Predicting Successful Phase Advancement and Regulatory Approval in Multiple Myeloma From Phase I Overall Response Rates

Purpose Drug development in oncology is resource intensive, time consuming, and frequently unsuccessful. Here, we hypothesized that therapeutic benefit of published phase I studies of antimyeloma investigational agents was associated with advancement to phase II and future regulatory approval.

Patients and Methods Seventy four phase I trials that treated patients with multiple myeloma (n = 2,408) conducted from 2004 to 2015 were analyzed to assess drug safety, efficacy, phase advancement, and regulatory approval.

Results The median overall response rate (ORR) for all single-agent trials evaluated was 13.2%. However, the ORR in trials that advanced to phase II was 19%, whereas it was only 4% in trials that failed to advance. The median ORR was 23% for trials testing agents that were ultimately approved by the US Food and Drug Administration compared with only 8% for trials testing agents that were not approved (hazard ratio, 2.21; 95% CI, 2.01 to 2.61; \( P = .012 \)). Importantly, the absolute number of phase I trials in multiple myeloma, but not the success rate, significantly increased over the period studied. The proportion of industry-sponsored trials also steadily increased over that same period. The ratio of initial dose to maximum tolerated dose was 0.29, suggesting that many patients were undertreated.

Conclusion Investigational agents with higher ORRs in phase I trials were more likely to advance to phase II trials and achieve US Food and Drug Administration approval. Our results suggest that designing phase I trials to maximize the antimyeloma efficacy of a given compound may lead to more successful and cost-effective drug development.

INTRODUCTION

Multiple myeloma (MM) is a fatal blood cancer that accounted for more than an estimated 12,600 deaths in the United States in 2016.\(^1,2\) Greater understanding of the molecular basis of MM has led to the successful development of numerous treatments for this challenging disease.\(^3,4\) Despite the development of novel biologic and immunomodulatory therapies and significant extension of life expectancy for patients during the last decade, MM remains largely incurable, causing most patients with MM to undergo a relapse-remission course.\(^5,6\) Indeed, because of an aging population, longer survival, and lack of a curative therapy, MM prevalence is predicted to increase by 57% in 2030 compared with 2010.\(^7,8\) Therefore, even in the era of robust drug development, there is an urgent need to develop more effective agents that can be used alone or in combination with other therapies to attain a cure for MM.\(^9\)

The recent number of small molecules and immunomodulatory agents that have received regulator approval in the United States and Europe for MM treatment is unprecedented.\(^10\) The US Food and Drug Administration (FDA) approved panobinostat in combination with bortezomib and dexamethasone for patients who have received at least two prior regimes in early 2015.\(^11\) By the end of the year, the FDA had approved three more agents: single-agent daratumumab, elotuzumab in combination with lenalidomide and dexamethasone, and ixazomib in combination with lenalidomide and dexamethasone.\(^12-14\) It also expanded the indication for carfilzomib from use as monotherapy only to use in combination with lenalidomide and dexamethasone in patients with relapsed disease.\(^15\)
These approvals were part of a record seven new agent approvals and 16 regulatory approvals during the past 12 years for MM.

First-in-human phase I trials are the first step in the clinical translation of preclinical findings. The primary goal is to assess agent safety and toxicity, investigate pharmacokinetics, and determine the maximum tolerated dose (MTD). The advancement of an investigational agent from bench to bedside is largely dependent on conducting a successful phase I trial. However, the relationship between antineoplastic activity observed in phase I MM trials and the early success (ie, advancement to phase II phase I trial) is largely dependent on conducting a successful phase I trial. Here, we hypothesized that the overall success (ie, advancement to phase II trials) and late success of such agents (ie, final regulatory approval) has not been previously evaluated. Here, we hypothesized that the overall response rate (ORR) of antamyeloma agents evaluated in phase I trials correlated with advancement to phase II and future regulatory approval.

PATIENTS AND METHODS

Data Sources

First, we identified all phase I abstracts on MM presented between 2004 and 2015 at annual meetings of the American Society of Hematology, American Society of Clinical Oncology, and the European Hematologic Association. We started with meeting abstracts to decrease the selection bias toward published trials and extended our search to the published manuscripts reporting these trials. We chose to create our own database because there were no appropriate datasets available for this type of analysis. Next, we used MEDLINE and the Cochrane Library to find all phase I studies in MM published before December 2015. The “related articles” function in PubMed was used to identify additional, potentially relevant articles. Furthermore, we searched Clinicaltrials.gov by using the keywords “multiple myeloma” and “phase I” and limited our inclusion to trials with “completed” or “with results” status.

