Phase III Trials of Targeted Anticancer Therapies: Redesigning the Concept

Alberto Ocana, Eitan Amir, Francisco Vera-Badillo, Bostjan Seruga, and Ian F. Tannock

Abstract

Randomized phase III trials provide the gold-standard evidence for the approval of new drugs: an experimental treatment is compared with the current standard of care to identify clinically relevant differences in a predefined endpoint. However, there are several problems relating to the current role of phase III trials in drug development including the limited clinical benefit observed for some approved agents, the necessity for large trials to detect these differences, the inability of such trials to identify rare but important toxicities, and high cost. The design of phase III trials evaluating drug combinations, and those including biomarkers, presents additional challenges. Here, we review these problems and suggest that phase III trials with adaptive designs in selected prescreened populations could reduce these limitations. Clin Cancer Res; 19(18); 4931–40. ©2013 AACR.

Introduction

Phase III randomized clinical trials (RCT) have been used to generate evidence in support of the approval of most new agents in the treatment of cancer (1, 2). In phase III studies, an experimental treatment is compared with the standard of care to identify relevant differences in predefined endpoints. In cancer drug development, these are usually time-to-event endpoints such as overall (OS), progression-free (PFS), or disease-free survival (DFS; refs. 1, 2). If the magnitude of difference is statistically significant, the experimental treatment is usually approved by regulatory authorities and can then be incorporated into the therapeutic armamentarium (1).

In the last decade, numerous targeted therapies have been evaluated in clinical trials and many have been approved for the treatment of cancer. For most of these agents, phase III trials were undertaken to detect significant differences in a predefined endpoint. However, for a small group of new agents, impressive results observed in early studies led to approval without the need to perform a randomized study (reviewed by Tsimberidou and colleagues; ref 3).

The limited activity of some targeted agents, the necessity of large phase III trials to show significant differences in endpoint, and the high cost at which they are marketed, have raised questions about the way these agents are developed, including the necessity of conducting phase III trials to show improved outcomes compared with standard treatment (4–6). In the present article, we review the role of phase III trials in the development of targeted therapies, identify problems associated with them, and propose ideas to improve the process of drug development. We suggest that modifications to the design of phase II–III trials, including adaptive models in a preselected screened population, could help to circumvent some of these problems (4, 5).

Problems associated with drug development: role of randomized trials

Limited clinical benefit in large RCTs. The magnitude of difference in clinical benefit between experimental and standard treatment is the key factor in convincing regulatory agencies, and some clinicians, of the utility of a given drug. Although there is no consensus as to what should be considered a sufficient magnitude of benefit from use of a new agent to recommend its adoption, for most oncologists, a gain in survival of at least 3 to 4 months for patients with incurable metastatic disease is clinically important, especially if toxicity is acceptable and no deterioration in quality of life is observed (6). However, there are examples of targeted agents that have been approved by regulatory agencies with very limited improvement in absolute benefit: an example was the approval of erlotinib in pancreatic cancer with an improvement in median survival of around 10 days (see Table 1, ref 7), a difference that was statistically significant but less than prespecified in the protocol as clinically important. A positive study should not be based only on a statistical test alone but also on an improvement in a clinically relevant endpoint that will translate into substantial patient benefit (6). This benefit should be described in absolute terms because relatively impressive reductions in HR (i.e., in relative benefit) may translate into very small differences in an absolute measure such as median survival.
Clinical trials have become larger with time (8), and large sample sizes are often used in clinical trials to detect small benefits in predefined endpoints which meet conventional levels of statistical significance and allow drug registration. For example, studies evaluating erlotinib and bevacizumab for non–small cell lung cancer used large sample sizes to detect small but statistically significant differences in outcome (9, 10). Similarly, the recent approval of

