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Evaluation of Daratumumab for the Treatment of Multiple Myeloma in Patients With High-risk Cytogenetic Factors
A Systematic Review and Meta-analysis

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+ **Supplemental content**

IMPORTANCE The addition of daratumumab to backbone multiple myeloma (MM) regimens is associated with improved response rates and progression-free survival (PFS). Whether improved outcomes are also associated with this regimen among patients with cytogenetically defined high-risk MM (HRMM) remains unclear.

OBJECTIVE To measure PFS associated with adding daratumumab to backbone MM regimens among patients with HRMM.

DATA SOURCES For this systematic review and meta-analysis, MEDLINE, Embase, PubMed, Scopus, Web of Science Core Collection, Cochrane Library, clinical trials registries, and meeting libraries were searched from inception to January 2, 2020, using terms reflecting multiple myeloma and daratumumab.

STUDY SELECTION Included studies were phase 3 randomized clinical trials that compared backbone MM regimens with the same regimen plus daratumumab in newly diagnosed or relapsed or refractory MM, such that the only difference between the intervention and control groups was use of daratumumab and reported outcomes by cytogenetic risk. High-risk MM was defined as the presence of t(4;14), t(14;16), or del(17p).

DATA EXTRACTION AND SYNTHESIS Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline, 2 investigators independently extracted study data, with disagreements resolved by a third investigator. Quality was assessed by the Cochrane risk-of-bias method.

MAIN OUTCOMES AND MEASURES Data on effectiveness were extracted using hazard ratios (HRs) for PFS. Relative log-HRs were pooled using a DerSimonian-Laird random-effects model. Heterogeneity was assessed using the Cochran Q and the I^2 statistic.

RESULTS Of 5194 studies screened, 6 phase 3 trials were eligible, including 3 trials for newly diagnosed MM (2528 patients; 358 with HRMM) and 3 trials for relapsed or refractory MM (1533 patients; 222 with HRMM). Among patients with newly diagnosed HRMM, the addition of daratumumab to backbone regimens was associated with improved PFS (pooled HR, 0.67; 95% CI, 0.47-0.95; $P = .02$), with little evidence of heterogeneity (Cochran Q, $P = .77$; $I^2 = 0\%$). Similar results were seen among patients with relapsed or refractory HRMM (pooled HR, 0.45; 95% CI, 0.30-0.67; $P < .001$), again with little evidence of heterogeneity (Cochran Q, $P = .63$; $I^2 = 0\%$).

CONCLUSIONS AND RELEVANCE This study suggests that incorporating daratumumab to backbone regimens may be associated with improved PFS among patients with newly diagnosed HRMM or relapsed or refractory HRMM.

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Multiple myeloma (MM) has great variability in clinical presentation and biological characteristics. Several features are associated with worse outcomes, including high β2-microglobulin levels,[1] high lactate dehydrogenase levels,[2] gene expression profile,[3] and recurrent cytogenetic abnormalities.[4-6] For instance, the presence of t(4;14), t(14;16), or del(17p) is uniformly accepted as a marker of worse prognosis[4-6] and is incorporated in the Revised International Staging System for MM.[2]

Although the biological heterogeneity of MM has long been recognized, clinical trials are rarely performed to study the effect of a new agent or intervention in patients with a specific biological subset of MM. Instead, trials are designed with eligibility dictated by prior therapies for relapsed or refractory MM or, in the case of newly diagnosed MM, by age and suitability for high-dose therapy and autologous hematopoietic cell transplantation.[7]

Daratumumab is a human immunoglobulin Gκ monoclonal antibody that targets CD38, which is present ubiquitously on the surface of MM cells and normal plasma cells. Daratumumab has reasonable single-agent activity among patients with MM[8] and has been combined successfully with several backbone MM regimens both in newly diagnosed[9-13] and in relapsed or refractory disease.[14-18] However, a subset analysis of patients with cytogenetically defined high-risk MM (HRMM) did not show improvement of progression-free survival (PFS) in 4 studies,[11-13,16] whereas 2 studies[18,19] showed improved PFS in this subgroup of patients. As a result, there is reasonable concern that daratumumab may not improve outcomes among patients with HRMM, particularly in the context of newly diagnosed disease.