Trial Selection

We excluded trials from analysis that involved allogeneic bone marrow transplantation, combined a new agent with autologous bone marrow transplantation, used radiation therapy, did not separate phase I from phase II data of phase I/II trials, or only reported supportive care or bone-directed therapies (eg, anti-RANKL). The type of phase I trial design was not part of the exclusion criteria. When there were multiple reports from the same trial in subsequent years, the first year of publication was used to analyze time trends. The study selection strategy focused on the earliest experimental agent reports, which were expected to have low benefit-to-risk ratios and higher scrutiny by institutional review boards and the FDA.

Data Extraction

The data were extracted manually by two reviewers (C.S. and R.Y.) based on the selection criteria. To assess interobserver variability, each trial was assigned to two separate reviewers. Two authors (E.M. and B.-G.K.) reviewed the data and resolved conflicts by discussing with a third author (J.J.D.). Trials were grouped based on the mechanism of action of the study drug as follows: immunomodulators, proteasome inhibitors, histone deacetylase inhibitors, AKT inhibitors, cytotoxic agents, mammalian target of rapamycin inhibitors, heat shock protein inhibitors, immunosuppressors, immunotherapies, and tyrosine kinase inhibitors. Each group was further subdivided into combination versus single-agent therapy. When a study abstract did not include adequate details of clinical outcome, we relied on the manuscript. If the trial was not published as a full manuscript, data were extracted from the abstract only (Appendix).

Outcomes, Definitions, and Explanatory Variables

The potential therapeutic benefit of investigational agents was classified as very good partial response or better (≥ VGPR), partial response (PR), progressive disease (PD), or stable disease according to the response criteria of the International Myeloma Working Group (IMWG) and the European Group for Blood and Marrow Transplant. The ratio of PD or overall response was calculated by dividing the number of patients with PD or response by the total number of enrolled patients in that trial (regardless of dose level). The ORR was calculated by combining rates of PR and ≥ VGPR. Serious adverse events (SAEs) were defined as grade 3 or 4 as assessed by the universal Common Terminology Criteria for Adverse Events. The SAE rate was assigned as a continuous variable per trial. For cross-trial comparisons of performance status, Karnofsky performance scores ≥ 80% were assigned to Eastern Cooperative Oncology Group (ECOG) scores of 0 to 1, and Karnofsky performance scores ≤ 70% were assigned ECOG scores of ≥ 2. To study the effect of prior lines of therapy on ORR in phase I trials in MM, the trials were dichotomized based on median number of prior lines of therapy for all trials (ie, > four or ≤ four). Reported MTD was assigned to each phase I trial as a continuous variable. The advancement of a given agent to a phase II trial was evaluated by confirming a recruiting phase II trial listed on Clinicaltrials.
Both generic and chemical names of the investigational agent were used as keywords without any time limitation.

**Statistical Analysis**

The primary objective of the study was to assess the value of ORR in phase I trials in MM to predict early and late successful clinical development of given agents, which was defined as phase II advancement and FDA approval, respectively. Each trial was counted as a single unit to analyze the ORR correlation with phase II advancement and FDA approval. A χ² test was used to analyze the differences in patients’ characteristics as a categorical variable. Response type, death, and grade 3 to 4 toxicity rates were analyzed for individual trials in each category. We used a t test to evaluate differences in ORR of an agent that advanced to phase II versus those that did not and did the same for an FDA-approved agent versus non-FDA-approved agents. Analysis of variance was used to compare the ORR and SAEs. Because the treatment-related death rates demonstrated a skewed distribution, a Kruskal-Wallis test was used. For multivariable analysis, stepwise logistic regression with statistical significance at \( P < .05 \) was required for inclusion in the model. To determine the trends over the time period, we used a multivariable regression model excluding time, then examined for the independent correlation of time with ORR or treatment-related death. The 12-year study period was divided into four 3-year periods, and findings were unchanged using time as a continuous variable, except where noted. Statistical analysis was performed using SAS software (version 9.4; SAS Institute, Cary, NC).

**RESULTS**

**Study Set for Analysis and Trial Characteristics**

We initially identified 156 phase I, phase I with extension cohort, or phase I/II studies (Fig 1). After careful review, 32 trials were excluded because of the enrollment of other hematologic malignancies or solid tumors. Thirty-two trials were excluded in which the phase I component could not be interpreted separately from the phase II component or the extension cohort. An additional 18 trials were excluded because they involved radiation therapy or stem-cell transplantation. Among the remaining 74 eligible trials, 17 had never been published as full-length manuscripts, and data were extracted from the abstracts only. The rate of full publication (77%) was similar to that which has been reported in other comparable fields.21,22 Trials evaluated a heterogeneous group of experimental agents from different drug categories and mechanisms of action (Appendix Table A1).