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Study design</th>
<th>HR: PFS/OS</th>
<th>Median PFS (mos) exp/ control difference</th>
<th>Median OS (mos) exp/ control difference</th>
<th>Ratio of median differences in OS/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (38)</td>
<td>Gemcitabine + paclitaxel vs. paclitaxel</td>
<td>0.70/0.78</td>
<td>6.1/4.0</td>
<td>18.6/15.8</td>
<td>1.33</td>
</tr>
<tr>
<td>Breast (39)</td>
<td>Albumin-bound paclitaxel vs. paclitaxel</td>
<td>0.73/0.75</td>
<td>5.8/4.2</td>
<td>16.3/13.9</td>
<td>1.50</td>
</tr>
<tr>
<td>Breast (40)</td>
<td>Ixabepilone + capecitabine vs. capecitabine</td>
<td>0.79/0.90</td>
<td>6.2/4.2</td>
<td>16.4/15.6</td>
<td>0.40</td>
</tr>
<tr>
<td>Breast (41)</td>
<td>Capcitabine + docetaxel vs. docetaxel</td>
<td>0.65/0.77</td>
<td>6.1/4.2</td>
<td>14.5/11.5</td>
<td>1.58</td>
</tr>
<tr>
<td>Breast (42)</td>
<td>Letrozole + lapatinib vs. letrozole + placebo</td>
<td>0.71/0.74</td>
<td>8.2/3.0</td>
<td>33.3/32.3</td>
<td>0.19</td>
</tr>
<tr>
<td>CRC (43)</td>
<td>Capcitabine vs. 5FU-LV</td>
<td>0.95</td>
<td>5.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>CRC (44)</td>
<td>IFL vs. FOLFOX vs. IROX</td>
<td>0.74/0.66</td>
<td>8.7/6.9</td>
<td>19.5/15.0</td>
<td>2.50</td>
</tr>
<tr>
<td>CRC (45)</td>
<td>IFC vs. FC</td>
<td>0.64/0.78</td>
<td>7.0/4.3</td>
<td>14.8/12.6</td>
<td>0.81</td>
</tr>
<tr>
<td>CRC (46)</td>
<td>IFL vs. FL vs. I</td>
<td>0.71/0.74</td>
<td>6.7/5.5</td>
<td>13.8/11.1</td>
<td>2.25</td>
</tr>
<tr>
<td>Gastric cancer (47)</td>
<td>Capcitabine or FU + cisplatin + trastuzumab</td>
<td>0.71/0.74</td>
<td>6.7/5.5</td>
<td>13.8/11.1</td>
<td>2.25</td>
</tr>
<tr>
<td>HNC (48)</td>
<td>TPF vs. PF</td>
<td>0.72/0.73</td>
<td>11.8/2</td>
<td>18.8/14.5</td>
<td>1.53</td>
</tr>
<tr>
<td>HCC (49)</td>
<td>Sorafenib vs. placebo</td>
<td>1.08/0.69</td>
<td>4.9/4.1</td>
<td>10.7/7.9</td>
<td>3.50</td>
</tr>
<tr>
<td>Mesothe lioma (50)</td>
<td>Pemetrexed + cisplatin vs. cisplatin</td>
<td>0.68/0.77</td>
<td>5.7/3.9</td>
<td>12.1/9.3</td>
<td>1.55</td>
</tr>
<tr>
<td>NSCLC (10)</td>
<td>Erlotinib vs. Placebo</td>
<td>0.61/0.70</td>
<td>2.2/1.8</td>
<td>6.7/4.7</td>
<td>5.00</td>
</tr>
<tr>
<td>NSCLC (9)</td>
<td>Paclitaxel–carboplatin + bevacizumab</td>
<td>0.66/0.79</td>
<td>6.2/4.5</td>
<td>12.3/10.3</td>
<td>1.18</td>
</tr>
<tr>
<td>Pancreas (7)</td>
<td>Gemcitabine + erlotinib vs. gemcitabine + placebo</td>
<td>0.77/0.82</td>
<td>3.8/3.6</td>
<td>6.2/5.9</td>
<td>1.50</td>
</tr>
<tr>
<td>Prostate (51)</td>
<td>Mitoxantrone + pred vs. cabazitaxel + pred</td>
<td>0.74/0.70</td>
<td>2.8/1.4</td>
<td>15.1/12.7</td>
<td>1.71</td>
</tr>
<tr>
<td>Renal (52)</td>
<td>Temsirolimus vs. IFN-α vs. combination</td>
<td>0.74/0.70</td>
<td>2.8/1.4</td>
<td>15.1/12.7</td>
<td>1.71</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancer; FU, fluorouracil; mos, months; HNC, head and neck cancer; I, irinotecan; IROX, irinotecan and oxaliplatin; LV, leucovorin; NR: not recorded; NSCLC, non–small cell lung cancer; PF, platinum compound, fluorouracil; TPF, taxotere, platinum compound, fluorouracil.

aTTP: time to treatment progression used instead of PFS.

