Historic Evidence and Future Directions in Clinical Trial Therapy of Solid Tumors

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Although improved survival is the "gold standard" for proving clinical benefit of oncologic therapy, the US Food and Drug Administration (FDA) has accepted significant results in clinical trials using surrogate endpoints as the basis for drug approval. One surrogate is the amount of tumor reduction, or tumor response. Although tumor shrinkage would seem to be a necessary precondition for improved survival, clinical studies of a variety of oncologic agents have not consistently demonstrated a correlation between the two in patients with renal cell carcinoma. Moreover, tumor response may not be an appropriate endpoint for evaluating the effects of the new targeted therapies, whose putative mechanisms are generally cytostatic rather than cytotoxic. Clinical trials suggest that some patients with other solid tumors, such as lung cancer, may derive clinical benefit from treatment that helps stabilize their disease. There is also controversy as to whether the Response Evaluation Criteria in Solid Tumors (RECIST) provides the most appropriate instrument for assessing tumor burden. Ultimately, use of a variety of endpoints as well as different trial designs may provide an adequate basis for investigating the benefits/risks of newer therapies.

In clinical trials evaluating the efficacy of oncology drugs, improved survival has been the "gold standard" accepted by the US Food and Drug Administration (FDA) for establishing clinical benefit.[1] Yet survival itself is not an ideal endpoint for clinical trials because it necessitates designing large, long studies; may be affected by crossover therapy; does not capture symptom improvement; and may include noncancer deaths.[1] Thus, over the past decade, clinical trials of oncologic therapies have used surrogate endpoints which, by reducing the duration and size of the trials, facilitate accelerated approval. Tumor shrinkage is a logical endpoint, since advancing tumor burden is the predominant mechanism by which the disease causes morbidity and mortality.

Objective response rate (ORR) has been considered a measure of drug antitumor activity, even in single-agent studies.[1] There are several reasons that ORR has been widely used as an endpoint. First, tumor shrinkage is likely to be attributable to a direct effect of the agent under investigation. Second, tumor response has been widely accepted as a means of guiding cancer treatment. Finally, ORR would seem to be likely to predict clinical benefit, assuming the response rate (RR) is high enough and the responses are of sufficient duration. Despite its logical appeal, reduction in tumor burden has proven to be a controversial endpoint. Typically, many recent trials have assessed tumor response using the recently developed Response Evaluation Criteria in Solid Tumors (RECIST). These criteria are derived from a retrospective analysis of measurements obtained from eight clinical trials in which patients were assessed for tumor response.[2] To simplify tumor assessment, RECIST uses unidimensional measurement of the longest diameter of a tumor. Such measurements have reportedly underestimated response to chemotherapy in pleural-based masses, such as malignant pleural mesothelioma,[3,4] tumors with significant surrounding fibrosis, and other tumors, especially in light of current imaging technologies and multimodality approaches.[5] The limitations of this unidimensional approach are illustrated in Figure 1.
In addition, tumor response may underestimate treatment effects on clinical endpoints, including survival, by failing to reflect the magnitude, breadth, and duration of effects on tumor burden.[6] Alternatively, tumor response can overestimate impact on survival if the response is brief or if it does not capture unintended harmful mechanisms of action of the tested treatment. The question of whether ORR correlates with overall survival (OS) and, thus, whether it is an appropriate endpoint is still open to significant debate.

A number of factors influence the effect of tumor response on OS in randomized clinical trials. One obvious consideration is the magnitude of the response difference between arms. For example, a 20% response in one treatment arm and 10% in the other may be clinically significant, but in a small trial the difference will not translate into a significant OS benefit. Quality of response is also important: complete response (CR), partial response (PR), or stable disease (SD) may all impact survival differently. The durability of response, which sometimes is overlooked, obviously can affect progression-free survival (PFS) or OS. Durability of response must be evaluated in the context of the rate of disease progression for the specific disease. With renal cell cancer (RCC), for example, tumors classified as low-, intermediate-, or high-risk according to the Sloan-Kettering classification system progress at different rates. Thus, a brief response in patients whose disease progresses slowly may not necessarily affect PFS or OS. In contrast, with a rapidly progressing tumor, a large number of responses (even if relatively brief) may influence PFS.

