

Review of Phase II Trial Designs Used in Studies of Molecular Targeted Agents: Outcomes and Predictors of Success in Phase III

Robert H. El-Maraghi and Elizabeth A. Eisenhauer

A B S T R A C T

Purpose

Because the appropriate design and end points for phase II evaluation of targeted anticancer agents are unclear, we undertook a review of recent reports of phase II trials of targeted agents to determine the types of designs used, the planned end points, the outcomes, and the relationship between trial outcomes and regulatory approval.

Methods

We retrieved reports of single-agent phase II trials in six solid tumors for 19 targeted drugs. For each, we abstracted data regarding planned design and actual results. Response rates were examined for any relationship to eventual success of the agents, as determined by US Food and Drug Administration approval for at least one indication.

Results

Eighty-nine trials were identified. Objective response was the primary or coprimary end point in the majority of trials (61 of 89 trials). Fourteen reports were of randomized studies generally evaluating different doses of agents, not as controlled experiments. Enrichment for target expression was uncommon. Objective responses were seen in 38 trials; in 19 trials, response rates were more than 10%, and in eight, they were more than 20%. Agents with high response rates tended to have high nonprogression rates; renal cell carcinoma was the exception to this. Higher overall response rates were predictive of regulatory approval in the tumor types reviewed ($P = .005$).

Conclusion

In practice, phase II design for targeted agents is similar to that for cytotoxics. Objective response seems to be a useful end point for screening new targeted agents because, in our review, its observation predicted for eventual success. Improvements in design are recommended, as is more frequent inclusion of biological questions as part of phase II trials.

J Clin Oncol 26:1346-1354. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Recently, there has been a veritable explosion of knowledge with respect to the molecular biology of malignancy. This has led to the identification of potential new targets for cancer therapy and, subsequently, to the rational design of agents created to affect those targets in a clinically meaningful way. However, as a growing number of agents targeting molecular pathways are tested in the clinic, there has been increasing pressure to rethink the standard drug development paradigm, specifically early trial design, to ensure that these promising new drugs are appropriately evaluated.

The ultimate goal of drug development in oncology is to identify new agents that provide a meaningful clinical benefit for patients, with the gold standard being the prolongation of patient survival.

This is both a time- and resource-intensive process, with an estimated monetary cost to bring new drugs to market of \$800 million (or more)^{1,2} with equally important, although perhaps less definable, costs to participating clinical subjects. With this in mind, it is understandable that there is pressure to optimize early clinical trial design so as to minimize the resources expended on drugs that are likely to fail in later development.

The primary objective of phase II trials, regardless of the nature of the compound, is to screen for preliminary evidence of efficacy in a given tumor type. For cytotoxic agents, the standard approach has been to enroll small numbers of patients in a nonrandomized design, often of two or more accrual stages, and use objective tumor regression assessed by standard criteria^{3,4} as the end point to identify drugs with potential efficacy. Retrospective

From the Royal Victoria Hospital, Barrie; and National Cancer Institute of Canada Clinical Trials Group, Queen's University, Kingston, Ontario, Canada.

Submitted July 18, 2007; accepted November 1, 2007; published online ahead of print at www.jco.org on February 19, 2008.

The National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) is supported by a core grant from the National Cancer Institute of Canada with funds received from the Canadian Cancer Society. R.H.E.-M. was a Drug Development Fellow at NCIC CTG from 2005 to 2006 whose salary was supported by a Transdisciplinary Training Program Grant from the Canadian Institutes of Health Research as well as a Drug Development Fellowship grant from AstraZeneca.

Presented in part at the 42nd Annual Meeting of the American Society of Clinical Oncology, June 2-6, 2006, Atlanta, GA; and the National Cancer Research Institute Cancer Conference, October 8-11, 2006, Birmingham, United Kingdom.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Elizabeth Eisenhauer, MD, FRCPC, National Cancer Institute of Canada Clinical Trials Group, Queen's University, 10 Stuart St, Kingston, Ontario, Canada K7L 3N6; e-mail: eisenhauer@ctg.queensu.ca.

© 2008 by American Society of Clinical Oncology

0732-183X/08/2608-1346/\$20.00

DOI: 10.1200/JCO.2007.13.5913

data support the use of the response end point for studies of cytotoxic agents⁵⁻⁷ and the efficiency of the nonrandomized design. The inherent differences in the mechanism of action between traditional cytotoxic drugs and molecularly targeted agents, coupled with interest in increasing the reliability of phase II results in identifying truly active agents, have led to considerable discussion about the so-called traditional approach to screening trials, particularly in regards to patient selection criteria, end points, and study design.

With respect to patient selection, it is reasonable to expect that not all patients with a given tumor type will have similar levels of target protein activity or expression, and thus, efficacy of the targeted agent may vary according to which subpopulation is evaluated. Enriching the population to maximize possible activity could be achieved through restriction of study entry to those with a specific tumor histology or those whose tumors (over)express a molecular target. However, at the time of early clinical studies, such predictors of activity are by definition hypothetical, unless the agent affects a target that has had validated predictors identified through earlier clinical trials of other drugs affecting the same target.

The appropriate end point for phase II trials of targeted agents has also been debated.⁸⁻¹² Because many of these agents may affect tumor cells by reducing proliferation, rather than by causing cell death, the impact on tumor growth may be stabilization of disease or minor tumor shrinkage. Thus, it is argued that focusing only on objective response could result in overlooking some agents that could improve survival by causing disease stabilization. Indeed, in lung cancer, attainment of stable disease, in addition to responses, has been shown to contribute to improved survival.¹³

The design of phase II trials and the choice of which end point is to be used are closely linked; the use of a nonrandomized design in the traditional phase II trial is reasonable because objective responses are unlikely to be due to natural disease processes, rendering a control group unnecessary. However, even if response is believed to be a reasonable end point for trials of particular agents, the sample size of a nonrandomized trial may need adjustment. This is necessary if the hypothesized response rate of interest for the targeted agent is lower than what might be considered standard for cytotoxic agents, as would be the case if the trial population is unselected for predictive markers.

When objective response alone is not foreseen to be a useful end point, novel designs have been proposed for phase II screening trials. Included is a multinomial design in which decisions about early stopping and conclusions on activity are based not only on the number of responses seen, but also on the proportion of patients demonstrating early disease progression.^{14,15} Another approach of interest is the randomized discontinuation trial where patients are treated with a new agent for a specified period of time, after which those with stable disease are randomly assigned to continue or discontinue therapy.^{16,17} The end point for this type of trial is either time to event (eg, progression) or the proportion of patients progression free at a specific time point after random assignment. This design also provides information on the activity of the drug in terms of rates of response and progression at the end of the run-in phase. The randomized discontinuation design has been promoted to be of particular help in screening cytostatic drugs, such as molecularly targeted agents, by permitting early assessment of whether delays in progression are related to treatment or disease and whether they are of sufficient magnitude to suggest that the drug may be effective.

