original report

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

abstract

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.

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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 predicated 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 regulatory 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 regimens 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 trials) and late success of such agents (ie, final regulatory approval) has not been previously evaluated.[16] Here, we hypothesized that the overall response rate (ORR) of antimyeloma 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.[17] We chose to create our own database because there were no appropriate datasets available for this type of analysis.[18] 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

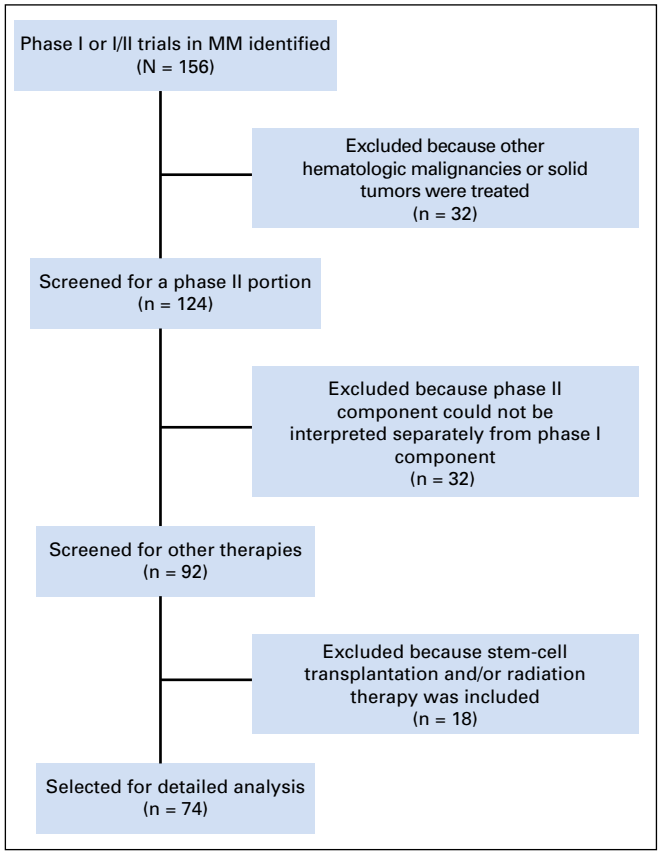
The potential therapeutic benefit of investigational agents was classified as very good partial response or better ($\geq$ VGPR), partial response (PR), progressive disease (PD), or stable disease according to the response criteria of the International Myeloma Working Group (IMWG) and the European Group for Blood and Marrow Transplant.[19] 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 $\geq$ VGPR. Serious adverse events (SAEs) were defined as grade 3 or 4 as assessed by the universal Common Terminology Criteria for Adverse Events.[20] The SAE rate was assigned as a continuous variable per trial. All deaths were listed as drug-related toxicities. For cross-trial comparisons of performance status, Karnofsky performance scores $\geq$ 80% were assigned to Eastern Cooperative Oncology Group (ECOG) scores of 0 to 1, and Karnofsky performance scores $\leq$ 70% were assigned ECOG scores of $\geq$ 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 $\leq$ 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.

gov. 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 χ^2 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).

Fig 1. Flowchart for studies of multiple myeloma (MM) included in or excluded from detailed analysis.



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

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 4.37)	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.

[six trials], and four agents [one trial]). 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% *v* 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 antimyeloma 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, 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, > eightfold), 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 2. Characteristics of Phase I Trials in MM

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).

(R^2 = 0.17; P = .41) or combinational therapies (R^2 = 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 (R^2 = 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% *v* 5%, respectively), with significantly lower toxicity-related mortality (0.2% *v* 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

