Clinical Cancer Research

Use of Expansion Cohorts in Phase I Trials and Probability of Success in Phase II for 381 Anticancer Drugs

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Abstract

Purpose: Evaluate the association between the use of phase I expansion cohorts (ECs) and drug performance in phase II as well as time to approval by the FDA.

Experimental Design: We performed a systematic search of MEDLINE for single-agent dose-finding adult oncology phase I trials published in 2006 to 2011 and subsequent phase II trials. Successful phase II trials were those that met their primary endpoints. Dates of approval were obtained from the Drugs@FDA website in April 2014. A logistic regression model was used to determine the associations between variables and success in phase II.

Results: We identified 533 phase I trials evaluating 381 drugs; 112 drugs had at least one phase I trial with an expansion cohort. Phase I trials with expansion cohorts of two to 20 patients were associated with a higher rate of successful phase II trials than those with no expansion cohort [48% vs. 27%; OR, 2.1; 95% confidence interval (CI), 1.1–4.0; $P = 0.037$]. Phase II success rates were the same for expansion cohort with two to 20 and more than 20 patients (48% vs. 52%). Other positive associations were disease-specific trials (OR, 1.7; 95% CI, 1.0–2.9; $P = 0.037$), industry sponsorship (OR, 2.9; 95% CI, 1.5–5.7; $P = 0.0024$), and response rate of 6% to 20% (OR, 2.89; 95% CI, 1.6–5.2; $P = 0.0007$). Drugs tested in phase I trials with expansion cohorts had a higher rate of 5-year approval (19% vs. 5%; HR, 4.4; 95% CI, 2.2–8.8; $P < 0.001$).

Conclusions: The use of expansion cohorts in phase I trials was associated with success of subsequent phase II trials. However, confounders may play a role in this association. *Clin Cancer Res; 23(15); 4020–6. ©2017 AACR.*

Introduction

The need for improvement in the efficiency of cancer drug development has led to new innovative phase I trial designs (1, 2). One strategy is the use of expansion cohorts, in which additional patients are enrolled in a phase I trial after the MTD or recommended phase II dose has been defined. The main goals of expansion cohorts are more accurate estimation of the MTD and more accurate assessment of drug activity. On the other hand, the use of expansion cohorts has been criticized (3, 4) because many trials using expansion cohorts lack clear objectives, proper statistical design, and independent data and safety monitoring boards. The actual value of expansion cohorts for drug development remains unknown.

Manji and colleagues (5) reviewed all single-agent dose-finding phase I oncology trials in adults listed in the MEDLINE database during 2006 to 2011 and found that the proportion of trials with expansion cohorts increased over the study period, from 12% in 2006 to 38% in 2011. For this study, we have expanded their database by systematically searching for the corresponding published phase II trials for all those phase I studies. We also searched the FDA website for the approval status of each drug. Our goal was to evaluate the association between the use of phase I expansion cohorts and drug performance in phase II trials or eventual regulatory approval.

Materials and Methods

Search strategy and study selection

The search strategy for the phase I trials included in this study has been described elsewhere (5). In summary, we searched MEDLINE for trials published from January 1, 2006, through December 31, 2011, that were prospective, single-agent dose-finding phase I studies performed in adults and involving systemic administration of antineoplastic agents for the treatment of solid or hematologic malignancies. If an author defined its trial as "phase I/II," it was included only if it had a dose-finding cohort.

There were no exclusion criteria based on therapeutic class (e.g., cytotoxic therapy, targeted therapy, or immunotherapy), but trials whose interventions included radiotherapy, surgery, or stem cell transplantation were excluded. We then used the Medical Subject Headings terms assigned to each report, the Drugs@FDA website (www.accessdata.fda.gov/scripts/cder/drugsatfda/), and the full text of the phase I articles to identify the experimental compound codes and chemical, generic, and trade names for each drug.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Phase I expansion cohorts are common in drug development, especially in oncology. However, two main questions remain unanswered: what is the optimal design for a phase I expansion cohort and what is their real impact in the drug development process. In this article, we have reviewed 381 cancer drugs, focusing on their original phase I trials, subsequent phase II studies, and eventual FDA approval. After correcting for possible confounders, we have shown that phase I expansion cohorts are associated with a higher likelihood of success in phase II and that in general, a sample size of 20 patients is enough for defining the MTD and providing enough efficacy information for adequate design of phase II trials. Therefore, this article supports the role of phase I expansion cohorts in drug development and provides important information on their optimal size.