Given the additional toxic effects and costs associated with daratumumab, we sought to clarify its role among patients with HRMM. We performed a systematic review and meta-analysis of randomized clinical trials to evaluate the association of daratumumab treatment with progression-free survival among patients with newly diagnosed HRMM or relapsed or refractory HRMM.

Methods

This systematic review and meta-analysis was performed in accordance with a previously published protocol (CRD42020165055). This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[20]

Search Strategy and Selection Criteria

The search strategy was designed and conducted by a medical librarian (A.G.) with input from study investigators using the following databases: Ovid MEDLINE, Ovid Embase, PubMed, Scopus, Web of Science Core Collection, and the Cochrane Library from inception of each database to January 2, 2020. We used a combination of controlled vocabulary (MeSH [Medical Subject Headings] and Emtree terms) and key words with various synonyms that reflect the following concepts: "multiple myeloma OR plasmacytoma" combined

Key Points

Question Is there a benefit associated with adding daratumumab to backbone myeloma treatment regimens among patients with cytogenetically defined high-risk multiple myeloma (HRMM)?

Findings This systematic review and meta-analysis identified 6 clinical trials involving 4061 patients, of which 580 had HRMM. The addition of daratumumab to backbone multiple myeloma regimens was associated with significantly improved progression-free survival among patients with newly diagnosed HRMM or relapsed or refractory HRMM.

Meaning The findings suggest that addition of daratumumab to established myeloma regimens may be associated with improved outcomes among patients with HRMM.

with "daratumumab OR Darzalex OR HuMax CD38." Our search result was limited to English-language studies. No filters or hedges for publication type were used. The search strategy was peer reviewed by a second librarian using Peer Review for Electronic Search Strategies (PRESS).[21] In addition, we performed a search of the gray literature through manual hand search of (1) bibliographies of identified randomized clinical trials, (2) trial registries (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform search portal, controlled-trials.com, and the National Institutes of Health database of funded studies for ongoing or unpublished trials), and (3) conference proceedings and abstracts of the American Society of Hematology, American Society of Clinical Oncology, European Hematology Association, and European Society for Medical Oncology from 2016 to 2019. Details of the search strategy are provided in the eMethods in the Supplement.

Citations from all databases were imported into an EndNote X9 database (Clarivate Analytics). After removing duplicates in EndNote, the remaining set of articles was imported into Covidence, a screening and data extraction tool.[22] Two independent screeners performed title and abstract review (S.G. and P.K.), and a third screener (L.J.C.) resolved ties. Overall, there was excellent agreement between the 2 screeners, with a Cohen κ statistic of 0.85.

Selection Criteria

After preliminary screening, the full text of potentially eligible studies was reviewed independently by 2 of us (S.G. and P.K.) to confirm final eligibility for qualitative and quantitative synthesis using the following selection criteria: (1) all phase 3 randomized clinical trials comparing the effectiveness of 2 or more systemic treatment regimens (comparator may include placebo) for the treatment of patients with newly diagnosed or relapsed or refractory MM; (2) phase 3 trials comparing backbone MM regimens with the same regimen plus daratumumab, such that the comparative effectiveness between the 2 groups was primarily caused by the addition of daratumumab, and (3) phase 3 studies reporting comparative effectiveness data stratified by cytogenetic risk status in the primary or subgroup analysis. Cytogenetically defined HRMM was defined as the presence of t(4;14), t(14;16), or del(17p)

irrespective of the method used in the study and the proportion of cells exhibiting the cytogenetic abnormality.

