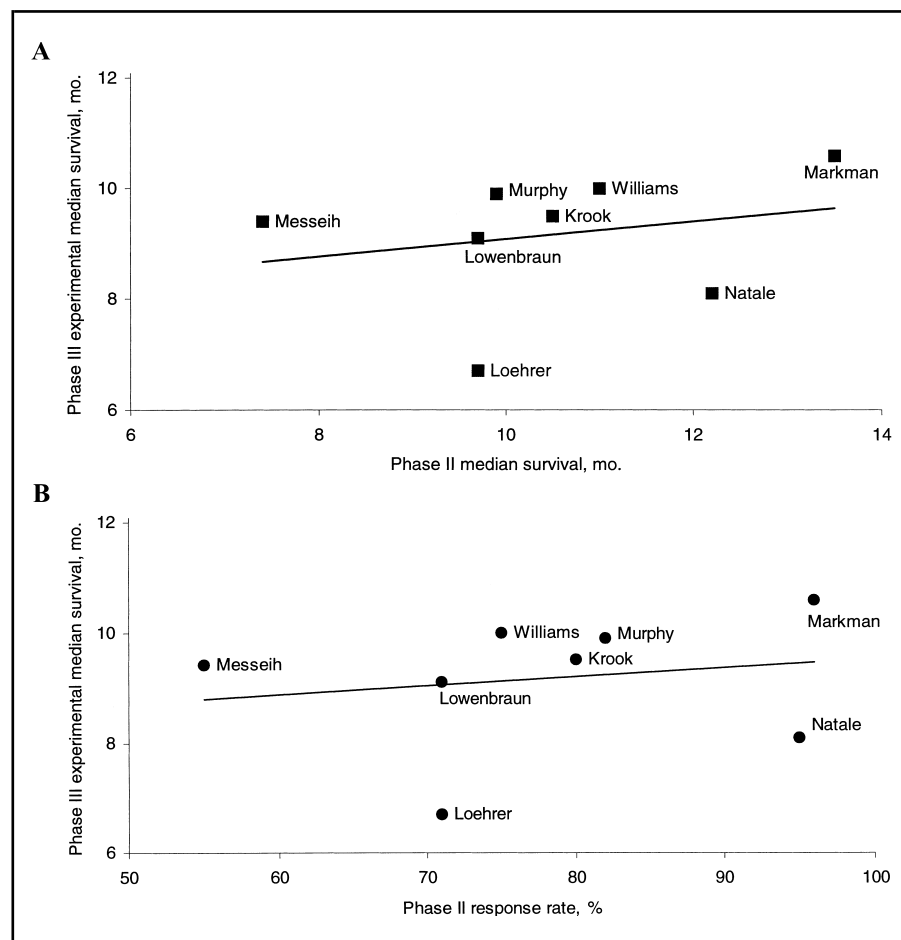


## Re: A Model to Select Chemotherapy Regimens for Phase III Trials for Extensive-Stage Small-Cell Lung Cancer

Chen et al. (1) recently argued that the results of phase II trials of new therapeutic regimens for extensive-stage small-cell lung cancer (SCLC) could be used to predict the statistical power of subsequent phase III trials of the same regimens. Furthermore, they concluded that the median survival of patients on phase II trials was more useful than their response rate to predict the outcome of subsequent phase III trials. We believe, however, that their data call for more prudent conclusions.

