Failures in Phase III: Causes and Consequences

Bostjan Seruga[1], Alberto Ocana[2], Eitan Amir[3], and Ian F. Tannock[3]

Abstract

Phase III randomized controlled trials (RCT) in oncology fail to lead to registration of new therapies more often than RCTs in other medical disciplines. Most RCTs are sponsored by the pharmaceutical industry, which reflects industry's increasing responsibility in cancer drug development. Many preclinical models are unreliable for evaluation of new anticancer agents, and stronger evidence of biologic effect should be required before a new agent enters the clinical development pathway. Whenever possible, early-phase clinical trials should include pharmacodynamic studies to demonstrate that new agents inhibit their molecular targets and demonstrate substantial antitumor activity at tolerated doses in an enriched population of patients. Here, we review recent RCTs and found that these conditions were not met for most of the targeted anticancer agents, which failed in recent RCTs. Many recent phase III RCTs were initiated without sufficient evidence of activity from early-phase clinical trials. Because patients treated within such trials can be harmed, they should not be undertaken. The bar should also be raised when making decisions to proceed from phase II to III and from phase III to marketing approval. Many approved agents showed only better progression-free survival than standard treatment in phase III trials and were not shown to improve survival or its quality. Introduction of value-based pricing of new anticancer agents would dissuade the continued development of agents with borderline activity in early-phase clinical trials. When collaborating with industry, oncologists should be more critical and better advocates for cancer patients. *Clin Cancer Res; 21(20); 4552–60. ©2015 AACR.*

See all articles in this *CCR Focus* section, "Innovations to Speed Drug Development."

Introduction

New anticancer agents are approved by regulatory agencies on the basis of proven efficacy and safety, which usually (but not always) need to be demonstrated in phase III randomized controlled trials (RCT; ref. 1). It is estimated that current development of a single new drug costs pharmaceutical companies up to $2.6 billion (2). Before a particular new anticancer agent enters evaluation in a RCT, its mechanism of action, antitumor activity, and safety should be demonstrated in preclinical models and in early-phase clinical trials. The overall failure rate of oncologic RCTs is about 60% and is higher than in other medical disciplines (3).

New agents often add toxicity, and RCTs that are unlikely to demonstrate benefit to patients should be avoided. Here, we explore causes and discuss consequences of negative RCTs and whether some of these failures could be avoided. For the purpose of this review, we analyzed recently published RCTs, which evaluated targeted agents for treatment of solid tumors and the corresponding data from preclinical and early-phase clinical trials.

A Snapshot of Recently Published Phase III RCTs

We searched MEDLINE (Host: PubMed) for phase III RCTs, which evaluated targeted anticancer agents (used alone or in combination with chemotherapy or hormonal therapy) for advanced solid tumors and were published between January, 2010 and December, 2014 in *Journal of Clinical Oncology* (JCO), *Lancet Oncology*, *Lancet*, or *New England Journal of Medicine*. We defined positive or negative RCTs as those reporting (or not) a statistically significant difference between arms in the primary time-to-event endpoint. Search terms were: cancer, phase III, randomized, and the Journal name. We excluded phase II studies, studies evaluating supportive agents, cytotoxic chemotherapy or endocrine therapy used alone, maintenance therapy, trials with radiotherapy, studies for hematologic malignancies or early-stage cancer, biomarker analyses, smaller studies (<150 participants), pooled analyses, noninferiority trials, studies evaluating investigational agents in both arms, and studies without a time-to-event primary endpoint. We searched publications reporting these RCTs for supporting evidence from preclinical and early-phase clinical studies. We also searched MEDLINE (Host: PubMed) and Google for published and unpublished early-phase studies supporting the phase III trial. Of note, phase III RCTs included in our analysis may not be representative of currently designed and ongoing RCTs.

Our search identified 112 RCTs (see Fig. 1; Supplementary Tables S1 and S2), among which 60 (54%) were negative, consistent with other reports (3). Fifty-two (87%) negative and 48 (92%) positive RCTs were sponsored at least in part by pharmaceutical companies. Thirty-nine (65%) negative and 25 (48%) positive RCTs were conducted in patients with non–small cell lung cancer (NSCLC), prostate, breast, and colorectal cancer, which are the most common, lethal cancers in wealthy countries (Table 1; ref. 4).

Endpoints of the RCTs

Overall survival (OS) is the most reliable measure of efficacy of a new anticancer drug. Progression-free survival (PFS) and similar intermediate endpoints may be considered appropriate but oncologists may overinterpret the value of improvement in PFS if it is not validated as a surrogate endpoint for duration or quality of

[1]Department of Medical Oncology, Institute of Oncology Ljubljana and University of Ljubljana, Ljubljana, Slovenia. [2]Translational Oncology Unit, Albacete University Hospital, Albacete, Spain. [3]Princess Margaret Cancer Centre and University of Toronto, Toronto, Canada.