Characteristics of the trials analyzed are listed in Table 1. A total of 2,408 patients were enrolled in the 74 analyzed trials. The median number of patients enrolled per trial was 29 (mean, 26; standard deviation, 24; interquartile range, 16 to 36 patients). Fifty-six percent of patients were male, and 44% were female. The median age of study participants was 67.8 years, with an increase toward the end of the study period. ECOG performance status was >2 in all trials; however, because of a lack of more granular data (ie, patient-level data), an analysis of performance status effect on clinical outcome was not possible. The median number of treatment lines before trial enrolment was four (mean, 3.92; standard deviation, 1.9 lines). Ninety percent of the trials were conducted using escalating dose levels in three to five cohorts of patients before establishing the MTD or before stopping the trial. The median ratio of initial dose level to final MTD was 0.29 across all phase I trials (range, 0.08 to 0.69), suggesting that a large fraction of enrolled patients in these trials were undertreated (Table 2). Thirty trials (41%) investigated single agents (with or without corticosteroids) and 44 (59%) studied combination therapies (two agents [37 trials], three agents
A majority of combination therapies were proteasome inhibitor (20 trials) or immunomodulatory drug based (19 trials). Most of the trials used oral drug administration (Table 2).

### Phase I ORR Correlates With Advancement to Phase II and Regulatory Approval

Response rates in 10 of the 74 trials were assessed based on European Group for Blood and Marrow Transplant response criteria, 58 were based on IMWG response criteria, and six trials did not mention the criteria used. A total of 1,007 of the 2,408 patients responded to agents under study, resulting in an ORR of 42% (range, 0% to 91%; Table 1). The median ORR was significantly lower in trials with single agents versus combination therapies (13.2% vs 48.3%, respectively; $P < .01$; Appendix Fig A1). Agents that advanced to phase II trials demonstrated a median ORR of 19%, compared with 4% for agents that did not advance to phase II (hazard ratio, 2.79; 95% CI, 2.12 to 3.32; $P = .001$; Fig 2). Daratumumab, ixazomib, pomalidomide, isatuximab, marizomib, oprozomib, filanesib, dinaciclib, venetoclax, and LGH-447 had single-agent antmyeloma activity and proceeded to phase II/III clinical trials (Fig 2). The median ORR was 23% for trials testing agents that were ultimately FDA approved, compared with only 8% for trials testing agents that were not approved (hazard ratio, 2.21; 95% CI, 2.01 to 2.61; $P = .012$).

### ORR Determinants

Next, we investigated the effect of different phase I parameters on ORR. To achieve a significant number adequate for running a robust statistical analysis, we extended our evaluation to the past 12 years; however, time may be a main cofounding factor influencing the interpretation of the results (ie, whether later trials had different characteristics or ran differently than earlier trials). To study a temporal trend of the format of phase I trials in MM, we divided the period between 2004 and 2015 into four 3-year periods (2004 to 2006, 2007 to 2009, 2010 to 2012, and 2013 to 2015) and built a regression model to assess the ORR, adjusted for time and other variables. Although a significant increase in the number of phase I trials conducted in MM occurred between 2004 and 2015 (ie, $>8$-fold), there was no specific pattern throughout the study period to indicate that the therapeutic benefit from phase I trials in MM of single agents