Finally, in assessing whether tumor response influences OS or PFS in randomized clinical trials (RCTs), an important consideration is the type of comparator arms. A study that compares active drug with placebo or observation will yield different information from studies that compare two drugs with similar mechanisms of action or two drugs with markedly different mechanisms of action. Single-arm studies have occasionally provided the basis for FDA approval when no effective therapy is available and spontaneous tumor regressions are rare.[1] In contrast, trials using historical controls have rarely been successful unless the survival outcomes differ markedly in the active comparator arm.

Following is an overview of the efficacy and limitations of using tumor response as an endpoint in key clinical studies of various agents used to treat renal cell carcinoma, melanoma, lung cancer, breast cancer, and other solid tumors.

Renal Cell Carcinoma

Cytokines

The response data for high-dose interleukin-2 (IL-2; Aldesleukin, Proleukin) highlight an interesting dichotomy observed between the durability and quality of responses in RCC vs melanoma. In both cancers, CRs can be quite durable. In a study of 86 patients with RCC treated with high-dose IL-2,
more than one-half of the 17 patients who had a CR remained essentially disease-free for more than 10 years. Median response lasted 54 months in the 43 patients who had an objective CR and 20 months in those with a PR.[7] These results represented a clear improvement over the response to chemotherapy, which historically lasted 4 to 6 months.[8-10]

A somewhat different pattern emerged from a study by Atkins et al of 270 evaluable melanoma patients treated with high-dose IL-2 in 8 trials.[11] Twelve (28%) of the responding patients, including 10 (59%) of the patients who achieved a CR, remained progression-free at the time of publication; duration of reported response ranged between 24 and 106 months, and there was no progressive disease (PD) in patients responding for more than 30 months. However, the median duration of response for those who had a PR was 5.9 months. Thus, the value of a PR to high-dose IL-2 is different in melanoma vs RCC.

The influence of the magnitude of response can be illustrated by studies comparing treatment with combination cytokine therapy vs a drug with a different mechanism of action (Table 1).[12-16] In the first study, Pyrhonen et al accrued 160 RCC patients and randomized them to receive either interferon-α 2a (Intron A, 3 million U tid for week 1, then 18 million U tid thereafter) plus vinblastine (Velban, 0.1 mg/kg every 3 weeks) or vinblastine alone.[12] Historically, vinblastine has very little single-agent activity, inducing only a 5% to 10% major RR in renal cancer.[10] RR was 16.5% (8.9% CR, 7.6% PR) in the interferon-α 2a plus vinblastine arm compared with 2.4% in the vinblastine arm ($P = .0025$). The median duration of a CR was 27 weeks and of a PR was 24 weeks in the interferon-α 2a plus vinblastine arm.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Treatment Regimens</th>
<th>Overall Response Rate</th>
<th>Median Overall Survival</th>
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<tr>
<td>Pyrhonen et al[12]</td>
<td>160</td>
<td>Interferon-α 2a plus vinblastine, Vinblastine alone</td>
<td>16.5%</td>
<td>67.6 wk</td>
</tr>
<tr>
<td>MCRRC[13]</td>
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<td>Interferon-α 2b Medroxyprogesterone</td>
<td>14%</td>
<td>8.5 wk</td>
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<tr>
<td>Negrin et al[14]</td>
<td>425</td>
<td>Interferon-α 2a High-dose IL-2, Combination interferon-α 2a plus high-dose IL-2</td>
<td>7.5%</td>
<td>13 mo</td>
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<tr>
<td>Yang et al[15]</td>
<td>156</td>
<td>High-dose IL-2, Low-dose IL-2</td>
<td>21%</td>
<td>Not reported</td>
</tr>
<tr>
<td>McDermott et al[16]</td>
<td>190</td>
<td>High-dose IL-2, Combination low-dose IL-2 plus interferon-α 2b</td>
<td>23.2%</td>
<td>17.5 mo</td>
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IL-2 = interleukin-2; MCRRC = Medical Research Council Renal Cancer Collaborators.

There was a modest but still significant improvement in median TTP: 13 weeks compared with 9 weeks ($P = .0001$). Median survival (MS) also improved, 67.6 weeks for the interferon-α 2a plus vinblastine arm compared with 37.8 weeks for vinblastine alone ($P = .0049$).

