pathways were activated by carfilzomib treatment, as indicated by increases in cleaved caspase 8 and caspase 9, respectively (Figure 1H), and to some extent the cells appeared more resistant to spontaneous endogenous apoptosis ex vivo following ibrutinib therapy.

In summary, this pilot study provides some foundation to further investigate carfilzomib-ibrutinib combination therapy for CLL.

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**Acknowledgments:** The authors gratefully acknowledge Dr Bryant G. Darnay for critical comments and for reading the manuscript, and Kathryn B. Carnes for editing the manuscript. The authors thank Benjamin Hayes for collection, Yuling Chen, Min Fu, and Vrushali Datar for transportation of samples, and Susan Smith for providing patient characteristics. V.G. and W.G.W. are members of the CLL Research Consortium.

This work was supported in part by grant P01 CA81534 from the National Cancer Institute at the National Institutes of Health, a CLL Global Research Foundation Alliance grant award, a sponsored research agreement from Pharmacyclics, and generous philanthropic contributions to The University of Texas MD Anderson Cancer Center Moon Shot Program.

**Contribution:** B.L. designed and performed most of the experiments, analyzed the data, and wrote the manuscript; F.C.-G. performed part of the experiments corresponding to Figure 1A-B; M.S., M.J.K., and W.G.W. provided clinical and patient-related input; V.G. conceptualized and coordinated the project, supervised F.C.-G., and obtained funding; and all authors reviewed and approved the final version of the manuscript.

**Conflict-of-interest disclosure:** V.G. received a sponsored research agreement from Pharmacyclics. The remaining authors declare no competing financial interests.

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# To the editor:

## Future distribution of multiple myeloma in the United States by sex, age, and race/ethnicity

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States (US), representing 1.4% of all new cancers,[1] and is twice as common among African Americans as it is among other racial or ethnic groups.[2] Although the absolute burden (or number) of new MM cases per year is expected to be higher in future years because of changes in the demographic profile of the US,[3] to date, no study has estimated the future distribution of MM by sex, age, and racial group. Therefore, we constructed such forecasts for 2011 to 2034 using (1) age-specific MM case and population data (from 1993 to 2010) among men and women for non-Hispanic whites, Hispanics of all races, blacks, and Asians or Pacific Islanders (API) obtained from the nationally representative and authoritative SEER 13 Registries Database (November 2013 submission; http://www.seer.cancer.gov/seerstat); (2) age-period-cohort incidence rate forecasting models[4,5]; and (3) official projections of population sizes produced by the US Bureau of the Census (http://www.census.gov/population/projections/data/national/2012). We multiply the projected incidence rate (Figure 1A) by the projected population size to estimate the number of new MM cases (Figure 1B).

From 2011 to 2013, there were an estimated 11 200 new MM cases per year in men and 8500 new cases per year in women. For