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

Corresponding Author: Ian F. Tannock, Princess Margaret Cancer Centre and University of Toronto, 610 University Avenue, Toronto, ON M5G 2M9, Canada. Phone: 1-416-946-2245; Fax: 1-416-946-4563; E-mail: ian.tannock@uhn.ca

doi: 10.1158/1078-0432.CCR-15-0124

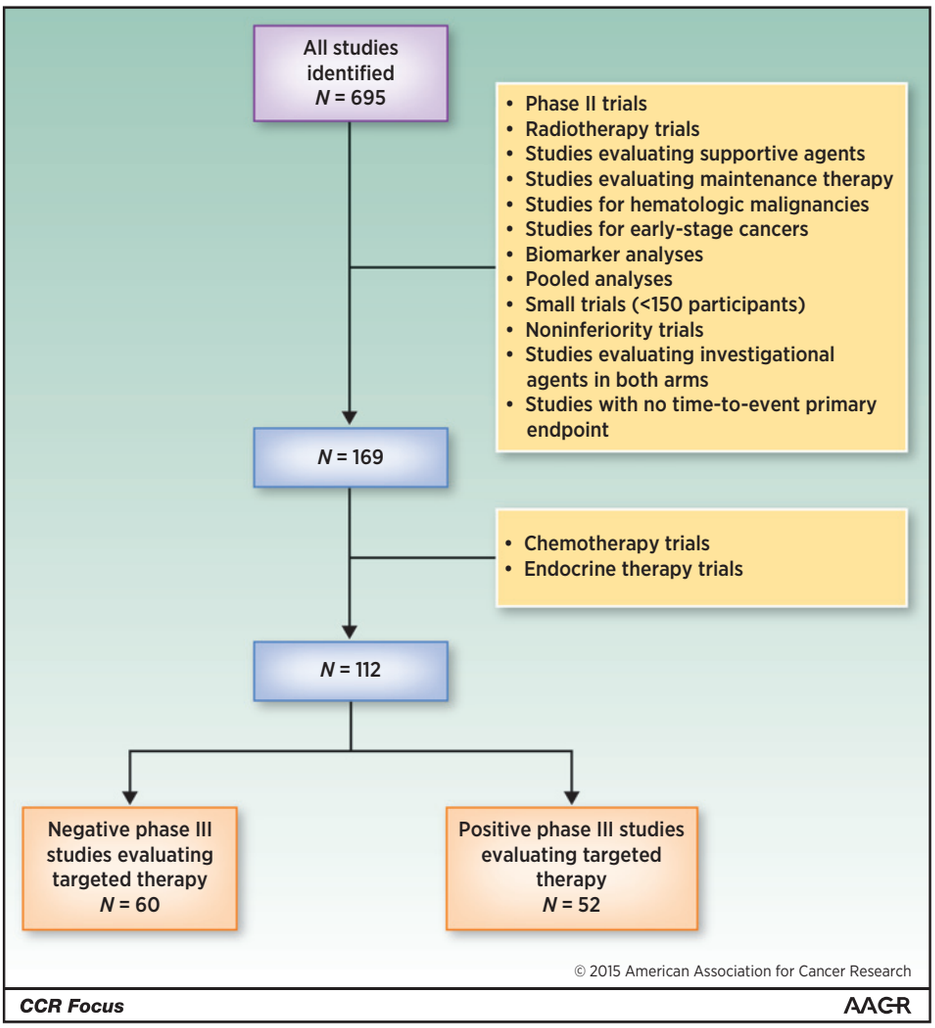

Figure 1.
Search strategy.

survival (5). In our cohort of RCTs, OS was the sole primary endpoint in 23% of positive and in 65% of negative trials, whereas PFS or time-to-progression (TTP) was the sole positive endpoint in 71% of positive and in 23% of negative trials ($P < 0.001$; Table 1). In 18 (46%) of negative studies that did not show a difference in the primary endpoint of OS, PFS was significantly superior for the experimental arm whereas only 12 (32%) of 37 positive studies with PFS as the primary endpoint showed at least a trend toward improvement in OS. However, in some positive studies, crossover was allowed or OS data were immature (Supplementary Tables S1 and S2). Thus, description of trials as positive or negative depends on whether their primary endpoint is OS or PFS (5). Only survival and its quality are true measures of benefit to patients and acceptance of PFS as a primary endpoint may lead to substantial overestimation of the number of new agents for treatment of cancer that meet the criterion of improving survival or its quality in phase III RCTs.

Preclinical cancer research to support drug development

For some of the negative RCTs, which were evaluated in our cohort, we were unable to identify appropriate preclinical studies. This was particularly true for studies evaluating combinations of chemotherapy and targeted agents where the corresponding preclinical studies evaluated targeted agents used alone. For some trials there was simply a claim of sufficient preclinical evidence to conduct such trials (6–8). Appropriate preclinical studies may have been conducted, but were not reported.

Efficient drug development should initiate with robust preclinical findings from cell lines and animal models. It is essential to show in preclinical studies that new agents can inhibit their molecular target at concentrations achievable in humans, although valid preclinical models are lacking for evaluation of some therapies, especially immunotherapy and antiangiogenic agents. There is evidence of poor reproducibility from preclinical studies: two surveys found that only 11% to 25% of published results of preclinical studies could be reproduced (9, 10). One reason may be the bias to publish positive results: Career development and research funding are promoted by positive studies, which are more likely to be published, and published in high impact journals, as compared with negative studies. Scientists should be encouraged to present whole datasets, not only positive results (10). Clinical trials evaluating drug combinations are often stimulated by claims of synergistic interactions in preclinical models. We have shown that inappropriate methods for