In a second study, conducted by the Medical Research Council Renal Cancer Collaborators, 335 patients with RCC received treatment with interferon-α 2b (three doses, 5 MU, 5 MU, 10 MU for the first week, then 10 MU tid for 11 wks) or with medroxyprogesterone (300 mg qd for 12 wks).[13] The
RRs were not high in either the cytokine arm (14%) or the hormone arm (2%), but there was a sevenfold difference between them. There was a 28% reduction in the risk of death in the interferon-α 2b group (hazard ratio [HR] for OS, 0.72; \( P = .017 \)), with only a 1 month absolute improvement in PFS. One-year survival was 43% in the interferon-α 2b group compared with 31% in the medroxyprogesterone group; MS was 8.5 months and 6 months, respectively. Thus, while neither combination cytokine study demonstrated a high RR in either treatment arm, the magnitude of the difference enabled researchers to conclude that addition of a cytokine to an agent with a different mechanism of action translates into an improvement in TTP and OS. Notably, despite the reported increase in magnitudes of up to seven times in RRs, the corresponding differences in PFS and OS (clinical benefit parameters) were not large.

Three randomized phase III studies comparing different cytokine therapies for RCC yielded varying results concerning the correlation between RR and survival. In the first, differences in RR translated into an improved PFS but not MS. Negrier et al compared three regimens-interferon-α 2a, continuous infusion of high-dose IL-2, and a combination of both in 425 RCC patients.[14] RR was significantly higher (\( P < .01 \)) in the combination therapy group (18.6%) than in the interferon alone (7.5%) or high-dose IL-2 (6.5%) groups. This difference in RR translated into a difference in 1-year PFS of 20% compared with 15% or 12% (\( P = .01 \)). But the MS rates—respectively, 17, 13, and 12 months—were not significantly affected (\( P = .55 \)). These data indicate that even if RRs are positively impacted by therapy, a corresponding benefit in MS (eg, increased survival duration or percentage) is not necessarily seen.

In a second cytokine comparison trial, Yang et al administered either high-dose IL-2 (720,000 U/kg given by bolus every 8 hours) or low-dose IL-2 (72,000 U/kg) to 156 patients with metastatic RCC.[15] RR was 21% (7% CR, 14% PR) in the high-dose IL-2 group and 13% (4% CR, 9% PR) in the low-dose IL-2 group. The difference was significant by Chi-square analysis (\( P = .048 \)) but not Fisher’s exact test (\( P = .067 \)). There was no difference in median OS. Median follow-up was 7.4 years for all patients on study. In patients who had a CR, the duration of response and survival were significantly better with high-dose IL-2 compared with low-dose IL-2 (\( P = .04 \)). Thus, in this trial, higher doses of IL-2 provided greater clinical activity yet did not improve survival. The authors concluded that high-dose IL-2 may have a curative potential that can be realized only when limiting immunological factors have been identified. These data similarly demonstrated that RRs are not correlated to survival benefit.

In a third study comparing cytokine regimens, McDermott and coworkers randomized 192 patients to treatment with either high-dose IL-2 (600,000 U/kg/dose intravenously [IV] every 8 hours on days 1-5 and 15-19 every 12 weeks) or combination therapy of low-dose IL-2 (5 MIU/m2 subcutaneously [SC] every 8 hours for three doses on day 1, then daily 5 d/wk for 4 wks) plus interferon-α 2b (5 MIU/m2 SC tid for 4 weeks) every 6 weeks.[16] Respective RRs were 23.1% (8.4% CR, 14.7% PR) and 9.9% (3.3% CR, 6.6% PR; \( P = .018 \)) for the high-dose and the combination low-dose arms. Ten patients receiving high-dose IL-2 were progression-free at 3 years vs three receiving IL-2 and interferon-α 2b (\( P = .082 \)). The median response duration was 24 and 15 months (\( P = .18 \)) and MS was 17.5 and 13 months (\( P = .24 \)), respectively. The durable 3-year CR rate was 7.4% and 0% (\( P = .014 \), although this may not be considered an important endpoint in studies evaluating overall outcome. Thus, although median duration of response and MS did not differ significantly between treatment groups, the authors found sufficient evidence of benefit from a high-dose IL-2 regimen to justify using it despite increased toxicity and cost.

Subset analysis did show a link between RR and OS in patients who fell into poor prognostic categories. Historic data suggested that patients with bone and liver metastases or patients with primary tumors in place would not respond well to cytokine therapy. However, in the study of McDermott et al,[16] patients with liver or bone metastases exhibited an RR of 2.6% for those receiving combination IL-2 and interferon-α 2b therapy compared with 22.7% for those receiving high-dose IL-2. The respective RRs were 0% and 20.7% for those patients whose primary tumor was in place. MS was 8.0 months in those with liver or bone metastases receiving IL-2 plus interferon-α 2b compared with 14.7 months for those receiving high-dose IL-2 (\( P = .001 \)). Similarly, MS was 8.2 and 12.4 months for those with remaining primary tumor (\( P = .0040 \)).