Clinical trials have become larger with time (8), and large sample sizes are often used in clinical trials to detect small benefits in predefined endpoints which meet conventional levels of statistical significance and allow drug registration.

For example, studies evaluating erlotinib and bevacizumab for non–small cell lung cancer used large sample sizes to detect small but statistically significant differences in outcome (9, 10). Similarly, the recent approval of...
ziv-aflibercept in metastatic colon cancer was based on a clinical trial involving 1,226 patients where the difference in median overall survival was only 6 weeks (11).

**Predicting a successful phase III trial from phase II data.** The completion of a randomized phase II trial with positive results does not guarantee a subsequent positive phase III study. This may be due to more stringent selection of patients in phase II studies, the use of different endpoints in phase II and III studies (e.g., PFS in the phase II and overall survival in the phase III), lack of understanding how they relate to each other, low statistical power in smaller phase II studies, or simply regression to the mean. Estimation of the sample size for a phase III trial will depend on the magnitude of benefit expected, and will be influenced by that observed in phase II trials. Ideally, however, the sample size should not be set by the likelihood of obtaining an effect that is statistically significant, but by detecting or ruling out one that is clinically important.

**Are RCTs sufficient to determine toxicity?** Phase III trials should be designed to obtain information about toxicities related to the investigational treatment as well as benefit. Phase III trials tend to capture frequent but mild toxicity and sometimes less frequent but more severe toxicities not identified in previous phase I and II studies (12). However, many phase III trials fail to capture this information adequately. Approximately 40% of fatal adverse drug reactions of approved targeted agents reported in updated drug labels were not described in any published report of the phase III trial(s) used for the approval of that drug (13); thus, phase III trials are not sufficiently powered to detect infrequent but serious toxicities of targeted agents or those that may occur after completion of the trial (14). In addition, phase III trials have limited ability to detect toxicity in vulnerable subgroups of patients, who are often excluded from phase III studies but may receive the drug once it is approved. Furthermore, our group has reviewed data using meta-analyses, which show that newly approved anticancer drugs are associated with increased drug-induced morbidity and mortality when compared with the standard treatment received by control groups. These toxicities became evident only when data were pooled from multiple RCTs (15). We do not suggest enlarging the sample size of RCTs to increase their probability of showing less common types of toxicity, but we do recommend strict requirements for reporting of toxicity as a condition of marketing approval.

**Pitfalls in the design of studies with drug combinations.** Although the design of studies with drug combinations should be based on preclinical data to support an interaction leading to improved therapeutic index, a recent analysis from our group shows that to be uncommon: there is rarely preclinical information to suggest a synergistic interaction between the agents evaluated in phase II trials (16). Because the activity of targeted drugs as single agents has been modest, most of them have been developed in association with standard chemotherapy, and they have usually been given concomitantly. Scheduling of a primarily cytostatic-targeted agent to be given concurrently with cycle-dependent cytotoxic chemotherapy makes little biologic sense, because chemotherapy will be less active if cells are put out of cycle by the targeted agent, although combined activity against multiple pathways might overcome this antagonistic effect. Scheduling the targeted agent between cycles of chemotherapy to inhibit tumor cell repopulation could be an option to improve therapeutic outcome (17, 18). This approach has not been explored adequately in clinical trials.

Phase I and early phase II trials provide opportunities to investigate dose and schedule for a drug combination before launching a large randomized phase II or a phase III trial, but this is often not undertaken. The U.S. Food and Drug Administration (FDA) Critical Path Initiative addresses the limited foundation of early drug development studies (19). For example, a recent phase IIB trial involving 229 patients with HER2-negative breast cancer evaluated the combination of sorafenib and capecitabine compared with capecitabine alone; the combination showed unacceptable toxicity that could have been detected in a smaller study (20). Similarly, the phase III trial that compared standard chemotherapy (doxorubicin/cyclophosphamide or paclitaxel) versus standard chemotherapy with trastuzumab in metastatic breast cancer showed unacceptable toxicity in the doxorubicin/cyclophosphamide-containing arm, a combination that was never evaluated in a phase I or phase II trial (21). These examples highlight the importance for the redesign of phase II–III trials with drug combinations to facilitate the early identification of toxic combinations and to select the most appropriate dose and schedule to obtain the best balance between clinical benefit and toxicity. Schedule is as important as dose, as has been shown recently when evaluating different schedules of sunitinib in renal cell carcinoma (22). The design of phase II trials to find the best schedule is challenging, as resources are not usually available to evaluate various schedules, so that one schedule is chosen with limited prior information. However, there could be greater emphasis on dose scheduling in preclinical studies that could be refined in the phase I trials.