Data Extraction

Data extracted included study characteristics (first author, year of publication, journal, country of origin, study design, sample size, treatment regimens, and duration of follow-up), baseline characteristics of the participants (age, sex, race/ethnicity, and distribution by stage and performance status), and outcome data (effectiveness data). Quality assessment was done using the Cochran risk of bias assessment tool.[23]

Definition of Outcomes

The primary outcome was PFS, defined as the time from randomization to the date of first confirmed progression or date of death, whichever occurred earlier. We quantified associations in terms of hazard ratios (HRs) and 95% CIs. If multiple publications were available from the same study, the publication with the longest available follow-up results was used to extract the summary effect.

Statistical Analysis

We conducted statistical analyses according to the prepublished protocol. After extracting the PFS HRs and 95% CI for each cytogenetic subgroup (HRMM vs standard-risk MM [SRMM]), we pooled relative log-HRs using a DerSimonian-Laird random-effects model. We chose to pool effect size using a random effects model a priori because we anticipated that eligible studies would involve varying backbone regimens. We conducted separate analyses for cytogenetic SRMM vs HRMM and for newly diagnosed and relapsed or refractory disease. Given the small number of studies included in this analysis and concerns for imprecision or biased estimates using the DerSimonian-Laird estimator,[24,25] we conducted a sensitivity analysis using alternative approaches to random-effects modeling including the Knapp-Hartung method and small sample profile likelihood estimator, as suggested by Cornell et al,[24] and a robust inverse variance heterogeneity model, as suggested by Doi et al.[25] We assessed study-level heterogeneity using the Cochran Q and the I^2 statistic and planned to explore evidence of any substantial heterogeneity with appropriate sensitivity and subgroup analyses. We evaluated for the presence of publication bias using funnel plots and the Egger regression intercept. Statistical analyses were performed using the *admetan* package on Stata, version 13.0 (StataCorp LLC) and Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration). All *P* values were 2 sided, and results were deemed statistically significant at *P* < .05.

Results

The bibliographic search resulted in 5193 citations; 1 additional conference abstract was found through hand searching.[26] After removing duplicates, 3057 articles were screened in the title and abstract review. Of these, 78 articles met the criteria and were reviewed in full text, of which 6 randomized phase 3 clinical trials including 4061 patients were selected for quali-

Figure 1. PRISMA Flow Diagram
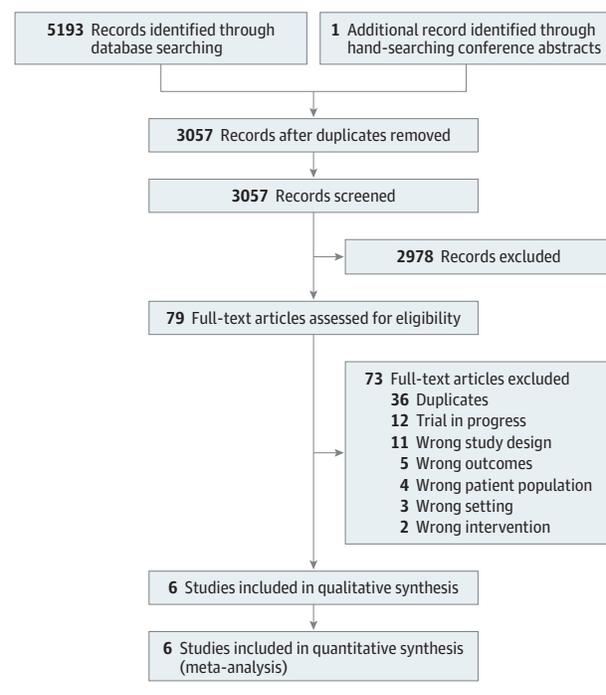
tative and quantitative analysis (**Figure 1** and eTable 2 in the Supplement). This included 3 trials of patients with newly diagnosed MM (ALCYONE,[11] MAIA,[10] and CASSIOPEIA[12]) (2528 patients; 358 with HRMM) and 3 trials of patients with relapsed or refractory MM (CASTOR,[14] POLLUX,[15] and CANDOR[16]) (1533 patients; 222 with HRMM). The proportion of patients with HRMM in these trials ranged from 15% to 33%. The overall summary characteristics of these 6 studies are shown in eTable 1 in the Supplement.

