy PL. Should Overall Survival Remain an Endpoint for Multiple Myeloma Trials? Curr Hematol Malig Rep. 2019;14(1):31-8.
8. Abrams Kaplan D. Multiple Myeloma: Top 10 Advances in the Past 10 Years. Targeted Therapies in Oncology. 2022;11(4):70.
9. Avet-Loiseau H, Ludwig H, Landgren O, Paiva B, Morris C, Yang H, et al. Minimal Residual Disease Status as a Surrogate Endpoint for Progression-free Survival in Newly Diagnosed Multiple Myeloma Studies: A Meta-analysis. Clin Lymphoma Myeloma Leuk. 2020;20(1):e30-e7.
10. Bahlis NJ, Dimopoulos MA, White DJ, Benboubker L, Cook G, Leiba M, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia. 2020;34(7):1875-84.
11. Costa LJ, Chhabra S, Medvedova E, Dholaria BR, Schmidt TM, Godby KN, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. Journal of Clinical Oncology. 2021;40(25):2901-12.
12. Landgren O, Iskander K. Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes. J Intern Med. 2017;281(4):365-82.
13. San-Miguel J, Avet-Loiseau H, Paiva B, Kumar S, Dimopoulos MA, Facon T, et al. Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE. Blood. 2022;139(4):492-501.
14. Landgren O, Gormley N, Turley D, Owen RG, Rawstron A, Paiva B, et al. Flow cytometry detection of minimal residual disease in multiple myeloma: Lessons learned at FDA-NCI roundtable symposium. Am J Hematol. 2014;89(12):1159-60.
15. Munshi NC, Avet-Loiseau H, Anderson KC, Neri P, Paiva B, Samur M, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv. 2020;4(23):5988-99.

16. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e46.
17. Kumar SK, Callander NS, Adekola K, Anderson L, Baljevic M, Campagnaro E, et al. NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY: Multiple Myeloma, Version 3.2021. Journal of the National Comprehensive Cancer Network. 2020;18(12):1685-717.
18. Administration UDoHaHSFaD. Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment. 2020.
19. Cavo M, San-Miguel J, Usmani SZ, Weisel K, Dimopoulos MA, Avet-Loiseau H, et al. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA. Blood. 2022;139(6):835-44.
20. Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. Bone Marrow Transplant. 2016;51(12):1565-8.
21. Munshi NC, Avet-Loiseau H, Rawstron AC, Owen RG, Child JA, Thakurta A, et al. Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis. JAMA Oncol. 2017;3(1):28-35.
22. Administration UDoHaHSFaD. Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry 2020 [Available from: https://www.fda.gov/media/86377/download.
23. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e46.
24. Burzykowski T, Molenberghs G. The validation of surrogate end points by using data from randomized clinical trials: a case-study in advanced colorectal cancer. J R Statist Soc. 2004;167(1):103-24.
25. Paiva B, Gutierrez NC, Rosinol L, Vidriales MB, Montalban MA, Martinez-Lopez J, et al. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood. 2012;119(3):687-91.
26. Paiva B, Martinez-Lopez J, Vidriales MB, Mateos MV, Montalban MA, Fernandez-Redondo E, et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. J Clin Oncol. 2011;29(12):1627-33.
27. Paiva B, Vidriales MB, Cervero J, Mateo G, Perez JJ, Montalban MA, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood. 2008;112(10):4017-23.
28. Hultcrantz M, Rustad EH, Yellapantula V, Jacob A, Akhlaghi T, Korde N, et al. Capture rate of V(D)J sequencing for minimal residual disease detection in multiple myeloma. Clin Cancer Res. 2022;28(10):2160-6.