### Table 1. Univariable and Multivariable Predictors of Response to Therapy

| Variable                  | No. of Trials | No. of Patients | ORR* No. (%) | OR (95% CI)          | Univariable Predictors | Multivariable Predictors |
|---------------------------|---------------|-----------------|--------------|----------------------|------------------------|--------------------------|
| Total                     | 74            | 2,408           | 1,007 (42)   |                      |                        |                          |
| Year of publication       |               |                 |              |                      |                        |                          |
| Period 1, 2004-2006       | 4             | 141             | 76 (54)      | Reference            | Reference              |                          |
| Period 2, 2007-2009       | 6             | 498             | 249 (50)     | 0.94 (0.72 to 1.16)  | 0.96 (0.73 to 1.19)    |                          |
| Period 3, 2010-2012       | 17            | 562             | 213 (38)     | 0.66 (0.38 to 0.96)  | 0.70 (0.42 to 1.01)    |                          |
| Period 4, 2013-2015       | 47            | 1,207           | 591 (49)     | 0.79 (0.53 to 1.10)  | 0.82 (0.56 to 1.16)    |                          |
| Industry funded           |               |                 |              |                      |                        |                          |
| Yes                       | 49            | 1,427           | 405 (41)     | Reference            | Reference              |                          |
| No                        | 25            | 981             | 602 (60)     | 1.39 (1.07 to 1.62)  | 1.12 (0.89 to 1.32)    |                          |
| Combination type          |               |                 |              |                      |                        |                          |
| PI based                  | 20            | 732             | 409 (56)     | Reference            | Reference              |                          |
| IMiD based                | 19            | 634             | 336 (53)     | 0.98 (0.81 to 1.23)  | 0.96 (0.79 to 1.24)    |                          |
| No. of prior lines of therapy† |      |                 |              |                      |                        |                          |
| ≤ 4                       | 24            | 699             | 342 (49)     | Reference            | Reference              |                          |
| > 4                       | 50            | 1709            | 563 (33)     | 0.63 (0.42 to 0.87)  | 0.61 (0.40 to 0.85)    |                          |
| No. of involved agents    |               |                 |              |                      |                        |                          |
| Single                    | 30            | 621             | 81 (13.2)    | Reference            | Reference              |                          |
| Combination               | 44            | 1787            | 864 (48.3)   | 2.15 (1.48 to 3.47)  | 2.35 (1.63 to 4.57)    |                          |

Abbreviations: IMiD, immunomodulatory drug; OR, odds ratio; ORR, overall response rate; PI, proteasome inhibitor.

*Trial as the primary unit of analysis.
†Median prior lines of therapy was used.
R² = 0.17; P = .41) or combinational therapies (R² = 0.21; P = .21) had significantly changed during this period (Appendix Fig A1). The median number of prior treatment lines increased from the beginning to the end of the study period (Fig 3A) and was inversely correlated with response rate (R² = 0.2569; P = .009; Fig 3B). The effect that the number of prior lines of therapy had on response rates remained significant after multivariable analysis adjusted for age, year of publication, and ratio of initial dose to MTD. The proportion of industry-sponsored trials increased progressively during the study period, with significant increases in the last 3-year period compared with the first period (Table 1; Appendix Fig A1). Univariable analysis showed that patients enrolled in industry-sponsored trials had significantly lower response rates than their counterparts enrolled in trials with other funding sources. This difference was not significant when the model was adjusted for trial status based on single versus combinational agents (Appendix Table A3). The univariable and multivariable predictors of response to therapy according to the trial characteristics are listed in Appendix Table A3.

### DISCUSSION

Here, we present a comprehensive review of phase I trials in MM reported between 2004 and 2015 to determine if ORR could predict phase advancement and eventual FDA approval. The study period includes the era of emerging novel antimyeloma therapies and demonstrated an eight-fold increase in the number of trials conducted. Our analysis shows that the median ORR from these trials, even those that evaluated single agents, was higher than that previously reported in phase I clinical trials of anticancer agents (42% vs 5%, respectively), with significantly lower toxicity-related mortality (0.2% vs 0.49%, respectively).23 The primary objective of a phase I trial is to evaluate safety and determine the MTD or recommended phase II dose of an experimental agent. Interestingly, despite using trial design methodology that did not formally test antitumor efficacy, our cohort of phase I trials in MM showed that the observed efficacy was an important determinant of ultimate successful licensing. Moreover, as expected, our results indicate an inverse correlation between the number of prior lines of therapy and response rates. Therefore, designing phase I trials appropriate for treatment early in the course of disease may further enhance the chance of advancement to later-phase clinical trials for given compounds. Our analysis showed that despite an increase in the number of compounds tested in phase I trials in MM during the past 12 years, the antimyeloma efficacy in these trials, reflected in the ORR, did not improve over this period. The seemingly unaffected antitumor effect of compounds entered in phase I trials in MM could be interpreted as an indication of unchanged efficacy or poor compound selection for phase I trials in MM throughout the 12 years of study. This observation does not negate the significant scientific