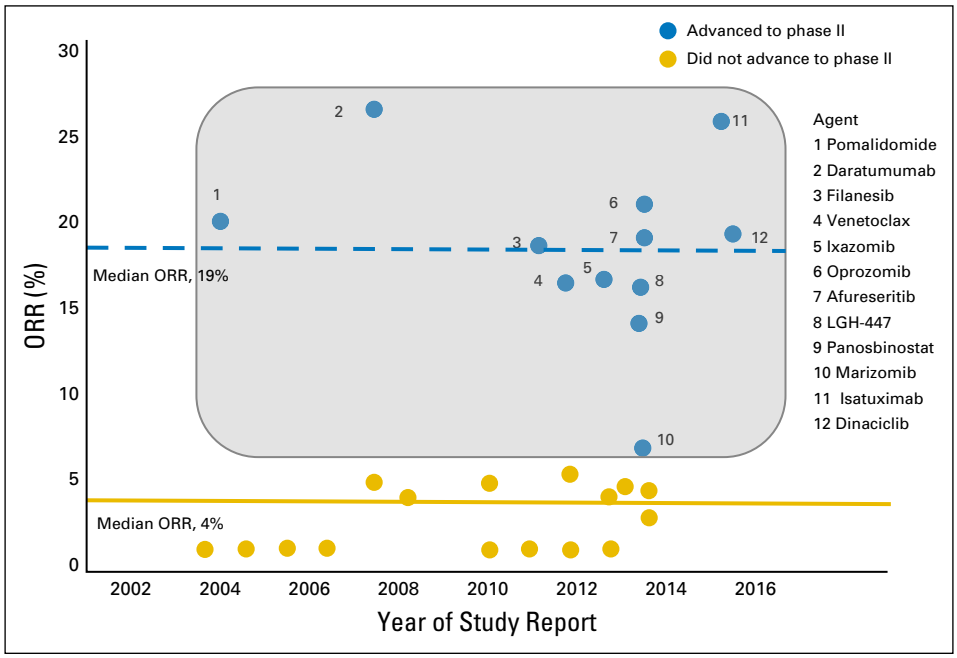


Fig 2. Overall response rate (ORR) from single-agent phase I trials correlates with advancement to phase II. Agents with significant single-agent antimyeloma activity that proceeded to later-phase trials are shown as blue dots; those that did not advance are represented by gold dots.

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

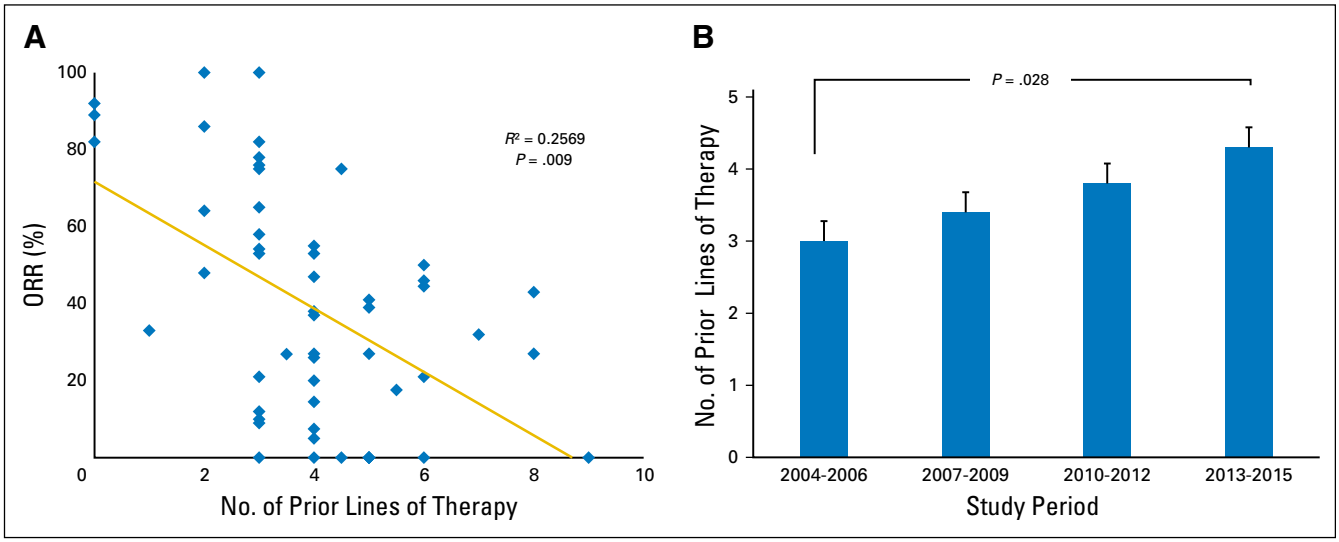


Fig 3. (A) Overall response rate (ORR) inversely correlates with the median number of lines of therapy received before phase I trial enrollment. (B) Median number of prior lines of therapy per trial by period. Error bars represent SE of the median for each 3-year period calculation.

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 antimyeloma 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.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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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% *v* 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
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 *v* 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 *v* 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.

Table A2. Compounds Tested in Phase I Trials According to Mechanism of Action

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
ZI0-101 (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 inhbitors		
Panobinostat	2	4
Ricolinostat		
Vorinostat		
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)		
MFGR1877S (anti- FGFR3)		
Milatuzumab (anti-CD74)		
Anti-KIR		
CNTO328 (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;

Table A3. Trial As the Primary Unit of Analysis

Variable	Study Period				*P*
	2004-2006	2007-2009	2010-2012	2013-2015	
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.

