Rates of Influenza and Pneumococcal Vaccination and Correlation With Survival in Multiple Myeloma Patients

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Abstract

We analyzed vaccination rates and associated outcomes of patients with multiple myelom in the INSIGHT MM study. Influenza vaccination in the prior 2 years and pneumococcal vaccination in the prior 5 years impacted overall survival versus no vaccination. Additionally, deaths due to infections were lower among vaccinated versus non-vaccinated patients. Vaccination status should be recorded in prospective clinical trials as it may affect survival.

Background: Infections are a common reason for hospitalization and death in multiple myeloma (MM). Although pneumococcal vaccination (PV) and influenza vaccination (FV) are recommended for MM patients, data on vaccination status and outcomes are limited in MM. **Materials and Methods:** We utilized data from the global, prospective, observational INSIGHT MM study to analyze FV and PV rates and associated outcomes of patients with MM enrolled 2016-2019. **Results:** Of the 4307 patients enrolled, 2543 and 2500 had study-entry data on FV and PV status. Overall

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vaccination rates were low (FV 39.6%, PV 30.2%) and varied by region. On separate multivariable analyses of overall survival (OS) by Cox model, FV in the prior 2 years and PV in the prior 5 years impacted OS (vs. no vaccination; FV: HR, 0.73; 95% CI, 0.60-0.90; $P = .003$; PV: HR, 0.51; 95% CI, 0.42-0.63; $P < .0001$) when adjusted for age, region, performance status, disease stage, cytogenetics at diagnosis, MM symptoms, disease status, time since diagnosis, and prior transplant. Proportions of deaths due to infections were lower among vaccinated versus non-vaccinated patients (FV: 9.8% vs. 15.3%, $P = .142$; PV: 9.9% vs. 18.0%, $P = .032$). Patients with FV had generally lower health resource utilization (HRU) versus patients without FV; patients with PV had higher or similar HRU versus patients without PV. **Conclusion:** Vaccination is important in MM and should be encouraged. Vaccination status should be recorded in prospective clinical trials as it may affect survival. This trial was registered at www.clinicaltrials.gov as #NCT02761187.

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Introduction

Multiple myeloma (MM) affects plasma cells, a cell population within the immune system. Immunity in patients with MM is impaired due to a combination of disease-, patient-, and treatment-related factors, including age and B-cell dysfunction (leading to hypogammaglobulinemia).[1,2] Therefore, patients with MM tend to be more susceptible to vaccine-preventable infections, including influenza and *Streptococcus pneumoniae*.[3-8] Infections are a significant cause of morbidity and deaths in patients with MM,[9,10] and infection rates are increasing in this population[10] due to, among other factors, the rise in life expectancy, particularly among those aged ≥ 65 years at diagnosis.[11]

Increased median overall survival (OS) in MM has been associated with the use of high-dose melphalan followed by autologous stem cell transplant (SCT) along with the introduction of novel agents including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. Additional agents with differing mechanisms of action, such as BCL2 inhibition (venetoclax), nuclear export inhibition (selinexor), and immuno-oncology approaches (bispecific T-cell engaging antibodies, CAR T-cell therapies, antibody-drug conjugates) are also under investigation or recently approved. These therapies are associated with toxicities that increase immunosuppression and susceptibility to infection, a particularly important issue in the modern era of continuous therapy in which patients may receive prolonged treatment with novel anti-myeloma agents.[12,13]

Understanding the importance of infections in the context of the treatment-emergent/drug-related adverse event (AE) profile – and their prevention – is critical, given they can lead to increased death rates. In the phase 3 BELLINI study, treatment with venetoclax plus bortezomib-dexamethasone resulted in 8 (4%) treatment-emergent fatal infections, prompting the implementation of antibiotic prophylaxis in ongoing studies of venetoclax plus a proteasome inhibitor, as well as exclusion of patients without t(11;14), in whom the largest imbalance in mortality was observed.[14] Similarly, in the phase 3 MAIA and ALCYONE studies, high rates of grade 3 of 4 and serious infections with daratumumab-based combinations versus standard-of-care regimens led to the development of a predictive model to identify patients most at risk of infection during treatment with daratumumab.[15]

Vaccination against *S. pneumoniae* (13-valent pneumococcal conjugate vaccine) and the influenza virus (inactivated trivalent influenza vaccine) is feasible in patients with MM;[16-21] these prophylactic vaccinations are among those recommended by the European Myeloma Network.[22,23] However, the effectiveness of these vaccines is poorly characterized in MM, especially when administered concomitantly with anti-MM therapies.[24,25] Data on the vaccination status of patients with MM are also limited. A US retrospective study[25] and analysis of data collected via a patient self-report online portal[26] showed that vaccination in US patients with MM is not administered consistently. A retrospective cohort study using data from the French national health insurance database revealed a similar trend in France.[27]

To our knowledge, no previous studies have looked at vaccination rates and associated outcomes in patients with MM at a global level. We analyzed data on influenza and pneumococcal vaccination status and associated clinical outcomes in patients with MM enrolled in the global, prospective, observational INSIGHT MM study (NCT02761187). We assessed vaccination rates, the association between vaccination status and OS and deaths due to infections, healthcare resource utilization (HRU) including outpatient clinic visits, hospitalizations, emergency room (ER) visits, intensive care unit (ICU) admissions, and hospitalizations/ER visits/ICU admissions due to infections.

Patients and Methods

Trial Design and Oversight

The primary objective of the INSIGHT MM study (NCT02761187)[28] is to describe real-world patterns of MM patient and disease characteristics at diagnosis and relapse, treatment patterns, and clinical outcomes including effectiveness and tolerability. Other objectives include assessment of quality of life and HRU.[28] The study has enrolled 4307 adult patients with MM from 15 countries worldwide, across 4 regions (Europe, the US, Latin America, and Asia); patients are being followed prospectively for ≥ 2 years.[28,29] The full list of countries and previously reported study design[28] are summarized in the Supplemental Additional Methodology. INSIGHT MM is being conducted in accordance with the Declaration of Helsinki, European Network of Centers for Pharmacoepidemiology and Pharmacovigilance Guidelines, Good

Pharmacoepidemiology Practice guidelines, European directives on protection of human patients in research, and local relevant guidelines, laws, or regulations. Local or central independent review boards or independent ethics committees at each site approved the research and the protocol. All patients provided written informed consent. All authors had access to the data; M.A.T., R.H.F., K.R., D.M.S., and A.C. analyzed the data.