**Cost associated with development of targeted drugs.** Recently approved drugs are marketed at a high price despite many of them having only modest activity; thus, many new drugs do not fall within a range of cost-effectiveness used for evaluating other health interventions. In the approval process of a drug by some regulatory authorities, market price and cost-effectiveness are not taken into consideration. There are concerns about long-term affordability of new anticancer drugs for both patients and healthcare providers (including public health systems and private insurers), and health providers may not be willing to fund the costs of drugs if they do not meet standards of cost-effectiveness (23). What is considered cost-effective differs between countries (24). For developed countries, up to $100,000 is often considered a reasonable maximum cost per quality adjusted life year gained (24–27), but it will be far less in developing countries.

Renal cell carcinoma is one of the solid tumors where several new targeted agents have been approved. Table 2 shows prices associated with each new treatment, including those for the control and experimental arms of the pivotal
Can adaptive phase II–III trial designs in a molecularly prescreened population help to resolve these problems?

An adaptive trial uses data obtained while the trial is ongoing to modify the course of the trial (28, 29). As suggested by the FDA and European Medicines Agency (30), all potential adaptations should be preplanned and registered before the trial is initiated. Examples of adaptive measures include early stopping rules in case of lack of efficacy or unacceptable toxicity, adapting doses or schedules that will lead to a more efficient benefit-toxicity relationship, stopping arms in a multi-arm trial, changing accrual, selection and/or order of primary and secondary end-points, or modification of concomitant treatments (28–30). In addition, adaptive trials can use outcome-adaptive randomization in which the ratio of patients randomly assigned to the experimental arm versus the control arm changes over time from the standard 1:1 to increase the proportion of patients randomized to the arm that is doing better (28).

There are advantages to designing a study with various arms, including those with different dose and schedule of a combination. With emerging (albeit imperfect) evidence that one arm of the phase II–III trial is superior (i.e., has more activity and/or less toxicity in a predefined interim analysis), increased accrual to that arm can augment the statistical power to detect a relevant magnitude of clinical benefit. An example of this multi-arm approach is the STAMPEDE trial in prostate cancer (31): an increased benefit in biochemical (i.e., PSA) response or PFS as an interim endpoint is used to support increased accrual to the selected arms while maintaining OS as the final endpoint. Accrual to a phase III trial can be designed to identify uncommon but serious toxicities or even to increase the accrual for a specific vulnerable population.

The incorporation of several arms in a randomized trial with different doses and/or schedules can facilitate identification of the best ratio of benefit to toxicity. This approach could have been used to identify the best dose and schedule for the combination of sunitinib and capecitabine in patients with HER2-negative metastatic breast cancer (20). In contrast, the large phase III study concluded that the combination was clinically active but toxic, and another trial was necessary to evaluate the combination using lower doses (20). An adaptive design would have saved time and resources, as early stopping rules would have led to dropping of toxic or ineffective arms.

Although adaptive clinical trials can be more expensive initially as they may include more scenarios and treatment arms, their ability to prevent the undertaking of further clinical studies can reduce the total cost of drug development.

Incorporation of biomarkers in adaptive designs

The incorporation of biomarkers in phase III studies should be exploratory unless a validated marker is identified and it should then be evaluated (quantified) for all included patients. The incorporation of biomarkers in studies of approved drugs in the last decade is summarized in Table 3. We previously reviewed the magnitude of relative benefit in phase III trials used for the approval of new drugs: although all studies were powered to detect about a 20% to 30% reduction in relative risk, drugs designed to interact with a specific target, and especially those that used predictive biomarkers, were able to produce the highest relative improvement in overall survival and PFS (ref. 32; Fig. 1). Thus, the sample size needed to detect this difference was smaller for these studies (32). Adaptive phase III trials using biomarkers and a preselected population may not need a large sample to detect a relevant clinical benefit, and they can have early stopping rules in case the study arm meets the predefined magnitude of benefit.