We used those terms to identify published phase II trials for each drug using the PubMed search engine with the "clinical trial" filter (January 1, 2005–April 30, 2014; ref. 6). One reviewer (D.D.G. Bugano) analyzed all the trial abstracts to identify phase II studies. Studies were included if (i) they were not among the phase I trials identified; (ii) they were classified as phase I/II, or had no available classification but enrolled more than 15 patients and had no dose escalation; (iii) the abstract was available in English; (iv) they evaluated single-agent systemic antineoplastic therapy; and (v) the study population consisted of adults with cancer, or results were reported separately for adult subgroups. We then excluded studies that (i) had duplicate publications; (ii) were only published in conference proceedings; or (iii) used interventions that included stem cell transplantation, radiotherapy, or surgery.

Drug approval data were obtained from Drugs@FDA on April 30, 2014 (7). We excluded any drug for which the date of electronic publication of the first phase I trial was 6 months after the first FDA approval for any indication for that drug. This exclusion was necessary because our search results included phase I studies of new indications for previously approved drugs for which the original phase I studies could not be found and because many trials did not specify the actual start date of the study. The study selection process is summarized in Fig. 1.

Endpoints of interest

Drugs were classified in two groups depending on whether their phase I trials used expansion cohorts. Expansion cohorts were classified as any patients enrolled after the MTD or the recommended phase II dose had been defined. It was not possible to estimate how each individual phase I trial influenced the design of the corresponding phase II trials; therefore, we combined data for all phase I trials for each drug into single measurements. For example, if a drug was tested in three phase I trials and two of those had expansion cohorts, that drug was categorized in the expansion cohort group. The resulting "pooled trial" had patients from three trials in its dose escalation phase and from two trials in its expansion cohort.

Our primary endpoint was the probability of a drug's success in phase II. To be considered successful, drugs had to be tested in at least one phase II study meeting the following criteria: (i) the primary endpoint of the trial, as described in its methods section, included some measurement of drug efficacy; and (ii) the results section stated that the primary endpoint was met. Trials without a clear efficacy endpoint were excluded.

The secondary endpoint was time to first FDA approval, measured from the date of electronic publication of the earliest phase I study of a drug to the date of the first FDA approval for treatment of a solid or hematologic malignancy. Date of first electronic publication was chosen because most phase I trials in the database did not report on the date of first patient enrolled.

We also studied the impact of multiple variables on the two endpoints: therapeutic class, drug-specific trials, response rates, determination of an MTD, publication date, industry sponsorship, inclusion of multiple centers in the phase I trial, the number of patients enrolled, cancer type, the rate of grade 3–4 toxic effects, and occurrence of any grade 5 toxic effect.

Therapeutic classes were categorized as cytotoxic (traditional chemotherapy) or noncytotoxic (immunotherapies, mAbs, tyrosine kinase inhibitors, viral vectors, and vaccines). Response rates were based on the definitions in the different trials. The responses for the dose escalation and dose expansion cohorts were combined and classified into four groups: 0% (no responders), >0% but <6% (average response rates for phase I single-agent oncology trials; refs. 8–10), $\geq$6% but <20%, and $\geq$20% (unusually high response rates). The rates of toxic effects were included in the analysis if the Common Terminology Criteria for Adverse Events version 3.0 or later had been used. We considered the MTD to have been reached if at least one phase 1 trial for a drug mentioned a value for the MTD.

Data extraction

Three authors (D.D.G. Bugano, D.L.F. Jardim, and A. Zer) reviewed full-text versions of all the phase I studies and collected information on response rates, toxic effects, and MTD. One author (D.D.G. Bugano) reviewed all full-text publications for discrepancies. The remaining information from the phase I trials had been previously extracted (5).

A single author (D.D.G. Bugano) extracted the data for the phase II studies from their abstracts and obtained the date of first approval from the Drugs@FDA website.

