

# Chromosome 1 abnormalities and survival of patients with multiple myeloma in the era of novel agents

Smith Giri,<sup>1,2</sup> Scott F. Huntington,<sup>2,3</sup> Rong Wang,<sup>2,4</sup> Amer M. Zeidan,<sup>2,3</sup> Nikolai Podoltsev,<sup>2,3</sup> Steven D. Gore,<sup>2,3</sup> Xiaomei Ma,<sup>2,4</sup> Cary P. Gross,<sup>2,4</sup> Amy J. Davidoff,<sup>2,5,\*</sup> and Natalia Neparidze<sup>2,3,\*</sup>

<sup>1</sup>Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL; <sup>2</sup>Cancer Outcomes, Public Policy, and Effectiveness Research Center and <sup>3</sup>Department of Internal Medicine, Yale School of Medicine, New Haven, CT; and <sup>4</sup>Department of Chronic Disease Epidemiology and <sup>5</sup>Department of Health Policy and Management, Yale School of Public Health, New Haven, CT

## Key Points

- Nearly one-quarter of patients with MM have C1As at diagnosis.
- C1As are associated with inferior survival, independent of other high-risk chromosomal abnormalities, despite therapy with novel agents.

Chromosome 1 abnormalities (C1As) are common genetic aberrations among patients with multiple myeloma (MM). We aimed to evaluate the significance of C1As among a contemporary cohort of patients with MM in the United States. We used electronic health records from the Flatiron Health database to select patients newly diagnosed with MM from January 2011 to March 2018 who were tested using fluorescence in situ hybridization within 90 days of diagnosis. We characterized patients as having documented C1As or other high-risk chromosomal abnormalities (HRCAs) as defined by the Revised-International Staging System (R-ISS) such as del(17p), t(14;16), and t(4;14). We used Kaplan-Meier methods to compare overall survival (OS) of patients with or without C1As and stratified log-rank tests (with the presence of HRCAs as a stratifying variable). We used Cox proportional hazards regression models to compare OS, adjusting for age, sex, stage, HRCAs, and type of first-line therapy. Of 3578 eligible patients, 844 (24%) had documented C1As. Compared with patients without C1As, patients with C1As were more likely to have higher stage (R-ISS stage III; 18% vs 12%), to have HRCAs (27% vs 14%), and to receive combinations of proteasome inhibitors and immunomodulatory agents (41% vs 34%). Median OS was lower for patients with C1As (46.6 vs 70.1 months; log-rank  $P < .001$ ). C1As were independently associated with worse OS (adjusted hazard ratio, 1.42; 95% confidence interval, 1.19-2.69;  $P < .001$ ), as were older age, higher R-ISS stage, HRCAs, and immunoglobulin A isotype. C1As were associated with inferior OS, independent of other HRCAs, despite greater use of novel therapies. Clinical trials testing newer therapies for high-risk MM should incorporate patients with C1As.

## Introduction

Each year, more than 30 000 individuals are diagnosed with multiple myeloma (MM) in the United States.<sup>1</sup> The disease trajectory for these patients is highly variable, with survival ranging from a few months to more than 10 years.<sup>2</sup> The number of treatment options is increasing, and patients may receive multiple lines of therapy. Prognostic markers that stratify patients with varying clinical outcomes are essential for developing appropriately tailored therapeutic strategies.

Several markers of high-risk disease have already been identified and were incorporated into the Revised-International Staging System (R-ISS) in 2015.<sup>3</sup> The R-ISS incorporates information on albumin,  $\beta$ -2 microglobulin, and lactate dehydrogenase levels as well as 3 high-risk chromosome abnormalities (HRCAs): del(17p), t(4;14), and t(14;16). Patients with newly diagnosed MM can be classified according to 3 distinct R-ISS stages (I-III) with reported 5-year overall survival (OS) of 82%, 62%, and

Submitted 30 December 2019; accepted 20 April 2020; published online 22 May 2020. DOI 10.1182/bloodadvances.2019001425.

\*A.J.D. and N.N. are joint senior authors.

Presented in part at the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, 31 May to 4 June 2019.

Requests for data may be sent to Smith Giri (smithgiri@uabmc.edu).

© 2020 by The American Society of Hematology

40%, respectively.<sup>4</sup> However, recent research has identified additional cytogenetic abnormalities that may predict worse outcomes among MM patients independent of the R-ISS risk factors.<sup>5</sup>

Chromosome 1 abnormalities (C1As) are among the most common recurrent chromosomal aberrations observed in patients with MM.<sup>6</sup> A variety of abnormalities involving both short and long arms of chromosome 1 have been described, including gains, deletions, and balanced or jumping translocations; patients with relapsed MM have a greater prevalence of these abnormalities compared with newly diagnosed patients.<sup>6</sup> Previous studies of C1As indicate an association with poor prognosis, although there is uncertainty about the magnitude of the effects of C1As relative to other HRCAs.<sup>7-11</sup> Many of these studies involve highly selected and often younger patients enrolled in clinical trials that are not representative of real-world populations.<sup>7,11-13</sup> Meanwhile, studies of patients treated outside of clinical trials are limited by either small sample size<sup>14,15</sup> or the inclusion of very few patients treated with combinations of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs).<sup>16,17</sup> It remains unclear whether combination regimens using novel agents can ameliorate the adverse prognostic impact of C1As.