Table 1. Characteristics of the phase III clinical trials

Characteristics	Negative RCTs (total *N* = 60), *n* (%)	Positive RCTs (total *N* = 52), *n* (%)	*P*
Cancer site			
NSCLC	19 (32)	11 (21)	0.04
Prostate	8 (13)	1 (2)	
Breast	7 (12)	9 (17)	
Esophagus/gastric	6 (10)	3 (6)	
Colon/rectum	5 (8)	4 (8)	
Pancreas	4 (7)	1 (2)	
Melanoma	3 (5)	9 (17)	
Other	8 (13)	14 (27)	
Double-blind study			
Yes	37 (62)	30 (58)	0.67
No	23 (38)	22 (42)	
Sponsor			
Industry	46 (78)	47 (90)	0.11
Cooperative group/government	8 (13)	4 (8)	
Industry and cooperative group	6 (10)	1 (2)	
Type of targeted agent studied			
Antiangiogenic agent	28 (47)	23 (44)	0.92
EGFR and/or other HER members	17 (28)	12 (23)	
Immunotherapy	4 (7)	4 (8)	
mTOR inhibitor	4 (7)	5 (10)	
Other	7 (12)	8 (15)	
Enriched population of patients			
No	52 (87)	29 (56)	<0.001
Yes, based on clinical or pathologic characteristics	6 (10)	7 (13)	
Yes, based on molecular characteristics	2 (3)	16 (31)	
Type of therapy in experimental arm			
CTx/endocrine th. + small molecule	23 (38)	5 (10)	
CTx/endocrine th. + mAb	15 (25)	18 (35)	
Small molecule	14 (23)	21 (40)	0.005
Other	8 (14)	8 (15)	
Type of therapy in control arm			
CTx	41 (68)	32 (62)	0.25
BSC or Placebo	8 (13)	12 (23)	
Small molecule	6 (10)	7 (13)	
Other	5 (8)	1 (2)	
Primary endpoint			
OS	39 (65)	12 (23)	<0.001
PFS/TTP	19 (32)	37 (71)	
OS/PFS co-primary	2 (3)	3 (6)	
Prior phase II trials*			
No appropriate phase II trial	21 (35)	15 (29)	0.19
SA-II study only	22 (37)	27 (52)	
RP-II study only	11 (18)	9 (17)	
Both SA-II and RP-II	6 (10)	1 (2)	
Single-arm phase II studies*			
Primary endpoint			
ORR	18 (64)	21 (75)	0.12
PFS	4 (14)	6 (21)	
PSA response	4 (14)	0	
Other	2 (7)	1 (4)	
Randomized phase II studies[a]			
Screening design	9 (53)	7 (70)	0.38
Selection (pick-the-winner) design	8 (47)	3 (30)	
Randomized phase II studies			
Primary endpoint			
PFS	7 (41)	9 (90)	0.09
ORR	5 (29)	1 (10)	
PSA response	2 (12)	0	
Other or not defined	3 (18)	0	
Metric of success defined and met			
Single-arm phase II studies	14 (23)	22 (42)	0.14
Randomized phase II studies	8 (13)	6 (12)	0.77
Phase III RCTs with supporting PD analyses[b]			0.18
In phase II studies	11 (18)	5 (10)	0.88
In phase I studies	20 (33)	18 (34)	

(Continued on the following page)

Table 1. Characteristics of the phase III clinical trials (Cont'd)

Characteristics	Negative RCTs (total $N = 60$), *n* (%)	Positive RCTs (total $N = 52$), *n* (%)	*P*
Phase III RCTs with supporting correlative analyses			
In phase II studies	17 (28)	33 (63)	<0.001
In phase I studies	8 (13)	17 (33)	<0.001

NOTE: Asterisks indicate that for some phase III RCTs more than one single-arm phase II trial was identified.

Abbreviations: BSC, best supportive care; CTx, chemotherapy; RP-II, randomized phase II; SA-II, single-arm phase II; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; mTOR, mammalian target of rapamycin; mAb, monoclonal antibody; PSA, prostate-specific antigen.

[a]No phase II studies with the randomized discontinuation design were identified. Screening design enables preliminary comparisons of an experimental treatment regimen, generally composed of a standard regimen with an experimental agent added, to an appropriate control, which is usually the standard regimen. This design is especially useful when PFS is an endpoint. In contrast, selection design compares two experimental regimens, usually incorporating comparison of each with the historical control, and usually involving a tumor response endpoint.

[b]For only six positive and one negative phase III, we were able to identify the corresponding PD analyses in both phase I and II studies.

evaluation of synergy and poor assessment of therapeutic index have been used in many preclinical articles, leading to inaccurate claims of synergy (11).

In addition to the requirement for reproducibility from preclinical research, new research tools are needed for more efficient drug development (12). Dispersed cells in tissue culture do not reflect the microenvironment in solid tumors and immunodeficient mice bearing transplanted human tumor cell lines do not faithfully predict histology-specific antitumor efficacy of targeted drugs (13, 14). Examples of new *in vitro* models are the development of 3D cultures or cancer organoids, whereas genetic approaches have produced more sophisticated *in vivo* models of human cancer, and xenografts in mice can be generated from surgical or biopsy samples taken directly from patients (15–17).

Early-phase clinical trials

Characteristics of the phase II studies that preceded the phase III trials in our review are presented in Table 1; Supplementary Tables S1 and S2. Twenty-one (35%) negative and 15 (29%) positive phase III RCTs in our survey were not preceded by any identifiable and context-appropriate phase II study ($P = 0.19$). However, some phase II trials may have been conducted, but results were never published. At least one context-appropriate corresponding single-arm phase II study was identified for 28 (47%) negative and 28 (54%) positive RCTs at the time they were initiated. At least one randomized phase II study was identified for 17 (28%) negative and for 10 (19%) positive RCTs. For 6 (10%) negative and one (2%) positive RCTs, we identified both single-arm and randomized studies. A metric of success (a stated threshold of activity in phase II to proceed to phase III was both defined and met in only a small proportion of phase II trials; Table 1).