The issues we have just highlighted illustrate the fact that numerous proposals regarding changes to traditional phase II trial design and end points have been made in recent years. However, there is little information on the impact of these discussions on the actual end points and designs used for the evaluation of novel targeted agents in phase II trials. In this article, we report the results of a review of phase II designs, end points, and outcomes of a series for targeted agents that have been studied in clinical trials in the last few years. In particular, we were interested in determining the planned design and end point(s) in these trials, what the observed results were, and, when possible, whether the results of phase II trials of individual agents were useful in predicting which agents achieve regulatory approval. Our interest in this last point speaks to the ultimate goal of phase II screening trials regardless of design: Is the output of the trials useful in identifying those agents likely to succeed in phase III trials?

METHODS

Agents

For this review, we focused on the 31 targeted agents that were the basis of a review of phase I trial design published in 2004.¹⁸ These agents have distinct intracellular or extracellular targets in pathways and can be grouped into major classes on the basis of the chemistry of the agent (small molecule, antisense oligonucleotide, or antibody) as well as the expected molecular target (Table 1).¹⁹⁻⁸³ All of these agents completed phase I investigation long enough in the past that phase II trials, if undertaken, should now be reported.

Tumor Types and Search Strategy

We defined six common solid tumor types (breast, colorectal, lung, ovarian, prostate, and renal cell carcinomas) on which to focus. We performed a MEDLINE search for published articles of completed phase II single-agent studies for all of the 31 drugs limited to the six tumor types noted. Studies using the agents in combination and studies in progress were excluded from the review. The search terms included the name of the agent (including trade name, if applicable) and the molecular target, with the limit of clinical trials, phase II. A cutoff date of April 30, 2006 was used for retrieving publications.

In addition to full publications, we also attempted to identify final reports of phase II studies published as abstracts that were not yet reported in full article form. Abstracts were identified using an electronic search of the proceedings of the American Society of Clinical Oncology, the American Association for Cancer Research, and the San Antonio Breast Cancer Symposia meetings until the end of 2005. Identified abstracts were excluded if they indicated continuing patient accrual or incomplete efficacy results. Abstract data were verified against data presented at the actual scientific meeting, when possible.

Definition of Trial Versus Report

Each publication, whether abstract or full article, was considered a report. A small number of reports included more than one trial. Examples were reports in which multiple tumor types were included (each analyzed separately), multiple targeted agents were evaluated (in a noncomparative randomized design), or multiple doses of the same targeted agent were tested. To describe the outcomes of each active arm of targeted therapy appropriately, we considered a study with n prospective active treatment groups in which there was no intent to conduct a formal statistical comparison to be n trials within a single report. For those few reports where random assignment was to standard therapy or placebo, the study arms with no active targeted therapy or placebo were not considered as separate trials, and the reported outcome was that which was planned for the overall study.

Data Abstraction

All data were abstracted independently for each trial by both authors, with any discrepancies resolved by consensus. A summary of abstract data is found in Appendix Table A1 (online only). All planned primary and secondary

Table 1. Targeted Agents From 2004 Phase I Review Subjected to Search for Phase II Results

Target Category	Phase I Review Agents			This Phase II Review			
	Target	Agent	Drug Type	No. of Single-Agent Phase II Reports Identified	No. of Single-Agent Phase II Trials in Selected Tumors* Reviewed	Reference No.	
EGFR/HER-2 signaling pathways	Farnesyltransferase	BMS-214662	SM	5	6	19-23	
		R115777	SM				
		L778, 123	SM				
		SCH 66336	SM				
	MEK	CI-1040	SM	1	1	24	
	mTOR	CCI-779 (temsirolimus)	SM	1	3	25	
	Raf kinase	ISIS 5132	AS	3	7	26-28	
		BAY 43-9006 (sorafenib)	SM	4	5	29-32	
				1	2	33	
Cell surface receptors	EGFR	ZD1839 (gefitinib)	SM	14	17	34-47	
		OSI-774 (erlotinib)	SM	5	5	48-52	
		C225 (cetuximab)	AB	3	3	53-55	
		MAb225	AB				
		EMD 72000	AB				
		EKB 569	SM				
	RG83852	AB					
	HER-2	Trastuzumab	AB	8	9	56-63	
	c-kit	STI-571 (imatinib)	SM	7	9	64-70	
Angiogenesis	VEGF	Bevacizumab	AB	2	5	71,72	
		VEGFR (plus other targets)	ZD6474	SM	1	2	73
			PTK787	SM			
			SU6668	SM			
			SU5416 (semaxanib)	SM	2	2	74,75
			SU11248 (sunitinib)	SM	2	2	76,77
	Other	Endostatin	Other				
Extracellular matrix	Matrix metalloproteinase	BB-2516 (marimastat)	SM	1	3	78	
		BAY 12-9566 (tanomastat)	SM				
		COL-3	SM				
		BMS-275291	SM	1	2	79	
Other	BCL-2	G3139	AS				
	PKC α	ISIS 3521 (aprinocarsen)	AS	5	5	29,32,80-82	
	DNA methyltransferase	MG98	AS	1	1	83	
Total No.		31†		65‡	89		

Abbreviations: EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor 2; SM, small molecule; MEK, mitogen-activated protein-Erk kinase; mTOR, mammalian target of rapamycin; AS, antisense oligonucleotide; AB, antibody; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PKC α , protein kinase C alpha.

*Selected tumors were breast, lung (small-cell and non-small-cell), prostate, colorectal, renal, and ovary.

†Nineteen agents identified for this review.

‡Actual total is 67, but two reports have been counted twice because they each included two agents and thus are found twice in this table (ISIS 5312 and ISIS 3521).

end points (eg, response, change in target expression, progression-free survival, either individually or in a multinomial combination) were abstracted, as were the actual outcome measures (eg, number of patients enrolled/eligible, number of patients with complete response, partial response, stable disease, progressive disease [PD], median time to progression, and overall survival). Data were not collected with respect to sex, age, or nature of the prior systemic treatment of patients.