To address this important knowledge gap, we used clinical and genomic data from a large, unselected group of real-world patients with MM to examine the prevalence of C1As in those patients as well as the pattern of care and survival of those with C1As compared with those of other cytogenetic risk subgroups.

## Methods

### Data source

We used electronic health records (EHRs) from the Flatiron Health database, a nationwide database comprising de-identified, longitudinal patient-level demographic, clinical, and outcomes data extracted from the source EHR system.<sup>18</sup> The database includes structured data as well as data elements that were abstracted from unstructured data and processed according to internal protocols. Structured data (including demographics, performance status, laboratory results, and medication administrations) are harmonized and normalized to a standard ontology across different source systems. Experienced oncology nurses and tumor registrars (with oncologist oversight) process unstructured data (eg, clinical data, pathology reports, treatment history, reason for treatment discontinuation, and adverse events) according to a modular, technology-enabled chart abstraction methodology supplemented by a manual review. Meanwhile, dates of death are obtained from a composite mortality variable generated from multiple data sources that include EHR data supplemented with external commercial and US Social Security Death Index data.<sup>19</sup> At the time of our analysis, the database comprised data from >2 million patients with cancer seen at more than 265 cancer clinics in the United States (at ~800 sites of care), both academic and community-based, in both urban and rural areas. Our study cohort comprised 194 unique practice sites from 42 different states including Hawaii and from US territories such as Puerto Rico. Within the continental United States, the geographic distributions of the practices were 41.9% from the Southern region, 23.5% from the Northeast, 16.6% from the Midwest, and 18% from the Western region. Institutional Review Board approval with a waiver of informed consent was obtained before the study started.

### Study cohort

Our primary study cohort included patients age 18 years or older with a histologically confirmed diagnosis of MM between January 2011 and March 2018. Eligible patients were required to have at least 2 clinic encounters on or after their date of diagnosis (defined as the first day of month in which patient was diagnosed), known first-line therapy, and fluorescence in situ hybridization (FISH) testing from 30 days before to 90 days after the date of diagnosis. All patients were observed until death (defined as first day of month in which patient was deceased) or the end of study period (31 March 2018).

### Definition of outcome

OS was defined as the time from date of diagnosis until death. Patients were censored if they were alive at the end of study period (31 March 2018); patients without any visits or therapy in the 6 months before the end of the study period were censored at the time of their last recorded activity.

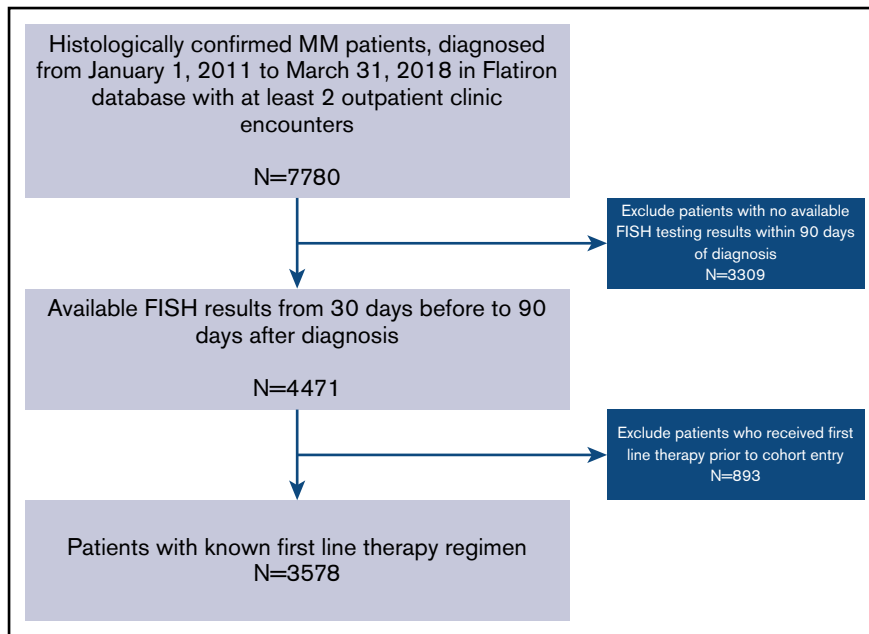
### Key variables

The primary variable of interest was documentation of the presence of C1As as identified by FISH. We created an indicator for the documented presence of other HRCAs that are incorporated into the R-ISS. Because patients with C1As are also more likely to have HRCAs, we also created a 4-level measure that combined the 2 entities: neither C1As nor HRCAs; HRCAs present but no C1As; C1As present but no HRCAs; and both C1As and HRCAs present. Additional variables of interest included socio-demographic characteristics (age, sex, race/ethnicity), clinical characteristics (type of M-protein, performance status, and disease stage), and treatment characteristics (first-line treatment regimen and receipt of autologous stem cell transplantation [ASCT]). We used a composite variable for self-reported race/ethnicity, classified as Hispanic, non-Hispanic white, non-Hispanic African American, and other (Pacific Islander, American-Indian, or Alaska Native).<sup>20</sup> Baseline performance status was measured by using the Eastern Cooperative Oncology Group (ECOG) performance score that was recorded closest to the date of MM diagnosis. ECOG performance scores were grouped into 0-2 and 3-4; because of the large number of missing values, we created an indicator for missing values. Information on comorbidity was not available. We used R-ISS to measure disease stage at the time of initial diagnosis, based on either an abstracted R-ISS report or constructed by using laboratory results (albumin and  $\beta$ -2 microglobulin) within 90 days of diagnosis. Lack of data on lactate dehydrogenase levels limited our ability to construct the R-ISS. First-line therapy was defined on the basis of the first episode of anti-myeloma therapy initiated up to 14 days before or after the diagnosis date and after the initial visit. First-line therapy was further categorized into PI- or IMiD-based therapy or therapy using only older agents. Information on the receipt and timing of ASCT was also incorporated into the characterization of lines of therapy.