Early-phase clinical trials are critical in drug development and their goal is to facilitate decision making by identifying anticancer agents with the highest probability of succeeding in phase III RCTs. Because of the limited size and statistical uncertainty of phase II trials, that decision will always be imperfect but it will be strengthened by (i) the observation of a predefined threshold of activity, and (ii) pharmacodynamic (PD) studies confirming proof-of-concept that the agent is inhibiting its target (18). Results of our survey indicate that many phase III trials proceed despite a threshold of activity not being reached in phase II evaluation, and few include PD studies to confirm target inhibition. An example is provided by the nine phase III RCTs, which have evaluated new anticancer agents in combination with docetaxel for men with metastatic castrate-resistant prostate cancer: These trials randomized about 10,000 men to receive (or not) treatments that added toxicity without improving survival and cost several billion dollars. For new agents evaluated in these trials there was a lack of supporting evidence of activity from early-phase clinical trials (19).

A debate regarding the optimal design of phase II clinical trials in oncology focuses on whether they should be single-arm or randomized (20, 21). A recent review showed that a majority of phase II trials evaluating targeted agents are single-arm studies and that objective response rate (ORR), as used in most phase II trials evaluating chemotherapy, predicts (albeit imperfectly) eventual success in phase III trials (22). However, ORRs in most phase III RCTs were lower than those in preceding phase II studies, with a mean absolute difference of 12.9% (23). There are examples of success with agents that showed a substantial and durable ORR in single-arm phase II trials, including some immunotherapeutic agents, and examples of failures despite showing improvement in OS in randomized phase II studies (24–26). In one analysis more complex randomized, double-blind, and multi-arm phase II trials did not translate to positive phase III RCTs more often than single-arm phase II studies (27).

Another major omission in early-phase clinical studies is failure to confirm proof-of-concept that targeted agents can inhibit their target in people. Often, this can be done by evaluating molecular targets in circulating white cells or from superficial biopsies of normal tissue (28). Cancer patients are often willing to undergo tumor biopsy if this is important to demonstrate biologic activity (29), but this is done rarely in early-phase trials. For only 11 (18%) and 20 (33%) negative and 5 (10%) and 18 (34%) positive phase III studies in our review, we were able to identify PD studies to determine whether the experimental agent inhibited its target in the preceding phase II and I studies, respectively ($P < 0.01$). Of note, in studies evaluating vascular-disrupting or antiangiogenic agents (the most frequently studied drugs) dynamic contrast-enhanced (DCE)-MRI was used rather than blood or tissue-based PD analyses. Although DCE-MRI evaluates properties of tumor vessels such as leakiness, it is not well established as a valid PD marker for antiangiogenic therapy (30). Selected examples of negative and positive phase III trials are presented in Table 2.

In summary, many new agents are not properly evaluated in phase II clinical trials, and some of them proceed to phase III when a pre-defined threshold of activity is not met. Moreover, confirmation of mechanism of action of new agents in phase I and II trials is undertaken rarely, despite the fundamental importance of demonstrating target inhibition. The oncologic community, regulatory agencies, and industry should jointly set higher standards

Table 2. Selected examples of negative and positive RCTs

Author/study	Cancer site/ setting	Sample size (treated) all/exp. am	Comparison arms	Targets	Enriched population?	Sponsor	Primary endpoint (secondary endpoint)	Efficacy results	Safety results Exp vs. control arm	Supporting evidence from early-phase clinical studies, biomarker correlative and PD analyses
Negative RCTs										
Mackey et al. (39) ROSE/TRIO-12	Breast ca., HER2 neg, 1st line	1,144/752	Ramucirumab + Doce vs. placebo + Doce	Angiogenesis (VRGFR2)	No	Eli Lilly /ImClone Systems.	PFS (OS)	HR PFS, 0.88; $P = 0.077$ HR OS, 1.01; $P = 0.915$	G≥3: 61% vs. 52% Toxic deaths: not reported	No appropriate phase II study, ramucirumab subsequently studied with eribulin in the RP-II in 3rd -5th line, results negative (results not available when study was initiated). In phase I but (monotherapy) PD analyses done.
Scagliotti et al. (35) ESCAPE	NSCLC, 1st line	922/463	Sorafenib + PacliCarbo vs. placebo + PacliCarbo	Angiogenesis (multikinase inhibitor)	No	Bayer HealthCare and Onyx Pharm.	OS (PFS)	HR OS, 1.15; $P = 0.915$ HR PFS, 0.99; $P = 0.433$	G3: 32% vs. 17% G4: 9% vs. 5% G5: 3% vs. 1%	No appropriate phase II study, this combination studied in phase I studies only, no biomarker correlative or PD analyses. SA-II studies and RP-II discontinuation study evaluated sorafenib in monotherapy (in previously treated patients), no biomarker correlative or PD analyses.
Kelly et al. (57) CALGB 90401	CRPC, docetaxel naïve	1,009/504	Bevacizumab + DocePred vs. placebo + DocePred	Angiogenesis (VEGF)	No	CALGB and Roche/ Genentech	OS (PFS)	HR OS, 0.91; $P = 0.181$ PFS, 9.9 vs. 7.5 mo; $P = 0.001$	G3: 41% vs. 31% G4: 30% vs. 24% Toxic deaths: 4.0% vs. 1.2%	SA-II, primary endpoint PFS, a metric of success not met (median PFS 8 mo, target median PFS ≥ 16 mo); in this study bevacizumab combined with estarmustine and docetaxel, no biomarker correlative and PD analyses.
Vermorken et al. (58) SPECTRUM	Head and neck ca., 1st line	657/327	Panitimumab + Cis/5-FU vs. Cis/5-FU	EGFR	No	Amgen	OS (PFS)	HR OS, 0.873 $P = 0.1403$ HR PFS, 0.780 $P = 0.0036$	G3/4: 67% vs. 66% Toxic deaths: 4% vs. 2%	No phase II reported, phase I evaluated panitimumab, carboplatin and radiotherapy, no biomarker correlative and PD analyses done.