Tables and Figures

Table 1. PFS and OS Data for Studies in Patients with Newly Diagnosed Multiple Myeloma Included in the Meta-Analysis

Study/Sponsor	Treatment: n (%)	N	Median Follow-up**, months	Median PFS, months	Median OS, months	MRD Assay***
TE NDMM						
Randomized Phase III Trial for Previously Untreated Multiple Myeloma to Evaluate Two Regimens of Bortezomib Based Induction Therapy and Lenalidomide Consolidation Followed by Lenalidomide Maintenance Treatment (MM5)/ University Hospital Heidelberg[Error! Reference source not found.] https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-019173-16/DE	A1*: 149 (24.8%) A2*: 151 (25.1%) B1*: 150 (25%) B2*: 151 (25.1%)	601	57.1 (IQR:44.4-64)	40.5 (95% CI: 36.5-43.2)	Not reached	MFC
Phase 2, Randomized, Open-label Study Comparing Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) versus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Subjects with Newly Diagnosed Multiple Myeloma Eligible for High-dose Chemotherapy and Autologous Stem Cell Transplantation (GRIFFIN-MMY2004)/Janssen R&D[Error! Reference source not found.] NCT02874742	D-RVd: 120 (53.8%) RVd: 103 (46.2%)	223	25.4 (IQR:22.1-28.3)	Not reached (95% CI: 34.1-NR)	Not reached	NGS
Study of Daratumumab in Combination with Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTD) in the First Line Treatment of Transplant Eligible Subjects with Newly Diagnosed Multiple Myeloma (CASSIOPEIA-MMY3006)/Intergroupe Francophone du Myelome (IFM)[Error! Reference source not found.,Error! Reference source not found.] NCT02541383	D-VTd: 543 (50%) VTd: 542 (50%)	1085	18.2 (IQR:13.7-24)	Not reached	Not reached	NGS
TIE NDMM						
A Randomized, Open-label Phase 3 Study of Carfilzomib, Melphalan, and Prednisone versus Bortezomib, Melphalan, and Prednisone in Transplant ineligible Patients with Newly Diagnosed Multiple Myeloma (CLARION)/Amgen[Error! Reference source not found.] NCT01818752	KMP: 428 (50.2%) VMP: 425 (49.8%)	853	22.3 (IQR:19.1-27.6	22.2 (95% CI: 21-24.2)	Not reached	MFC

Study/Sponsor	Treatment: n (%)	N	Median Follow-up**, months	Median PFS, months	Median OS, months	MRD Assay***
A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination with VMP (D-VMP) in Subjects with Previously Untreated Multiple Myeloma Who are Ineligible for High-dose Therapy (ALCYONE-MMY3007) Janssen R&D[Error! Reference source not found.,Error! Reference source not found.] NCT02195479	D-VMP: 350 (49.6%) VMP: 356 (50.4%)	706	39.9 (IQR:37.4-42.9)	24 (95% CI: 21.6-27.4)	Not reached	NGS
A Phase 3, Randomized, Double-blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone (Rd) versus Placebo Plus Lenalidomide and Dexamethasone (Rd) in Adult Patients with Newly Diagnosed Multiple Myeloma (TOURMALINE-MM2)/Takeda[Error! Reference source not found.] NCT01850524	IRd: 351 (49.8%) Rd: 354 (50.2%)	705	54.6 (IQR:22-60.7)	27.9 (95% CI: 23.9-35.8)	Not reached	MFC
A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma Who are Ineligible for High Dose Therapy (MAIA-MMY3008)/Janssen R&D[Error! Reference source not found.,Error! Reference source not found.] NCT02252172	DRd: 368 (49.9%) Rd: 369 (50.1%)	737	62.4 (IQR:57.9-66.8	44.8 (95% CI: 40.9-52.4)	73.7 (95% CI: 69.7-NA)	NGS
A Phase 3, Multicenter, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination With VMP (D-VMP), in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High-Dose Therapy (Asia Pacific Region-OCTANS-MMY3011)/Janssen R&D NCT03217812	D-VMP: 146 (66.4%) VMP: 74 (33.6%)	220	22.9 (IQR:19-30)	28.2 (95% CI: 24.4-NR)	41.6 (95% CI: 41.6-NA)	MFC

CI, confidence interval; DRd, daratumumab, lenalidomide, and dexamethasone; D-RVd,daratumumab, lenalidomide, bortezomib, and dexamethasone; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone**;** D-VMP, daratumumab, bortezomib, melphalan, and prednisone; IRd, isatuximab, lenalidomide, and dexamethasone; Janssen R&D, Janssen Research & Development, LLC; KMP, **c**arfilzomib, melphalan, and prednisone; NA, not available; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; RVd, lenalidomide, bortezomib, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VTd, bortezomib, thalidomide, and dexamethasone; TE, transplant eligible; TIE, transplant ineligible; NR, not reached.