### Statistical analysis

We compared baseline characteristics between patients with and without documented C1As using appropriate bivariate statistics ( $\chi^2$  test for categorical variables and independent sample Student *t* test for continuous variables). We used the Kaplan-Meier method to compare the survival distribution of patients stratified by presence

**Figure 1. Cohort selection process.** Eligible patients were required to have undergone FISH testing of their bone marrow aspirate within 90 days of diagnosis and have known first-line therapy.



of either C1As and/or HRCAs. The difference between survival distribution of MM patients with and without C1As was then compared using stratified log-rank tests (with the presence of HRCAs as a stratifying variable). We performed multivariable analysis using Cox proportional hazards regression to examine the association of C1As with OS, adjusting for potential confounders including age, sex, race/ethnicity, type of first-line therapy, and use of ASCT. The proportional hazards assumption was confirmed by using evaluation of Cox Snell's residuals. Furthermore, we tested for interactions between C1As and type of first-line therapy. Because there were several missing values for R-ISS stages and ECOG scores, they were not included in our primary regression models; however, we controlled for these potential confounders in a separate sensitivity analysis. Similarly, because many practice sites may not have adopted C1A testing, particularly during the early study period, we conducted a sensitivity analysis by running separate Cox regression models, limiting our study cohort to the second half of the study period (ie, 2015 and after). All statistical tests were 2-sided with an  $\alpha$  of 0.05. All analyses used STATA 13.0 (STATA, College Station, TX).

## Results

A total of 7780 patients with MM were identified, and 3578 patients from 194 practice sites met the eligibility criteria for inclusion in this analysis (Figure 1). The median age of the overall cohort was 69 years (interquartile range, 31-85 years) with 54% males and 60% non-Hispanic whites; 24% had documented C1As. Patients with C1As were more likely to have other high-risk indicators compared with patients without C1As. For example, higher prevalence of R-ISS stage III disease (18% vs 12%), presence of any HRCA (27% vs 14%), and individual HRCAs such as del(17p), 14% vs 8%; t(4;14), 10% vs 5%; and t(14;16), 5% vs 2%, all significantly different at  $P < .001$ . However, patients with C1As were less likely to harbor t(11;14) compared with those without C1As (9% vs 15%;  $P < .001$ ). Patients with C1As were more likely

to receive therapy with PI and IMiD combinations compared with those without C1As (41% vs 34%;  $P < .001$ ). The use of ASCT was similar in the 2 groups (26% vs 28%;  $P = .14$ ) (Table 1).

During a median follow-up of 29.3 months (95% confidence interval [CI], 28.4-31.4 months), 958 patients (27%) had died. The median OS of the overall cohort was 66.9 months (95% CI, 60.9-73.1 months). The median OS for each of the 4 cytogenetic categories was 75.1 months for no documented C1As or HRCAs; 59.9 months for HRCAs present/no C1As; 46.7 months for C1As present/no HRCAs; and 46.7 months for both C1As and HRCAs present. The median OS was significantly lower for patients with C1As compared with the median OS for those without C1As (46.7 vs 70.1 months) after adjusting for presence of other HRCAs (stratified log-rank  $P < .001$ ) (Figure 2).