Definitions of High-risk MM

The methods for the assessment of HRMM varied across the included trials. The CASSIOPEIA trial[12] defined HRMM as either the presence of del(17p) (≥50% abnormal cells) or t(4;14) (≥30% abnormal cells) using fluorescence in situ hybridization (FISH), which was confirmed by centralized analysis. Patients for whom cytogenetic testing failed (ie, the test did not provide a result) were considered to have SRMM. The ALCYONE[11] and MAIA[10] studies similarly defined HRMM by the finding of t(4;14), t(14;16), or del(17p) on results of FISH or karyotype testing irrespective of the proportion of abnormal cells, but no centralized confirmation was mandated in the protocol. The CASTOR[14] and POLLUX[15] studies defined HRMM based on the presence of 1 or more of t(4;14), t(14;16), or del(17p) (using a >50% deletion cutoff) using next-generation sequencing conducted in a centralized laboratory. These analyses were done during the screening period for the study at the time of disease relapse and additionally involved FISH or karyotype testing at the local laboratory. The details of HRMM testing in the CANDOR study[16] were not available. Although all trials included a preplanned subgroup analysis based on cytogenetic

Figure 2. Outcomes Associated With the Addition of Daratumumab to Backbone Multiple Myeloma Regimens for Patients With High-risk Multiple Myeloma

Source	Log (hazard ratio)	SE	Daratumumab total	Control total	Hazard ratio (95% CI) IV, random	Favors daratumumab / Favors control	Weight, %
Newly diagnosed high-risk multiple myeloma							
ALCYONE,[11] 2018	-0.2485	0.3038	53	45	0.78 (0.43-1.42)		35.0
CASSIOPEIA,[12] 2019	-0.4005	0.3313	82	86	0.67 (0.35-1.28)		29.4
MAIA,[13] 2019	-0.5621	0.301	48	44	0.57 (0.32-1.03)		35.6
Subtotal			183	175	0.67 (0.47-0.95)		100
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.54$; $P = .76$; $I^2 = 0\%$							
Overall effect: $z = 2.25$; $P = .02$							
Relapsed or refractory high-risk multiple myeloma							
CANDOR,[16] 2019	-0.5447	0.3364	48	26	0.58 (0.30-1.12)		35.6
CASTOR,[19] 2019	-0.8916	0.3414	41	37	0.41 (0.21-0.80)		34.6
POLLUX,[18] 2019	-0.9943	0.3676	35	35	0.37 (0.18-0.76)		29.8
Subtotal			124	98	0.45 (0.30-0.67)		100
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.93$; $P = .63$; $I^2 = 0\%$							
Overall effect: $z = 3.98$; $P < .001$							

Hazard ratio (95% CI) IV, random (scale 0.1 – 1 – 10)

Significant improvement in progression-free survival was seen among patients with first-line and relapsed or refractory disease. Squares represent mean values, with the size of the squares representing the weight, and horizontal lines represent 95% CIs. Diamonds are pooled means with the points representing 95% CIs. IV indicates inverse variance.

group, the latter was used as a stratification variable during randomization only in the CASSIOPEIA study[12]; the distribution of patients with high-risk disease was well balanced between the 2 groups in all the other trials.

Risk of Bias
Five of 6 studies had a low risk for bias in random sequence generation (selection bias, 83%) and allocation concealment (selection bias, 83%). For the CANDOR study,[16] the risk of bias could not be evaluated owing to the availability of limited published data in abstract form only.[16] All included studies were open-label studies and none reported blinding of outcome assessment, potentially indicating the presence of detection bias, although 3 studies (MAIA,[10] CASTOR,[14] and POLLUX[15]) reported using a validated computer algorithm to evaluate treatment response and progression. All included studies had a low risk for bias of incomplete outcome data (attrition bias) or selective reporting (reporting bias) (eFigure in the Supplement). All studies reported survival analysis using intention-to-treat analysis and response rates and toxic effect results with per-protocol analysis.