*A1, bortezomib, doxorubicin, and dexamethasone, high-dose melphalan, autologous blood stem cell transplantation and lenalidomide consolidation followed by lenalidomide maintenance therapy for 2 years

B1, bortezomib, doxorubicin, and dexamethasone, high-dose melphalan, autologous blood stem cell transplantation and lenalidomide consolidation followed by lenalidomide

maintenance until achievement of complete response
A2, bortezomib, cyclophosphamide, and dexamethasone, high-dose melphalan, autologous blood stem cell transplantation and lenalidomide consolidation followed by lenalidomide maintenance therapy for 2 years
B2, bortezomib, cyclophosphamide, and dexamethasone, high-dose melphalan, autologous blood stem cell transplantation and lenalidomide consolidation followed by lenalidomide maintenance until achievement of complete response

** Follow-up is calculated for the endpoint of progression-free survival using the reverse Kaplan-Meier estimate.
*** multiparameter flow cytometry (MFC) or next generation sequencing (NGS).

Table 2. Trial-Level R^2 Estimates for PFS – Sensitivity Analyses (All-NDMM Population)

Sensitivity Analysis	Total Follow-up, months (IQR)	R^2_{copula} (95% CI)	$R^2_{WLS\ (inverse\ variance)}$ (95% CI)
Adding study 2.1* to all NDMM	28.6 (19,56.4)	0.82 (0.62,1.03)	0.68 (0.45,0.91)
All NDMM without study 1.1A and 1.1B	26.9 (18,53.4)	0.72 (0.35,>0.99)	0.53 (0.22,0.83)
All NDMM without study 1.2	28.2 (18.8,55.6)	0.87 (0.69,>0.99)	0.69 (0.47,0.92)
All NDMM without study 1.3	43.8 (24.3,61.1)	0.91 (0.79,>0.99)	0.88 (0.78,0.98)
All NDMM without study 1.4	38 (18.9,59.5)	0.82 (0.58,>0.99)	0.56 (0.27,0.86)
All NDMM without study 1.5	27.4 (18.1,58.9)	0.84 (0.63,>0.99)	0.62 (0.36,0.89)
All NDMM without study 1.6	26.5 (18,44.4)	0.88 (0.72,>0.99)	0.82 (0.67,0.96)
All NDMM without study 1.7	30.5 (18.9,58.3)	0.78 (0.47,>0.99)	0.64 (0.39,0.9)

Note: The 2004 comparison was not included in the primary analysis due to >20% of patients being assigned a value of missing for the primary endpoint definition based on MRD. All-NDMM (i.e., transplant eligible and transplant ineligible combined) includes studies 1.1A, 1.1B, 1.2, 1.3, 1.4, 1.5, 1.6, and 1.7. Transplant-eligible NDMM includes studies 1.1A, 1.1B, and 1.3.

Table 3. Concordance of Significance for MRD with PFS and OS (All-NDMM Population)

Study	Treatment Effect on MRD[a] (2-sided test) p-value	Treatment Effect on PFS[a] (2-sided test) p-value	Treatment Effect on OS[a] (2-sided test) p-value
Transplant-eligible NDMM			
1.1A	0.98	0.385	0.686
1.1B	0.131	0.605	0.901
1.3	<0.001	<0.001	0.008
Transplant-ineligible NDMM			
1.4	0.629	0.399	0.232
1.2	0.264	0.038	0.806
1.5	<0.001	<0.001	<0.001
1.6	<0.001	<0.001	<0.001
1.7	<0.001	<0.001	0.377

MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; NDMM, newly diagnosed multiple myeloma; TE, transplant eligible; TIE, transplant ineligible.
[a]Does not include stratification factors used in randomization.