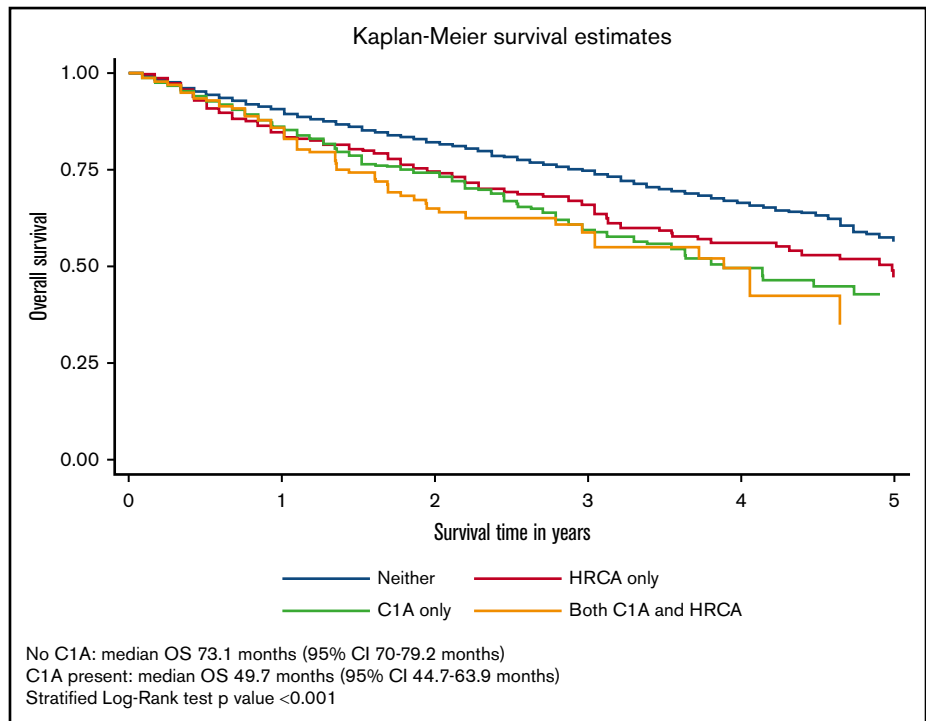
In multivariable analysis, compared with patients without either type of chromosomal abnormality, those with C1As had an increased risk of mortality regardless of the presence of HRCAs (hazard ratio [HR], 1.84; 95% CI, 1.42-2.39;  $P < .001$  for those with HRCAs; HR, 1.42; 95% CI, 1.19-1.69;  $P < .001$  for those without HRCAs). C1As remained an independent predictor of worse survival after adjusting for multiple covariates, including age, sex, race/ethnicity, M-protein subtype, type of first-line therapy, and use of ASCT. As detailed in Table 2, the HRs are quite similar between patients with C1As only and patients with HRCAs only, with nearly identical CIs. Furthermore, we tested the interaction between documented C1As and type of first-line therapy (IMiD plus PI vs other) as well as C1As and the use of ASCT in our multivariable models and found no evidence of a statistically significant interaction (Table 2). Sensitivity analyses incorporating R-ISS stage and ECOG performance status as additional covariates showed similar results, with C1As remaining an independent predictor of worse survival (HR, 1.45; 95% CI, 1.22-1.73;  $P < .001$ ) (Table 3). Similarly, C1As remained an independent predictor of worse survival (HR, 1.34; 95% CI, 1.03-1.74;  $P = .029$ ), even after limiting our study cohort to years 2015 and after (Table 4).

**Table 1. Characteristics of patients with MM with or without documented C1As**

Variable	With C1As		Without C1As		P
	No.	%	No.	%	
No. of patients	844		2734		
Median age (IQR), y	69 (62-77)		68 (60-76)		.002
Female	406	48.1	1237	45.2	.150
<b>Race/ethnicity</b>					.496
Non-Hispanic white	493	58.4	1656	60.6	
Non-Hispanic African American	131	15.5	437	15.9	
Hispanic	65	7.7	183	6.7	
Other	75	8.9	241	8.8	
Missing	80	9.5	217	7.9	
<b>Practice type</b>					.511
Academic	80	9.5	239	8.7	
Community	764	90.5	2495	91.3	
<b>M-protein type</b>					<.001
IgG	386	49.2	1511	58.8	
IgA	219	27.9	505	19.7	
Light chain	171	21.8	515	20.1	
Other	9	1.1	37	1.4	
Missing	59	7	166	6.1	
<b>R-ISS stage</b>					<.001
I	140	16.6	435	15.9	
II	129	15.3	437	15.9	
III	148	17.5	322	11.8	
Missing	427	50.6	1540	56.3	
<b>ECOG PS</b>					.903
0-2	534	63.3	1713	62.6	
3-4	22	2.6	78	2.8	
Missing	288	34.1	943	34.5	
<b>HRCA</b>					
Any HRCA	227	26.9	376	13.8	<.001
del(17 p)	121	14.3	231	8.4	<.001
t(4;14)	87	10.3	130	4.8	<.001
t(14;16)	41	4.9	47	1.7	<.001
Non-HRCA					
del(13q)	414	49.1	768	28.1	<.001
t(11;14)	78	9.2	411	15	<.001
<b>First-line therapy</b>					<.001
PI + IMiD combination	342	40.5	916	33.5	
PI-based	151	17.9	615	22.5	
IMiD-based	284	33.6	871	31.9	
Other	67	7.9	332	12.1	
ASCT	215	25.5	768	28.1	.140

HRCA is defined as the presence of 1 of the following: del (17p), t4;14, or t14;16). IgG, immunoglobulin G; IQR, interquartile range; PS, performance status.

**Figure 2. OS of patients with MM and with or without C1As.** Survival distributions were plotted using Kaplan-Meier methods. Because patients with C1As were also more likely to have HRCAs, we created a 4-level measure that combined them: neither C1As nor HRCAs, HRCAs present/no C1As, C1As present/no HRCAs, and C1As and HRCAs present. Differences in survival distributions between those with and without C1As were tested with log-rank statistics, accounting for HRCAs as a stratifying variable, and the results were statistically significant ( $P < .001$ ).



## Discussion

In this large retrospective study with a contemporary, real-world cohort of adult patients with MM, we found that patients with documented C1As had worse survival compared with those without C1As, independent of previously identified HRCAs. Furthermore, this adverse impact does not seem to be ameliorated by the use of combinations of PIs and IMiDs, with or without ASCT as first-line therapy. To our knowledge, this is the first large-scale, real-world study that shows the prognostic significance of C1As in a cohort of unselected patients, treated predominantly with novel therapies as first-line agents.