The above features can be included in a continuous phase II–III study design (Fig. 2). This approach would exclude the majority of single-arm trials that have no intention to

### Table 2. Total cost of control and experimental arms, and estimated incremental cost per life-year gained for OS (or PFS if cross-over or if OS was not given), for new agents approved for the treatment of renal cell carcinoma

<table>
<thead>
<tr>
<th>Targeted agent</th>
<th>Design</th>
<th>Total price: control arm (US$)</th>
<th>Total price: experimental arm (US$)</th>
<th>Primary endpoint</th>
<th>Δ in median OS/PFS (mo)</th>
<th>Incremental cost per life-year gained (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (53)</td>
<td>Bev + IFN-α vs. IFN-α + placebo</td>
<td>31,260</td>
<td>157,220</td>
<td>PFS</td>
<td>Not reported/4.8</td>
<td>314,900</td>
</tr>
<tr>
<td>Everolimus (54)</td>
<td>Everolimus vs. placebo</td>
<td>Placebo</td>
<td>27,730</td>
<td>PFS</td>
<td>Not reached/2.1</td>
<td>158,450</td>
</tr>
<tr>
<td>Sorafenib (55)</td>
<td>Sorafenib vs. placebo</td>
<td>Placebo</td>
<td>34,700</td>
<td>OS</td>
<td>3.4/2.7</td>
<td>122,500</td>
</tr>
<tr>
<td>Sunitinib (56)</td>
<td>Sunitinib vs. IFN-α</td>
<td>7,720</td>
<td>52,260</td>
<td>PFS</td>
<td>Not reached/6.0</td>
<td>89,000</td>
</tr>
<tr>
<td>Temsirolimus (52)</td>
<td>Temsirolimus vs. IFN-α</td>
<td>5,870</td>
<td>21,440</td>
<td>OS</td>
<td>3.6/1.9</td>
<td>51,900</td>
</tr>
<tr>
<td>Targeted agent</td>
<td>Publication year phase I</td>
<td>Target</td>
<td>Tumor type</td>
<td>Biomarker</td>
<td>Selection of patients based on biomarker in phase I</td>
<td>Biomarker included in phase II-III trials</td>
</tr>
<tr>
<td>----------------</td>
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<td>----------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Trastuzumab (57)</td>
<td>1999</td>
<td>HER2</td>
<td>Breast</td>
<td>HER2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gefitinib (58)</td>
<td>2002</td>
<td>EGFR</td>
<td>Solid tumors, express EGFR</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Erlotinib (59)</td>
<td>2001</td>
<td>EGFR</td>
<td>Solid tumors</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cetuximab (60)</td>
<td>2002</td>
<td>EGFR</td>
<td>Solid tumors with EGFR overexpression</td>
<td>EGFR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bevacizumab (64)</td>
<td>2001</td>
<td>VEGF</td>
<td>Solid tumors</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sorafenib (67)</td>
<td>2005</td>
<td>Multi TKI</td>
<td>Solid tumors</td>
<td>pERK in PBL</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sunitinib (68)</td>
<td>2006</td>
<td>Multi TKI</td>
<td>Solid tumors</td>
<td>VEGF, VEGFR2</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Panitumumab (70)</td>
<td>2008</td>
<td>EGFR</td>
<td>Solid tumors</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Temsirolimus (72)</td>
<td>2004</td>
<td>mTOR</td>
<td>Solid tumors</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Everolimus (73)</td>
<td>2008</td>
<td>mTOR</td>
<td>Solid tumors</td>
<td>pS6 in PBMC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vemurafenib (37)</td>
<td>2010</td>
<td>B-RAF</td>
<td>Solid tumors</td>
<td>Erk1/2</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Crizotinib (36)</td>
<td>2009</td>
<td>ALK</td>
<td>Solid tumors</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Abbreviations:** TKI, tyrosine kinase inhibitor; RCC, renal cell carcinoma; EGFR, EGF receptor; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; PBMC, peripheral blood mononuclear cells; PBL, peripheral blood lymphocytes; VEGFR, VEGF receptor.
Figure 1. Forest plot showing meta-analyses of HR for progression-free survival based on mechanism of action of targeted agents. Reproduced from "Oncogenic Targets, Magnitude of Benefit, and Market Pricing of Antineoplastic Drugs" by Amir E et al. J Clin Oncol. 2011 Jun 20;29(18):2543–9, under permission of the American Society of Clinical Oncology (number: 317351452218).
proceed to a phase III trial; this is a positive feature as most such trials represent a waste of resources (33). In the phase II part, different arms can be evaluated, but only the arm with signs of major activity and acceptable toxicity will be included in the final phase III part that will be compared with standard treatment. An example of this approach is the I-SPY2 trial in breast cancer (34). The phase II part is exploratory and gives information about how to design the phase III and what might be the expected magnitude of benefit and its uncertainty. In addition, the endpoint for the phase II part could be a surrogate for the endpoint used in the phase III trial. However, this assumption is often not justified: for example, there is rather poor correlation between improvements in PFS and in overall survival. The total number of patients to be included can also be higher as they will be combined with those included in the phase II part, so the identification of a meaningful ratio of clinical benefit to toxicity will be easier (Fig. 2). This approach can reduce time and cost. An example will be a multi-arm trial in metastatic breast cancer in which a specific experimental treatment arm shows an increase in PFS of more than 6 to 8 months, like the results recently reported with pertuzumab in HER2-positive breast cancer that has led to FDA approval of this drug (35). The preliminary result could give confidence to continue or increase accrual in that arm, and stop the other experimental arms, and aim for an improvement in overall survival of at least 3 to 4 months.