Calculations

Once data abstraction was completed, several computations were undertaken. To determine the total response rate for a given trial, the total number of patients achieving either complete or partial response was divided by all eligible patients. Trials without response reported or collected were classified as not reported for this outcome. Although we initially planned to report stable disease rate, because substantially differing duration requirements were used to define stable disease across the trials reviewed, we elected to calculate the nonprogression rate as a means of better standardizing the output of our review. To determine the percentage of patients with nonprogression, patients with PD as best response were subtracted from the number of eligible patients

entered to give the total number of nonprogressors (non-PD). This figure was then divided by the total number of eligible patients. Although we recognized that assignment of PD as a best response was somewhat dependent on the timing of follow-up (usually between 6 and 12 weeks), this was less variable than the duration used to define stable disease (which ranged from a few weeks to > 6 months).

Once the response rate and PD rate for each trial was calculated, additional summary information was generated for presentation in tabular form. This included the calculation of overall rates of response (and nonprogression), which were determined for each drug by grouping all patients in all trials of a given agent with either complete or partial response (or nonprogression) and then dividing by the total number of eligible patients.

Response rates for trials and for drugs were categorized in the following range groupings: 0%, more than 0% to \leq 10%, more than 10% to \leq 20%, and more than 20%. Nonprogression rates were categorized as follows: \leq 30%, more than 30% to \leq 50%, more than 50% to \leq 65%, and more than 65%. The numbers of trials with response rates or non-PD rates in the ranges noted were displayed in table format according to a variety of groupings of the trial data.

This included tables representing the number of trials in the various response categories by disease type, by individual drugs, by drugs grouped by target, and by population enrichment.

Drug Approval

Information on whether the agents under evaluation had received accelerated or full US Food and Drug Administration (FDA) approval for use in any of the six tumor types as of June 2007 was also identified. A table was then created that listed the number of drugs with overall response rates in the ranges described earlier versus the number of drugs in each grouping that had achieved regulatory approval. The relationship between the four response categories and the probability of FDA approval was assessed by the exact Cochran-Armitage linear trend test.

Agents With No Phase II Trials

There were 12 agents from the original list of 31 for which no phase II trials in any of the six tumor types were found. Every reasonable effort was made to determine the reasons for this (eg, drug stopped development, skipped phase II altogether, was evaluated in other diseases than those we focused on, or went into combination phase II immediately after phase I). However, not all agents could be traced.

RESULTS

Agents and Trials

Of the 31 agents surveyed, reports on single-agent phase II evaluation were retrieved for 19 in at least one of the prespecified tumor types (Table 1).¹⁹⁻⁸³ Altogether, 65 reports were identified (53 articles and 12 abstracts). Several reports contained results of evaluation of more than one tumor type or involved several different agents or dose levels; thus, the final tally of trials was 89. These were spread across all six tumor types, with the largest numbers in breast (21 trials) and lung cancers (13 trials in non-small-cell lung cancer and nine trials in small-cell lung cancer), followed by renal (15 trials), prostate (14 trials), and ovarian cancers (six trials; Appendix Table A2, online only).

Trial Design

Randomized versus nonrandomized designs. In the majority of reports (51 of 65 reports; 78%), the investigational agent was evaluated using a nonrandomized single-arm design (Table 2). Randomization

was used in 14 (22%) of 65 reports. However, in only two reports was there random assignment to a placebo (this included the randomized discontinuation phase of the BAY 43-9006 renal cell carcinoma trial³³ and a randomized phase II study of gefitinib v placebo in prostate cancer⁴⁵). One study in prostate cancer randomly assigned patients between an experimental agent and an active corticosteroid control arm.⁷⁴ In two reports,^{29,32} patients were randomly assigned between two different investigational drugs; in both, the random assignment was between ISIS 3521 (aprinocarsen) and ISIS 5132 in a noncomparative phase II design. Finally, in nine reports, the random assignment was between various dose levels of the same investigational drug.

End points. The primary end point on which the trial design was based was most commonly objective response (51 trials; 57%; Table 2). In addition, 10 studies used a multinomial end point incorporating both response and nonprogression. Thus, objective response was the primary or coprimary end point in 61 trials. Only 16 trials were designed with end points of progression-free survival or the proportion of patients progression free at a prespecified time point. Some of the remaining studies were in prostate cancer and used measures of prostate-specific antigen (PSA) change (eg, PSA response, change in slope of PSA increase) as the primary end point. In addition, in two reports, toxicity was the primary end point.

Population enrichment. Efforts to enrich the population under evaluation by restricting entry to patients of a particular molecular or histologic tumor subtype were undertaken in 18 (20%) of 89 trials. As can be seen in Table 3, in 14 studies, enrichment was on the basis of a molecular marker assessed in tumor.

Hypotheses used in design. For those trials in which objective response was the primary end point, we attempted to identify the hypotheses used to derive the sample size from the methods sections of articles because we postulated that response rates of interest might be lower for targeted agents than those that have been traditionally used for phase II trials of cytotoxic drugs. Unfortunately, of the 51 trials in which response was indicated to be the primary end point, only 27 described the hypotheses that had led to design and the planned sample size. Of these, 20 based the sample size and, thus, stopping rules on response rates of interest of 20% or higher. In seven trials, response rates in the 10% to 15% range were targeted.

Sample size. Not surprisingly, the mean planned sample size for the trials reviewed depended on the design. For trials in which objective response was the end point, the mean maximum sample size planned was 56 patients (based on the data reported for 35 trials). When progression-free survival or non-PD was the end point used, the mean maximum sample size planned was 115, and for the multinomial design, the mean maximum sample size was 41.

Trial Results: Response and Nonprogression

Response rates. Seventy-six of 89 trials reported objective response outcomes. In total, 38 trials had overall response rates of 0%. In the other 38 trials, objective responses were seen; in 19 trials, response rates were more than 10%, and in eight trials, response rates were more than 20%.