Meta-analysis for the Association of Daratumumab With PFS in HRMM
Among the 3 trials studying the addition of daratumumab to backbone regimens among patients with newly diagnosed HRMM, the HRs for PFS using the most recent follow-up data were 0.57 (95% CI, 0.32-1.04) in the MAIA study,[13] 0.78 (95% CI, 0.43-1.43) in the ALCYONE study,[11] and 0.67 (95% CI, 0.35-1.30) in the CASSIOPEIA study[12]; none of the findings were statistically significant. Among patients with relapsed or refractory MM, analysis of the most recent data from both the CASTOR[19] (HR, 0.41; 95% CI, 0.21-0.83) and POLLUX[18] studies (HR, 0.37; 95% CI, 0.18-0.76) showed that PFS was associ-

ated with the addition of daratumumab. In the CANDOR study,[16] the association of daratumumab with PFS did not reach statistical significance (HR, 0.58; 95% CI, 0.3-1.12).

In our meta-analysis, the addition of daratumumab to first-line backbone regimens among patients with HRMM was associated with improved PFS (pooled HR, 0.67; 95% CI, 0.47-0.95; $P = .02$), with little heterogeneity (Cochran Q, $P = .76$; $I^2 = 0\%$). Consistent results were obtained by using alternative models for pooling effect sizes, including the Knapp-Hartung method (pooled HR, 0.67; 95% CI, 0.45-0.99; $P = .04$), the partial likelihood method (pooled HR, 0.67; 95% CI, 0.46-0.97; $P = .04$), and the inverse variance heterogeneity model (pooled HR, 0.67; 95% CI, 0.47-0.95; $P = .03$).

Similar results were seen for relapsed or refractory disease, again with no significant heterogeneity (pooled HR, 0.45; 95% CI, 0.30-0.67; $P < .001$; Cochran Q, $P = .63$; $I^2 = 0\%$). (Figure 2). Similar results were obtained using alternative pooling methods.

Meta-analysis for the Association of Daratumumab With PFS in SRMM
Among patients with newly diagnosed SRMM, all 3 trials showed significant improvement in PFS in the daratumumab-containing groups (ALCYONE: HR, 0.39 [95% CI, 0.28-0.55][11]; MAIA: HR, 0.50 [95% CI, 0.38-0.65][13]; and CASSIOPEIA: HR, 0.41 [95% CI, 0.26-0.62][12]). Similar results were seen among patients with relapsed or refractory SRMM, with significant PFS benefit in the daratumumab group reported in the CASTOR (HR, 0.26; 95% CI, 0.18-0.36),[19] POLLUX (HR, 0.42; 95% CI, 0.32-0.56),[18] and CANDOR (HR, 0.55; 95% CI, 0.31-0.97) studies.[16]

In the meta-analysis, the addition of daratumumab to backbone regimens in newly diagnosed MM among patients with SRMM was associated with improved PFS (pooled HR, 0.45;

Figure 3. Outcomes Associated With the Addition of Daratumumab to Backbone Multiple Myeloma Regimens for Patients With Standard-Risk Multiple Myeloma

Source	Log (hazard ratio)	SE	Daratumumab total	Control total	Hazard ratio (95% CI) IV, random	Favors daratumumab / Favors control	Weight, %
Newly diagnosed standard-risk multiple myeloma							
ALCYONE,[11] 2018	-0.9416	0.1691	261	257	0.39 (0.28-0.54)		32.8
CASSIOPEIA,[12] 2019	-0.8916	0.2324	460	454	0.41 (0.26-0.65)		17.4
MAIA,[13] 2019	-0.6931	0.1373	271	279	0.50 (0.38-0.65)		49.8
Subtotal			992	990	0.45 (0.37-0.54)		100
Heterogeneity: $\tau^2 = 0.00$; $\chi_2^2 = 1.45$; $P = .48$; $I^2 = 0\%$							
Overall effect: $z = 8.35$; $P < .001$							
Relapsed or refractory standard-risk multiple myeloma							
CANDOR,[16] 2019	-0.5978	0.2925	104	52	0.55 (0.31-0.98)		24.4
CASTOR,[19] 2019	-1.3471	0.1876	140	137	0.26 (0.18-0.38)		35.0
POLLUX,[18] 2019	-0.8675	0.1387	193	176	0.42 (0.32-0.55)		40.6
Subtotal			437	365	0.38 (0.26-0.56)		100
Heterogeneity: $\tau^2 = 0.08$; $\chi_2^2 = 6.19$; $P = .05$; $I^2 = 68\%$							
Overall effect: $z = 4.83$; $P < .001$							