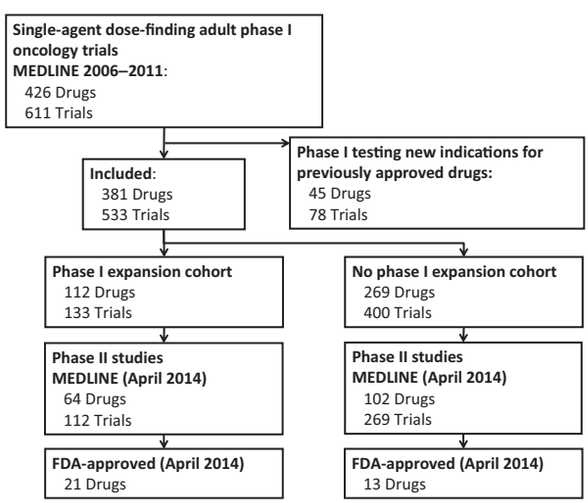

Figure 1.
Flow diagram of study selection.

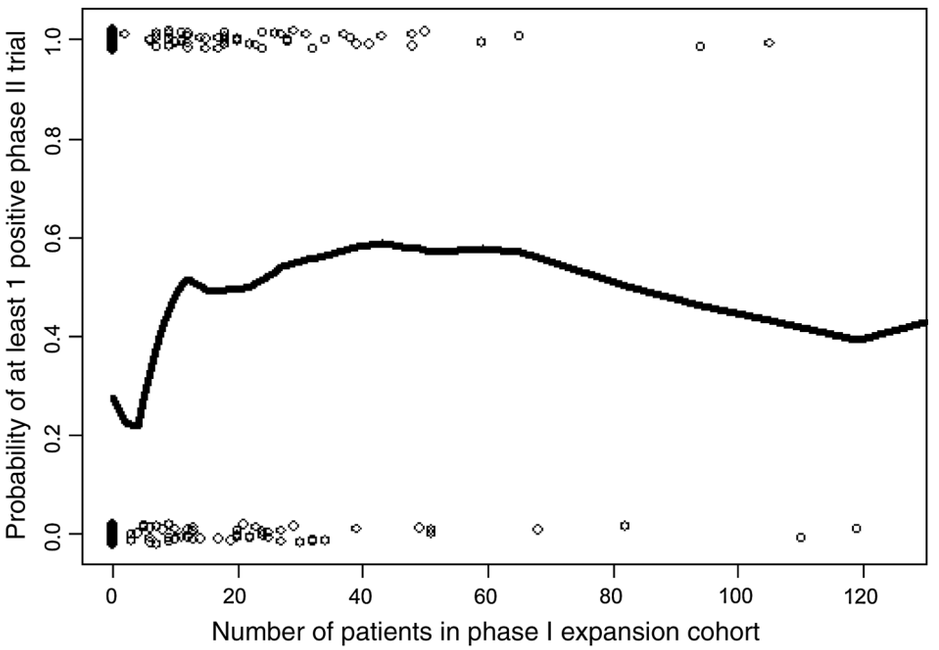

Figure 2.
Scatterplot of probability of success in a phase II trial relative to the size of the phase I expansion cohort.

Data synthesis and statistical analysis

Study factors were compared between the expansion cohort and nonexpansion cohort groups using χ^2 tests. A logistic regression model was used to determine the associations between each of the study variables and the probability of success in subsequent phase II trials. The cutoff for "total number of patients in phase I trials" was based on values that would create a more balanced distribution; cutoffs for "response rate" and "toxicity rate" were based on the literature and clinical judgment. For size of the expansion cohorts, subgroups were created on the basis of visual analysis of a scatterplot with smooth fitted lines of the probability of success in phase II relative to the size of the expansion cohort (Fig. 2).

Cox proportional hazards regression models were used to evaluate the associations between independent variables and time to first FDA approval. Data were censored on April 30, 2014. The probabilities of FDA approval as a function of time since the publication of the phase I study were estimated using the Kaplan–Meier method.

All statistical analyses were performed using Spotfire S+ 8.2 for Windows (TIBCO Software Inc.). Unless otherwise specified, the significance threshold was set at 0.05.