Appendix Table A3 (online only) shows the reported response rates categorized in the ranges shown for all trials sorted by agent. Appendix Table A4 (online only) displays the same data but sorted by tumor type. Trial response results for all agents affecting the same target are shown in Appendix Table A5 (for example, all epidermal growth factor receptor inhibitors trials are displayed in one line in the

Table 2. Trial Design and End Points

Design and End Point	No. of Reports (N = 65)	Trials (N = 89)	
		No.	%
Nonrandomized	51	62	70
Randomized	14	27	30
Comparator arms:			
Placebo/standard		3	
Other investigational drug		4	
Other dose of same agent		20	
Primary end point			
Objective response		51	57
Multinomial (response and progressive disease)		10	11
Proportion progression free		8	9
Progression-free survival		8	9
Other		12	13

Table 3. Population Enrichment

Basis for Enrichment	No. of Trials (n = 18)	Agent*	Tumor Type*	Reference No.
EGFR expression	3	Erlotinib (n = 2); cetuximab (n = 1)	Lung (n = 1); ovary (n = 1); CRC (n = 1)	50,51,53
HER-2 expression	7	Trastuzumab	Breast (n = 5); lung (n = 1); ovary (n = 1)	56-59,61,62
Histology				
BAC	1	Erlotinib	Lung	49
Clear cell	2	Bevacizumab	Renal cell carcinoma	72
c-kit	4	Imatinib	Lung (n = 3); ovary (n = 1)	65,67,68
Other (SD at 12 weeks)	1	Sorafenib	Renal cell carcinoma	33
Total	18	Trastuzumab (n = 7); imatinib (n = 4); erlotinib (n = 3); bevacizumab (n = 2); sorafenib (n = 1); cetuximab		

Abbreviations: EGFR, epidermal growth factor receptor; CRC, colorectal cancer; HER-2, human epidermal growth factor receptor 2; BAC, bronchioloalveolar carcinoma; SD, stable disease.
*Numbers in parentheses represent No. of trials.

table; table online only). Finally, Table 4 provides the overall response rate by agent, pooling results for all trials (across all tumor types).

Nonprogression rates. Results for nonprogression rates were also tabulated, but not all are shown. Table 4 lists the non-PD rates by agent (pooling across all trials for each particular agent). As can be seen, non-PD rates were variable, but several agents (sorafenib, cetuximab, temsirolimus, trastuzumab, and gefitinib) had non-PD rates of 50% or more overall.

Although in most tumor types the ranking of agents by response rates or non-PD rates was similar (data not shown), renal cell carcinoma trials seemed to display a different pattern. Appendix Table A6 (online only) shows overall response rate and non-PD rates in renal cell carcinoma studies by agent. High non-PD rates were seen with four agents (sunitinib, sorafenib, temsirolimus, and imatinib), but

only one of these, sunitinib, had a response rate that was more than 20%; the remainder had observed response rates less than 10%.

Response and Non-PD Rates by Disease Type and Regulatory Approval

To identify whether there were tumor-related patterns in the response or non-PD results and regulatory approval (as of June 2007), we examined overall rates of non-PD and response by agent in each tumor type in the trials reviewed, as shown in Appendix Tables A7 and A8 (online only). Numbers within each tumor type are too small to apply statistics, but it was observed that no agent with a 0% response rate in a given tumor type received approval in that tumor type. Similarly, no agent with non-PD rates less than 30% in a given tumor type received approval in that tumor type.

Table 4. Overall Response and Non-PD Rates by Agent

Agent	No. of Trials	Overall Response Rate (%)	Total No. of Patients in Response Rate Denominator*	Overall Non-PD Rate (%)	Total No. of Patients in Non-PD Rate Denominator*
Sorafenib	2	4	202	75	202
Marimastat	3	NR	NA	NR	NA
Bevacizumab	5	5.3	97	NR	NA
BMS-275291	2	0	80	36	80
Cetuximab	3	3	169	60	58
Temsirolimus	7	8	190	66	190
CI-1040	3	0	52	12	52
Aprinocarsen	5	0	87	13	60
ISIS 5132	5	0	71	27	71
MG98	1	0	15	40	15
Erlotinib	5	12	200	39	150
R1155777	6	5	208	23	208
SCH 66336	1	0	21	14	21
Imatinib	9	0	112	21	112
Sunitinib	2	28	127	0	63
Semaxanib	2	5	45	0	29
Trastuzumab	9	18	562	53	420
Gefitinib	17	10	698	50	627
ZD6474	2	0	46	NR	NA
Total	89				

Abbreviations: PD, progressive disease; NR, not reported in any trial; NA, not applicable.

*Response and non-PD rate denominators may not match if some trials had one or the other not reported. Only trials with data reported were used to calculate rates.

Noteworthy was the observation that three of four agents in renal cell carcinoma with non-PD rates of more than 65% have been approved for renal cell carcinoma.

Overall Response Rate and Regulatory Approval

A number of the agents reviewed in this article had received FDA approval by June 2007. Figure 1 graphically displays the relationship between overall response rate for each agent (including all trials and all tumor types) and regulatory approval. Table 5 provides the same information clustering agents into the four response categories used earlier. Overall, seven of the 19 agents reviewed have received full FDA approval; one (gefitinib) received accelerated approval but failed to achieve full approval on the basis of randomized data. The *P* value of the exact Cochran-Armitage trend test for the relationship between response category into which agents fell and regulatory approval was *P* = .005 if the accelerated approval for gefitinib was not counted as FDA approved and was *P* < .0001 if the accelerated approval for gefitinib was included in the calculation.

DISCUSSION

Debate continues as to the most efficient and reliable approach to clinical development of targeted agents in oncology. When or how to enrich populations for putative predictors of activity, how to design and size screening studies, and which end points to use have been the subject of many articles and editorials in the last decade. The results of single-agent trials of targeted agents reviewed here may help to shed some light on these difficult issues.

The majority of phase II trials in this review have been conducted using traditional designs (nonrandomized) and end points (objective response). However, some evidence of innovation was evident in several reports; random assignment was occasionally used (although largely with noncomparative intent), and primary end points other than objective response were used in several studies. Population enrichment was uncommon; this may reflect the fact that, with many agents, the marker for activity of the targeted agent was uncertain and/or that the agents in question were expected to have activity not defined by a particular marker (eg, angiogenesis inhibitors).

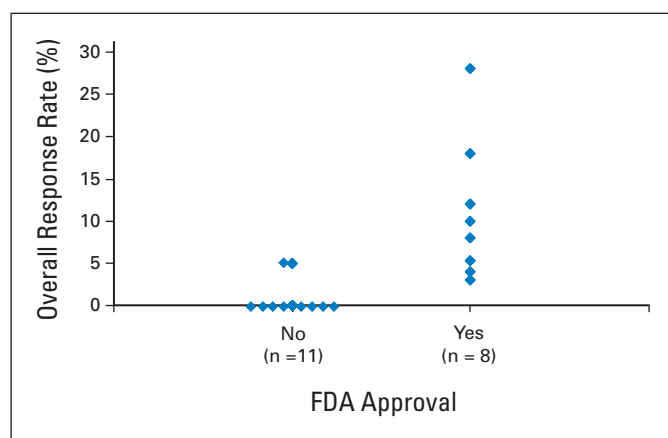


Fig 1. Overall single-agent phase II response rate for each agent versus US Food and Drug Administration (FDA) approval (as of June 2007) in at least one of the reviewed tumor types.