Chemotherapy
There are few data on chemotherapy responses in RCC. Rini et al[17] studied gemcitabine (Gemzar) plus fluorouracil (5-FU), comparing DFS with that of historic controls treated with other chemotherapy. RR was increased in the treatment arm (17% vs 5%). However, the small sample size (\( n = 41 \)) and use of historic controls (especially in studies of this tumor type) were serious flaws.
Tumor Response in RCC Trials

This brief overview of randomized trials comparing treatments of RCC suggests that overall superior RR did not consistently translate into improved median OS (Table 1).[12-16] The only exception occurred in the patients with a poor prognosis in the McDermott et al study.[16] Nonetheless, these findings do not necessarily negate the value of a major response and the impact it may have on PFS and OS in RCC. Possibly, IL-2 and interferon-α may affect the natural history of advanced RCC without eliciting major responses (CR or PR). The cytokine studies rarely assessed trends in clinical benefit such as minor responses or SD that are typically observed in the clinic. Hypothetically, this bias in data collection may dilute the effect of objective response on PFS and OS. Major responders may exhibit a high response, but since cytokine-induced PRs are relatively more durable than chemotherapy-induced rates, even larger differences in overall RR/CR rate (and/or clinical benefit parameters, such as minor response and SD) might be taken into account to reflect actual differences in efficacy between therapies. It has also been observed that in tumor types such as RCC, historical controls may not be adequate to assess RR or clinical benefit, in light of the natural history of disease.

Moreover, it may also be hypothesized that RRs and OS in the RCC setting have reached a "plateau" during administration of standard regimens (and may not significantly differ), similar to the observation about conventional therapy and lung cancer. Schiller and colleagues[18] at the Eastern Cooperative Oncology Group (ECOG) compared four different first-line regimens in the treatment of advanced non-small-cell lung cancer (NSCLC) (n = 1,207). The RR for all 1,155 eligible patients was 19%, MS of 7.9 months, 1-year OS rate of 33%, and 2-year OS of 11%. They found statistically similar response and survival data for the varied regimens of conventional chemotherapy used both in the United States and Europe, and concluded that none of four frontline regimens offered a significant advantage over the others in the treatment of advanced NSCLC.[18]

Melanoma

Melanoma generally progresses more rapidly than RCC. Thus, a therapeutic regimen that produces a high number of short-lived responses may make it possible to document significantly improved PFS or TTP in this malignancy.

For example, the addition of cytokines to chemotherapy produced a significant series of short-term responses associated with encouraging results in a study by Eton et al.[19] Treatment regimens for the 190 enrolled patients included CVD (cis platin/vinblastine/dacarbazine [DTIC]) or sequential biochemotherapy with CVD plus IL-2 and interferon-α 2b. RR was 25% in CVD-treated patients compared with 48% of CVD-biochemotherapy-treated patients (P = .001). TTP was 2.4 months compared with 4.9 months (P = .004), but OS was 9.2 months compared with 11.9 months (P = .079). The authors concluded that cytokines substantially augment the antitumor efficacy of chemotherapy.

By contrast, the RRs were comparable across treatment arms in three randomized phase III studies of biochemotherapy vs chemotherapy in metastatic melanoma. None of these studies demonstrated a difference in PFS and OS. Atkins et al reported RRs of 11.9% in patients treated with CVD and 16.6% in patients receiving CVD-biochemotherapy.[20] PFS lasted 3.1 months in CVD patients, and OS lasted 9.1 months. In CVD-biochemotherapy, the respective outcomes were 5.0 and 8.4 months. Del Vecchio et al found an RR of 21% with OS of 12 months in CVD-treated patients. RR was 27% and OS was 11 months in patients receiving CVD/IL-2.[21] Finally, Keilholz et al reported an RR of 22.8% in patients receiving CVD/interferon-α 2b; PFS was 3 months, and OS was 9 months.[22] For those receiving CVD/interferon-α 2b/IL-2 therapy, the RR was 20.8%, PFS 3.9 months, and OS 9 months. Some data suggest that the lack of improved survival among patients receiving biochemotherapy may be attributable at least in part to a high incidence of subsequent cerebral metastasis in responders.[23-25]