Figure Legends

Figure 1. PRISMA Flowchart of the Systematic Literature Review Search Strategy and Article Selection

The literature review was conducted in adherence with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Medline and EMBASE databases were searched for articles published in English up to 8 June 2019; there was no date limit on the indexed database searches. Details of the search strategy were performed as follows: medical subject heading (MeSH) terms for MM were “multiple myeloma” and “neoplasm, residual.” Non-MeSH search terms were “Kahler disease” (or “Kahler’s disease” or “myelomatosis” or “plasma cell myeloma”) and “minimal residual disease” (or “MRD”). Selected congress abstracts published between 2016 and 2019, including additional literature, were manually reviewed. Bibliographies of SLR articles on multiple myeloma published between 2014 and 2019 were reviewed manually to identify additional potentially relevant publications. Additional sources were used for validation, including studies identified in public assessment reports published by the European Medicines Agency and the US Food and Drug Administration. Population, interventions, comparisons, outcomes, and study design (PICOS) criteria were used to define eligibility. Patients could have received any type of therapy except allogeneic stem cell transplantation. Studies with PFS or OS data that could not be extracted or reconstructed were excluded. Studies with patients who did not have a primary diagnosis of multiple myeloma were also excluded, as were those with MRD measured only in peripheral blood or assessed only by positron emission tomography-(PET)-computed tomography-(CT)-scanning. Two independent investigators selected the articles for potential inclusion. Randomized controlled trials and observational studies that reported PFS or OS rates stratified by MRD status in patients with MM following therapy were eligible for inclusion (supplemental Table 1). Methodological quality of the studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting recommendations. A manual search was conducted to identify any updated publications on selected studies.

Figure 2, Panel A. Correlation Between Treatment Effect on 12-month MRD Negativity and Treatment Effect on PFS Scaled by Sample Size – All-NDMM Population

MRD, minimal residual disease; PFS, progression-free survival; NDMM, newly diagnosed multiple myeloma; HR, hazard ratio; OR, odds ratio. Note: All-NDMM combines transplant eligible and transplant ineligible patients. Study 2.1 was not included in the primary analysis due to >20% of patients being assigned a value of missing for the primary endpoint definition based on MRD. This study was included in sensitivity analyses.

Figure 2, Panel B. Forest Plot of Treatment Effect on MRD and PFS

MRD, minimal residual disease; PFS, progression-free survival; CI, confidence interval; N/D, newly diagnosed; R/R, relapsed/refractory.

Figure 1. PRISMA Flowchart of the Systematic Literature Review Search Strategy and Article Selection