Hazard ratio (95% CI) IV, random — axis: 0.1, 1, 10

Significant improvement in progression-free survival was seen among patients with first-line and relapsed or refractory disease. Squares represent mean values, with the size of the squares representing the weight, and horizonal lines represent 95% CIs. Diamonds are pooled means with the points representing 95% CIs. IV indicates inverse variance.

95% CI, 0.37-0.54; $P < .001$), with little evidence of heterogeneity (Cochran Q, $P = .48$; $I^2 = 0\%$). Similar results were seen for relapsed or refractory disease (pooled HR, 0.38; 95% CI, 0.26-0.56; $P < .001$) albeit there was some evidence of heterogeneity (Cochran Q, $P = .05$; $I^2 = 68\%$) (**Figure 3**). Similar results were obtained using alternative pooling methods.

Overall Survival

Among the included studies, mature overall survival data stratified by cytogenetic group were only available for the ALCYONE study,[9] with less-pronounced benefits associated with daratumumab among patients with HRMM (HR, 0.91; 95% CI, 0.50-1.65) than in patients with SRMM (HR, 0.49; 95% CI, 0.35-0.69). Therefore, we were unable to report pooled overall survival data.

Discussion

The findings from this systematic review and meta-analysis suggest that incorporating daratumumab into backbone myeloma regimens is associated with significantly improved PFS for patients with newly diagnosed HRMM or relapsed or refractory HRMM. Furthermore, the benefit appears to be consistent irrespective of the backbone anti-myeloma regimen. These findings are of direct clinical relevance and may help clinicians choose an optimal anti-myeloma regimen for patients with high-risk cytogenetic factors.

The presence of t(4;14), t(14;16), or del(17p) is associated with double the risk of death in patients with newly diagnosed MM.[2] These patients are less likely to achieve deep responses to therapy[27-30] and are at increased risk for early progression, even with autologous hematopoietic cell transplantation.[31] Therefore, this subset of patients has greater

need for novel treatments and improvements in outcomes.[32] Daratumumab is changing the management of MM. Several phase 3 trials have shown that adding daratumumab to a proteasome inhibitor, immunomodulatory agent, or proteasome inhibitor plus immunomodulatory agent backbone regimen improves the rate and depth of responses and PFS.[12,14,16,18] More recently, daratumumab has also been shown to improve overall survival in non–transplant-eligible patients with newly diagnosed MM based on updated results of the ALCYONE trial.[9]

The benefit (or lack thereof) of a given MM agent is modulated by many patient and disease characteristics, including cytogenetic risk. It is therefore important to examine the performance of a new drug across cytogenetic subsets. Among patients with relapsed or refractory disease, the most recent follow-up of the CASTOR trial showed improved PFS with the addition of daratumumab to bortezomib plus dexamethasone for HRMM (HR, 0.41; 95% CI, 0.21-0.83) and SRMM (HR, 0.26; 95% CI, 0.18-0.36).[19] Similar findings were seen in the POLLUX trial, in which the HR for PFS among patients with HRMM was 0.37 (95% CI, 0.18-0.76) and among those with SRMM was 0.42 (95% CI, 0.32-0.56)[18] when daratumumab was added to lenalidomide plus dexamethasone. More recently, the CANDOR trial compared daratumumab plus carfilzomib and dexamethasone vs carfilzomib and dexamethasone.[16] The addition of daratumumab led to improved PFS for patients with SRMM (HR, 0.55; 95% CI, 0.31-0.97); however, no significant improvement was noted among patients with HRMM (HR, 0.58; 95% CI, 0.30-1.12).