Notably, only the cytokines IL-2 and interferon-α 2b and chemotherapy with single-agent dacarbazine have been approved by the FDA for treatment of malignant melanoma. However, there is a lack of a conventional therapeutic agent that significantly prolongs survival in patients with this disease. While cytokine therapy achieved durable responses in some patients with metastatic melanoma, it is associated both with a high toxicity rate and high cost. Thus, novel treatment agents that target metabolic pathways, angiogenesis inhibitors, antisense therapies, gene therapies, and innovative vaccines are currently under investigation.[26,27]

Lung Cancer and Other Solid Tumors

Chemotherapy

While some clinical trials of chemotherapeutic regimens have demonstrated a correlation between RR and survival in patients with a variety of other solid tumors, the results remain mixed overall. A
lack of connection between tumor response and OS has been demonstrated in a clinical trial in which 699 eligible patients with stage IV NSCLC were treated with MVP (mitomycin-C [Mutamycin]/vinblastine/cisplatin) or carboplatin (Paraplatin).[28] RR was 20% in the MVP group compared with 9% in the carboplatin group (P = .03). However, treatment with carboplatin was associated with longer survival (median survival time [MST], 31.7 wks; P = .008) while initial treatment with MVP was associated with a trend for shorter survival (MST, 22.7 wks; P = .09); none of these regimens appeared to produce a clinically meaningful prolongation of survival. Indeed, the 1-year survival rate was significantly worse in the MVP group (12%) than in the carboplatin group (25%). Thus, the regimen that provided a significantly lower RR actually was associated with an absolute improvement of survival.

Several clinical trials of new chemotherapeutic agents have reached different conclusions about the prognostic implications of tumor response, including data typically obtained using RECIST criteria.[29] For example, in 334 patients with NSCLC, Sederholm and colleagues demonstrated an RR of 11.3% in patients treated with single-agent gemcitabine (1,250 mg/m2/d1,8) compared with 29.6% in patients given gemcitabine plus carboplatin (area under the curve [AUC] of 5, d1).[30] MS was 39 weeks compared with 47.7 weeks. One-year survival rates were 32% and 41%, respectively, and 2-year rates were 5% and 15%. Similarly, in a study of 522 patients with NSCLC, Sandler et al reported ORRs in 11.1% of patients receiving cisplatin monotherapy (100 mg/m2 IV/d1 of a 28-day cycle) compared with 30.4% for gemcitabine (1,000 mg/m2 IV/d1,8,15 of a 28-day cycle) plus cisplatin-treated patients (P < .0001).[31] Median time to progressive disease was 3.7 months in the monotherapy group compared with 5.6 months with combination therapy (P = .0013), and respective OS was 7.6 months compared with 9.1 months (P = .004).

In metastatic breast cancer, the achievement of an OR may be associated with a true survival benefit, according to a meta-analysis of 10 randomized trials including 2,126 patients.[32] Patients were treated with either standard or intensified epirubicin (Ellence)-containing chemotherapy. The intensified chemotherapy was associated with a significantly higher tumor RR compared with standard chemotherapy. The intensified regimens also led to a trend for better, although not significantly longer, survival (P = .22). In the authors’ meta-analysis, tumor response was a significant predictor of survival (P < .0001). The MST of patients with CR and PR was 28.8 months and 21.3 months; by contrast, the MST of patients with no response was 14.6 months. These data can be interpreted to suggest that individual patients may benefit from a tumor response, although this benefit is not observed across the entire trial population.

Likewise, in colorectal cancer, a similar meta-analysis of 25 studies (3,791 patients) demonstrated a connection between major RR and survival.[33] Buyse et al compared the standard bolus IV fluoropyrimidines with experimental treatments, including 5-FU plus leucovorin, 5-FU plus methotrexate, 5-FU continuous infusion, or hepatic-arterial infusion of fluoruridine. The experimental fluoropyrimidines provided significantly higher tumor RRs than did standard bolus treatment (odds ratio 0.48; P < .0001) and improved survival (HR, 0.90; P = .003). The survival benefits could be attributable to the improved tumor RR with experimental treatment. However, the authors noted that treatment that lowered the odds of failure to respond by 50% would be expected to decrease the odds of death by only 6%. Moreover, less than one-half of the variability in OS could be explained by the variability of the response benefits. They concluded that while an increase in tumor RR apparently translated into an increase in OS, knowledge that a treatment improves RR does not permit accurate prediction of the ultimate effect on survival.