| Characteristic                          | Value          |
|----------------------------------------|----------------|
| Time to publication, months*           |                |
| Mean (SD)                              | 25 (15)        |
| Median (IQR)                           | 22 (13-34)     |
| No. of patients per trial              |                |
| Mean (SD)                              | 26 (14)        |
| Median (IQR)                           | 29 (16-36)     |
| Median age of enrolled patients, years |                |
| 2004-2006                              | 66.7           |
| 2007-2009                              | 67.1           |
| 2010-2012                              | 67.9           |
| 2013-2015                              | 68.3           |
| Mean (median) No. of prior regimens    |                |
| 2004-2006                              | 3.4 (3)        |
| 2007-2009                              | 3.5 (3.6)      |
| 2010-2012                              | 4.2 (4.0)      |
| 2013-2015                              | 4.4 (4.06)     |
| Mean (median) No. of dosing cohorts    | 5.1 (4.8)      |
| Ratio of initial dose to MTD           | 0.29           |
| Original year of publication, No. (%)  |                |
| 2004-2006                              | 5 (5.8)        |
| 2007-2009                              | 13 (15.1)      |
| 2010-2012                              | 22 (25.6)      |
| 2013-2015                              | 46 (53.5)      |
| Publication journal, No. (%)           |                |
| Blood                                  | 12 (16)        |
| Journal of Clinical Oncology           | 7 (9)          |
| Clinical Cancer Research               | 7 (9)          |
| British Journal of Hematology         | 8 (10)         |
| Haematologica                          | 5 (7)          |
| Other                                  | 18 (24)        |
| Unpublished                            | 17 (23)        |
| Route of drug administration           |                |
| Parenteral                             | 34 (46)        |
| Oral                                   | 40 (54)        |

Abbreviations: IQR, interquartile range; MM, multiple myeloma; MTD, maximum tolerated dose; SD, standard deviation.

*Time from study start date listed on Clinicaltrials.gov to publication time (abstract or manuscript).
discoveries in the biology of MM and the tumor microenvironment. However, it does suggest that the new understanding of myeloma biology has yet to enhance compound selection for agents that have higher antimyeloma effect for phase I trials. This could be the result of a possible time lag between preclinical bench discoveries and testing in early-phase clinical trials. These results are consistent with earlier reviews of single-agent phase I trials of all malignancies, which demonstrate that the antitumor effects of targeted agents in phase I trials are not superior to those of older therapies, probably because of the high heterogeneity of the targeted agent compounds.24

Therapeutic benefit was reported in a slightly different format across the trials analyzed here. Although most trials used IMWG response criteria, which list five response categories (PD, stable disease, PR, VGPR, and complete response), a number of trials reported a group of patients experiencing minimal clinical response (MCR), with less than 50% response to define a PR. We recognize that combining MCR with other response categories in defining the ORR could overestimate the true response rate. However, the sensitivity analysis showed that there was no difference when analysis was restricted to the trials with response assessment without MCR as compared with the
ones that used MCR classifications. Therefore, we bundled all response categories to calculate the cumulative ORR.

In a standard 3 + 3 design, a low dose of an experimental agent is administered to an initial cohort of participants. Successive cohorts then receive escalating doses of the agent until a predetermined portion of patients develop dose-limiting toxicities. The inherent drawback in this method is that a significant number of participants may be underdosed. Earlier studies showed that most clinical responses were achieved with dose levels between 80% and 120% of the MTD.25 Our analysis demonstrates a ratio of initial dose to final MTD of 0.29, which suggests the potential undertreatment of a significant number of patients enrolled in these trials, most likely because of a dominance of the 3 + 3 trial design.26,27 Alternative strategies (eg, more rapid dose-escalation schema, intrapatient dose escalation, and implementation of newer adaptive Bayesian designs) may lead to the achievement of therapeutic dosage for a larger portion of enrolled patients and improve the therapeutic benefit of these trials.28 Although these strategies may decrease the number of patients and resources, as well as the amount of time, needed to complete the studies, this must be balanced against the potential for higher risk of SAEs.26,29 Importantly, we should consider that participants may be willing to accept greater risk of toxicity in return for a higher chance of therapeutic benefit.30

Taken together, the results of our analysis indicate that ORR in phase I trials in MM from 2004 to 2015 was a strong predictor for successful clinical development of investigational agents. Therefore, designing a phase I trial to maximize the antmyeloma efficacy of a given compound may lead to more successful and cost-effective drug development. Our data demonstrate that response rate declines significantly when trials are performed late in the course of the disease. This can be relevant to the success of phase I trials in MM in the new era, in which the number of possible combinational therapies available for relapsed MM is rapidly increasing. Reserving phase I trial enrollment as a last-resort treatment approach significantly compromises the chances of success for a compound.

DOI: https://doi.org/10.1200/CCI.17.00055
Published online on ascopubs.org/journal/cci on November 9, 2017.