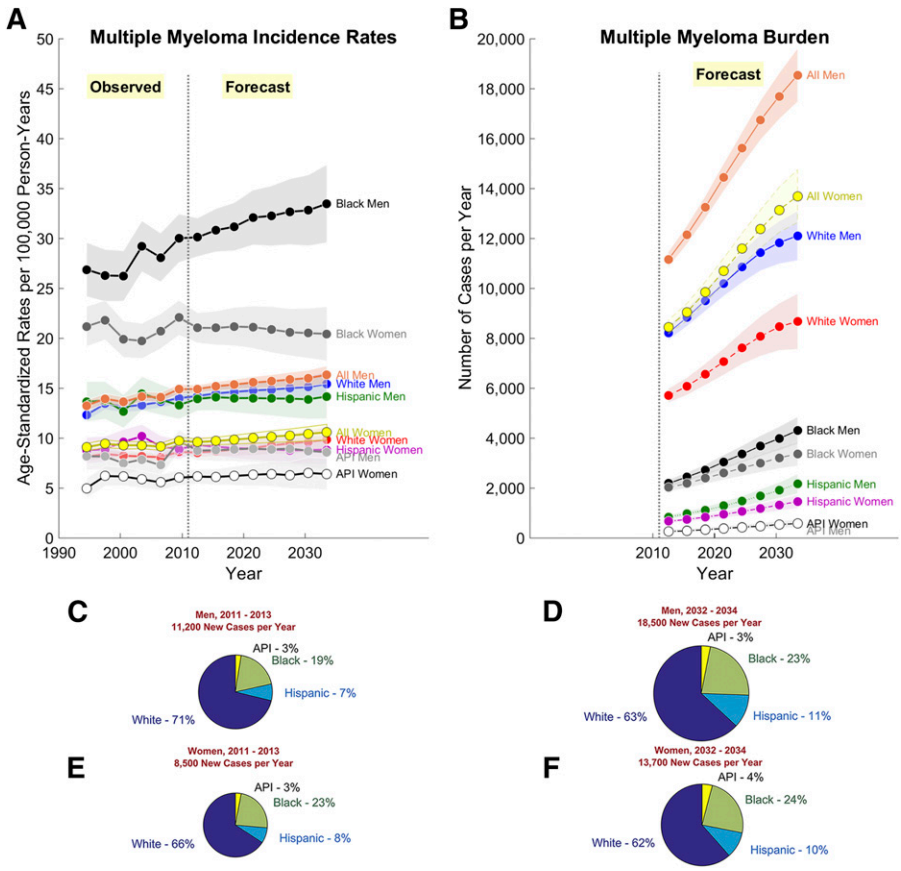


**Figure 1. Observed and projected burden of multiple myeloma in the US by sex and race/ethnicity.** (A) Age-standardized rates per 100 000 person-years (2000 US Standard Population) by sex and race/ethnic group, as labeled. The dotted line separates the observed data for 1993 to 2010 from the 2011 to 2034 forecast periods. Data points show age-standardized rates based on 3-year age groups and calendar periods. Shaded regions show point-wise 95% confidence intervals. Forecasts are based on age-period-cohort model for each sex and race/ethnic group. (B) Number of new multiple myeloma cases per year in the US, 2011 to 2034, by sex and race/ethnic group, as labeled. (C-F) Distribution of multiple myeloma burden in the US among men (C-D) and women (E-F), by race/ethnicity; observed for 2011 to 2013 and projected for 2032 to 2034, respectively. Panels show pie charts sized in proportion to the total number of new cases per year. Slices show percentage distribution by race/ethnic group.

2032 to 2034, we forecast a total of 18 500 new cases per year in men and 13 700 new cases per year in women (increases of 65% and 61%, respectively). Our models also forecast similarly large increases in new MM cases among Americans ages 64 to 84: 7300 male and 5400 female cases observed per year in 2011 to 2013 increasing by 93% and 91%, respectively, to projected 14 100 male and 10 300 female cases per year in 2032 to 2034. These estimates are very similar to those of Smith et al[3] and will be conservative if the MM surveillance definition is expanded.

As we show here, the age-standardized incidence rates (ASRs) of MM by sex and race/ethnicity for 1993 to 2010 are stable or slightly increasing (Figure 1A). Similar to the observed ASRs, our projected ASRs for 2011 to 2034, based on age-specific forecasts, are also stable or they slightly increase. In contrast, the number of new MM cases per year is expected to increase substantially over time in each sex and race/ethnic group (Figure 1B), primarily because of the expected changes in the demographic profile of the US. Importantly, in the Census Bureau projections, the black and Hispanic populations will increase much more rapidly than the white population. Consequently, the future distribution of new MM cases is expected to include more minorities. Among men, the percentage of black patients is expected to increase from 19% to 23%, and the percentage of Hispanic patients is expected to increase from 7% to 11% (Figure 1C-D). Smaller shifts are expected among women (Figure 1E-F). Including API, the percentage of MM patients who are racial or ethnic minorities is expected to increase, from 29% to 37% among men and from 34% to 38% among women. Hence, the percentage of patients who are white is expected to decrease from 71% to 63% among men and from 66% to 62% among women.

In sum, to a greater extent in the future than now, MM will primarily be a disease that affects older persons ages 64 to 84 years. Indeed, circa 2032 to 2034, we estimate that 3 of every 4 newly diagnosed MM patients will be aged 64 to 84 years, an increase from ~2 of every 3 patients diagnosed today. These results highlight the need for more effective MM therapies, especially for patients aged 64 to 84 years, who have a worse prognosis despite recent advances.[6-9] Our analyses also suggest for the first time that the percentage of MM patients who are racial or ethnic minorities is expected to increase, from 29% to 37% among men and from 34% to 38% among women. Therefore, our results strongly suggest that future clinical trials should be representative of the patient population, which increasingly will include larger numbers of racial and ethnic minorities.