Targeted Therapies

In general, the putative mechanisms of action of novel targeted therapies have been thought to be cytostatic rather than cytotoxic. Thus, tumor response would seem to be a poor reflection of the clinical efficacy of these agents. Yet results of some phase II trials with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in NSCLC have suggested that these agents may cause tumor regression. At the same time, results of these studies vary widely with regard to any correlation between tumor regression and survival. Fukuoka et al in the Iressa (gefitinib) Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 study of 210 patients in whom one or two chemotherapy regimens (at least one platinum-based therapy) had failed reported that gefitinib at 250 mg per day, was associated with an 18% RR, PFS of 2.7 months, OS of 7.6 months, and 1-year survival rate of 35%.[34] A second phase II study of gefitinib (250 mg per day) in 221 patients with previously treated advanced NSCLC, achieved PRs in 12% of patients. OS at 1 year was 25%.[35] Similarly, a phase II study by Perez-Soler et al of erlotinib (Tarceva) at 150 mg/day in 57 NSCLC patients reported an RR of 12.3%, MS of 8.4 months, and 1-year survival of 40%.[36] A subsequent randomized, double-blind, placebo-controlled phase III study by Shepherd et al in 731
patients with previously treated NSCLC provided proof of principle for the survival benefit of erlotinib. While objective response was relatively low at 8.9% in the erlotinib arm vs < 1% in the placebo group, MS of 6.7 months in the erlotinib arm was significantly increased from 4.7 months reported for placebo (**P < .001**). Moreover, median PFS was significantly increased in the erlotinib arm (2.2 vs 1.8 months (**P < .001**); respective 1-year survival rates were 31% and 21%. Clearly, use of an EGFR inhibitor significantly prolonged survival, albeit demonstrating a relatively low RR in this disease.[37] There is a question as to whether use of an EGFR inhibitor should be limited to a subset of patients, since only about 10% of patients with NSCLC possess mutations in EGFR sites that render the tumors sensitive to treatment.[38-40] Hypothetically, treatment might provide an objective response in the 10% of patients who have exquisitely sensitive tumors. Other patients may have minor regressions and relief of symptoms. Thus, given the continuum of response, limiting treatment to patients who have the mutation would be inappropriate.

Because both the EGFR inhibitors and chemotherapy cause tumor regression and the toxicity associated with each does not absolutely overlap, there was considerable hope that combining both types of agent would produce a significant step forward in the treatment of one cancer. Researchers progressed rapidly from phase I to phase III studies comparing combination chemotherapy and EGFR inhibitors with chemotherapy alone.

Unfortunately, by using survival as the endpoint, four clinical studies of EGFR tyrosine kinase inhibitors plus chemotherapy were considered failures, since there was a trend toward worsening (or unchanged) survival among patients receiving combination therapy.[38,39] One such phase III trial, the Iressa NSCLC Trials Assessing Combination Therapy (INTACT) 1, enrolled 1,093 chemotherapy-naïve patients with advanced NSCLC.[41] Treatment consisted of up to six cycles of chemotherapy (cis platin 80 mg/m2/d1 and gemcitabine, 1,250 mg/m2/d1,8,18 of the 3-week cycle) plus either gefitinib (250 mg or 500 mg/d) or placebo. For the gefitinib 500 mg, gefitinib 250 mg, and placebo groups, respectively, neither MSTs were significantly different at 9.9, 9.9, and 10.9 months nor RRs at 49.7%, 50.3%, and 44.8%. Indeed, the initial segments of the survival curves showed trends for shorter survival in patients receiving the combination therapy. Hypothetically, putative mechanisms impacting survival appeared distinct from those influencing objective RR when using combinations of targeted and conventional agents. It has also been hypothesized that the dosing schedule may not have taken advantage of the unique cytostatic mechanism(s) of the EGFR inhibitor.

Other trials in which different targeted therapies, such as an angiogenesis inhibitor, were combined with chemotherapy reported that patients with a significantly improved RR also had a significantly longer survival. In a phase II study, Johnson et al randomly assigned 99 patients with stage IV lung cancer to treatment with carboplatin (AUC = 6) and paclitaxel 200 mg/m2 every 3 weeks, with or without the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin) (7.5 mg or 15 mg/kg).[42] In comparison with patients receiving carboplatin and paclitaxel, the group that was also given bevacizumab 15 mg/kg experienced improved RR (18.8% vs 31.5%), longer median TTP (4.2 mo vs 7.4 mo), and increased survival (14.9 mo vs 17.7 mo).