We observed important differences in clinical characteristics between patients with and without C1As. Patients with C1As were more likely to have immunoglobulin A (IgA) subtype, higher R-ISS stage, and HRCAs, all of which are associated with inferior outcomes among patients with MM.<sup>4,21</sup> This is consistent with previous observations,<sup>15,16</sup> suggesting that clustering of high-risk features among patients with C1As may account for inferior outcomes seen among those patients. In fact, C1As and HRCAs were independent predictors of inferior survival. When we considered joint indicators for C1As and HRCAs, we found very similar hazards of death associated with C1As or HRCAs alone, compared with having neither, whereas patients with both C1As and HRCAs had the worst OS. These findings underscore the importance of incorporating C1As into future risk stratification models for MM.

Our results provide important real-world evidence of inferior outcomes for patients with C1As despite treatment regimens that include novel therapies. Most previous studies of C1As included patients treated with first- and second-generation drugs.<sup>12,13,16,17,22,23</sup> Only a few small single-institution studies have evaluated the prognostic impact of C1As

among a more contemporary cohort of MM patients treated with newer treatment combinations.<sup>14,15,24,25</sup> In a series of 95 patients with MM, Shah et al<sup>15</sup> showed that gain of chromosome 1q independently predicted worse progression-free survival (PFS) and OS, despite receiving an ASCT. In another series of 201 MM patients treated at Emory University with first-line therapy based on lenalidomide, bortezomib, and dexamethasone, patients with +1q (vs those without) had a shorter median PFS and worse OS.<sup>24</sup> Varma et al<sup>25</sup> reported similar results among a cohort of 100 patients with +1q and/or del(1p) treated with high-dose therapy and ASCT. In an analysis of the CoMMpass study, Christofferson et al<sup>26</sup> showed that gain of chromosome 1q exhibited poor PFS and OS regardless of hyperdiploid status. Finally, Biran et al<sup>14</sup> analyzed 28 MM patients with gain of chromosome 1q and reported a median OS of only 37 months, despite use of combination therapies with novel agents. Aside from small sample sizes,<sup>14,15,24,25</sup> the study by Shah et al<sup>15</sup> lacked comparison groups, and the study by Biran et al<sup>14</sup> did not account for concomitant HRCAs. Although our findings are generally consistent with these previous studies, our study has a substantially larger cohort of more than 3500 patients, most of whom were treated with novel agents, and we accounted for covariates, including the presence of HRCAs.

Previous studies have suggested that certain novel therapies may ameliorate the adverse impact of high-risk cytogenetics. In several clinical trials, bortezomib has been shown to partly overcome the adverse effect of t(4;14) and del(17p).<sup>5,27,28</sup> In another open-label study of lenalidomide and dexamethasone, patients with t(4;14) experienced a median OS similar to that of patients without any cytogenetic abnormalities, suggesting that lenalidomide may overcome the adverse impact of t(4;14).<sup>29</sup> However, it is less clear how these novel agents impact the prognosis of patients with C1As. In a series of 290 patients with newly diagnosed MM, gain of 1q21

**Table 2. Predictors of OS in patients with MM (n = 3353)**

Variable	HR*	95% CI*	P
<b>Cytogenetic group</b>			
Neither C1A nor HRCA	Ref	—	
HRCA present/no C1A	1.57	1.30-1.91	<.001
C1A present/no HRCA	1.42	1.19-1.69	<.001
Both C1A and HRCA present	1.84	1.42-2.38	<.001
Age, y	1.03	1.02-1.03	<.001
Male	1.26	1.11-1.44	<.001
<b>Race/ethnicity</b>			
Non-Hispanic white	Ref	—	
Hispanic or Latino	0.65	0.47-0.88	.006
Non-Hispanic African American	0.85	0.70-1.02	.084
Other	0.91	0.72-1.15	.446
Unknown	1.27	1.00-1.61	.046
<b>M-protein subtype</b>			
IgG	Ref	1.18-1.63	<.001
IgA	1.38	1.13-1.58	.001
Other	1.33	2.04-3.25	<.001
Unknown	2.57		
<b>First-line therapy</b>			
IMiD + PI based	Ref	0.84-1.24	.866
IMiD based	1.02	1.25-1.75	<.001
PI based	1.48	0.90-1.39	.314
Non-IMiD/PI	1.12		
ASCT	0.33	0.26-0.40	<.001

HRCA is defined as presence of 1 of the following: del(17p), t4;14, or t14;16).  
Ref, reference.

\*HRs and 95% CIs were derived from a multivariable Cox proportional hazards regression model; all variables in the table were included in the same model simultaneously. The interaction terms between first-line treatment and cytogenetic group as well as ASCT and cytogenetic group were not statistically significant (results not shown).

had no impact on survival in patients receiving thalidomide-based treatment, suggesting that IMiDs could overcome resistance to thalidomide.<sup>30</sup> However, several subsequent studies reported inferior survival among patients with C1As who received therapy with combinations of novel agents or ASCT.<sup>14,15,23</sup> Consistent with these observations, we did not see a significant interaction between C1As and type of first-line treatment or ASCT with OS, suggesting that neither novel agent combinations nor ASCT can mitigate the adverse impact of C1As.