(Continued on the following page)

Table 2. Selected examples of negative and positive RCTs (Cont'd)

Author/study	Cancer site/ setting	Sample size (treated) all/exp. am	Comparison arms	Targets	Enriched population?	Sponsor	Primary endpoint (secondary endpoint)	Efficacy results	Safety results Exp vs. control arm	Supporting evidence from early-phase clinical studies, biomarker correlative and PD analyses
Positive RCTs										
Verma et al. (59) EMILIA	Breast ca., previously treated with trastuzumab and taxane	991/495	T-DM1 vs. LapatinibCapec	HER-2	Yes, HER-2^{+}	Hoffmann La Roche	PFS (OS: sign. improved, no cross-over)	HR PFS, 0.65, $P < 0.001$ HR OS, 0.68, $P < 0.001$	G3/4: 40.8% vs. 57% SAEs: 15.5% vs. 18% Toxic deaths: 1 vs. 4 deaths	Two SA-II studies, primary endpoint ORR, metric of success defined and met in at least one study. Biomarker correlative analyses included, no PD analyses. In phase I no biomarker correlative or PD analyses
Sequist et al. (60) LUX-Lung 3	NSCLC, 1st line	340/229	Afatinib vs. CisPem	EGFR, HER-2 and HER-4	Yes, EGFR mutated	Boehringer Ingelheim	PFS (OS: data immature, cross-over allowed)	HR PFS, 0.47 $P < 0.001$	G3/4: 49% vs. 48% Toxic deaths: 4 vs. 0 toxic deaths	SA-II study, in enriched population of EGFR mutated patients, previously treated with chemo and chemo-naïve, primary endpoint ORR, metric of success defined and met (ORR 66%, target ORR 55%), biomarker correlative analyses done, no PD analyses. In phase I studies biomarker correlative and PD analyses done.
Hauschild et al. (61)	Melanoma, 1st line	250/187	Dabrafenib vs. dacarbazine	BRAF	Yes, mutated BRAF^{V600E}	GlaxoSmithKline	PFS (OS: trend toward improved OS; cross-over allowed)	HR PFS, 0.30 $P < 0.0001$ HR OS, 0.61; 95% CI 0.25–1.48	G3/4 AEs rare in both groups No toxic deaths reported	SA-II study, primary endpoint ORR; metric of success not defined, ORR 59% Biomarker correlative analysis done, no PD analyses. In phase I study biomarker correlative and PD analysis done.
Chapman et al. (62) BRIM-3	Melanoma, 1st line	675/337	Vemurafenib vs. dacarbazine	BRAF	Yes, patients with BRAF^{V600E} mutation	Hoffmann–La Roche	OS and PFS	HR PFS, 0.26, $P < 0.001$ HR OS, 0.37, $P < 0.001$	G3/4 AEs rare in both groups No toxic deaths reported	SA-II study in patients with BRAF^{V600E} mutation, primary endpoint ORR, metric of success defined and met (ORR 52.3%), PD analyses done.

Abbreviations: CALGB, Cancer and Leukemia Group B; CAPOX, capecitabine and oxaliplatin; Cis, cispatin; Carbo, carboplatin; CTx, chemotherapy; Capec: capecitabine; CRPC, castration-resistant prostate cancer; Doce, docetaxel; FOLFOX: oxaliplatin with fluorouracil (5FU) and folinic acid; G, grade; HR, Hazard Ratio; Oxali, oxaliplatin; Pacli, paclitaxel; Pem: pemetrexed; Pred, prednisone; R: receptor; RP-II, randomized phase II; SAE, serious adverse event; SA-II, single-arm phase II study; TKI, tyrosine kinase inhibitor; T-DM1, trastuzumab–emtansine.

for the design of early-phase clinical studies and for transition of investigational agents to phase III RCTs.

Biomarkers

For seventeen (28%) negative and 33 (63%) positive phase III trials included in our survey, a correlative blood or tissue biomarker was used in prior phase II studies (Table 1). For several positive but only one negative phase III RCT, correlative biomarker analyses were performed already in phase I trials (Supplementary Tables S1 and S2; ref. 31). Eight (13%) of 60 negative and 23 (44%) of 52 positive phase III studies evaluated new agents in an enriched population of patients ($P < 0.001$; Table 1). Among phase III studies using PFS as a primary endpoint, those with positive results more often enrolled an enriched population of patients as compared with negative studies ($P < 0.0008$; data not shown); however, we did not observe any such association in phase III trials using OS as a primary endpoint. Because of the small number of patients further sensitivity analyses were not feasible.

As many of the most successful anticancer drugs are those with companion diagnostics, efforts to identify biomarkers early in the development of new anticancer drugs should be made. Such an approach should inform the design and conduct of early-phase clinical trials and allow consistency between populations in early-phase and phase III clinical trials. A recent study showed that anticancer drugs that were used to treat an enriched population selected by a biomarker progressed from one phase to another phase, and ultimately to regulatory approval, more often than drugs, which were evaluated without biomarkers (32). However, development of biomarkers may be hindered by intratumor heterogeneity (33), and for some drugs, such as antiangiogenic agents, serum or tumor levels of possible biomarkers such as vascular endothelial growth factor have not proven helpful in selecting patients (34).