Eligibility

Adult patients with newly diagnosed MM (NDMM) who were within 3 months of treatment initiation, and patients with relapsed/refractory MM (RRMM) who had received 1-3 prior lines of therapy, were eligible for enrollment.[28] See the Supplemental Additional Methodology for additional, previously reported[28] eligibility criteria. Patients for whom data on FV and PV status were available (FV status in the 2 years and PV status in the 5 years prior to study discontinuation, death, or data cutoff), and who were enrolled between July 2016 and July 2019, were included in the analysis.

Endpoints, Assessments, and Analyses

Retrospective data on prior vaccinations received before enrollment were collected at study entry with prospective follow-up data on vaccination status collected yearly for all NDMM and RRMM patients during participation in INSIGHT MM. Prospective HRU data are collected quarterly.[28] For patients with vaccination status information available, we extracted and analyzed individual patient-level data on FV and PV status, demographics, baseline disease characteristics, HRU, deaths due to infections, and OS. HRU during study was evaluated through assessment of outpatient visits, hospitalizations, ER visits, ICU admissions, length of stay, and events due to infections.

Statistical Analysis

All data were summarized descriptively for all patients with vaccination data available, by FV and PV status. Baseline (study entry) vaccination rates were determined in all patients with data on FV receipt in the 1 year prior to study entry and in all patients with data on PV receipt in the 5 years prior to entry; these rates were also summarized by region and by year of enrollment. Vaccination rates were calculated based on patients who provided any answers to vaccinations questions at enrollment.

For OS analyses, deaths due to infections, and HRU, patients were analyzed in subgroups according to known FV status in the past 2 years and known PV status in the past 5 years prior to study discontinuation, death, or data cutoff; demographics and disease characteristics (at diagnosis or study entry) were similarly analyzed in these subgroups. Deaths due to infections included deaths due to influenza or pneumonia, pneumonia only, or other infections. OS was defined as time from study entry to death from any cause or last follow-up and was estimated using Kaplan–Meier methodology. Data cutoff for this analysis was July 28, 2020. Univariable and multivariable analyses of OS incorporating FV or PV status (assessed in the past 2 and 5 years, respectively) were conducted; analyses were performed using Cox proportional hazards modeling to evaluate the association of FV/PV status, as well as demographics and disease characteristics, with OS. The following parameters were included: region, age, Eastern Cooperative Oncology Group performance status (ECOG PS) score, International Staging System (ISS) disease stage, cytogenetic abnormalities at diagnosis, CRAB criteria (calcium level, renal function per creatinine clearance, anemia [hemoglobin level], and destructive bone lesions), disease status (NDMM, RRMM), time since diagnosis, and receipt of prior SCT. Separate univariable and multivariable analyses of OS were performed for Europe and the US, but not for Asia or Latin America due to the small numbers of patients in these regions. For HRU data analyses, exposure-adjusted event rates (EAERs) were calculated as total number of events divided by total risk exposure in years and multiplied by 100. Analyses were conducted using SAS version 9.4.

Data-sharing Statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be available 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Results

FV and PV Rates

Data on FV status in the 1 year prior to, and PV status in the 5 years prior to study entry were available for 2543 and 2500 patients, respectively; most patients were from Europe and the US (Figure 1). Overall vaccination rates were low: 39.6% (n = 1007) of patients had received FV in the past 1 year and 30.2% (n = 754) had received PV in the past 5 years (Figure 1). Vaccination rates were generally stable throughout the enrollment period and varied by region, with the highest rates reported in the US (FV: 55.8% [n = 510]; PV: 42.83% [n = 375]) and the lowest in Asia (FV: 4.3% [n = 12]; PV: 4.7% [n = 13]) (Figure 1).

Patient Demographics and Baseline Disease Characteristics

Patient demographics and disease characteristics at diagnosis or study entry by FV status in the 2 years prior to and PV status in the 5 years prior to study discontinuation, death, or data cutoff are reported in Table 1; data for patients enrolled in Europe and in the US are reported in the Supplemental Additional Results and Supplemental Tables 1 and 2. Overall, median age at study entry was 67 versus 66 years for patients who had versus had not received FV, with 19.2% versus 16.9% aged > 75 years. Most patients were white/Caucasian; the percentage of white/Caucasian patients was higher in the subgroup who had (82.9%) versus had not (64.3%) received FV. Conversely, the majority of Asian patients had not received FV and constituted a larger proportion of this subgroup (22.2%) than the subgroup that had received FV (2.1%). Median time on study for all patients was 22 months.

Among patients who had versus had not received FV, 48.7% versus 52.7% of patients had NDMM, and median time since diagnosis was 1.1 versus 0.8 years; 30.7% versus 20.4% of all FV patients had received a prior SCT. In the FV versus no FV groups,

Figure 1 Percentage of patients who received FV in the year prior and PV in the 5 years prior to study entry (overall, by region and by year of enrollment in INSIGHT MM). Abbreviations: FV, influenza vaccination; PV, pneumococcal vaccination.