AUTHOR CONTRIBUTIONS
Conception and design: Ehsan Malek, James J. Driscoll
Collection and assembly of data: Ehsan Malek, Caner Saygin, Rebecca Ye, Fahrettin Covut
Data analysis and interpretation: Ehsan Malek, Byung-Gyu Kim, Jeffrey Welge, Neal J. Meropol, Marcos De Lima, James J. Driscoll
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Ehsan Malek
Consulting or Advisory Role: Takeda Pharmaceuticals
Speakers’ Bureau: Celgene, Takeda Pharmaceuticals, Amgen, Sanofi
Research Funding: Cumberland Pharmaceuticals

Caner Saygin
No relationship to disclose

Rebecca Ye
No relationship to disclose

Fahrettin Covut
No relationship to disclose

Byung-Gyu Kim
No relationship to disclose

Jeffrey Welge
No relationship to disclose

Neal J. Meropol
Employment: Flatiron Health
Research Funding: Genomic Health

Marcos De Lima
Consulting or Advisory Role: Celgene, Pfizer, Amgen
Research Funding: Celgene

James J. Driscoll
No relationship to disclose
REFERENCES

1. Costa LJ, Brill IK, Omel J, et al: Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv 1:282-287, 2017

2. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2016. CA Cancer J Clin 66:7-30, 2016

3. D’Agostino M, Palumbo A: Moving toward a tailored therapy in multiple myeloma. J Oncol Pract 12:293-294, 2016

4. Munshi NC, Anderson KC: Minimal residual disease in multiple myeloma. J Clin Oncol 31:2523-2526, 2013

5. Mimura N, Hideshima T, Anderson KC: Novel therapeutic strategies for multiple myeloma. Exp Hematol 43:732-741, 2015

6. 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 33:2863-2869, 2015

7. Smith BD, Smith GL, Hurria A, et al: Future of cancer incidence in the United States: Burdens upon an aging, changing nation. J Clin Oncol 27:2758-2765, 2009

8. Rosenberg PS, Best A, Anderson WF, et al: Multiple myeloma will become a common cancer in the era of modern therapy. Cancer Res 76, 2016 (abstr 5231)

9. Bianchi G, Richardson PG, Anderson KC: Best treatment strategies in high-risk multiple myeloma: Navigating a gray area. J Clin Oncol 32:2125-2132, 2014

10. Kapoor P, Rajkumar SV: Multiple myeloma in 2016: Fresh perspectives on treatment and moments of clarity. Nat Rev Clin Oncol 14:73-74, 2017

11. Alsina M, Lonial S, Weber D, et al: PANORAMA 2: A phase II study of panobinostat (LBH589) in combination with bortezomib (BTZ) and dexamethasone (DEX) in patients with relapsed and BTZ-refractory multiple myeloma (MM). J Clin Oncol 28, 2010 (suppl; abstr TPS308)

12. Moreau P, Masszi T, Grzasko N, et al: Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 374:1621-1634, 2016

13. Lonial S, Dimopoulos M, Palumbo A, et al: Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 373:621-631, 2015

14. Hofmeister CC, Lonial S: How to integrate elotuzumab and daratumumab into therapy for multiple myeloma. J Clin Oncol 34:4421-4430, 2016

15. Moreau P, Palumbo A, Stewart A, et al: A randomized, multicenter, phase (Ph) III study comparing carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (Dex) to LEN and Dex in patients (Pts) with relapsed multiple myeloma (MM). J Clin Oncol 29, 2011 (suppl; abstr TPS225)

16. Kortuem KM, Zidich K, Schuster SR, et al: Activity of 129 single-agent drugs in 228 phase I and II clinical trials in multiple myeloma. Clin Lymphoma Myeloma Leuk 14:284.e5-290.e5, 2014

17. Krzyzanowska MK, Pintilie M, Tannock IF: Factors associated with failure to publish large randomized trials presented at an oncology meeting. JAMA 290:495-501, 2003

18. Agrawal M, Emanuel EJ: Ethics of phase 1 oncology studies: Reexamining the arguments and data. JAMA 290:1075-1082, 2003

19. Durie BG, Harousseau JL, Miguel JS, et al: International uniform response criteria for multiple myeloma. Leukemia 20:1467-1473, 2006

20. Trotti A, Colevas AD, Setser A, et al: CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176-181, 2003

21. Goldman L, Loscalzo A: Fate of cardiology research originally published in abstract form. N Engl J Med 303:255-259, 1980

22. Chalmers I, Adams M, Dickersin K, et al: A cohort study of summary reports of controlled trials. JAMA 263:1401-1405, 1990

23. Horstmann E, McCabe MS, Grochow L, et al: Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med 352:895-904, 2005

24. Roberts TG Jr, Goulart BH, Squillieri L, et al: Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. JAMA 292:2130-2140, 2004
25. Von Hoff DD, Turner J: Response rates, duration of response, and dose response effects in phase I studies of antineoplastics. Invest New Drugs 9:115-122, 1991