An Example of Failed Drugs—Inhibitors of Angiogenesis

Inhibitors of angiogenesis are anticancer agents that have often failed to meet criteria of success in phase III RCTs (Table 1). Fifteen different antiangiogenic agents, including multikinase inhibitors and monoclonal antibodies, owned by 11 pharmaceutical companies, were evaluated in 28 (47%) negative and 23 (44%) positive RCTs from our cohort (Table 1; Supplementary Tables S1 and S2). Overall, 22 of 37 phase III RCTs (59%) evaluating antiangiogenic agents were not preceded by appropriate phase II studies. In some of these studies results of the prior phase I clinical trials were considered sufficiently promising to conduct phase III RCTs (35–38). Furthermore, investigators sometimes justified evaluation of a new anticancer therapy on the basis of preclinical data, or on results of RCTs, which evaluated the same treatment in different cancer types (39). In recent published reports of RCTs, investigators openly stated that results of phase II trials were not available when phase III RCTs were initiated (40, 41). Enrollment periods sometimes overlapped for phase II and III studies, and results of the phase II study, later found to be negative, were not available when the phase III RCT was initiated (42, 43).

In patients with advanced NSCLC, antiangiogenic agents were evaluated in 10 (53%) of 19 negative RCTs in our survey. It is possible that the positive results of the Eastern Cooperative Oncology Group E4599 phase III RCT, which showed that bevacizumab in combination with chemotherapy improved OS modestly in patients with non-squamous NSCLC as compared with chemotherapy alone, led to the multiple RCTs evaluating angiogenesis inhibitors for this disease, which subsequently all failed (44).

Consequences of Failure of RCTs—Harm and Dollars

Although failures in RCTs generate knowledge and cannot be completely avoided, prevalent negative trials lead to increased costs for drug development and increased toxicity to patients. Overall, 44,655 patients with advanced cancer were treated within our cohort of negative RCTs and 23,598 of patients received experimental therapy within these trials. Patients enrolled into experimental arms of such trials may be exposed to harm. In 3 (5%) of negative RCTs in our survey, the overall population of patients assigned to the experimental arm had at least a trend to worse OS as compared with those in the control arm (Supplementary Table S1; refs. 45–47). In other studies, more patients receiving experimental therapy died of toxic effects of drugs compared with patients in the control arm, including studies without preceding phase II trials (Supplementary Table S2; refs. 6, 40, 41). Patients receiving experimental therapy may also suffer from increased non-fatal toxicity, which impairs the quality of their lives, and this was demonstrated for the majority of negative RCTs (Supplementary Table S1). Given our findings, continuing to embark on phase III RCTs without careful empirical analysis to improve the success rate of those RCTs is unethical.

Many approved new anticancer agents are not cost-effective (48). Furthermore, the cost of new drugs is not related to their effectiveness: For example, agents with specific molecular targets are clinically most beneficial, but their market price is not significantly different from those of less active anticancer agents (49). Before initial approval for marketing, 57% of oncology drugs are investigated for multiple indications, with 32% tested in at least four indications, and these strategies increase the cost of the approved drug (50). For example, in our survey, antiangiogenic agents such as sunitinib, sorafenib, and bevacizumab were evaluated in several different cancer types (Supplementary Tables S1 and S2). Market prices of new drugs are set to maximize the expected profits of pharmaceutical companies and one strategy to reduce costs of new drugs might be the introduction of value-based pricing. With such an approach, new drugs would be required to fall within a defined margin of cost-effectiveness (defined by cost per life-year gained in pivotal trials) after registration. This would dissuade the continued development of agents with borderline activity in phase II clinical trials. Many challenges for efficient, fast and less costly drug development still need to be addressed and are discussed elsewhere in this *CCR Focus* section (51, 52).

Role and Responsibility of the Pharmaceutical Industry

Pharmaceutical companies sponsor an increasing proportion of RCTs (53). Therapeutic advances such as agents targeting HER2/neu in women with breast cancer or agents directed against mutated B-RAF protein in patients with melanoma would not be possible without collaboration between industry and academia

(25, 54, 55). In contrast with these successes, many new anticancer therapies show only modest benefit or fail to improve patient outcome when studied in phase III RCTs.

The motivation for drug development by pharmaceutical companies is profit and there is, therefore, an emphasis on bringing products to market quickly to maximize the period of patent protection. Decisions about drug development are not only driven by science, but also by complex financial market forces, which may stimulate a transition of investigational cancer agents from preclinical and early-phase clinical studies to RCTs and are usually poorly understood by clinicians (56). Such an approach may have also an unfavorable impact on drug development.

Conclusions

RCTs evaluating new anticancer agents fail more often than RCTs in other areas of medicine. Most oncologic phase III RCTs are sponsored by industry and competitiveness may accelerate transition from early phases of drug development to phase III RCTs. Failed agents often show only borderline activity in early-phase clinical trials, and it is rare for such trials to include studies to ensure that new agents inhibit their putative molecular target. The threshold of success in phase II trials that informs the decision to proceed to phase III evaluation should be raised. Many agents that "succeed" in phase III do so because they were evaluated with a primary endpoint of PFS without significant improvement of OS, and often without demonstration of improvement in quality of survival. Negative RCTs expose cancer patients to harm: It is unethical to evaluate an anticancer agent in a phase III RCT if activity was not clearly demonstrated in preclinical and early-phase clinical studies. Value-based pricing of approved new anticancer agents would effectively reduce the rate of failures of phase III RCTs. The oncologic community should reflect on recently failed RCTs and aim for more successful drug development.

Disclosure of Potential Conflicts of Interest

B. Seruga reports receiving speakers bureau honoraria from Astellas Pharma, Janssen, and Sanofi-Aventis. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: B. Seruga, A. Ocana, I.F. Tannock
Development of methodology: B. Seruga
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Seruga
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B. Seruga, E. Amir, I.F. Tannock
Writing, review, and/or revision of the manuscript: B. Seruga, A. Ocana, E. Amir, I.F. Tannock
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B. Seruga, I.F. Tannock
Study supervision: I.F. Tannock

Received May 8, 2015; revised July 10, 2015; accepted August 20, 2015; published online October 15, 2015.