In our study, patients with Hispanic ethnicity seemed to have better outcomes on multivariable analysis after controlling for disease- and treatment-related risk factors. This is in contrast to previous reports of worse survival among Hispanic patients with MM compared with non-Hispanic whites,<sup>31,32</sup> largely attributed to limited access to novel therapeutics and clinical trials and lower rates of stem cell use<sup>33,34</sup> rather than disease biology.<sup>35</sup> Recent studies have shown that with equal access to novel therapies and transplantation, Hispanics may have a comparable or even better survival compared with non-Hispanic whites.<sup>36</sup> In our study, we found a comparable use of stem cell transplantation (28.6% vs 27.9%) and triplet combinations based on PIs plus IMiDs (33.5% vs 35.1%) among

**Table 3. Multivariable Cox regression model for OS incorporating R-ISS stage and ECOG PS as potential confounders**

Variable	HR*	95% CI*	P
<b>Cytogenetic group</b>			
Neither C1A nor HRCA	Ref	—	<.001
HRCA present/no C1A	1.48	1.23-1.81	<.001
C1A present/no HRCA	1.45	1.22-1.73	<.001
Both C1A and HRCA present	1.70	1.32-2.21	
Age, y	1.02	1.01-1.03	<.001
Male	1.23	1.08-1.40	.002
<b>Race/ethnicity</b>			
Non-Hispanic white	Ref	—	.002
Hispanic or Latino	0.61	0.45-0.84	.125
Non-Hispanic African American	0.86	0.71-1.04	.341
Other	0.89	0.71-1.13	.036
Unknown	1.29	1.02-1.63	
<b>M-protein subtype</b>			
IgG	Ref	—	.003
IgA	1.28	1.08-1.50	.001
Other	1.33	1.12-1.57	<.001
Unknown	2.56	2.03-3.23	
<b>R-ISS stage</b>			
I	Ref	1.16-2.01	.003
II	1.52	1.87-3.20	<.001
III	2.45	1.29-2.07	<.001
Unknown	1.63		
<b>ECOG PS</b>			
0-2	Ref	2.30-4.12	<.001
3-4	3.07	1.48-1.94	<.001
Unknown	1.69		
<b>First-line therapy</b>			
IMiD + PI based	Ref	0.81-1.21	.939
IMiD based	0.99	1.08-1.53	.004
PI based	1.29	0.82-1.29	.797
Non-novel	1.03		
ASCT	0.33	0.27-0.41	<.001

\*HRs and 95% CIs were derived from a multivariable Cox proportional hazards regression model; all variables in the table were included in the same model simultaneously. The interaction terms between first-line treatment and cytogenetic group as well as stem cell transplantation and cytogenetic group were not statistically significant (results not shown).

Hispanic patients compared with non-Hispanic white patients, which may partially explain superior survival seen among Hispanic patients.

Our study used a relatively new EHR database, Flatiron Health database, as a source, which has both strengths and limitations. The database is large and covers a broad geographic cross section of oncology patients cared for in the United States; our study population comprised MM patients seen in 198 cancer clinics across 44 states. Although the data set is not designed to generate nationally representative estimates, this should not bias study

**Table 4. Multivariable Cox regression model for overall survival limiting cases diagnosed from 2015 or later (n = 2033)**

Variable	HR*	95% CI*	P
<b>Cytogenetic group</b>			
Neither C1A nor HRCA	Ref	—	.094
HRCA present/no C1A	1.35	0.95-1.92	.029
C1A present/no HRCA	1.34	1.03-1.75	<.001
Both C1A and HRCA present	2.08	1.47-2.94	
Age, y	1.02	1.01-1.03	.006
Male	1.12	0.90-1.38	.304
<b>Race/ethnicity</b>			
Non-Hispanic white	Ref	—	.132
Hispanic or Latino	0.67	0.40-1.12	.399
Non-Hispanic African American	1.14	0.84-1.53	.944
Other	1.01	0.71-1.45	.281
Unknown	1.21	0.85-1.72	
<b>M-protein subtype</b>			
IgG	Ref	1.27-2.18	<.001
IgA	1.67	1.21-2.09	.001
Other	1.59	1.50-3.22	<.001
Unknown	2.20		
<b>First-line therapy</b>			
IMiD + PI based	Ref	0.88-1.67	.239
IMiD based	1.21	1.25-2.09	<.001
PI based	1.61	0.78-1.92	.378
Non-IMiD/PI	1.23		
ASCT	0.23	0.15-0.35	<.001

HRCA is defined as presence of 1 of the following: del(17p), t(4;14), or t(14;16).

\*HRs and 95% CIs were derived from a multivariable Cox proportional hazards regression model; all variables in the table were included in the same model simultaneously.

estimates of the association between C1As and clinical outcomes. The data set captured critical information on the results of FISH testing, which allowed us to identify patients with documented C1As. Unfortunately, the data do not allow for further categorization of patients on the basis of a specific subtype of C1A such as del(1p), +1q, copy number variations, or size of clones in this group. Although both del(1p) and +1q have been linked to an inferior prognosis, the magnitude of this impact may vary; our study results represent an average effect of C1As on outcomes. We also note that there may be some patients for whom C1A or HRCA status was not assessed, but we cannot distinguish between negative and missing results. It is possible that some laboratories may not uniformly evaluate C1As or even HRCAs as part of a standard myeloma diagnostic panel, although this would be quite rare in modern-day practices. Notably, nearly 80% of treatment centers (152 of 194) detected at least 1 patient with C1As, suggesting broad use of C1A testing; the remaining clinic practice sites (n = 42) contributed to less than 5% (n = 169) of total sample size (N = 3578). Thus, even if they were not including C1A in their FISH panel, that would be unlikely to influence the overall results. Nevertheless, the inclusion of very few patients from many sites may be associated with testing quality, data completeness, and selection bias for patients with less high-risk disease. Some sites

may not have adopted routine C1A testing during the earlier study period; however, our results were largely unchanged even after restricting the study cohort to those diagnosed in 2015 and after. Despite these limitations, our data set provided a contemporary cohort of patients with robust clinical and treatment information, including the presence of HRCAs, number of lines of therapy, and OS, which were often lacking in other real-world claims databases, which make it a unique resource for this study. Although extensive missing data for R-ISS stage and ECOG performance status precluded inclusion of these variables in our primary multivariable models, we were able to incorporate these measures during sensitivity analyses which yielded similar findings for other covariates.