Results

Study selection

The systematic review by Manji and colleagues (5) included 426 drugs tested in 611 unique phase I clinical trials. In our analysis, we excluded 45 of those 426 drugs because their first phase I trial was published more than 6 months after the date of their first FDA approval. Of the remaining 381 drugs, 112 (29%) were tested in at least one phase I expansion cohort. Our search strategy for phase II trials yielded 1,660 abstracts. After review, we identified 381 phase II studies evaluating 166 drugs (Fig. 1).

Drug characteristics

Table 1 summarizes drug characteristics and performance in phase I trials. Drugs in the expansion cohort group were less likely to be cytotoxic (12% vs. 25%, $P = 0.006$), more likely to have been tested in at least one trial that was multicenter (82% vs. 64%, $P < 0.001$), or industry-sponsored (89% vs. 72%, $P < 0.001$), and more likely to have a first publication during 2009 to 2011 rather than 2006 to 2008 (63% vs. 49%, $P = 0.013$). These drugs were also more likely to have been tested in two or more phase I trials (36% vs. 17%, $P = 0.002$) and more likely to have enrolled 47 or more patients in all phase I trials combined (63% vs. 21%, $P < 0.001$).

Compared with the drugs in the nonexpansion cohort group, drugs in the expansion cohort group had higher response rates in the phase I trials (72% vs. 43%% with any response, $P = 0.005$). Despite similar rates of grade 3–4 toxic effects between the groups, the drugs tested in expansion cohorts were more likely to lead to at least one event of grade 5 toxicity (21% vs. 8%, $P < 0.001$) and to have an MTD defined in a phase I trial (73% vs. 49%, $P < 0.001$).

Success rates

Of the 381 drugs included in our study, 166 were tested in phase II trials, and 132 had at least one successful phase II trial. Drugs in the expansion cohort group were more likely to have successful phase II trials (51% vs. 28%, $P < 0.001$; Fig. 3). The analysis of the scatterplot suggests that larger expansion cohorts were associated with a higher probability of success in phase II, but no additional benefit was seen for cohorts larger than 20 patients (Fig. 2).

Multivariate analysis showed that phase I trials with expansion cohorts of two to 20 patients were associated with a higher rate of successful phase II trials than phase I trials with no expansion cohorts [OR, 2.1; 95% confidence interval (CI), 1.1–4.0; $P = 0.037$). Other factors associated with successful phase

Table 1. Drug and trial characteristics according to whether at least one expansion cohort was used in phase I

Characteristics	No. of drugs (%)		P
	Not tested in an expansion cohort (total = 269)	Tested in an expansion cohort (total = 112)	
Publication year of first phase I trial			0.013
2006–2008	136 (51)	41 (37)	
2009–2011	133 (49)	71 (63)	
Disease specific	91 (34%)	48 (43%)	0.12
Cytotoxic drug class	68 (25)	14 (12)	0.006
Industry sponsorship	195 (72)	100 (89)	<0.001
Involvement of multiple centers in a phase I trial	171 (64)	92 (82)	<0.001
No. of patients in all phase I trials			<0.001
5–24	122 (45)	7 (6)	
25–46	92 (34)	35 (31)	
47–289	55 (21)	70 (63)	
Malignancy			0.28
Solid tumor	188 (70)	70 (62)	
Hematologic	35 (13)	21 (19)	
Mixed	46 (17)	21 (19)	
Pooled phase I response rate			0.005
Not available	17 (6)	3 (3)	
0%	137 (51)	28 (25)	
>0% and <6%	40 (15)	34 (30)	
≥6% and <20%	56 (21)	29 (26)	
≥20%	19 (7)	18 (16)	
Pooled grade 3–4 toxic effect rate			0.24
Not available	18 (7)	6 (5)	
≥0% and <10%	146 (54)	52 (47)	
≥10% and <30%	61 (23)	34 (30)	
≥30%	44 (16)	20 (18)	
Any trial with at least one grade 5 toxic effect	21 (8)	23 (21)	<0.001
MTD reached	133 (49)	82 (73)	<0.001

II trials were industry sponsorship (OR, 2.9; 95% CI, 1.5–5.7; $P = 0.0024$), phase I response rates 6% to 77% compared with a response rate of 0% (OR, 2.9; 95% CI, 1.6–5.2; $P = 0.0007$) and disease-specific phase I trials (OR, 1.7; 95% CI, 1.0–2.9; $P = 0.037$; Table 2).