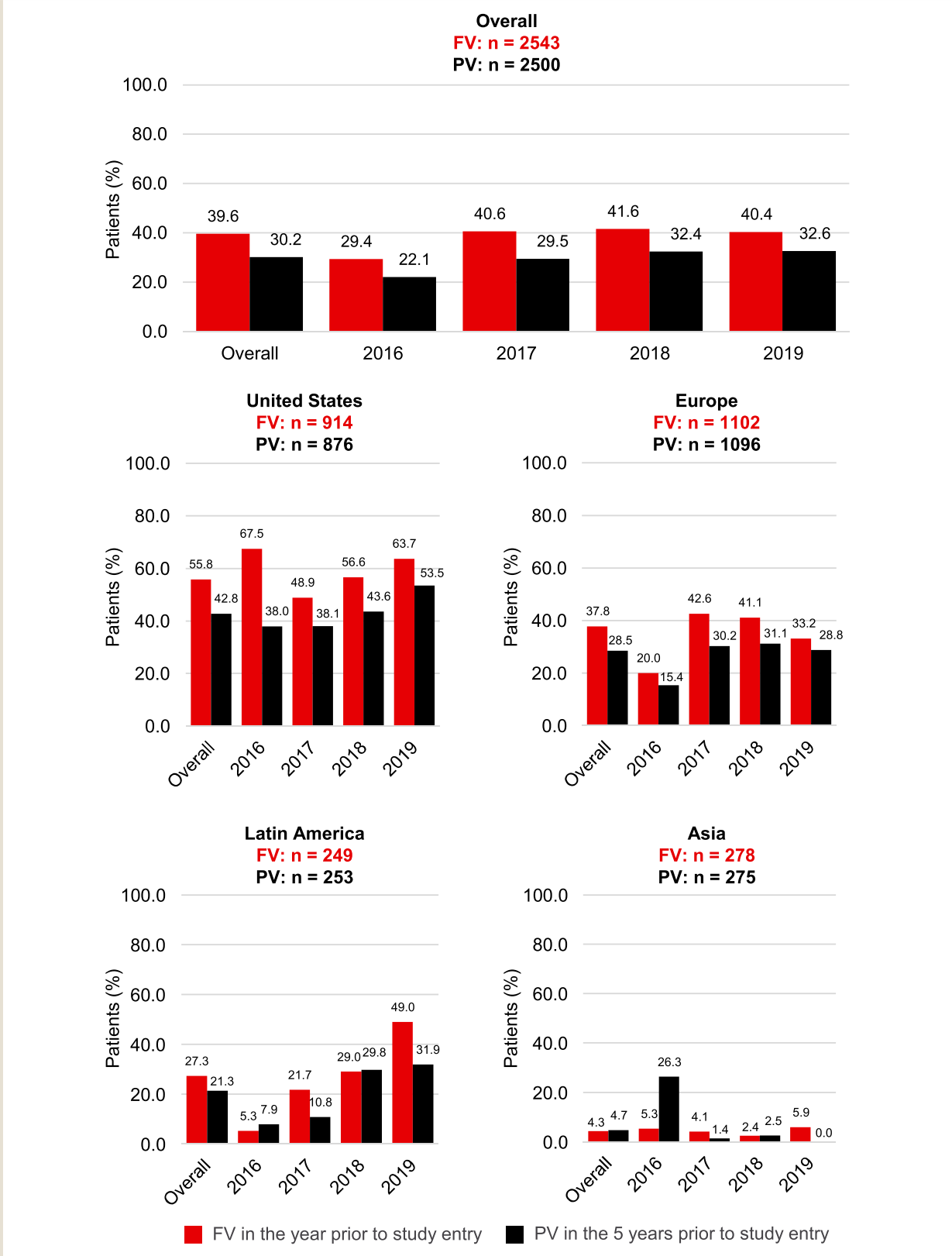

Table 1 Patient Demographics and Disease Characteristics by FV and PV Status Prior to and During the Study (see Supplemental Tables 1 and 2 for Patient Demographics and Baseline Disease Characteristics by Region)

Characteristic	FV[a] (N = 898)	No FV[a] (N = 902)	PV[b] (N = 956)	No PV[c] (N = 1192)
Age at study entry	n = 898	n = 901	n = 956	n = 1191
Median, years (range)	67 (27-96)	66 (33-95)	67 (27-95)	65 (33-96)
> 75 years, no. (%)	172 (19.2)	152 (16.9)	168 (17.6)	191 (16.0)
Male sex, no. (%)	528 (58.8)	521 (57.8)	552 (57.7)	684 (57.4)
Race, no. (%)	n = 794	n = 807	n = 850	n = 1040
White/Caucasian	658 (82.9)	519 (64.3)	702 (82.6)	638 (61.3)
Asian[d]	17 (2.1)	179 (22.2)	29 (3.4)	251 (24.1)
Black or African American	67 (8.4)	45 (5.6)	66 (7.8)	64 (6.2)
Other	41 (5.2)	55 (6.8)	39 (4.6)	81 (7.8)
Multiple	11 (1.4)	9 (1.1)	14 (1.6)	6 (0.6)
ISS disease stage at diagnosis, no. (%)	n = 618	n = 629	n = 628	n = 830
I	196 (31.7)	173 (27.5)	207 (33.0)	245 (29.5)
II	195 (31.6)	201 (32.0)	197 (31.4)	252 (30.4)
III	227 (36.7)	255 (40.5)	224 (35.7)	333 (40.1)
ECOG PS at diagnosis, no. (%)	n = 881	n = 895	n = 928	n = 1176
0	345 (39.2)	399 (44.6)	393 (42.3)	528 (44.9)
1-2	515 (58.5)	463 (51.7)	519 (55.9)	602 (51.2)
3-4	21 (2.4)	33 (3.7)	16 (1.7)	46 (3.9)
Cytogenetic features at diagnosis,[e] no. (%)	n = 620	n = 471	n = 612	n = 669
High-risk cytogenetic abnormalities	135 (21.8)	76 (16.1)	135 (22.1)	114 (17.0)
Standard-risk cytogenetic abnormalities	485 (78.2)	395 (83.9)	477 (77.9)	555 (83.0)
Bone lesions at diagnosis, no. (%)	n = 739	n = 746	n = 792	n = 970
0	231 (31.3)	244 (32.7)	238 (30.1)	314 (32.4)
1 to 3	174 (23.6)	177 (23.7)	194 (24.5)	237 (24.4)
> 3	236 (31.9)	244 (32.7)	264 (33.3)	301 (31.0)
Severe osteopenia and/or fractures	98 (13.3)	81 (10.9)	96 (12.1)	118 (12.2)
Calcium at diagnosis, no. (%)	n = 686	n = 669	n = 721	n = 895
> 11 mg/dL	76 (11.1)	83 (12.4)	79 (11.0)	123 (13.7)
≤ 11 mg/dL	610 (88.9)	586 (87.6)	642 (89.0)	772 (86.3)
Creatinine clearance at diagnosis, no. (%)	n = 687	n = 662	n = 730	n = 870
< 30 mL/min	81 (11.8)	88 (13.3)	74 (10.1)	135 (15.5)
30 to < 60 mL/min	167 (24.3)	168 (25.4)	181 (24.8)	199 (22.9)
≥ 60 mL/min	439 (63.9)	406 (61.3)	475 (65.1)	536 (61.6)
Hemoglobin at diagnosis, no. (%)	n = 768	n = 774	n = 810	n = 1021
≥ 12 (males) / 11 (females) g/dL	313 (40.8)	275 (35.5)	338 (41.7)	335 (32.8)
< 12 (males) / 11 (females) g/dL	455 (59.2)	499 (64.5)	472 (58.3)	686 (67.2)
Median time from diagnosis to study entry, years (IQR)	n = 896 1.1 (0.2-3.9)	n = 898 0.8 (0.1-3.4)	n = 954 1.5 (0.2-4.1)	n = 1186 0.6 (0.1-3.4)
Line of therapy at study entry, no. (%)	n = 859	n = 854	n = 917	n = 1100
1st	431 (50.2)	441 (51.6)	425 (46.3)	608 (55.3)
2nd	226 (26.3)	221 (25.9)	253 (27.6)	255 (23.2)
3rd	146 (17.0)	115 (13.5)	174 (19.0)	153 (13.9)
4th	46 (5.4)	67 (7.8)	57 (6.2)	73 (6.6)
> 4th	10 (1.2)	10 (1.2)	8 (0.9)	11 (1.0)
Disease status, no. (%)				
NDMM	437 (48.7)	475 (52.7)	441 (46.1)	651 (54.6)
RRMM	461 (51.3)	427 (47.3)	515 (53.9)	541 (45.4)
Prior SCT, no. (%)	276 (30.7)	184 (20.4)	320 (33.5)	219 (18.4)