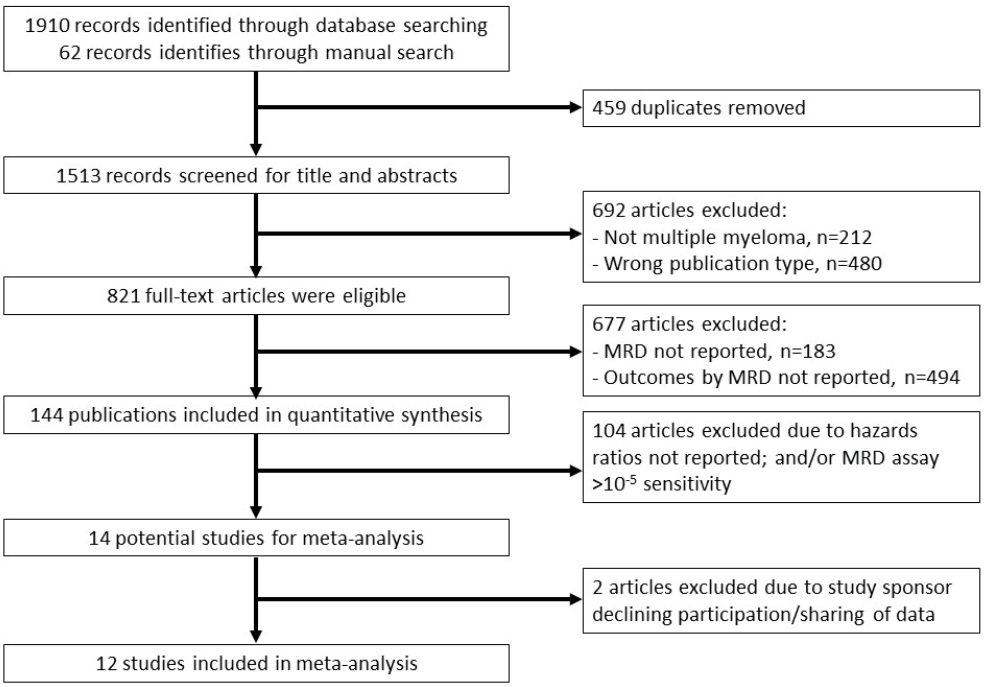


Figure 2, Panel A. Correlation Between Treatment Effect on 12-month MRD Negativity and Treatment Effect on PFS Scaled by Inverse Variance – All-NDMM Population

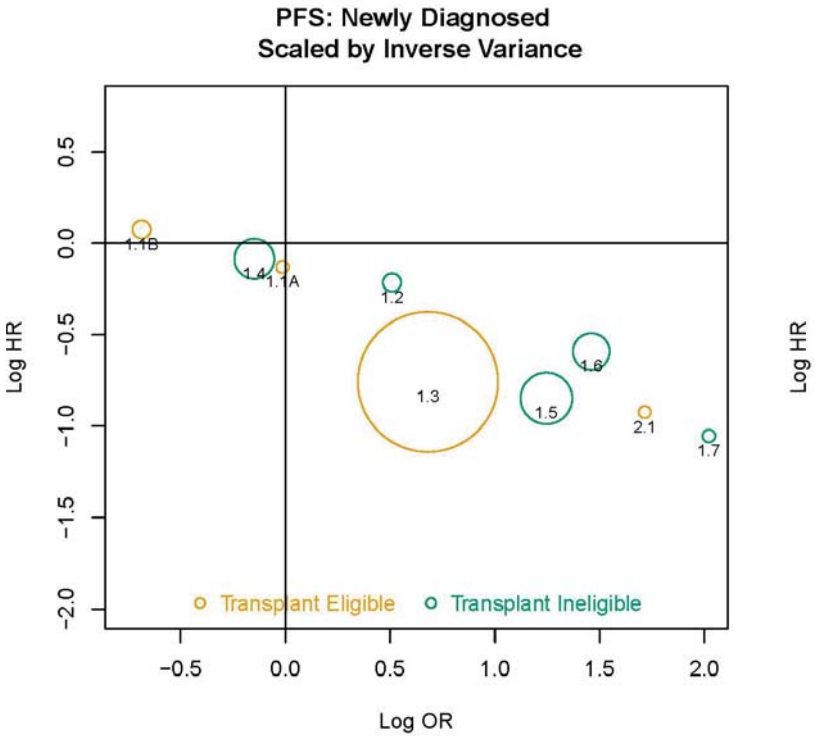
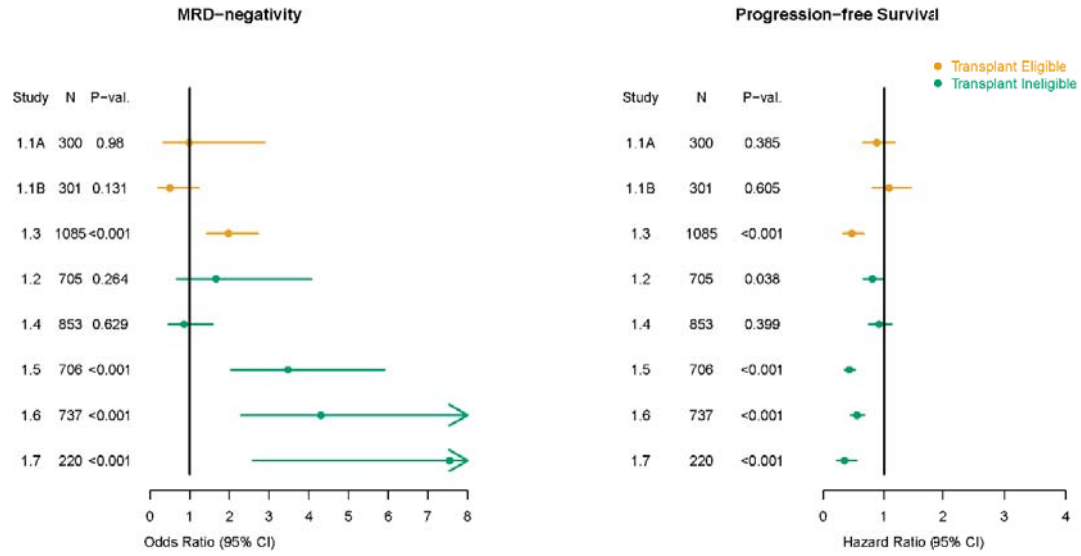