What seems of interest is that, despite the suggestion that targeted drugs could not be screened by assessment of tumor shrinkage, the evidence suggests otherwise; of the 89 trials, 38 documented objective tumor responses, and 19 had response rates of more than 10% (and eight had response rates of > 20%). When examined by drug, of the 19 drugs reviewed, 10 produced overall response rates (across all tumor types) ranging from 3% to 28%. Of these, seven have received full FDA approval for one or more indications. Furthermore, the data suggest a relationship between the level of the overall phase II response rate seen in the tumor types reviewed and the likelihood of achieving regulatory approval.

These results, although based on a relatively small number of targeted agents, are similar to a recent review of cytotoxic agents by Goffin et al.⁷ In that review, phase II outcomes of 46 cytotoxic drugs were compiled. The authors found a relationship between eventual regulatory approval and phase II response rate; drugs with overall response rates greater than 20% had a higher likelihood of approval than those with response rates of 10% to 20%, which, in turn, were more likely to receive approval than those with response rates of 0% or 0% to 10%. The relationship seemed to hold true for breast, non-small-cell lung, ovary, and colorectal cancers but not for renal cell carcinoma or melanoma, although the numbers of randomized trials actually conducted in the latter two tumor types were fewer. In an accompanying editorial, Ratain¹¹ argued that looking at the data as if the phase II response rates were diagnostic test results might be more appropriate. When he reanalyzed the data in this fashion, he identified that the negative predictive value of phase II results was quite high, but the positive predictive value was lower, being 0% in melanoma and renal cell carcinoma and from 33% to 75% for breast, ovarian, colorectal, and non-small-cell lung cancers when overall response rates were 20% or more. The problem with the approach of viewing the response rate outcome as if it were a diagnostic test is that it is guaranteed to achieve high negative predictive values if no randomized trials are ever performed to assess survival impact when response rates are zero or low.

Our review has limitations. First, not all targeted agents studied in the last decade were included. We identified phase II reports from the list of 31 targeted agents reviewed recently with respect to phase I design as a convenient approach to following up on the clinical development of those drugs. Second, we did not attempt to identify whether trials were conducted but never reported. Furthermore, we arbitrarily focused on six common solid tumor types. Thus, the overall single-agent response rates cited for each agent could be subject to some variation if data from unpublished studies or if trials in all tumor types had been included. In addition, our list of the original 31 agents was reduced to 19 because 12 drugs had no reported phase II single-agent studies in the tumor types that were of interest. Several of those agents were dropped from development after phase I, and others either remain in early phase II development or skipped phase II altogether to proceed into randomized combination studies.

Nonetheless, there are interesting messages here. First, even relatively low rates of objective response may signal that an agent has potential for achieving regulatory approval on the basis of subsequent randomized data. It can be inferred from this observation that agents affecting targets that are meaningful in one or more cancer types should reasonably be expected to cause tumor shrinkage in at least some patients. Failing to see any evidence of response at all suggests that the drug is likely to fail in subsequent development. There were no

Table 5. Overall Single-Agent Phase II Response Rates and Regulatory Approval* for Tumor Types Included in Review

Overall Response Rate†	No. of Agents	No. of Agents Approved by FDA	Comments
0%	9	0	Note: one of these agents, imatinib was approved in indications (CML, GIST) not included in this review
> 0% to ≤ 10%	6	4	Sorafenib; bevacizumab; cetuximab; temsirolimus
> 10% to ≤ 20%	3	2 (3)	Trastuzumab; erlotinib (gefitinib: accelerated approval only)
> 20%	1	1	Sunitinib
Total	19	7 (8)	$P = .005$ excluding gefitinib; $P = < .0001$ including gefitinib

Abbreviation: FDA, US Food and Drug Administration; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor.
 *Regulatory approval at FDA by June 2007.
 †Overall response rate calculated for each agent by pooling results of all trials across all tumor types included in the review. One agent (marimastat) did not have response outcomes reported in any of the three publications and is included as 0%.

exceptions to this observation in the studies we reviewed. If others confirm these findings, it would have important consequences in drug development because using response as the primary end point in phase II trials would mean nonrandomized designs could be used and, thus, fewer patients would need to be recruited.

Second, the pattern seen in renal cell carcinoma trials stands out as being somewhat different than the other tumor types reviewed. Four drugs (temsirolimus, sunitinib, sorafenib, and imatinib) had similar non-PD rates, but this was not reflected in the objective response rate data, where only sunitinib had a high level of response. Interestingly, renal cell carcinoma exhibited a similar pattern in the review of cytotoxic agents mentioned earlier.⁷ The biologic basis for this pattern is unclear, but in terms of trials of new agents in renal cell carcinoma in the future, designs using nonprogression end points may be more logical than ones using response.

Third, experience with enrichment in the phase II setting is limited. Except for trastuzumab, where enrichment by human epidermal growth factor receptor 2 status was undertaken, the results in those trials that were enriched by molecular marker or histology were not substantially different than the results of trials where no enrichment was attempted. This might mean that the biomarker used for patient selection in those trials was simply wrong and that more work was needed to identify the true biomarker. It may also be the case that the identification of human epidermal growth factor receptor 2 as a successful biomarker so early in development was as much the result of good fortune as good intent.

Finally, this review provides evidence that we should be doing better. If one accepts that tumor shrinkage is a marker that has validity in screening targeted agents, then it is clear that even low levels of response may be interesting. Designing trials using hypotheses based on a 20% response rate of interest (as has been traditional for cytotoxic agents) is not logical. Hypothesizing smaller response rates of interest means appropriate designs will result in larger sample sizes than the usual 15 to 30 patients. Increased enrollment, in turn, provides enhanced opportunity to undertake translational research as secondary end point(s) in the trial. Unfortunately, few of the trials included in this review incorporated biologic studies on patients or tumors that

related observed clinical outcomes with aspects of tumor biology. Until it is routine that such studies are incorporated in phase II designs, we will be held back in generating hypotheses about which biomarkers look most promising for selecting patients for treatment. It is only once such hypotheses are available based on real patient data from early trials that randomized trials evaluating the utility of putative biomarkers can be designed.