In conclusion, C1As are seen in almost a quarter of patients with newly diagnosed MM and seem to be much more common than other traditional HRCAs. The presence of C1As has an adverse impact on survival among patients with MM, similar in magnitude to that with other HRCAs. Our findings suggest the need to incorporate C1As into MM risk stratification tools, as recently proposed by the Mayo clinic group,<sup>37</sup> and highlight the need for development and testing of new therapies or regimens targeting patients with C1As.

## Authorship

Contribution: S.G., A.J.D., and N.N. conceptualized the study, the study design, and the methodology, curated and analyzed the data, and performed the analyses; A.J.D. and N.N. supervised and administered the project; and S.G., S.F.H., R.W., A.M.Z., N.P., S.D.G., X.M., C.P.G., A.J.D. and N.N. perform the investigation, wrote the original draft of the article, and reviewed and edited it.

Conflict-of-interest disclosure: A.J.D. and X.M. received research funding from Celgene. A.M.Z. received research funding (institutional) from Celgene, Acceleron, AbbVie, Otsuka, Pfizer, MedImmune/AstraZeneca, Boehringer-Ingelheim, Trovogene, Incyte, Takeda, and ADC Therapeutics; and served as a consultant for and received honoraria from AbbVie, Otsuka, Pfizer, Celgene, Ariad, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Seattle Genetics, BeyondSpring, and Takeda. N.P. served as a consultant for and received honoraria from Alexion, Pfizer, Agios Pharmaceuticals, Blueprint Medicines, Incyte, Novartis, and Celgene; and received research funding (all to the institution) from Boehringer Ingelheim, Astellas Pharma, Daiichi Sankyo, Sunesis Pharmaceuticals, Jazz Pharmaceuticals, Pfizer, Astex Pharmaceuticals, CTI biopharma, Celgene, Genentech, Al Therapeutics, Samus Therapeutics, Arog Pharmaceuticals, and Kartos Therapeutics. C.P.G. received research funding from the National Comprehensive Cancer Network (through Pfizer and AstraZeneca grants), from Johnson & Johnson for developing new approaches to data sharing, and from Flatiron Health for travel to and speaking at a scientific conference. The remaining authors declare no competing financial interests.

ORCID profiles: S.F.H., 0000-0001-7071-6475; N.P., 0000-0002-3657-778X; A.J.D., 0000-0001-8141-9249.

Correspondence: Smith Giri, Division of Hematology-Oncology, Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, 1600 7th Ave South, Lowder 500, Birmingham, AL 35233; e-mail: smithgiri@uabmc.edu.