Sandler et al reported a phase III trial involving the same treatment regimens, and likewise confirmed improved survival for NSCLC patients who received both chemotherapy and bevacizumab (n = 842).[43] At the second planned interim analysis (conducted upon 469 [72.2%] deaths), RR (10% vs 27%; **P < .0001**), PFS (4.5 mo vs 6.4 mo; **P < .0001**), and MS (10.2 mo vs 12.5 mo; **P = .0075**) favored the chemotherapy plus bevacizumab arm.[43]

A more ideal clinical-trial endpoint PFS was associated with a significant survival benefit in patients with advanced breast cancer who were treated with the combination of bevacizumab (10 mg/kg/d1,15) and paclitaxel (90 mg/m2/d1,8,15) administered as first-line therapy. The Intergroup trial E2100, coordinated by the Eastern Cooperative Oncology Group (ECOG), enrolled 715 eligible patients on study. The first interim analysis was conducted on 355 observed events, and reported by Miller et al.[44] The primary study endpoint, PFS, was 6.11 months in the paclitaxel group compared with 10.97 months in the paclitaxel plus bevacizumab group (HR, 0.498; **P < .001**), with a significant trend for improvement in OS (HR, 0.674; **P = .01**).

Studies of patients with colon cancer given combination therapy have also demonstrated that improved OS is predicted by improved PFS, ORR, and duration of response. With the addition of bevacizumab to chemotherapy regimens, Hurwitz et al conducted a phase III trial investigating two regimens for treatment of metastatic colorectal cancer (mCRC) in 923 patients: irinotecan (CPT-11, Camptosar) 125 mg/m2 IV once weekly for 4 weeks, bolus 5-FU 500 mg/m2 IV every 6 weeks, and leucovorin 20 mg/m2 IV (IFL); and IFL plus bevacizumab 5 mg/kg IV every 2 weeks; or 5-FU, leucovorin, and bevacizumab.[45] The primary endpoint, median OS, was 20.3 months in the IFL plus...
bevacizumab arm and 15.6 months in the IFL plus placebo arm ($P < .001$). Median PFS, a secondary endpoint, was 10.6 and 6.2 months ($P < .001$), respectively. Overall RRs were 44.8% and 34.8% ($P < .004$), and median response durations were 10.4 and 7.1 months ($P < .001$), for the IFL plus bevacizumab arm and the IFL plus placebo arm, respectively. Notably, all three endpoints were improved by targeted therapy (ie, RR, median OS, and median PFS).

Tumor Response in Lung Cancer and Other Solid Tumors: Rethinking Endpoints
While several studies of patients with lung, colon, and breast cancer have shown an apparently beneficial effect of tumor response on survival, this effect appears to be small. The number of patients who experience a complete response generally remains low and the responses are short lived, even in the most successful trial.[33]

As this review has noted, response is not consistently correlated with survival in RCC, lung cancer, and other solid tumors. Moreover, there is controversy on the appropriateness of using a measure of tumor burden as a primary endpoint in clinical studies of novel cytostatic agents.[46] Many years ago, the prevailing belief was that “if an agent did not cause tumor regression, it probably was not going to be effective.” However, with newer agents such as gefitinib, erlotinib, and bevacizumab providing the possibility of durable modest regressions or prolonged disease stability, it is important to rethink that principle and its implications for clinical trial endpoints.

Many clinicians favor use of PFS as an endpoint, partly because it may reflect the effects of cytostatic agents and partly because it is more relevant to how patients are treated in the real world.[47] Because PFS includes death, it would capture unanticipated effects of investigational agents on survival. Another alternative endpoint is TTP, which offers an objective, reliable, and practical alternative to OS. Use of both PFS and TTP is limited by the requirement to know the patient's progression history before treatment, the need for frequent and consistent assessment during trials, and the lack of historic comparators. A related issue is the value of historic data. Certainly, particular tumor types (eg, RCC) may not be amenable to the use of historic controls as a comparator. A statistical discussion by Sargent of the use of disease-free survival as a surrogate marker for OS from both a trial and regulatory perspective in colorectal cancer is presented elsewhere in the volume.