In summary, this review of phase II trials of targeted agents suggests that the most common screening approach remains that of using a nonrandomized trial design with objective response as the primary end point. Our observations suggest that objective response, if observed, signals that the agent may have sufficient activity to receive regulatory approval based on the outcomes of subsequent randomized trials. Thus, the use of objective response as an end point and, consequently, nonrandomized designs appear to retain utility for screening trials of targeted agents. Results from trials of other agents and in other tumor types should be reviewed to determine whether these findings are upheld. Further improvements in phase II design and trial conduct are needed, in particular with respect to the statistical considerations used to determine sample size and to the incorporation of biologic correlative studies to maximize the information about drug activity that can be obtained from this crucial step in drug development.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Elizabeth A. Eisenhauer
Collection and assembly of data: Robert H. El-Maraghi, Elizabeth A. Eisenhauer
Data analysis and interpretation: Robert H. El-Maraghi, Elizabeth A. Eisenhauer
Manuscript writing: Robert H. El-Maraghi, Elizabeth A. Eisenhauer
Final approval of manuscript: Robert H. El-Maraghi, Elizabeth A. Eisenhauer

REFERENCES

1. DiMasi JA, Hansen RW, Grabowski HG: The price of innovation: New estimates of drug development costs. *J Health Econ* 22:151-186, 2003

2. Adams CP, Brantner WV: Estimating the cost of new drug development: Is it really \$802 million? *Health Aff* 25:420-428, 2006

3. Therasse P, Arbuck S, Eisenhauer E, et al: New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 92:205-216, 2000

4. World Health Organization: WHO Handbook for Reporting Results of Cancer Treatment, World Health Organization Offset Publication No. 48. Geneva, Switzerland, WHO, 1979

5. Paesmans M, Sculier JP, Libert P, et al: Response to chemotherapy has predictive value for

Phase II Designs Used for Targeted Therapy

further survival of patients with advanced non-small cell lung cancer: 10 years experience of the European Lung Cancer Working Party. *Eur J Cancer* 33:2326-2332, 1997

6. Buyse M, Thirion P, Carlson RW, et al: Relation between tumor response to first-line chemotherapy and survival in advanced colorectal cancer: A meta-analysis—Meta-Analysis Group in Cancer. *Lancet* 356:373-378, 2000

7. Goffin J, Baral S, Tu D, et al: Objective responses in patients with malignant melanoma or renal cell cancer in early clinical studies do not predict regulatory approval. *Clin Cancer Res* 11:5928-5934, 2005

8. Eisenhauer EA: Phase I and II trials of novel anti-cancer agents: Endpoints, efficacy and existentialism. *Ann Oncol* 10:1047-1052, 1998

9. Gellon KA, Eisenhauer EA, Harris AL, et al: Anticancer agents targeting signaling molecules and cancer cell environment: Challenges for drug development? *J Natl Cancer Inst* 91:1281-1287, 1999

10. Korn EL, Arbuck SG, Pluda JM, et al: Clinical trial designs for cytostatic agents: Are new approaches needed? *J Clin Oncol* 19:265-272, 2001

11. Ratain MJ: Phase II oncology trials: Let's be positive. *Clin Cancer Res* 11:5661-5662, 2005

12. Ratain MJ, Eckhardt SG: Phase II studies of modern drugs directed against new targets: If you are fazed, too, then resist RECIST. *J Clin Oncol* 22:4442-4445, 2004

13. Murray N, Coppin C, Coldman A, et al: Drug delivery analysis of the Canadian multicenter trial in non-small cell lung cancer. *J Clin Oncol* 12:2333-2339, 1994

14. Dent S, Zee B, Dancey J, et al: Application of a new multinomial phase II stopping rule using response and early progression. *J Clin Oncol* 19:785-791, 2001

15. Zee B, Melnychuk D, Dancey J, et al: Multinomial phase II cancer trials incorporating response and early progression. *J Biopharm Stat* 9:351-363, 1999

16. Kopec JA, Abrahamowicz M, Esdaile JM: Randomized discontinuation trials: Utility and efficiency. *J Clin Epidemiol* 46:959-971, 1993

17. Rosner GL, Stadler W, Ratain MJ: Randomized discontinuation design: Application to cytostatic antineoplastic agents. *J Clin Oncol* 20:4478-4484, 2002

18. Parulekar WR, Eisenhauer EA: Phase I trial design for solid tumor studies of targeted, non-cytotoxic agents: Theory and practice. *J Natl Cancer Inst* 96:990-997, 2004

19. Johnston S, Hickish T, Ellis P, et al: Phase II study of the efficacy and tolerability of two dosing regimens of the farnesyl transferase inhibitor, R115777, in advanced breast cancer *J Clin Oncol* 21:2492-2499, 2003

20. Whitehead RP, McCoy S, Macdonald JS, et al: Phase II trial of R115777 (NSC #70818) in patients with advanced colorectal cancer: A Southwest Oncology Group study. *Invest New Drugs* 24:335-341, 2006

21. Adjei AA, Mauer A, Bruzek L, et al: Phase II study of the farnesyl transferase inhibitor R115777 in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 21:1760-1766, 2003

22. Heymach JV, Johnson DH, Khuri FR, et al: Phase II study of the farnesyl transferase inhibitor R115777 in patients with sensitive relapse small-cell lung cancer. *Ann Oncol* 15:1187-1193, 2004

23. Haas N, Peereboom D, Ranganathan S, et al: Phase II trial of R115777, an inhibitor of farnesyl-transferase, in patients with hormone refractory

prostate cancer. *Proc Am Soc Clin Oncol* 21:181a, 2002 (abstr 721)

24. Sharma S, Kemeny N, Kelsen DP, et al: A phase II trial of farnesyl protein transferase inhibitor SCH 66336, given by twice-daily oral administration, in patients with metastatic colorectal cancer refractory to 5-fluorouracil and irinotecan. *Ann Oncol* 13:1067-1071, 2002

25. Rinehart J, Adjei AA, LoRusso PM, et al: Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. *J Clin Oncol* 22:4456-4462, 2004

26. Chan S, Scheulen ME, Johnston S, et al: Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. *J Clin Oncol* 23:5314-5322, 2005

27. Pandya KJ, Levy DE, Hidalgo M, et al: A randomized, phase II ECOG trial of two dose levels of temsirolimus (CCI-779) in patients with extensive stage small cell lung cancer in remission after induction chemotherapy. A preliminary report. *J Clin Oncol* 23:622s, 2005 (suppl; abstr 7005)