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**Acknowledgments:** This research was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute (NCI), Division of Cancer Epidemiology and Genetics.

**Contribution:** P.S.R. developed the statistical methodology and software and designed the study; K.A.B. and W.F.A. assembled SEER 13 data; K.A.B.

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**Conflict-of-interest disclosure:** The authors declare no competing financial interests.

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# To the editor:

## First characterization of platelet secretion defect in patients with familial hemophagocytic lymphohistiocytosis type 3 (FHL-3)

Familial hemophagocytic lymphohistiocytosis (FHL), a rare autosomal recessive disorder of lymphocyte cytotoxicity, is caused by mutations in genes encoding perforin (FHL-2) or proteins important for intracellular trafficking/exocytosis of perforin-containing lytic granules: Munc13-4 (FHL-3), syntaxin 11 (FHL-4), and Munc18-2 (FHL-5).[1] FHL-1 is due to an unidentified gene defect located on chromosome 9. Munc13-4 (a Rab27a effector) coordinates exocytosis in hematopoietic cells.[2,3] Munc13-4 deficiency (FHL-3) results in defective cytolytic granule exocytosis.[4] Interestingly, platelets from Munc13-4–deficient mice showed a severe secretion defect of α- and dense granules.[5] In patients with FHL-3, bleeding symptoms have been rarely reported because patients may have not been challenged (ie, surgery).[6] An 8-month-old Chinese FHL-3 patient died because of gastrointestinal hemorrhage.[7] A platelet secretion defect in patients with FHL-5 has been described previously.[8,9]

Therefore, we analyzed platelet function in 2 unrelated male patients with genetically confirmed FHL-3. Both patients presented with clinical symptoms indicative of hemophagocytic lymphohistiocytosis (HLH) and fulfilled the diagnostic criteria.[10] Functional analyses showed absent degranulation of cytotoxic T cells and reduced degranulation of natural killer cells. Patient 1 (diagnosed at the age of 4 months) showed compound heterozygous mutations in the *UNC13D* gene accounting for FHL-3: c.551G>A (p.W184X) in exon 6 and c.118-308C>T in intron 1. After treatment according to the HLH 2004 protocol, haploidentical hematopoietic stem cell transplantation was performed at the age of 16 months.[10] Patient 2 (diagnosed at the age of 5 months) had severe central nervous system involvement and showed compound heterozygous splice donor site mutations of *UNC13D*: c.753+1G>T of exon 9 and c.1389+1G>A of exon 15. The patient received treatment according to the HLH 2004 protocol and underwent hematopoietic stem cell transplantation from a matched unrelated donor at the age of 9 months. He died of HLH relapse due to graft failure 4 months later. No major bleeding episodes were observed in either patient. The platelet studies were performed shortly before transplantation when patients were stable and did not receive medication, which induced secretion defects. Platelet count was normal at the time of platelet studies.

Flow cytometric analyses of platelets from both patients revealed severely diminished to absent platelet α- (CD62P) and dense granule (CD63) secretion in response to thrombin, collagen, and thrombin receptor activating peptide (TRAP) in platelet-rich plasma (Figure 1A-D; TRAP not shown). Collagen-induced adenosine triphosphate secretion (lumiaggregometry) in whole blood was absent (Figure 1E), whereas agonist-induced fibrinogen binding (data not shown) and aggregation (Figure 1F) were normal for a child of that age. In addition, flow cytometric analyses of platelets from patient 2 showed absent mepacrine uptake and release (a marker of uptake and release of dense body contents), as well as absent expression of the lysosomal marker CD107a (LAMP-1) in response to collagen and TRAP (data not shown).

These data demonstrate a selective impairment of platelet granule secretion in patients with FHL-3, and thus support an important role for Munc13-4 in human platelet degranulation. Although bleeding symptoms in FHL-3 patients can be mild, our findings clearly demonstrate that Munc13-4 deficiency is more than a genetic disorder of cytotoxicity.

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