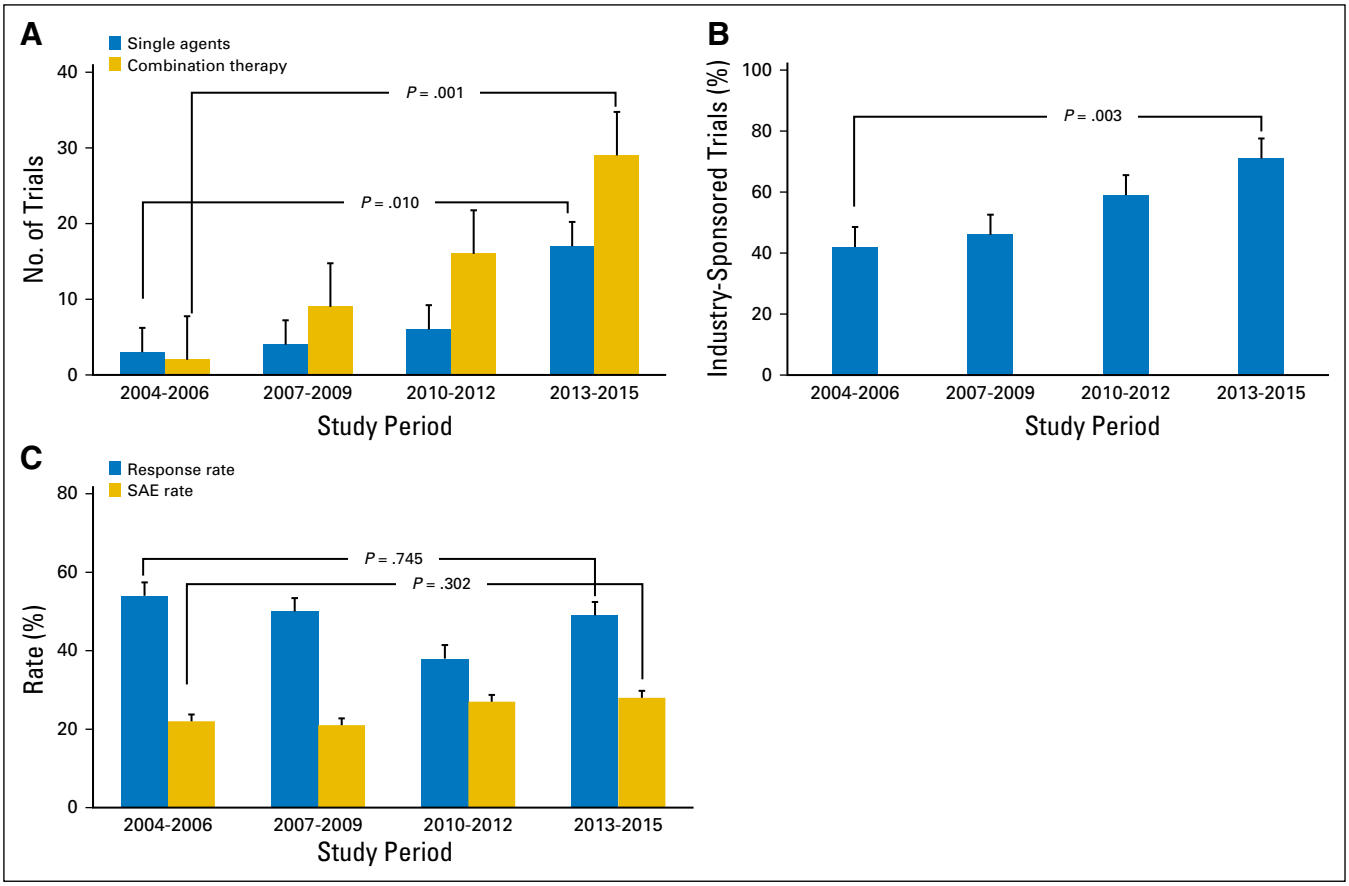

Fig A1. Data breakdown among the periods 2004 to 2006, 2007 to 2009, 2010 to 2012, and 2013 to 2015. (A) Number of single-agent or combination phase I trials in multiple myeloma, (B) percentage of industry-sponsored trials, and (C) median response rate and rate of serious adverse events (SAEs) per trial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