28. Atkins MB, Hidalgo M, Stadler WM, et al: Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 22:909-918, 2004

29. Cripps MC, Figueredo AT, Oza AM, et al: Phase II randomized study of ISIS 3521 and ISIS 5132 in patients with locally advanced or metastatic colorectal cancer: A National Cancer Institute of Canada Clinical Trials Group study. *Clin Cancer Res* 8:2188-2192, 2002

30. Coudert B, Anthoney A, Fiedler W, et al: Phase II trial with ISIS 5132 in patients with small-cell (SCLC) and non-small cell (NSCLC) lung cancer: A European Organization for Research and Treatment of Cancer (EORTC) Early Clinical Studies Group report. *Eur J Cancer* 37:2194-2198, 2001

31. Oza AM, Elit L, Swenerton K, et al: Phase II study of CGP 69846A (ISIS 5132) in recurrent epithelial ovarian cancer: An NCIC Clinical Trials Group study (NCIC IND. 116). *Gynecol Oncol* 89:129-133, 2003

32. Tolcher AW, Reyno L, Venner PM, et al: A randomized phase II and pharmacokinetic study of the antisense oligonucleotides ISIS 3521 and ISIS 5132 in patients with hormone-refractory prostate cancer. *Clin Cancer Res* 8:2530-2535, 2002

33. Ratain MJ, Eisen T, Stadler WM, et al: Final findings from a phase II, placebo-controlled, randomized discontinuation trial (RDT) of sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC). *J Clin Oncol* 23:388s, 2005 (suppl; abstr 4544)

34. Baselga J, Albanell J, Ruiz A, et al: Phase II and tumor pharmacodynamic study of gefitinib in patients with advanced breast cancer. *J Clin Oncol* 23:5323-5333, 2005

35. Robertson JF, Gutteridge E, Cheung KL, et al: Gefitinib (ZD1839) is active in acquired tamoxifen (TAM)-resistant estrogen receptor (ER)-positive and ER-negative breast cancer: Results from a phase II study. *Proc Am Soc Clin Oncol* 22:7, 2003 (abstr 23)

36. MacKenzie MJ, Hirte HW, Goss G, et al: A phase II trial of ZD1839 (Iressa) 750 mg per day, an oral epidermal growth factor receptor-tyrosine kinase inhibitor, in patients with metastatic colorectal cancer. *Invest New Drugs* 23:165-170, 2005

37. Rothenberg ML, LaFleur B, Levy DE, et al: Randomized phase II trial of the clinical and biological effects of two dose levels of gefitinib in patients

with recurrent colorectal adenocarcinoma. *J Clin Oncol* 23:9265-9274, 2005

38. Fukuoka M, Yano S, Giaccone G, et al: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 21:2237-2246, 2003

39. Niho S, Kubota K, Goto K, et al: First-line single agent treatment with gefitinib in patients with advanced non-small-cell lung cancer: A phase II study. *J Clin Oncol* 24:64-69, 2006

40. Reck M, Gatzemeier U, Bucholz E, et al: An open-label, multi centre, phase II, non-comparative trial of ZD1839 monotherapy in chemotherapy-naive patients with stage IV or stage III non-operable non-small cell lung cancer (NSCLC). *J Clin Oncol* 23:644s, 2005 (suppl; abstr 7098)

41. Spigel DR, Hainsworth JD, Burkett ER, et al: Single-agent gefitinib in patients with untreated advanced non-small-cell lung cancer and poor performance status: A Minnie Pearl Cancer Research Network Phase II Trial. *Clin Lung Cancer* 7:127-132, 2005

42. Chen YM, Perng RP, Tsai CM: Gefitinib treatment is highly effective in non-small-cell lung cancer patients failing previous chemotherapy in Taiwan: A prospective phase II study. *J Chemother* 17:679-684, 2005

43. Schilder RJ, Sill MW, Chen X, et al: Phase II study of gefitinib in patients with relapsed or persistent ovarian or primary peritoneal carcinoma and evaluation of epidermal growth factor receptor mutations and immunohistochemical expression: A Gynecologic Oncology Group study. *Clin Cancer Res* 11:5539-5548, 2005

44. Canil CM, Moore MJ, Winquist E, et al: Randomized phase II study of two doses of gefitinib in hormone-refractory prostate cancer: A trial of the National Cancer Institute of Canada-Clinical Trials Group. *J Clin Oncol* 23:455-460, 2005

45. Schröder FH, Wildhagen MF: ZD1839 (gefitinib) and hormone resistant (HR) prostate cancer: Final results of a double blind randomized placebo-controlled phase II study. *J Clin Oncol* 22:429, 2004 (suppl; abstr 4698)

46. Dawson NA, Guo C, Zak R, et al: A phase II trial of gefitinib (Iressa, ZD1839) in stage IV and recurrent renal cell carcinoma. *Clin Cancer Res* 10:7812-7819, 2004

47. Drucker B, Bacik J, Ginsberg M, et al: Phase II trial of ZD1839 (IRESSA) in patients with advanced renal cell carcinoma. *Invest New Drugs* 21:341-345, 2003

48. Townsley C, Major P, Siu LL, et al: Phase II study of OSI-774 in patients with metastatic colorectal cancer. *Br J Cancer* 94:1136-1143, 2006

49. Miller VA, Patel J, Shah N, et al: The epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (OSI-774) shows promising activity in patients with bronchioloalveolar cell carcinoma (BAC): preliminary results of a phase II trial. *Proc Am Soc Clin Oncol* 22:619, 2003 (abstr 2491)

50. Pérez-Soler R, Chachoua A, Hammond LA, et al: Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol* 22:3238-3247, 2004

51. Gordon AN, Finkler N, Edwards RP, et al: Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: Results from a phase II multicenter study. *Int J Gynecol Cancer* 15:785-792, 2005