Drug approval

The median time from first publication to FDA approval was 66 months (50–92 months) for the 34 drugs (9%) that were approved (Supplementary Table S1). Univariate analysis showed that drugs in the expansion cohort group had a higher 5-year probability of approval (19% vs. 5%, HR, 4.4; 95% CI, 2.2–8.8; $P < 0.001$).

Expansion cohorts with more than 20 patients were not associated with significantly higher drug approval rates than cohorts with two to 20 patients (22% vs. 15%; HR, 1.1; 95% CI, 0.33–2.47; $P = 0.84$; Fig. 4). Many other variables were associated with higher probability of approval over time, including industry sponsorship (HR, 4.9; 95% CI, 1.2–20; $P = 0.005$), enrollment of 47 or more patients in the phase I trials (HR, 4.7; 95% CI, 2.3–9.7; $P < 0.001$), testing in patients with hematologic malignancies (HR, 2.9; 95% CI, 1.4–6.0; $P = 0.0065$), disease-specific trials (HR, 7.1; 95% CI, 3.3–15.2; $P < 0.001$), any response seen in the phase I trials (HR, 9.2; 95% CI, 2.8–30.2; $P < 0.001$), and determination of an MTD in the phase I trials (HR, 3.1; 95% CI, 1.4–7.1; $P = 0.008$). However, because of the low number of events (approvals), we were not able to perform a multivariate analysis of study factors and time to approval.

Discussion

We reviewed 381 oncologic drugs and identified their first phase I trials, their success rates in subsequent phase II trials, and the status of their approval by the FDA. There was a positive association between the use of an expansion cohort in phase I and probability of success in phase II, but drugs with expansion cohorts larger than 20 did not seem to do better than drugs with expansion cohorts of two to 20 patients.

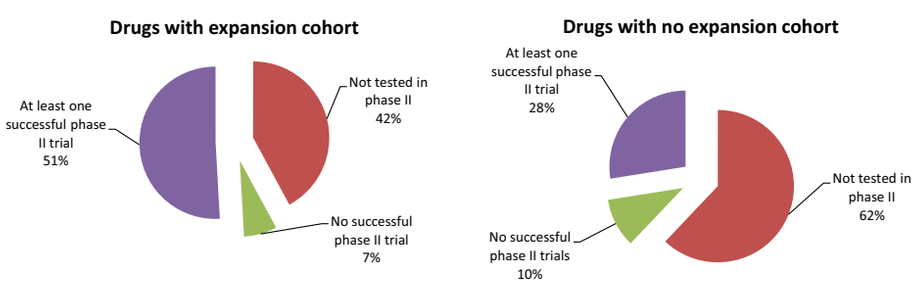

Figure 3.
Phase II outcomes for drugs tested in phase I trials with expansion cohorts compared with drugs tested in phase I trials without expansion cohorts.

Table 2. Univariate and multivariate logistic regression models of covariates associated with probability of success in phase II trials