Additional Issues in Trial Design
The debate over use of different surrogate endpoints is mirrored by a debate over the need to improve the rigor of phase II trials.[47] There is some pressure to institute randomized phase II trials that use survival as an endpoint. Small, randomized phase II trials comparing more than one experimental agent may help select those suitable for phase III and advanced-phase testing. Such an approach may produce a high type-I error rate, which will be used to justify false phase III trials, but it is more likely to prevent implementation of trials of ineffective agents.

Revised study designs may also need to address the question of inclusion and exclusion criteria. Many ECOG studies have very similar eligibility requirements: performance status of 0 to 1, and positive histologic findings, with clearly demonstrable disease; some allow the presence of metastatic disease. MS is consistently 8 months, and the 1-year survival is about 35% across all studies. However, one recent study of squamous cell carcinoma excluded patients with brain metastases, anticoagulation, and deep venous thrombosis or pulmonary emboli. MS for the control arm increased to 10 months and the 1-year survival for the control arm was almost 44%, an unexpected finding.

In RCC, other trial designs, such as the randomized discontinuation trial, were developed to differentiate drug effects from intrinsic growth patterns in patients with stable disease, select a more homogenous patient population in which to study drug activity, and to help distinguish treatment effect from the natural history of the disease.[46] Ratain et al used a randomized discontinuation trial design to evaluate the oral, small-molecule, multi-kinase inhibitor sorafenib (Nexavar) in 202 patients with RCC; all patients initially received sorafenib 400 mg bid for 12 weeks. Those whose tumor shrank by more than 25% remained on active treatment; those whose tumor shrank by less than 25% were randomly assigned to either continued treatment or placebo. Patients with tumor growth during initial therapy were taken out of the study. After 24 weeks, median PFS for sorafenib-treated patients was 23 vs 6 weeks in the placebo group (HR, 0.29; $P = .0001$); 50% vs 18% of patients were progression-free at 24 weeks, respectively.[46]

Notably, in RCC, the use of historical controls may not be useful as a comparator, presumably due to the natural history of disease. Thus, phase III randomized controlled trial (RCT) data are important to determine a role for promising agents. For example, Escudier et al reported the only phase III, prospective RCT of targeted therapy in RCC completed to date—the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs).[48,49] In this double-blind trial ($n = 769$), second-line
sorafenib was compared with placebo in advanced clear-cell RCC. (Further details of this pivotal trial are provided by Gore and Escudier elsewhere in this supplement.) On December 20, 2005, the FDA approved sorafenib to treat adults with advanced RCC.

Conclusions
This brief overview of clinical trials for treatment of patients with RCC, melanoma, and various solid tumors suggests the need for caution before concluding that the relationships between RR and PFS predict survival. Factors to be considered include different quality of responses; different rates of progression of the disease and the possibility of an interaction between response, quality of response and disease progression; and the natural history of the disease. Under certain circumstances, and with an appropriate clinical trial design using comparable patient populations, agents that produce fairly significant differences in response may evoke differences in survival. Based on historic data using cytotoxic chemotherapy and cytokines in RCC, the efficacy of these regimens has reached an apparent plateau. Similarly, it is apparent that the use of historic data for tumor types, such as RCC, in assessing clinical trial data may not allow for adequate measurement of the efficacy of novel agents or combinations. As in other tumor types (eg, colorectal, breast, lung cancer), novel molecularly targeted biologic agents offer significant potential, either as a single agent or likely in combination with standard regimens or other targeted agents. It may be prudent for trial designs using targeted therapy, along with new imaging technologies, to take into account putative cytostatic mechanisms of action of molecular agents (eg, sorafenib, bevacizumab); traditional response criteria may be inadequate to detect objective response if based solely on tumor measurement. Several recent trials and case reports, particularly in lung cancer, suggest that traditional RECIST does not adequately reflect changes in tumor burden. Use of different trial designs with different endpoints may provide an adequate basis for investigating the benefits (including survival benefit) and risks of some newer therapies.[6,50] The issue of whether traditional response is an adequate marker only for clinical trials, but not reflective of the community and clinical settings, warrants further investigation.

Disclosures:
Dr. Gollob is a consultant for and serves on the speakers bureau of Chiron Corporation. Dr. Bonomi receives research funding from and is on the speakers bureau of Genentech, OSI, and Astra Zeneca.

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