## References

1. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Myeloma. <https://seer.cancer.gov/statfacts/html/mulmy.html>. Accessed 20 August 2019.
2. Avet-Loiseau H, Durie BG, Cavo M, et al; International Myeloma Working Group. Combining fluorescent in situ hybridization data with ISS staging improves risk assessment in myeloma: an International Myeloma Working Group collaborative project. *Leukemia*. 2013;27(3):711-717.
3. Manier S, Salem KZ, Park J, Landau DA, Getz G, Ghobrial IM. Genomic complexity of multiple myeloma and its clinical implications. *Nat Rev Clin Oncol*. 2017;14(2):100-113.
4. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-2869.
5. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955-2962.
6. Marzin Y, Jamet D, Douet-Guilbert N, et al. Chromosome 1 abnormalities in multiple myeloma. *Anticancer Res*. 2006;26(2A):953-959.
7. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood*. 2007;109(8):3489-3495.
8. Fonseca R, Van Wier SA, Chng WJ, et al. Prognostic value of chromosome 1q21 gain by fluorescent in situ hybridization and increase CKS1B expression in myeloma. *Leukemia*. 2006;20(11):2034-2040.
9. Scott EC, Hari P, Sharma M, et al. Post-transplant outcomes in high-risk compared with non-high-risk multiple myeloma: A CIBMTR analysis. *Biol Blood Marrow Transplant*. 2016;22(10):1893-1899.
10. Shaughnessy JD Jr., Zhan F, Burington BE, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood*. 2007;109(6):2276-2284.
11. Caltagirone S, Ruggeri M, Aschero S, et al. Chromosome 1 abnormalities in elderly patients with newly diagnosed multiple myeloma treated with novel therapies. *Haematologica*. 2014;99(10):1611-1617.
12. Hanamura I, Stewart JP, Huang Y, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. *Blood*. 2006;108(5):1724-1732.
13. Boyd KD, Ross FM, Chiecchio L, et al; NCRI Haematology Oncology Studies Group. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. *Leukemia*. 2012;26(2):349-355.
14. Biran N, Malhotra J, Bagiella E, Cho HJ, Jagannath S, Chari A. Patients with newly diagnosed multiple myeloma and chromosome 1 amplification have poor outcomes despite the use of novel triplet regimens. *Am J Hematol*. 2014;89(6):616-620.
15. Shah GL, Landau H, Londono D, et al. Gain of chromosome 1q portends worse prognosis in multiple myeloma despite novel agent-based induction regimens and autologous transplantation. *Leuk Lymphoma*. 2017;58(8):1823-1831.
16. Grzasko N, Hajek R, Hus M, et al. Chromosome 1 amplification has similar prognostic value to del(17p13) and t(4;14)(p16;q32) in multiple myeloma patients: analysis of real-life data from the Polish Myeloma Study Group. *Leuk Lymphoma*. 2017;58(9):1-15.
17. Hebraud B, Leleu X, Lauwers-Cances V, et al. Deletion of the 1p32 region is a major independent prognostic factor in young patients with myeloma: the IFM experience on 1195 patients. *Leukemia*. 2014;28(3):675-679.
18. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR; Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2006;24(3):431-436.
19. Curtis MD, Griffith SD, Tucker M, et al. Development and validation of a high-quality composite real-world mortality endpoint. *Health Serv Res*. 2018;53(6):4460-4476.
20. Kish JK, Yu M, Percy-Laurry A, Altekruse SF. Racial and ethnic disparities in cancer survival by neighborhood socioeconomic status in Surveillance, Epidemiology, and End Results (SEER) Registries. *J Natl Cancer Inst Monogr*. 2014;2014(49):236-243.
21. Facon T, Avet-Loiseau H, Guillem G, et al. Chromosome 13 abnormalities identified by FISH analysis and serum beta2-microglobulin produce a powerful myeloma staging system for patients receiving high-dose therapy. *Blood*. 2001;97(6):1566-1571.
22. Hebraud B, Magrangeas F, Cleynen A, et al. Role of additional chromosomal changes in the prognostic value of t(4;14) and del(17p) in multiple myeloma: the IFM experience. *Blood*. 2015;125(13):2095-2100.
23. Nahi H, Våtsveen TK, Lund J, et al. Proteasome inhibitors and IMiDs can overcome some high-risk cytogenetics in multiple myeloma but not gain 1q21. *Eur J Haematol*. 2016;96(1):46-54.
24. Schmidt TM, Barwick BG, Joseph N, et al. Gain of chromosome 1q is associated with early progression in multiple myeloma patients treated with lenalidomide, bortezomib, and dexamethasone. *Blood Cancer J*. 2019;9(12):94.
25. Varma A, Sui D, Milton DR, et al. Outcome of multiple myeloma with chromosome 1q gain and 1p deletion after autologous hematopoietic stem cell transplantation: Propensity score matched analysis. *Biol Blood Marrow Transplant*. 2020;26(4):665-671.
26. Christofferson A, Skerget S, Aldrich J, et al. Unsupervised Clustering of DNA Copy Number Profiles Identifies a High-Risk Subtype of Hyperdiploid Multiple Myeloma: An MmrF Compass Analysis [abstract]. *Blood*. 2019;134(suppl 1):Abstract 1805.



27. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). *J Clin Oncol*. 2010;28(30):4630-4634.
28. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol*. 2012;30(24):2946-2955.
29. Reece D, Song KW, Fu T, et al. Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13. *Blood*. 2009;114(3):522-525.
30. An G, Xu Y, Shi L, et al. Chromosome 1q21 gains confer inferior outcomes in multiple myeloma treated with bortezomib but copy number variation and percentage of plasma cells involved have no additional prognostic value. *Haematologica*. 2014;99(2):353-359.
31. Pulte D, Redaniel MT, Brenner H, Jansen L, Jeffreys M. Recent improvement in survival of patients with multiple myeloma: variation by ethnicity. *Leuk Lymphoma*. 2014;55(5):1083-1089.
32. Ailawadhi S, Aldoss IT, Yang D, et al. Outcome disparities in multiple myeloma: a SEER-based comparative analysis of ethnic subgroups. *Br J Haematol*. 2012;158(1):91-98.
33. Ailawadhi S, Frank RD, Sharma M, et al. Trends in multiple myeloma presentation, management, cost of care, and outcomes in the Medicare population: A comprehensive look at racial disparities. *Cancer*. 2018;124(8):1710-1721.
34. Costa LJ, Huang JX, Hari PN. Disparities in utilization of autologous hematopoietic cell transplantation for treatment of multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21(4):701-706.
35. Jain T, Fonseca R, Chen R, et al. Racial differences in disease characteristics: Understanding multiple myeloma in Hispanics [abstract]. *Blood*. 2017;130(suppl 1). Abstract 864.
36. Kaur G, Mejia Saldarriaga M, Acuna-Villaorduna A, et al. Multiple myeloma in Hispanics is associated with better survival than non-Hispanic African Americans and Whites: Analysis from a large single center minority rich cohort [abstract]. *Blood*. 2018;132(suppl 1). Abstract 3601.
37. Kumar SK, Greipp P, Gertz MA, et al. A novel approach to risk stratification in multiple myeloma using ISS stage and FISH [abstract]. *Blood*. 2019;134(suppl 1). Abstract 1800.