Abbreviations: ECOG PS , eastern cooperative oncology group performance status; FV, influenza vaccination; IQR , interquartile range; ISS ,international staging system; NDMM , newly diagnosed multiple myeloma; PV , pneumococcal vaccination; RRMM , relapsed/refractory multiple myeloma; SCT , stem cell transplant.

[a] Patients received / did not receive FV in the 2 years prior to study discontinuation, death, or data cutoff.

[b] PV: patients received PV in the 5 years prior to study discontinuation, death, or data cutoff.

[c] No PV: patients did not receive PV in the 5 years prior to study discontinuation, death, or data cutoff.

[d] In the FV, no FV, PV, and no PV groups 8/17 (47.1%), 172/179 (96.1%), 14/29 (48.3%), and 242/251 (96.4%) Asian patients, respectively were enrolled in the region of Asia.

[e] High-risk cytogenetic abnormalities were detected by fluorescence *in situ* hybridization and were defined as chromosome 17p deletion (del[17p[), translocation between chromosomes 4 and 14 ([t(4;14]), and translocation between chromosomes 14 and 16 (t[14;16]). The standard-risk group comprised patients without these three abnormalities.

68.3% versus 72.5% of patients had ISS stage II or III disease, and 2.4% and 3.7%, respectively, had an ECOG PS score of 3-4; 11.1% versus 12.4% of patients had hypercalcemia, 36.1% versus 38.7% had renal impairment (creatinine clearance < 60 mL/min), and 59.2% versus 64.5% had anemia (Table 1).

Among patients who received PV in the 5 years prior to study discontinuation, death, or data cutoff versus those who did not, median age was 67 versus 65 years, and 17.6% versus 16.0% of patients were aged > 75 years. There was a higher percentage of white/Caucasian patients in the subgroup who had (82.6%) versus had not (61.3%) received PV, and a much lower percentage of Asian patients (3.4% vs. 24.1%). Among patients who had versus had not received PV, 46.1% versus 54.6% of patients had NDMM, and median time since diagnosis was 1.5 versus 0.6 years; 33.5% versus 18.4% of all PV patients had received a prior SCT. Among patients who had versus had not received PV, 67.0% versus 70.5% had ISS stage II or III disease, and 1.7% versus 3.9% had an ECOG PS score of 3-4; 11.0% versus 13.7% of patients had hypercalcemia, 34.9% versus 38.4% had renal impairment, and 58.3% versus 67.2% had anemia (Table 1).

Univariable and Multivariable Analysis of OS

Univariable and multivariable analyses of OS, by Cox proportional hazards model, were conducted for patients with vaccination status data available, to identify any associations between OS and vaccination status, age, region, ECOG PS, ISS stage, cytogenetics at diagnosis, CRAB criteria, disease status, time since diagnosis, and prior SCT. On univariable analysis of the overall population, having received 1 or 2 FV in the past 2 years or ≥ 1 PV in the past 5 years was associated with better OS (FV: HR, 0.67; 95% CI, 0.55-0.81; $P < .0001$; PV: HR, 0.50; 95% CI, 0.42-0.61; $P < .0001$) (Figure 2). When restricted to patients in Europe, FV (1 or 2 doses received in the past 2 years; HR, 0.52; 95% CI, 0.39-0.70; $P < .0001$) and PV (≥ 1 dose received in the past 5 years; HR, 0.45; 95% CI, 0.33-0.60; $P < .0001$) were both associated with improved OS (Supplemental Figure 1). In the US, having received 1 or 2 doses of FV in the past 2 years was not associated with OS (HR, 1.30; 95% CI, 0.92-1.84; $P = .143$), but having received ≥ 1 PV dose in the past 5 years was associated with improved OS (HR, 0.70; 95% CI, 0.50-0.97; $P = .034$) (Supplemental Figure 2). Overall data for age, region (other regions vs. US), ECOG PS (1-2 or 3-4 vs. 0), ISS stage (II or III vs. I), high-risk cytogenetics (vs. standard-risk), hypercalcemia, renal impairment, anemia, and RRMM (vs. NDMM) disease status showed that these factors were also associated with poorer OS on univariable analysis (Figure 2).

On multivariable analyses, both FV and PV status in the past 2 and 5 years, respectively, impacted OS when adjusted for the other parameters, overall (FV: HR, 0.73; 95% CI, 0.60-0.90; $P = .003$; PV: HR, 0.51; 95% CI, 0.42-0.63; $P < .0001$) and in Europe (FV: HR, 0.54; 95% CI, 0.39-0.74; $P = .0001$; PV: HR, 0.41; 95% CI, 0.30-0.56; $P < .0001$) (Figure 2 and Supplemental Figure 1). In the US, FV in the past 2 years was not associated with OS (HR, 1.26; 95% CI, 0.88-1.82; $P = .205$), but PV in the past 5 years was associated with improved OS (HR, 0.67; 95% CI, 0.48-0.95; $P = .026$) (Supplemental Figure 2).