Variable	No. of drugs (total = 381)	No. of successful phase II trials (total = 130)	OR (95% CI) Univariate analysis	*P*	Multivariate analysis	*P*
Total no. of patients in expansion cohorts						
0	269	74	1 (reference)		1 (reference)	
2–20	62	30	2.47 (1.40–4.35)	0.002	2.13 (1.14–3.98)	0.019
≥20	50	26	2.85 (1.54–5.29)	0.001	1.91 (0.97–3.753)	0.063
Disease specific						
No	242	70	1 (reference)		1 (reference)	
Yes	139	60	1.87 (1.21–2.89)	0.0050	1.72 (1.04–2.85)	0.037
Cytotoxic drug class						
Yes	82	25	0.81 (0.48–1.37)	0.43		
No	299	105	1 (reference)			
Publication year of first phase I trial						
2006–2008	177	59	1 (reference)			
2009–2011	204	71	1.07 (0.70–1.63)	0.77		
Malignancy						
Hematologic	56	26	1.59 (0.89–2.85)	0.12		
Mixed	37	13	0.44 (0.29–0.85)	0.015		
Solid tumor	258	91	1 (reference)			
Industry sponsorship						
Yes	295	111	2.13 (1.21–3.73)	0.009	2.88 (1.46–5.66)	0.0024
No	86	19	1 (reference)		1 (reference)	
Involvement of multiple centers in a phase I trial						
Yes	263	91	1.07 (0.68–1.70)	0.77	0.63 (0.36–1.09)	0.098
No	118	39	1 (reference)		1 (reference)	
Total no. of patients in phase I trials						
5–24	129	29	1 (reference)			
25–46	127	45	1.89 (1.09–3.28)	0.024		
47–289	125	56	2.80 (1.63–4.82)	0.002		
Pooled phase I response rate						
0%	165	35	1 (reference)		1 (reference)	
>0% and <6%	74	29	2.39 (1.32–4.35)	0.0045	1.92 (1.02–3.62)	0.043
≥6% and <20%	85	39	3.15 (1.79–5.55)	<0.001	2.87 (1.57–5.24)	0.0007
≥20%	37	19	3.92 (1.86–8.26)	<0.001	2.46 (1.07–5.64)	0.035
Pooled rate of grade 3–4 toxic effects in phase I trials						
≥0% and <10%	198	65	1 (reference)			
≥10% and <30%	95	29	0.90 (0.53–1.52)	0.69		
≥30%	64	28	1.59 (0.89–2.83)	0.11		
MTD reached						
No	166	49	1 (reference)			
Yes	215	81	1.44 (0.94–2.22)	0.097		
Any grade 5 toxic effect						
Yes	44	14	0.89 (0.45–1.74)	0.73		
No	337	116	1 (reference)			

There is much discussion about the value of expansion cohorts for characterizing the safety profiles of drugs. In the systematic review by Manji and colleagues (5), 54% of the phase I trials with expansion cohorts in the database (which we also used in the current review) identified a new toxic effect that had not been reported in the dose escalation phase, and 13% led to a change in the recommended phase II dose. Our study showed that the proportion of drugs causing grade 5 toxic effects and reaching a defined MTD was higher in the expansion cohort group. Even though we did not differentiate between toxic effects occurring during the dose escalation phase and those occurring during the dose expansion phase, this finding suggests that expansion cohorts allow early identification of toxic effects that would otherwise be identified only in phase II.

To our knowledge, the current study is the first to evaluate the correlation between the size of expansion cohorts and an efficacy endpoint, the probability of success in phase II trials. Interestingly, our analysis showed no benefit of increasing the size of an expansion cohort above 20 patients. This finding is similar to the previously reported results of a series of mathematical simulations suggesting that a cohort size of 20 patients would have a 96% probability of identifying a new dose-limiting toxic effect (11, 12) and an up to 50% likelihood of resulting in a change in the MTD (13). Those results are consistent with the study by Jardim and colleagues (14), which showed a direct correlation between the size of a phase I trial and its ability to predict toxic effects in phase III trials but demonstrated that sample sizes above 60 rarely provide additional information.

Therefore, it is reasonable to limit the size of expansion cohorts to 20 to 30 patients when a phase II or III trial is planned. However, when no further trials are planned and investigators want to obtain efficacy data from a phase I study, probably more patients are needed. This could explain why expansion cohorts with more than 20 patients were not associated with more positive phase II: it is possible that they were not followed by further trials, and drugs were either approved or abandoned.