References

1. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003;22:151–85.
2. How the Tufts Center for the Study of Drug Development pegged the cost of a new drug at $2.6 billion [PDF on the Internet]. Boston: Tufts Center for the Study of Drug Development; 2014 [cited 2015 10 Jul]. Available from: http://csdd.tufts.edu/files/uploads/cost_study_backgrounder.pdf.
3. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004;3:711–5.
4. Seruga B, Hertz PC, Le LW, Tannock IF. Global drug development in cancer: a cross-sectional study of clinical trial registries. Ann Oncol 2010;21: 895–900.
5. Ocaña A, Amir E, Vera F, Eisenhauer EA, Tannock IF. Addition of bevacizumab to chemotherapy for treatment of solid tumors: similar results but different conclusions. J Clin Oncol 2011;29:254–6.
6. Paz-Ares LG, Biesma B, Heigener D, von Pawel J, Eisen T, Bennouna J, et al. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/ cisplatin alone or with sorafenib for the first-line treatment of advanced non-squamous non–small cell lung cancer. J Clin Oncol 2012; 30:3084–92.
7. Scagliotti GV, Vynnychenko I, Park K, Ichinose Y, Kubota K, Blackhall F, et al. International, randomized, placebo-controlled, double-blind phase III study of motesanib plus carboplatin/ paclitaxel in patients with advanced nonsquamous non–small cell lung cancer: MONET1. J Clin Oncol 2012;30:2829–36.
8. Araujo JC, Trudel GC, Saad F, Armstrong AJ, Yu EY, Bellmunt J, et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. Lancet Oncol 2013;14:1307–16.
9. Prinz F, Schlange T, Asadullah K. Believe it or not: how much can we rely on published data on potential drug targets? Nat Rev Drug Discov 2011; 10:712.
10. Begley CG, Ellis LM. Drug development: raise standards for preclinical cancer research. Nature 2012;483:531–3.
11. Ocana A, Amir E, Yeung C, Seruga B, Tannock IF. How valid are claims for synergy in published clinical studies? Ann Oncol 2012;23:2161–6.
12. Doroshow JH, Kummar S. Translational research in oncology—10 years of progress and future prospects. Nat Rev Clin Oncol 2014;11: 649–62.
13. Minchinton AI, Tannock IF. Drug penetration in solid tumours. Nat Rev Cancer 2006;6:583–92.
14. Sausville EA, Burger AM. Contributions of human tumor xenografts to anticancer drug development. Cancer Res 2006;66:3351–4.
15. Sachs N, Clevers H. Organoid cultures for the analysis of cancer phenotypes. Curr Opin Genet Dev 2014;24:68–73.
16. Singh S, Sharma A, Robertson GP. Realizing the clinical potential of cancer nanotechnology by minimizing toxicologic and targeted delivery concerns. Cancer Res 2012;72:5663–8.
17. Tentler JJ, Tan AC, Weekes CD. Patient-derived tumour xenografts as models for oncology drug development. Nat Rev Clin Oncol 2012;9:338–50.
18. Goodwin R, Giaccone G, Calvert H, Lobbezoo M, Eisenhauer EA. Targeted agents: how to select the winners in preclinical and early clinical studies? Eur J Cancer 2012;48:170–8.
19. Antonarakis ES, Eisenberger MA. Phase III trials with docetaxel-based combinations for metastatic castration-resistant prostate cancer: time to learn from past experiences. J Clin Oncol 2013;31:1709–12.
20. Gan HK, Grothey A, Pond GR, Moore MJ, Siu LL, Sargent D. Randomized phase II trials: inevitable or inadvisable? J Clin Oncol 2010;28:2641–7.
21. Sharma MR, Stadler WM, Ratain MJ. Randomized phase II trials: a long-term investment with promising returns. J Natl Cancer Inst 2011;103: 1093–100.
22. El-Maraghi RH, Eisenhauer EA. Review of phase II trial designs used in studies of molecular targeted agents: outcomes and predictors of success in phase III. J Clin Oncol 2008;26:1346–54.
23. Zia MI, Siu LL, Pond GR, Chen EX. Comparison of outcomes of phase II studies and subsequent randomized control studies using identical chemotherapeutic regimens. J Clin Oncol 2005;23:6982–91.
24. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non–small cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011–9.

25. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;366:707–14.
26. O'Shaughnessy J, Osborne C, Pippen JE, Yoffe M, Patt D, Rocha C, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med 2011;364:205–14.
27. Thomas D. Oncology clinical trials – secrets of success. BIOtech Now 2014 Feb 24 [cited 2015 Mar 31]. Available from: http://www.biotech-now.org/business-and-investments/2012/02/oncology-clinical-trials-secrets-of-success.
28. Brunetto AT, Ang JE, Lal R, Olmos D, Molife LR, Kristeleit R, et al. First-in-human, pharmacokinetic and pharmacodynamic phase I study of Resminostat, an oral histone deacetylase inhibitor, in patients with advanced solid tumors. Clin Cancer Res 2013;19:5494–504.
29. Agulnik M, Oza AM, Pond GR, Siu LL. Impact and perceptions of mandatory tumor biopsies for correlative studies in clinical trials of novel anticancer agents. J Clin Oncol 2006;24:4801–7.
30. O'Connor JP, Jackson A, Parker GJ, Roberts C, Jayson GC. Dynamic contrast-enhanced MRI in clinical trials of antivascular therapies. Nat Rev Clin Oncol 2012;9:167–77.
31. Siu LL, Shapiro JD, Jonker DJ, Karapetis CS, Zalcberg JR, Simes J, et al. Phase III randomized, placebo-controlled study of cetuximab plus brivanib alaninate versus cetuximab plus placebo in patients with metastatic, chemotherapy-refractory, wild-type K-RAS colorectal carcinoma: the NCIC Clinical Trials Group and AGITG CO.20 Trial. J Clin Oncol 2013;31:2477–84.
32. Hayashi K, Masuda S, Kimura H. Impact of biomarker usage on oncology drug development. J Clin Pharm Ther 2013;38:62–7.
33. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366:883–92.
34. Jain RK, Duda DG, Willett CG, Sahani DV, Zhu AX, Loeffler JS, et al. Biomarkers of response and resistance to antiangiogenic therapy. Nat Rev Clin Oncol 2009;6:327–38.
35. Scagliotti G, Novello S, von Pawel J, Reck M, Pereira JR, Thomas M, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non–small cell lung cancer. J Clin Oncol 2010;28:1835–42.
36. Ramlau R, Gorbunova V, Ciuleanu TE, Novello S, Ozguroglu M, Goksel T, et al. Aflibercept and docetaxel versus docetaxel alone after platinum failure in patients with advanced or metastatic non–small cell lung cancer: a randomized, controlled phase III trial. J Clin Oncol 2012;30:3640–7.
37. Bergh J, Bondarenko IM, Lichinitser MR, Liljegren A, Greil R, Voytko NL, et al. First-line treatment of advanced breast cancer with sunitinib in combination with docetaxel versus docetaxel alone: results of a prospective, randomized phase III study. J Clin Oncol 2012;30:921–9.
38. Crown JP, Diéras V, Staroslawska E, Yardley DA, Bachelot T, Davidson N, et al. Phase III trial of sunitinib in combination with capecitabine versus capecitabine monotherapy for the treatment of patients with pretreated metastatic breast cancer. J Clin Oncol 2013;31:2870–8.
39. Mackey JR, Ramos-Vazquez M, Lipatov O, McCarthy N, Krasnozhon D, Semiglazov V, et al. Primary results of ROSE/TRIO-12, a randomized placebo-controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. J Clin Oncol 2015;33:141–8.
40. Hecht JR, Trarbach T, Hainsworth JD, Major P, Jäger E, Wolff RA, et al. Randomized, placebo-controlled, phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK 222584, an oral vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. J Clin Oncol 2011;29:1997–2003.
41. Van Cutsem E, Bajetta E, Valle J, Köhne CH, Hecht JR, Moore M, et al. Randomized, placebo-controlled, phase III study of oxaliplatin, fluorouracil, and leucovorin with or without PTK787/ZK 222584 in patients with previously treated metastatic colorectal adenocarcinoma. J Clin Oncol 2011;29:2004–10.
42. Scagliotti GV, Krzakowski M, Szczesna A, Strausz J, Makhson A, Reck M, et al. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non–small cell lung cancer: a phase III trial. J Clin Oncol 2012;30:2070–8.
43. Groen HJ, Socinski MA, Grossi F, Juhasz E, Gridelli C, Baas P, et al. A randomized, double-blind, phase II study of erlotinib with or without sunitinib for the second-line treatment of metastatic non–small cell lung cancer (NSCLC). Ann Oncol 2013;24:2382–9.
44. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non–small cell lung cancer. N Engl J Med 2006;355:2542–50.
45. Scher HI, Jia X, Chi K, de Wit R, Berry WR, Albers P, et al. Randomized, open-label phase III trial of docetaxel plus high-dose calcitriol versus docetaxel plus prednisone for patients with castration-resistant prostate cancer. J Clin Oncol 2011;29:2191–8.
46. Langer CJ, Novello S, Park K, Krzakowski M, Karp DD, Mok T, et al. Randomized, phase III trial of first-line figitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with advanced non–small cell lung cancer. J Clin Oncol 2014;32:2059–66.
47. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14:481–9.
48. Hillner BE, Smith TJ. Efficacy does not necessarily translate to cost effectiveness: a case study in the challenges associated with 21st-century cancer drug pricing. J Clin Oncol 2009;27:2111–3.
49. Amir E, Seruga B, Martinez-Lopez J, Kwong R, Pandiella A, Tannock IF, Ocaña A. Oncogenic targets, magnitude of benefit, and market pricing of antineoplastic drugs. J Clin Oncol 2011;29:2543–9.
50. DiMasi JA, Grabowski HG. Economics of new oncology drug development. J Clin Oncol 2007;25:209–16.
51. Siu LL, Conley BA, Boerner S, LoRusso PM. Next-generation sequencing to guide clinical trials. Clin Cancer Res 2015;21:4536–44.
52. Stewart DJ, Batist G, Kantarjian HM, Bradford J-P, Schiller JH, Kurzrock R. The urgent need for clinical research reform to permit faster, less expensive access to new therapies for lethal diseases. Clin Cancer Res 2015;21:4561–8.
53. Booth CM, Cescon DW, Wang L, Tannock IF, Krzyzanowska MK. Evolution of the randomized controlled trial in oncology over three decades. J Clin Oncol 2008;26:5458–64.
54. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
55. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372:724–34.
56. Fiorino T. Industry, clinical trials, and the cost of cancer drugs: an investor's perspective. J Clin Oncol 2007;25:e21–3.
57. Kelly WK, Halabi S, Carducci M, George D, Mahoney JF, Stadler WM, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. J Clin Oncol 2012;30:1534–40.
58. Vermorken JB, Stöhlmacher-Williams J, Licitra L, Winquist E, Villanueva C, et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. Lancet Oncol 2013;14:697–710.
59. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783–91.
60. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;3:3327–34.
61. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–65.
62. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16.