52. Beeram M, Rowinsky EK, Weiss GR, et al: Durable disease stabilization and antitumor activity

- with OSI-774 in renal cell carcinoma: A phase II, pharmacokinetic (PK) and biological correlative study with FDG-PET imaging. *J Clin Oncol* 22:207, 2004 (suppl; abstr 3050)
53. Saltz LB, Meropol NJ, Loehrer PJ Sr, et al: Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 22:1201-1208, 2004
54. Lilienbaum R, Bonomi P, Ansari R, et al: A phase II trial of cetuximab as therapy for recurrent non-small cell lung cancer (NSCLC): Final results. *J Clin Oncol* 23:629s, 2005 (suppl; abstr 7036)
55. Motzer RJ, Amato R, Todd M, et al: Phase II trial of anti-epidermal growth factor receptor antibody C225 in patients with advanced renal cell carcinoma. *Invest New Drugs* 21:99-101, 2003
56. Vogel CL, Cobleigh MA, Tripathy D, et al: Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 20:719-726, 2002
57. Cobleigh MA, Vogel CL, Tripathy D, et al: Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 17:2639-2648, 1999
58. Baselga J, Carbonell X, Castaneda-Soto N-J, et al: Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Oncol* 23:2162-2171, 2005
59. Baselga J, Tripathy D, Mendelsohn J, et al: Phase II study of weekly intravenous trastuzumab (Herceptin) in patients with HER2/neu-overexpressing metastatic breast cancer. *Semin Oncol* 26:78-83, 1999 (suppl 12)
60. Sun Y, Li LQ, Song ST, et al: Result of phase II clinical trial of Herceptin in advanced Chinese breast cancer patients. *Zhonghua Zhong Liu Za Zhi* 25:581-583, 2003
61. Clamon G, Herndon J, Kern J, et al: Lack of trastuzumab activity in nonsmall cell lung carcinoma with overexpression of *erb-B2* 39810: A phase II trial of Cancer and Leukemia Group B. *Cancer* 103:1670-1675, 2005
62. Bookman MA, Darcy KM, Clarke-Pearson D, et al: Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: A phase II trial of the Gynecologic Oncology Group. *J Clin Oncol* 21:283-290, 2003
63. Ziada A, Barqawi A, Glode LM, et al: The use of trastuzumab in the treatment of hormone refractory prostate cancer: Phase II trial. *Prostate* 60:332-337, 2004
64. Modi S, Seidman AD, Dickler M, et al: A phase II trial of imatinib mesylate monotherapy in patients with metastatic breast cancer. *Breast Cancer Res Treat* 90:157-163, 2005
65. Dy GK, Miller AA, Mandrekar SJ, et al: A phase II trial of imatinib (ST1571) in patients with c-kit expressing relapsed small-cell lung cancer: A CALGB and NCCTG study. *Ann Oncol* 16:1811-1816, 2005
66. Johnson BE, Fischer T, Fischer B, et al: Phase II study of imatinib in patients with small cell lung cancer. *Clin Cancer Res* 9:5880-5887, 2003
67. Krug LM, Crapanzano JP, Azzoli CG, et al: Imatinib mesylate lacks activity in small cell lung carcinoma expressing c-kit protein: A phase II clinical trial. *Cancer* 103:2128-2131, 2005
68. Coleman RL, Broaddus RR, Bodurka DC, et al: Phase II trial of imatinib mesylate in patients with recurrent platinum- and taxane-resistant epithelial ovarian and primary peritoneal cancers. *Gynecol Oncol* 101:126-131, 2006
69. Rao K, Goodin S, Levitt MJ, et al: A phase II trial of imatinib mesylate in patients with prostate specific antigen progression after local therapy for prostate cancer. *Prostate* 62:115-122, 2005
70. Vuky J, Isacson C, Fotoohi M, et al: Phase II trial of imatinib (Gleevec) in patients with metastatic renal cell carcinoma. *Invest New Drugs* 24:85-88, 2006
71. Cobleigh MA, Langmuir VK, Sledge GW, et al: A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. *Semin Oncol* 30:117-124, 2003
72. Yang JC, Haworth L, Sherry RM, et al: A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 349:427-434, 2003
73. Miller KD, Trigo JM, Wheeler C, et al: A multicenter phase II trial of ZD6474, a vascular endothelial growth factor receptor-2 and epidermal growth factor receptor tyrosine kinase inhibitor, in patients with previously treated metastatic breast cancer. *Clin Cancer Res* 11:3369-3376, 2005
74. Stadler WM, Dingcai C, Vogelzang NJ, et al: A randomized phase II trial of the antiangiogenic agent SU5416 in hormone-refractory prostate cancer. *Clin Cancer Res* 10:3365-3370, 2004
75. Kuenen BC, Taberero J, Baselga J, et al: Efficacy and toxicity of the angiogenesis inhibitor SU5416 as a single agent in patients with advanced renal cell carcinoma, melanoma, and soft tissue sarcoma. *Clin Cancer Res* 9:1648-1655, 2003
76. Miller KD, Burstein HJ, Elias AD, et al: Phase II study of SU11248, a multitargeted receptor tyrosine kinase inhibitor (TKI), in patients (pts) with previously treated metastatic breast cancer (MBC). *J Clin Oncol* 23:19s, 2005 (suppl; abstr 563)
77. Motzer RJ, Michaelson MD, Redman BG, et al: Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 24:16-24, 2006
78. Rosenbaum E, Zahurak M, Sinibaldi V, et al: Marimastat in the treatment of patients with biochemically relapsed prostate cancer: A prospective randomized, double-blind, phase I/II trial. *Clin Cancer Res* 11:4437-4443, 2005
79. Lara PN, Longmate J, Stadler W, et al: Angiogenesis inhibition in metastatic hormone refractory prostate cancer (HRPC): A randomized phase II trial of two doses of the matrix metalloproteinase inhibitor (MMPi) BMS-275291. *J Clin Oncol* 22:417, 2004 (suppl; abstr 4647)
80. Gradishar WJ, O'Neill A, Cobleigh M, et al: A phase II trial with antisense oligonucleotide ISIS 3521/Cgp 64128a in patients (Pts) with metastatic breast cancer (MBC): ECOG Trial 3197. *Proc Am Soc Clin Oncol* 20:44a, 2001 (abstr 171)
81. Marshall JL, Eisenberg SG, Johnson MD, et al: A phase II trial of ISIS 3521 in patients with metastatic colorectal cancer. *Clin Colorectal Cancer* 4:268-274, 2004
82. Advani R, Peethambaram P, Lum BL, et al: A phase II trial of aprinocarsen, an antisense oligonucleotide inhibitor of protein kinase C alpha, administered as a 21-day infusion to patients with advanced ovarian carcinoma. *Cancer* 100:321-326, 2004
83. Winquist E, Knox J, Ayoub J-P, et al: Phase II trial of DNA methyltransferase 1 inhibition with the antisense oligonucleotide MG98 in patients with metastatic renal carcinoma: A National Cancer Institute of Canada Clinical Trials Group investigational new drug study. *Invest New Drugs* 24:159-167, 2006

Acknowledgment

We thank National Cancer Institute of Canada Clinical Trials Group statistician Dongsheng Tu, PhD, for statistical advice.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).