In contrast to the above studies, all 3 randomized clinical trials of daratumumab for newly diagnosed MM (ALCYONE,[9] MAIA,[13] and CASSIOPEIA[12]) showed improvement in PFS among patients with SRMM, but the benefit for HRMM was not statistically significant. It is possible that the benefit of daratumumab for HRMM was not identified in those trials owing

to relatively small sample sizes. Patients with HRMM constituted only 15.9% of patients in the ALCYONE trial, 14.3% of patients in the MAIA trial, and 15.5% of patients in the CASSIOPEIA trial. Another possibility is that the effect of daratumumab on HRMM compared with SRMM was a smaller and nonsignificant. Although it appears contradictory that daratumumab would benefit patients with HRMM in the context of relapsed disease but not in the context of newly diagnosed disease, these are distinct populations. Patients with more aggressive high-risk disease may not be candidates for subsequent lines of therapy owing to early mortality and high attrition rates.[33,34]

The current meta-analysis combined multiple studies with similar design to increase the power to answer a scientifically and clinically relevant question. The method used to select studies for the meta-analysis ensured a consistent design in which the only difference between the control and experimental groups was the use of daratumumab. The findings suggest that daratumumab is associated with improved PFS among patients with newly diagnosed HRMM and SRMM. This finding was not weakened by the 3 trials entering the analysis having different backbone MM regimens and different age groups, as supported by the lack of significant heterogeneity in effect size.

Limitations

This study has limitations. There may have been imbalances in patient characteristics between the groups, potentially affecting the study outcome. This imbalance was minimized by all trials having been randomized and including stratification for other variables (such as disease stage) that affect risk of progression or death. Our analysis did not address the benefit associated with daratumumab in other subsets recognized as high risk, such as patients with extramedullary disease, high lactate dehydrogenase levels at diagnosis, stage 3 disease, and inferior performance status at enrollment. It also did not appraise the association of daratumumab with PFS among patients with a specific high-risk cytogenetic abnormality, such as del(17p). Different studies had varying cutoffs to identify high-risk chromosome abnormalities on FISH. In addition, there was no information about P53 mutation paired with del (17p). We did not have data stratified by cytogenetic group on

additional end points, including response rate, time to second objective disease progression, and overall survival. Some of these limitations could be overcome with an individual patient data meta-analysis, but some of these subsets may have too few participants to reach a satisfactory answer.

Although the HR was numerically lower for SRMM compared with HRMM in the context of both newly diagnosed and relapsed or refractory disease, such comparison could not be formally done and has limited clinical utility because the therapy given to a patient can be modulated but the biological characteristics of the disease cannot be modulated. However, no prior MM agent has been shown to have an association with PFS in patients with newly diagnosed HRMM. Few other agents, namely carfilzomib,[27,28] pomalidomide[26] and ixazomib,[30] have been associated with PFS among patients with relapsed or refractory HRMM, often with less impact than seen among patients with SRMM. This meta-analysis also did not find that daratumumab completely abrogated the prognostic impact of t(4;14), t(14;16), or del(17p), a high accomplishment that has not been reached by any MM agent to date.

The present analysis provided evidence that, when combined with backbone proteasome inhibitor and immunomodulatory agent–based regimens, daratumumab was associated with improved PFS among patients with HRMM and SRMM in the context of newly diagnosed and relapsed or refractory disease. However, it did not provide a comparison between daratumumab-based and non–daratumumab-based regimens. The identification of the best regimen and therapeutic strategy for patients with HRMM may be achieved by network meta-analysis, preferentially using individual patient data and by future well-designed randomized clinical trials.

Conclusions

The present study suggests that daratumumab-based regimens are associated with improved PFS among patients with HRMM and SRMM in the context of newly diagnosed and relapsed or refractory disease. Furthermore, lack of substantial heterogeneity suggests that the associated benefit is seen regardless of the underlying backbone myeloma regimen.

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