Death Due to Infections

Among patients for whom vaccination status was known, proportions of patients who died due to infections (including influenza and pneumonia) were numerically lower among patients who had a FV in the past 2 years versus patients who had not (9.8% vs. 15.3%, $P = .142$) and significantly lower among patients who had a PV in the past 5 years versus patients who had not (9.9% vs. 18.0%, $P = .032$) (Table 2). Regionally, percentages of patients who died due to infections were 4.8% in the US, 12.4% in Europe, 20.6% in Latin America, and 25.4% in Asia ($P < .001$, comparison across all regions) among patients for whom FV status was known; and 5.7% in the US, 13.3% in Europe, 21.6% in Latin America, and 31.4% in Asia ($P < .001$, comparison across all regions) among patients for whom PV status was known (Supplemental Table 3).

Healthcare Resource Utilization

Patients who did not receive FV in the past 2 years had numerically higher EAERs for hospitalization (59.6 vs. 31.6), ER visits (40.6 vs. 29.2), and ICU admissions (4.8 vs. 1.9) compared with patients who received FV (Table 3). The proportion of ER visits due to pneumonia (8.3% vs. 7.8%) or other infections (9.0% vs. 7.1%) were similar in patients who had or had not received FV, although the proportion of ICU admissions due to pneumonia was lower in patients who had versus had not received FV (11.5% vs. 20.0%) (Table 3). EAERs for hospitalizations (60.0 vs. 55.5), ER visits (48.5 vs. 36.3), and ICU admissions (4.1 vs. 4.6), as well as proportions of hospitalizations (11.2% vs. 8.1%), ER visits (9.0% vs. 7.5%), and ICU admissions (21.1% vs. 14.9%) due to pneumonia were numerically higher or similar among patients who had versus had not received PV in the past 5 years (Table 3).

Discussion

We demonstrate that global vaccination rates for influenza and *S. pneumoniae* in MM patients at the time of inclusion in the INSIGHT MM study were low and varied by geographical region. Vaccination rates were highest in the US and Europe, and the proportions of deaths due to infections were lowest in these regions, while the lowest vaccination rate and highest proportion of deaths due to infections were seen in Asia (China and Taiwan), suggesting the importance of vaccination for preventing infection-related mortality in patients with MM. Accordingly, the proportions of white/Caucasian patients were higher and proportions of Asian patients were lower in the vaccinated versus non-vaccinated subgroups, although most patients included in the study were white/Caucasian with a low proportion of Asian patients. Additionally, the proportion of patients aged > 75 years appeared slightly higher in the vaccinated versus non-vaccinated subgroups.

While direct comparisons between studies are confounded by multiple factors and should be interpreted with caution, vaccination rates in the US reported here from INSIGHT MM (55.8% FV in the past 1 year; 42.8% PV in the past 5 years) were similar to those reported in a previous US retrospective study of 411 patients with MM (15% optimal FV [twice in the previous 2 years]; 52% suboptimal FV [once in the previous 2 years]; 58% PV in the previous 5 years).[25] By contrast, a retrospective cohort study of 22,831 patients with MM in France found rates of FV and PV within 24 months of

Figure 2 Univariable and multivariable analysis of OS for patients with FV (A) and PV (B) status data available. Cox proportional hazards model was used for comparisons. Abbreviations: CI , confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH , fluorescence *in situ* hybridization; FV , influenza vaccination; HR . hazard ratio; ISS , international staging system; NDMM , newly diagnosed multiple myeloma; OS . overall survival; PV , pneumococcal vaccination; RRMM , relapsed/refractory multiple myeloma; SCT stem cell transplant. *Up to 2 years prior to study discontinuation, death, or data cutoff. FV yes: patients received one or two FV in the past 2 years. FV no: patients did not receive any FV in the past 2 years. †High-risk cytogenetic abnormalities were detected by fluorescence *in situ* hybridization and were defined as any of the following: chromosome 17p deletion (del[17p]), translocation between chromosomes 4 and 14 (t[4;14]), and translocation between chromosomes 14 and 16 (t[14;16]). The standard-risk group comprised patients without these three abnormalities. ‡Up to 5 years prior to study discontinuation, death, or data cutoff. PV yes: patients received at least one PV in the past 5 years. PV no: patients did not receive any PV in the past 5 years.