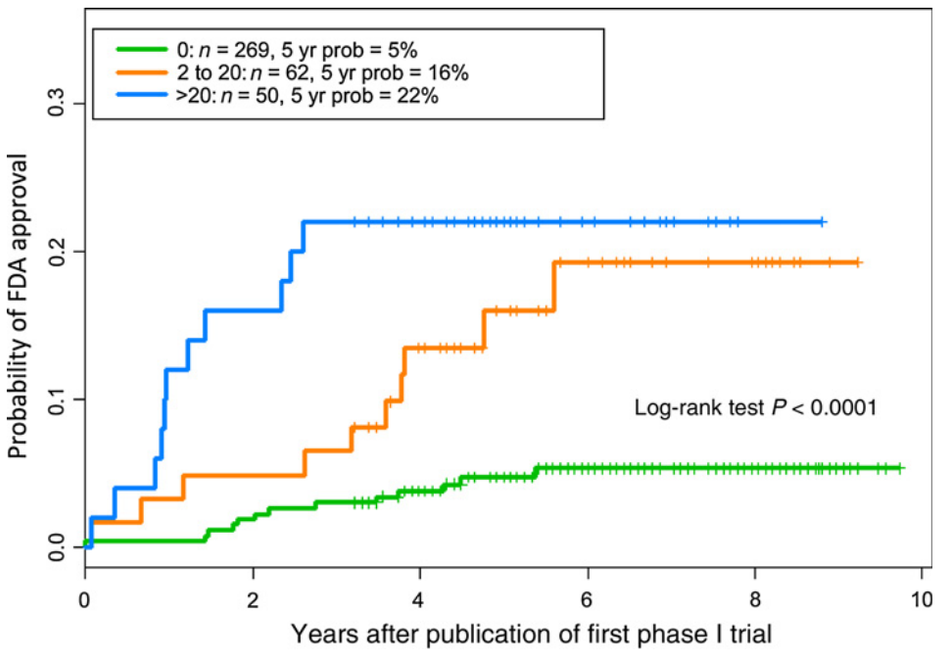

Figure 4.
Probability (prob) of FDA approval as a Kaplan–Meier failure function of time to first FDA approval and the number of patients in the phase I expansion cohort.

There is some concern that expansion cohorts may either stimulate researchers to move from phase I to phase III or simply delay the initiation of phase II trials, therefore prolonging the total period of drug development (15). We found that drugs in the expansion cohort group were actually more likely to be tested in phase II trials than drugs in the non–expansion cohort group (58% vs. 38%), suggesting that for most cases, phase II trials were performed, despite the expansion cohorts.

In a review of all phase I trials and corresponding phase II trials published in the Journal of Clinical Oncology during 2004 to 2014, Behtaj and colleagues (16) also described a positive association between the use of expansion cohorts, industry sponsorship, and study drugs being noncytotoxic agents. However, those authors found no association between the use of expansion cohorts and FDA approval. Comparison between both studies is challenging, because Behtaj and colleagues (16) used a narrower search strategy [positive phase I studies are more likely to be published in high-impact journals, such as the Journal of Clinical Oncology (17–19)] and included drug combination phase I studies [which usually have higher response rates and, therefore, approval rates (8)].

Our study has two main limitations. First, there might have been publication bias. It is possible that drugs that are more active are more likely to be tested in expansion cohorts and that expansion cohorts are more likely to be published than small, negative studies. This could have led to an overestimation of the outcomes in the expansion cohort group.

The second limitation is the fact that we were unable to determine the actual starting date or causality between the phase I dose escalation cohorts, dose expansion cohorts, and phase II trials. Therefore, we had to make choices in data analysis that can lead to bias. Drugs that are more active are more likely to be enrolled in multiple trials and, therefore, more likely to have at least one trial with an expansion cohort and to lead to successful phase II studies. By doing a pooled analysis of all phase I and phase II trials, this might also have overestimated the outcomes in the expansion cohort group. To ameliorate this effect, we corrected our analysis for response rates, but the effect will always remain a significant source of bias in our analysis.

In conclusion, our study has demonstrated an association between the use of expansion cohorts in phase I trials and successful drug performance in phase II trials. Our findings also suggest that when the objective of the expansion cohort is identifying toxicity and obtaining information for the design of a phase II trial, a sample size of 20 could be adequate. Future research should focus on optimizing sample size of multiple expansion cohorts or of biomarker-driven cohorts and on incorporating efficacy data from expansion cohorts in the design of phase II trials.

Disclosure of Potential Conflicts of Interest

D.D.G. Bugano reports receiving speakers bureau honoraria from Bristol-Myers Squibb and Roche. F. Meric-Bernstam reports receiving commercial research grants from Aileron, AstraZeneca, Bayer, Calithera, CytoMx, Debiopharma, Effective Pharma, Genentech, Novartis, Taiho, and Zymeworks and is a consultant/advisory board member for Clearlight Diagnostics, Darwin Health, Dialecta, Inflection Biosciences, and Pieris. No potential conflicts of interest were disclosed by the other authors.

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Writing, review, and/or revision of the manuscript: D.D.G. Bugano, K. Hess, D.L.F. Jardim, A. Zer, F. Meric-Bernstam, L.L. Siu, A.R.A. Razak, D.S. Hong
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Study supervision: A.R.A. Razak, D.S. Hong

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