The design of phase II–III trials in a molecularly pre-screened population can also help to overcome some of the problems described earlier. Impressive clinical activity observed in a phase I–II trial in a subgroup of patients with a specific molecular alteration could be the basis for the design of a phase II–III trial. This transition from a phase I–II trial to a phase III trial will save time and resources, thus speeding the development process. A phase I trial is designed to confirm a safe dose, and an extension cohort at the recommended phase II dose can evaluate efficacy in a specific subpopulation of prescreened patients, as conducted in the development of vemurafenib in b-RAF–mutated metastatic melanoma and crizotinib in anaplastic lymphoma kinase-mutated non–small cell lung cancer (36, 37).

Patients with newly diagnosed metastatic cancer could be prescreened, and when they progress on standard treatment, the molecular information could be used to randomize them in an adaptive phase II–III trial with drug combinations (Fig. 2). The trial might evaluate different arms that include a targeted agent alone, or in combination with

Figure 2. Schematic representation of phase II-III adaptive designs using prescreened populations.
another modulator of a defective molecular pathway, or with chemotherapy if there is preclinical evidence of a therapeutically beneficial interaction. Different doses or schedules might also be explored in different arms of the phase II part. A surrogate endpoint like PFS can be used in the phase II trial, but with an ambitious magnitude of benefit to select the best study arm for further development of the phase III trial. Those arms with lack of efficacy or substantial toxicity will be dropped, but the arm with more activity and better safety profile can be expanded to a phase III trial with increased accrual and with a more appropriate endpoint such as OS.

Adaptive designs also have limitations. There is no way to capture very rare toxicities or those that appear later, after the study has finished, and the logistics and interpretation of results can be more complicated. Indeed, their implementation has been slower than expected. Different reasons may explain this lack of endorsement by investigators, including the more complicated logistics, concerns about security, or increased chance of erroneous positive conclusions (see FDA guideline for adaptive designs). The incorporation of biomarkers also adds cost and requires a process of validation. Phase III trials could also be large, depending on the magnitude of the expected benefit. In addition, the final marketed price of a drug will be selected to maximize the profit that the pharmaceutical company has estimated for that drug, and has little or no relationship with the cost of drug development. However, even with these limitations, phase III trials with adaptive designs can overcome some of the problems associated with traditional phase III trials.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Ocana, E. Amir, F. Vera-Badillo
Analysis and interpretation of data (e.g., statistical analysis, biosafety, computational analysis): A. Ocana, F. Vera-Badillo, I.F. Tannock
Writing, review, and/or revision of the manuscript: A. Ocana, E. Amir, F. Vera-Badillo, B. Seruga, I.F. Tannock
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Study supervision: I.F. Tannock

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