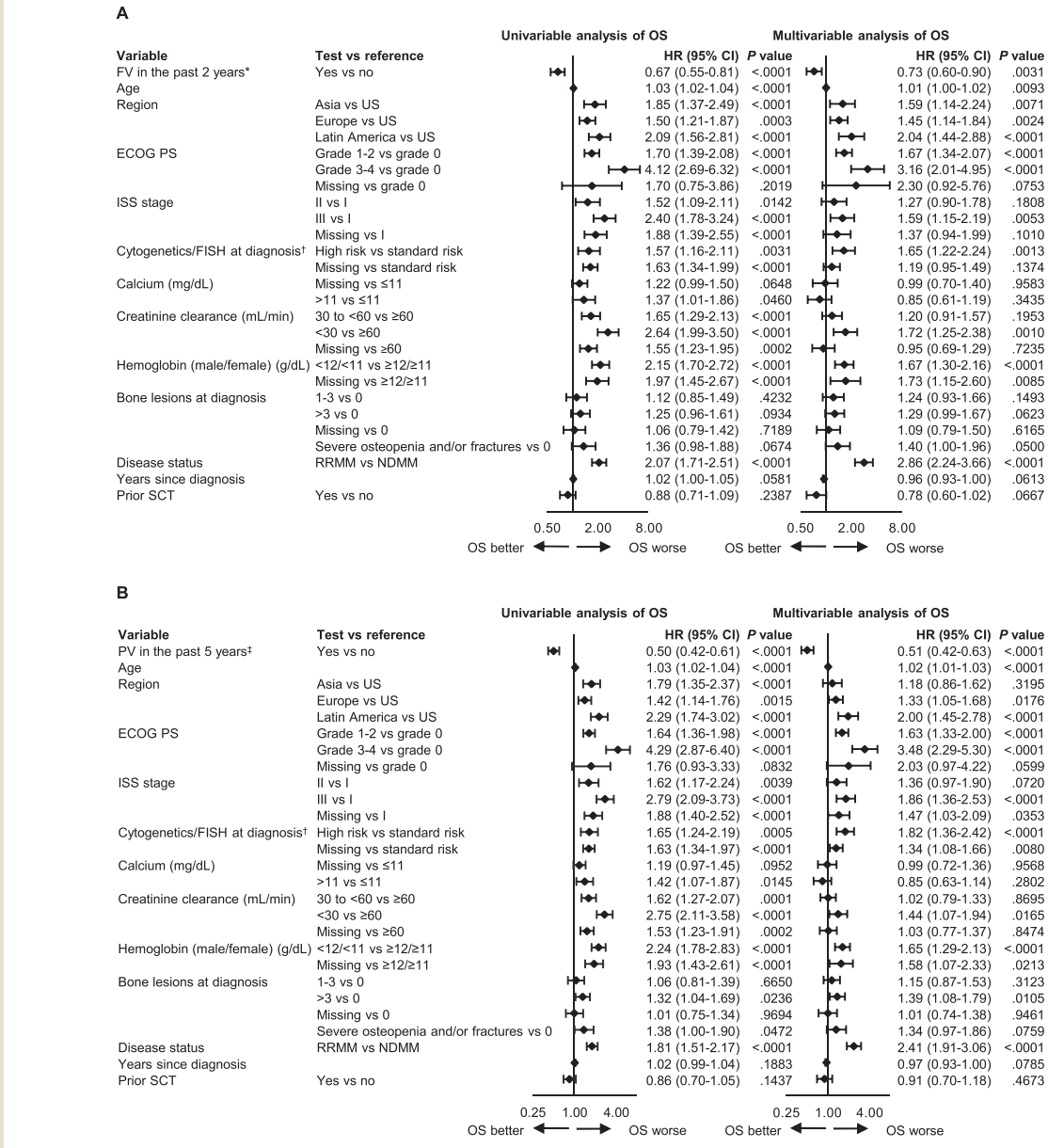

Table 2 Deaths Due to Infections, by FV and PV Status

	FV Status in the Past 2 years[a]			PV Status in the Past 5 years[b]		
Cause of Death,[c] no. (%)	Yes (≥ 1 FV) (N = 163)	No (0 FV) (N = 262)	*P* Value[d]	Yes (≥ 1 PV) (N = 152)	No (0 PV) (N = 311)	*P* Value[d]
Infections	16 (9.8)	40 (15.3)	.142	15 (9.9)	56 (18.0)	.032
Influenza/pneumonia	0	3 (1.1)	NA	0	3 (1.0)	
Pneumonia	12 (7.4)	21 (8.0)	NA	9 (5.9)	29 (9.3)	
Other infection	4 (2.5)	16 (6.1)	NA	6 (3.9)	24 (7.7)	

Abbreviations: FV , influenza vaccination; PV , pneumococcal vaccination.
[a] FV status in the past 2 years: up to 2 years prior to study discontinuation, death, or data cutoff. FV yes: patients received at least one FV in the past 2 years. FV no: patients did not receive any FV in the past 2 years.
[b] PV status in the past 5 years: up to 5 years prior to study discontinuation, death, or data cutoff. PV yes: patients received at least one PV in the past 5 years. PV no: patients did not receive any PV in the past 5 years.
[c] Deceased patients with missing cause of death (FV, n = 12; no FV, n = 18; PV, n = 12; no PV, n = 21) are not included.
[d] Analysis by Chi-squared test.

Table 3 Healthcare Resource Utilization During the Study Period, by FV and PV Status

	FV		PV	
Healthcare Resource Utilization During Study	FV[a] (N = 898)	No FV[b] (N = 902)	PV[c] (N = 956)	No PV[c] (N = 1192)
Patients with outpatient visits	n = 593	n = 841	n = 930	n = 1113
Mean total visits, no. (SD)	26.1 (18.29)	26.8 (23.80)	34.5 (29.82)	30.3 (29.68)
Mean visits for multiple myeloma therapy, no. (SD)	17.6 (15.68)	18.0 (17.37)	23.7 (24.48)	21.6 (23.21)
Hospitalizations				
Patients with ≥ 1 overnight hospitalization, no. (%)	229 (25.5)	363 (40.2)	480 (50.2)	508 (42.6)
Events, no. (EAER)[d]	431 (31.6)	804 (59.6)	1033 (60.0)	1126 (55.5)
Reason for hospitalization				
Pneumonia, no. (%) of events[e]	43 (10.0)	69 (8.6)	116 (11.2)	91 (8.1)
Other infections, no. (%) of events[e]	36 (8.4)	73 (9.1)	75 (7.3)	91 (8.1)
Mean total length of stay, days (SD)[f]	15.8 (15.71)	22.6 (24.08)	18.7 (19.32)	25.0 (26.22)
ER visits				
Patients with ≥ 1 ER visit, no. (%)	195 (21.7)	297 (32.9)	404 (42.3)	371 (31.1)
Events, no. (EAER)[d]	398 (29.2)	548 (40.6)	834 (48.5)	735 (36.3)
Reason for ER visit				
Pneumonia, no. (%) of events[e]	33 (8.3)	43 (7.8)	75 (9.0)	55 (7.5)
Other infections, no. (%) of events[e]	36 (9.0)	39 (7.1)	72 (8.6)	73 (9.9)
ICU admissions				
Patients with ≥ 1 ICU admission, no. (%)	22 (2.4)	55 (6.1)	61 (6.4)	78 (6.5)
Events, no. (EAER)[d]	26 (1.9)	65 (4.8)	71 (4.1)	94 (4.6)
Due to pneumonia, no. (%) of events[e]	3 (11.5)	13 (20.0)	15 (21.1)	14 (14.9)
Mean total length of stay, days (SD)[f]	5.2 (7.21)	7.7 (6.15)	6.3 (8.20)	7.9 (7.94)

Abbreviatons: EAER , exposure-adjusted event rates; ER , emergency room; FV , influenza vaccination; ICU , intensive care unit; PV , pneumococcal vaccination
[a] Patients received FV in the 2 years prior to study discontinuation, death, or data cutoff.
[b] Patients did not receive FV in the 2 years prior to study discontinuation, death, or data cutoff.
[c] PV / No PV: patients received / did not receive PV in the 5 years prior to study discontinuation, death, or data cutoff.
[d] EAER = total number of events divided by the total risk exposure in years and multiplied by 100; total risk exposure = time from baseline/study entry to data cutoff/death.
[e] Percentages were calculated using the number of events of hospitalization, ER visit, or ICU admission as denominator.
[f] If a patient has multiple hospitalizations or ICU admissions, the total length of stay is the sum of all hospitalization or ICU days for that patient.