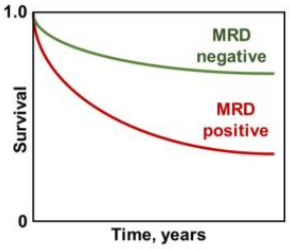
Figure 2, Panel B. Forest Plot of Treatment Effect on MRD and PFS



The EVIDENCE Meta-Analysis: Evaluating Minimal Residual Disease as an Intermediate Clinical Endpoint for Multiple Myeloma (MM)

Question

• Is minimal residual disease (MRD) negativity, measured as an intermediate endpoint, reasonably likely to predict long-term clinical benefit in patients with MM?



Methods

• FDA guidance

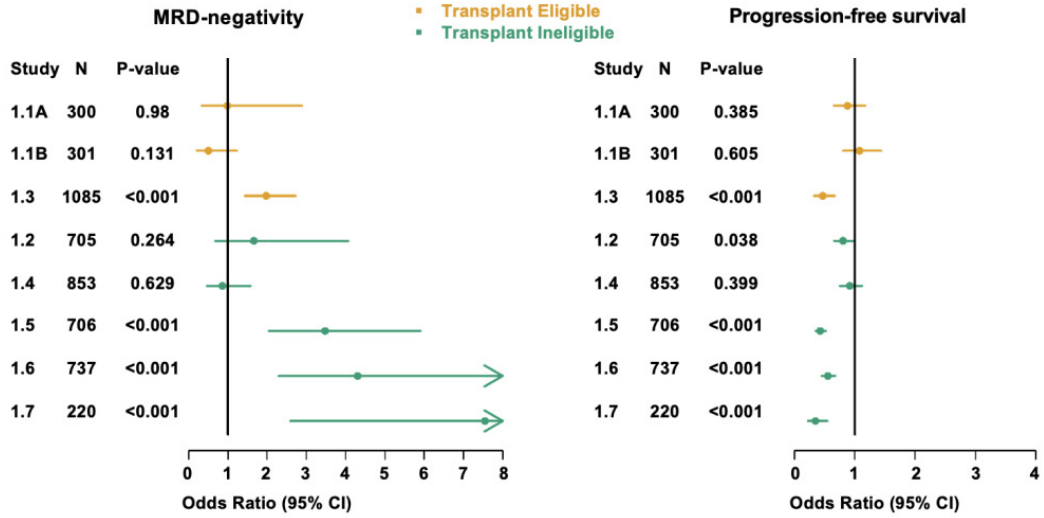
- MRD as a clinical endpoint

• Meta-analysis

- 12 phase 2 or 3 randomized controlled clinical trials measuring MRD negativity (using assays able to detect 1 myeloma cell in 100,000 cells, or better) as an endpoint in patients with MM

Main Findings

• Patients with newly diagnosed MM who were MRD-negative at 12 months had a reduced risk of progression



• The treatment effect on MRD was found to be correlated with that on progression-free survival (PFS) in both newly diagnosed and relapsed/refractory MM patients

Conclusions: MRD may serve as an early clinical endpoint that is likely to predict clinical benefit in MM. This endpoint may be utilized to support accelerated approval, thereby expediting the availability of new drugs to patients with MM.

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