26. Simon R, Freidlin B, Rubinstein L, et al: Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst 89:1138-1147, 1997

27. Le Tourneau C, Lee JJ, Siu LL: Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst 101:708-720, 2009

28. Braun TM, Wang S: A hierarchical Bayesian design for phase I trials of novel combinations of cancer therapeutic agents. Biometrics 66:805-812, 2010

29. Berry DA, Mueller P, Grieve AP, et al: Adaptive Bayesian Designs for Dose-Ranging Drug Trials, in Carlin B, Carriquiry A, Gatsonia C et al (eds): Case Studies in Bayesian Statistics. New York, , NY, , Springer, 2002, pp 99-XXXX

30. Daugherty CK, Ratain MJ, Minami H, et al: Study of cohort-specific consent and patient control in phase I cancer trials. J Clin Oncol 16:2305-2312, 1998
APPENDIX

Serious Adverse Events

Overall, seven therapy-related deaths were observed in the 2,408 recruited patients (overall death rate, 0.2%). Patients who participated in combination therapy versus single-agent studies experienced more serious adverse events (SAEs; 29% vs 16%, respectively; hazard ratio, 1.35; 95% CI, 1.12 to 1.61; \( P = .04 \)). The median SAE rate was 22% across all phase I trials (range, 0% to 44%; Appendix Fig A1). SAE rates were not statistically different between the four periods of the study (\( P = .302 \)), suggesting that the risk of an SAE remained stable through the study period (Appendix Fig A1).

Table A1. Parameters Included in Data Extraction

| Parameter | Details |
|-----------|---------|
| Regulatory data | |
| Author’s name | |
| Year of submission to ASH/ASCO/EHA | |
| Journal of publication | |
| Pharmaceutical funding (yes or no) | |
| Geographic location (United States, Europe, or Japan) | |
| Experimental agent | |
| Name (brand and generic) | |
| Mechanism of action | |
| Single-agent vs combination therapy* | |
| Route of administration (oral, subcutaneous, or intravenous) | |
| FDA approval until December 2015 (yes or no) | |
| Trial design | |
| Phase I or I/II† | |
| No. of lines of therapy as inclusion criterion | |
| Dose escalation (intrapatient vs interpatient)‡ | |
| 3 + 3 design (yes or no) | |
| Trial outcome | |
| No. of evaluable patients | |
| Serious adverse reaction rate | |
| ORR | |
| MTD | |
| No. of dose levels | |

Abbreviations: ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; EHA, European Hematology Association; FDA, US Food and Drug Administration; MTD, maximum tolerated dose; ORR, overall response rate.

*Combination therapy refers to the addition of a proteasome inhibitor, immunomodulatory agent, or cytotoxic agent. Addition of corticosteroids was not counted.
†Phase I/II denotes a trial with a phase II portion with the goal of efficacy testing as part of the trial design.
‡Trials with intrapatient dose-escalation design allowed each patient to receive a successively higher dose if they had not experienced a serious adverse event. Trials with interpatient dose-escalation design allowed a fixed dose of an experimental agent to each patient with dose escalation between groups.
| Agent                        | No. of Trials | Single Agent | Combination |
|------------------------------|--------------|--------------|-------------|
| **AKT inhibitors**          |              |              |             |
| Afuresertib                  |              | 1            | 1           |
| Perifosine                   |              |              |             |
| **Alkylating agents**       |              |              |             |
| Bendamustine                 |              | 1            | 2           |
| PM00104 (Zalypsis; PharmaMar, Madrid, Spain) | |  | |
| **Antibody-drug conjugates**|              |              |             |
| Lorvotuzumab (anti-CD56)    | 2            |              | 1           |
| Indatuximab (anti-CD138)    |              |              |             |
| **Arsenic derivatives**     |              |              |             |
| Arsenic trioxide             |              | 1            | 1           |
| ZIO-101 (dimethylarsinic glutathione) | |  | |
| **Aurora A kinase inhibitor**|              |              |             |
| Alisertib (MLN8237)         |              | 1            |             |
| **BCL-2 inhibitor**         |              |              |             |
| ABT199                       |              | 1            | 2           |
| **BTK inhibitors**          |              |              |             |
| Ibrutinib                    |              | 1            | 3           |
| ONO/GS-4059                  |              |              |             |
| **CDK inhibitor**            |              |              |             |
| Dinaciclib                   |              | 1            | 2           |
| **Cellular therapy**        |              |              |             |
| Expanded NK cell             |              | 1            | 0           |
| **Histone deacetylase inhibitors** | |  | |
| Panobinostat                 |              | 2            | 4           |
| Ricolinostat                 |              |              |             |
| Vornostat                    |              |              |             |
| ITF2357                      |              |              |             |
| Romidepsin                   |              |              |             |
| **IL-6 inhibitor**           |              |              |             |
| Siltuximab                   |              | 1            | 1           |
| **Immunomodulators**        |              |              |             |
| Pomalidomide                 |              | 1            | 5           |
| Thalidomide                  |              |              |             |
| Lenalidomide                 |              |              |             |
| **KSP inhibitor**            |              |              |             |
| Filanesib                    |              | 1            |             |
| **Oncoviral therapy**       |              |              |             |
| Reolysin                     |              | 1            | 0           |