MM diagnosis of 28.5% and 10.3%, respectively,[27] lower than the vaccination rates in Europe reported here (37.8% FV in the past 1 year, 28.5% PV in the past 5 years).

Overall, FV in the past 2 years and PV in the past 5 years prior to study discontinuation, death, or data cutoff were independent prognostic factors for OS on univariable and multivariable analysis, with vaccination associated with better OS. Similar findings were seen from the analyses in Europe and analysis of PV status in the US; however, in the US, FV in the past 2 years showed no significant association with OS, although the HRs from the univariable (1.30) and multivariable (1.26) analyses suggested poorer OS in vaccinated patients. The reasons for this divergent finding are unclear. According to the Organization for Economic Co-operation and Development, FV rates in the US are higher than in most other countries, except for Ireland, the UK, New Zealand, Greece, Chile, and Korea.[30] However, this may be partially driven by the common

practice of administering FV to patients upon admission to hospital in the US. Therefore, the subgroup of US patients who had received FV may have been enriched with those who had been hospitalized due to MM complications or other comorbidities, compared to the non-vaccinated subgroup. Consequently, with previous hospitalization suggesting a poorer prognosis, relative OS between subgroups favored non-vaccinated patients. Indeed, a recent Medicare and Medicaid claims database analysis of 4999 elderly patients found that uptake of influenza vaccine was highest among non-Hispanic white patients with > 9 somatic conditions.[31] While the focus should be on the overall population, in which vaccination status predicted OS, additional MM datasets should be analyzed to further understand this discrepant, although statistically non-significant, finding in the US subgroup.

Our findings are valuable as they indicate that routine vaccination as part of infection prophylaxis is feasible and important in patients with MM, given the apparent association with improved OS, and should be encouraged as part of standard supportive care. Evidence of the benefit of infection prophylaxis in MM has been previously reported from a double-blind, randomized, phase 3 study of prophylactic levofloxacin versus placebo for 12 weeks (commencing within 2 weeks of starting anti-myeloma therapy).[32] Patients receiving levofloxacin had a 34% reduction in the risk of death or of having a febrile episode versus placebo (HR, 0.66; 95% CI, 0.51-0.86; $P = .0018$), within the 12-week treatment period.

Currently, we are not aware of any prospective clinical trials in MM incorporating data collection on vaccination status; however, our results support such data collection, as imbalances in vaccination rates between treatment arms may confound interpretation of OS data. Vaccination rates may also impact interpretation of safety, as rates of treatment-emergent or treatment-related infections can be an important factor, especially when determining dosing or combination therapies. As infection risk can greatly impact drug development and result in compulsory concomitant infection prophylaxis and/or exclusion of patients with certain characteristics, as per the venetoclax example noted in "Introduction",[14] improved vaccination rates may help mitigate these risks. This will be important for studies of novel, potent agents known to increase infection risk, such as daratumumab,[33-35] and also in the context of the evolving treatment paradigm of continuous therapy.

Regarding the impact of vaccination on HRU, our descriptive, unadjusted data support an apparent association between receipt of FV and a generally lower rate of HRU, including HRU associated with infections. However, a similar effect was not observed with respect to PV status. A possible explanation for this discrepancy may be the lower prevalence of pneumococcal infections versus influenza.[36,37] Additionally, it is possible that the recommended schedule of initial and booster PV (in the US: https://www.cdc.gov/vaccines/vpd/pneumo/) may mean that some patients with historical PV (> 5 years prior to data cutoff, with no further recommended dose) were included in the "no PV" group, limiting the effect of PV status on HRU. This would not be the case with FV status due to the recommended annual vaccination schedule and shorter window for defining FV status (up to 2 years prior to data cutoff). Also, patients enrolled in the study without PV but who then received PV during the study would have been included in the "PV" rather than "no PV" group, and would have contributed HRU data for this analysis only from the time of PV until data cutoff; the shorter "exposure period" in these patients would have limited the potentially beneficial contribution of their data (ie, lower HRU) to the overall findings.

This study has limitations due to the real-world, non-randomized, observational nature of the data, and the findings reported here should be interpreted with caution. Firstly, data on several baseline characteristics, including hypogammaglobulinemia, were unavailable for a high proportion of patients or were not considered (eg, academic vs. non-academic sites of care); this may have impacted the univariable and multivariable analyses of OS. Relatedly, there may have been additional prognostic factors either not captured in the dataset/analysis or not temporally aligned to the vaccination data that may have had an impact on OS, including access/exposure to subsequent active therapies (eg, anti-CD38 antibodies), the variability of which may partially explain observed differences in the prognostic analyses among the geographical regions. Secondly, the definition of FV status used in our analysis (within the 2 years prior to data cutoff) does not reflect the "optimal" yearly vaccination schedule for influenza, nor does it account for the year-to-year variation in influenza virus strains and vaccine efficacy. Thirdly, HRU data analyses were descriptive and hence not adjusted for any parameters, such as age, that could have impacted HRU rates. Additionally, as noted above, HRU data could have been affected by "late" PV for some patients. Nevertheless, these data provide an important indication of the effect of FV and PV status on OS and HRU in patients with MM and should prompt further data collection and prospective studies.

Conclusion

In conclusion, these analyses from the INSIGHT MM study showed that FV in the past 2 years and PV in the past 5 years were associated with better OS, overall and in Europe, with similar results seen for the analysis of PV status in the US. The discrepant finding from the analysis of FV in the US, in which FV status was not a prognostic factor for OS, might be explained by higher FV rates in previously hospitalized patients, but further confirmatory studies are warranted. Despite infections being a leading cause of early mortality in MM,[9,10] global vaccination rates against influenza and pneumococcus in this analysis were low and varied by region. As most patients included in the study were white/Caucasian, further investigation into racial and other disparities, such as health system factors, in relation to vaccination access are recommended. Our finding that vaccination status may impact OS in patients with MM supports use of vaccination in routine practice as part of infection prophylaxis to prevent complications related to infections during treatment (which, in light of the recent pandemic, may also include vaccination against SARS-CoV-2), and the routine collection of data on vaccination status in future prospective studies in MM. Additionally, these data should be shared with the broader MM community, including patients and caregivers, to raise awareness of low vaccination rates and the importance and value of receiving vaccinations to decrease infectious complications, and to empower patients to be active participants in their care.