(continued on following page)
Table A2. Compounds Tested in Phase I Trials According to Mechanism of Action (continued)

| Agent                      | No. of Trials | Single Agent | Combination |
|----------------------------|---------------|--------------|-------------|
| **Monoclonal antibodies**  |               |              |             |
| Daratumumab                | 3             | 8            |             |
| Elotuzumab                 |               |              |             |
| Indatuximab                |               |              |             |
| SAR650984                  |               |              |             |
| BB-10901 (anti-CD56)       |               |              |             |
| AVE-1642 (anti-IGF)        |               |              |             |
| CP-751871 (anti-IGF)       |               |              |             |
| Dacetuzumab (anti-CD40)    |               |              |             |
| MFGIR1877S (anti-FGFR3)    |               |              |             |
| Milatuzumab (anti-CD74)    |               |              |             |
| Anti-KIR                   |               |              |             |
| CNT0328 (anti-IL-6)        |               |              |             |
| HuLuc63 (anti-CS1)         |               |              |             |
| **PI3K inhibitor**         |               |              |             |
| Perifosine                 |               |              |             |
| **Proteasome inhibitors**  |               |              |             |
| Carfilzomib                | 3             | 9            |             |
| Ixazomib                   |               |              |             |
| Marizomib                  |               |              |             |
| Oprozomib                  |               |              |             |
| **Immunosuppressant**      |               |              |             |
| Mycophenolic acid          | 1             |              |             |
| **mTOR inhibitors**        |               |              |             |
| RAD001                     | 2             | 2            |             |
| Temsirolimus               |               |              |             |
| **Bone-directed agent**    |               |              |             |
| Samarium lexidronam        | 2             | 1            |             |
| **HSP inhibitors**         |               |              |             |
| Tanespimycin (HSP90 inhibitor) | 2        | 1            |             |
| IPI-504 (retaspimycin)     |               |              |             |
| **Others**                 |               |              |             |
| Nelfinavir                 | 1             | 1            |             |
| Plitidepsin (Aplidin; PharmaMar) |          |              |             |

Abbreviations: FGFR, fibroblast growth factor receptor; HSP, heat shock protein; IGF, insulin-like growth factor; IL-6, interleukin-6; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase;
| Variable               | 2004-2006 | 2007-2009 | 2010-2012 | 2013-2015 | P     |
|------------------------|-----------|-----------|-----------|-----------|-------|
| Study Period           |           |           |           |           |       |
| No. of patients        | 141       | 498       | 562       | 1207      | .003  |
| Single agent           | 40        | 103       | 150       | 328       | .010  |
| Combination            | 101       | 395       | 412       | 879       | .001  |
| Sex                    |           |           |           |           |       |
| Men, No. of total (%)  | 80 (56)   | 266 (54)  | 310 (55)  | 680 (56)  | .342  |
| ORR, %                 | 54        | 50        | 38        | 49        | .745  |
| Single agent           | 14        | 7         | 9         | 16        | .213  |
| Combination            | 40        | 43        | 29        | 33        | .439  |
| Industry sponsored, %  | 40        | 46        | 60        | 71        | .003  |
| Single agent           | 25        | 26        | 38        | 49        | .011  |
| Combination            | 15        | 20        | 22        | 22        | .086  |
| Progressive disease, % | 9         | 21        | 19        | 20        | .197  |
| Single agent           | 5         | 13        | 11        | 13        | .210  |
| Combination            | 4         | 8         | 8         | 7         | .426  |
| Serious adverse effect, % | 22   | 21        | 27        | 28        | .302  |
| Single agent           | 8         | 8         | 10        | 9         | .612  |
| Combination            | 14        | 13        | 17        | 19        | .492  |

Abbreviation: ORR, overall response rate.
Fig A1. Data breakdown among the periods 2004 to 2006, 2007 to 2009, 2010 to 2012, and 2013 to 2015. (A) Number of single-agent or combination phase I trials in multiple myeloma, (B) percentage of industry-sponsored trials, and (C) median response rate and rate of serious adverse events (SAEs) per trial by each 3-year period.