Clinical Practice Points

- Although vaccination is important in MM, rates of influenza and pneumococcal vaccination are low in MM patients globally. To our knowledge, no previous studies have assessed vaccination rates and associated outcomes in multiple myeloma (MM) patients at a global level. Our analyses of data from the INSIGHT MM study on influenza and pneumococcal vaccination status and associated clinical outcomes show that vaccination status may impact overall survival in MM patients, supporting the use of vaccination in routine practice as part of infection prophylaxis during treatment (may include vaccination against SARS-CoV-2).

Disclosure

M.A.T. reports membership on advisory boards for Adaptive, BMS (Celgene), Epizyme, Janssen, Sanofi, and Takeda; is Co-chair of committees for Elsevier Clinical Path; holds stock in Doximity; travel expenses from Syapse; royalties from UpToDate. reports honoraria and research funding from Sanofi, Celgene, Amgen, Novartis, and BMS; honoraria, research funding, and membership on an advisory board for Janssen; honoraria from AbbVie; research funding from Mundipharma; membership on an advisory board for GSK. K.C.W. reports honoraria from AbbVie, Adaptive, Janssen, Karyopharm, Novartis, Oncopeptides, Pfizer, Roche Pharma, and Takeda; grants to institution and honoraria from Amgen, BMS/Celgene, GSK, and Sanofi. R.M.R. reports membership on advisory boards for Amgen, BMS/Celgene, Coherus, and Takeda; is Medical Director for Biosimilar (US Oncology Network) and McKesson. S.Z.U. reports grants and personal fees from Amgen, Celgene, Sanofi, Seattle Genetics, Janssen, Takeda, SkylineDX, Merck, and GSK; personal fees from Abbvie, MundiPharma, and Oncopeptides; grants from Pharmacyclics and BMS. R.H. reports personal fees from Janssen, Amgen, AbbVie, BMS, and Pharma Mar; grants and personal fees from Takeda and Novartis. K.E.M. reports travel and accommodation expenses from Takeda. S.-P.Y. reports advisory role for AbbVie, Amgen, Astellas, Astex, Janssen, Novartis, Takeda, and Sanofi. C.L.C. reports honoraria and research funding from BMS, Janssen, and Takeda. J.G.B. reports grants from Takeda during the conduct of the study; grants and consultancy fees from Bluebird, BMS, Celgene, CRISPR Therapeutics, and Janssen; grants from AbbVie, Amgen, Astex, Celularity, EMD Sorono, Genentech, GSK, Ichnos Sciences, Incyte, Novartis, Poseida, and Sanofi; consultancy fees from Legend and SecuraBio. F.E.D. reports membership on advisory boards for Sanofi, Takeda, BMS/Celgene, Oncopeptides, and Janssen. J.A.Z. reports participation on a steering committee for Takeda during the conduct of the study; grants from BMS; membership on advisory boards for Regeneron, Intellia, Alnylam, Janssen, Caelum, and Amgen; participation on a Data Safety Monitoring Committee for Pharmacyclics. H.C.L. reports consulting fees and research funding from Celgene Inc., GlaxoSmithKline, Janssen, and Takeda Pharmaceutical; consulting fees from Bristol Myers Squibb, Genentech, Immunitas, Legend Biotech, Karyopharm Pharmaceutical, Oncopeptides, and Sanofi; research funding from Amgen Inc, Regeneron, and Daiichi Sankyo. E.T. reports personal fees, nonfinancial support, and membership on a steering committee for Takeda; personal fees from BMS and Novartis; grants and personal fees from Amgen, Janssen, and Sanofi; personal fees and nonfinancial support from Celgene; grants, personal fees, and nonfinancial support from Genesis Pharma and GSK. V.T.M.H. reports personal fees from Amgen, BMS, Janssen, Sanofi, and Takeda. N.P. reports grants and personal fees for advisory role, travel, accommodation, and expenses from Amgen, Janssen, and Takeda; grants and personal fees for advisory role, speaker's bureau, travel, accommodation, and expenses from BMS/Celgene; personal fees for advisory role, travel, accommodation, and expenses from The Binding Site. R.H.F. reports employment with Takeda Pharmaceuticals U.S.A., Inc. K.R. reports employment with Takeda Development Center Americas, Inc. (TDCA). D.M.S. reports employment with Takeda Pharmaceuticals U.S.A., Inc. A.C. reports grants, research funding, membership on advisory board, and personal fees for consultancy from Janssen, BMS/Celgene, and Amgen; membership on advisory board for Karyopharm, Sanofi, Oncopeptides, Glaxo Smith Kline, Shattuck Labs, Genentech, and AbbVie; grants, research funding, and membership on advisory board for Seattle Genetics; grants, research funding, and personal fees for consultancy from Millennium/Takeda; personal fees for consultancy from Antengene; personal fees for consultancy and membership on advisory board for Secura Bio.

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Author Contributions

M.A.T., M.B., X.L., J.V.-O., R.M.R., S.Z.U., R.H., G.C., M.A., K.E.M., C.L.C., J.G.B., F.E.D., J.A.Z., J.O., A.S., E.T., V.T.M.H., D.M.S., and A.C. conceived and designed the study. M.A.T., M.B., X.L., J.V.-O., F.v.R., K.C.W., R.M.R., S.Z.U., R.H., G.C., R.A., M.A., K.E.M., C.L.C., J.G.B., F.E.D., J.A.Z., H.C.L., J.O., A.S., E.T., V.T.M.H., N.P., and A.C. were steering committee members for the study. M.A.T., M.B., X.L., F.v.R., K.C.W., R.M.R., S.Z.U., G.C., R.A., S.-P.Y., C.L.C., J.G.B., F.E.D., J.A.Z., H.C.L., E.T., V.T.M.H., N.P., C.F., and A.C. were study investigators; they enrolled patients and contributed to data acquisition. M.A.T., R.H.F., K.R., D.M.S., and A.C. analyzed the data; K.R. performed the statistical analysis. M.A.T., R.H., G.C., M.A., K.E.M., N.P., R.H.F., K.R., D.M.S., and A.C. interpreted the data. All authors had access to the data and contributed to drafting/editing the manuscript as well as providing their final approval and agreeing to be accountable for the content and its accuracy and integrity.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2022.12.003.

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