Phase II trials are typically performed with carefully selected patient populations and have often yielded impressive results that could not be reproduced in phase III trials (2). The results of phase II trials are imprecise because of a limited sample size and are unreliable because of the patient selection and the lack of a control group. The data presented by Chen et al. (1) suggest that the results of phase II trials in SCLC poorly predict the outcomes of patients on phase III trials (see Fig. 1). The authors found no correlation between the median survival of patients on phase II trials and the median survival of patients on phase III trials (Fig. 1, A;  $P = .57$ ) nor between the response rate of patients on phase II trials and the median survival of patients on phase III trials (Fig. 1, B;  $P = .67$ ). Moreover, the striking similarity of Fig. 1, A and B, suggests that the median survival of patients on phase II trials does not predict the median survival of patients on phase III trials any better than does the response rate of patients on phase II trials. In their analyses of these data, Chen et al. (1) used Bayesian techniques to incorporate external information to capture improvements in the median survival for patients treated on the control arm over



**Fig. 1.** Plots of phase II median survival versus the corresponding phase III experimental median survival (A) and phase II response rates versus the corresponding phase III experimental median survival (B). **x-axes** represent the median survival (in months) (A) and the overall response rates (B) of patients with extensive-stage SCLC treated in eight phase II studies for which response rates were available. **y-axes** represent the median survival of patients treated on subsequent phase III trials that compared the experimental regimen with standard chemotherapy. **Lines** represent the least-squares regression lines. The Pearson correlation coefficients are .38 ( $P = .57$ ) (A) and .13 ( $P = .67$ ) (B). This figure is identical to Fig. 1 of the original publication (1), with trials identified by the name of their first author, and without the trial of Zacharski et al. [reference (27) in (1)], for which no response data were available.

time (7.0 months before 1981 and 8.9 months after 1981). We do not know whether improvements were also seen in the response rates of control treatments over the same time period, in which case a Bayesian prediction based on phase II response rates could have been just as good (or just as bad) as that based on phase II median survival.

Chen et al. (1) should also be cautious in their conclusions because the choice of a 55% cutoff in expected power appears largely data derived. The authors excluded the phase II study by Natale et al. [reference (30) in (1)] from those that should have led to a phase III trial, even though this study had yielded both a long median survival (12.2 months) and a high response rate (95%) (Fig. 1). Our concerns, however, bear more on the general applicability of the

approach proposed by Chen et al. (1) than on the details of their data analyses. On the practical side, the authors do not discuss the great difficulty of obtaining reliable comparable survival data for patients on control treatments, should their approach be used in real time and not 10 years later. Nor do the authors consider the chief advantage of response rate over survival, which is that it is observed early after treatment initiation.

In an editorial appearing in the same issue of the Journal (3), Dr. Pazdur contrasts the conclusions of Chen et al. (1) with those of a meta-analysis performed by our group on 25 randomized trials studying the effects of various treatments on response and survival in advanced colorectal cancer (4). The two approaches differ in two important ways. First, the former used phase II

data to predict the survival outcome of patients on phase III trials and the latter used effects of randomized treatments on response to predict their effects on survival in the same patient population. Second, the former used data from 252 patients (187 deaths) and the latter used data from 3791 patients (3429 deaths). Admittedly, these analyses had different purposes and used different statistical methods, but the cautious conclusions of the latter ["there is much uncertainty in predicting treatment benefits on survival from treatment benefits upon response" (5)] may cast some doubts on the claims made by the former ["use of this model may expedite the randomized study of regimens that show promise" (1)]. Had the method proposed by Chen et al. (1) been available in the early 1980s at the time of planning phase III trials in SCLC, only two such trials would have been recommended on the basis of 25 deaths: seven deaths in the trial by Williams et al. [reference (25) in (1)] and 18 deaths in the trial by Markman et al. [reference (29) in (1)]. Intuition suggests that such a strategy would have been very risky. We quite agree with Dr. Pazdur that tumor response "is a puzzle in itself" (3), and we acknowledge that, for many new classes of agents, tumor response may no longer be a relevant endpoint to consider (3). However, alternative ways of expediting the development of effective anticancer therapies require validation, especially if, as proposed by Chen et al. (1), they are based primarily on nonrandomized evidence.

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## NOTES

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## RESPONSE

Most current phase III clinical trials are justified based on an informal review of phase II response rates for the same experimental regimen. This approach, while acceptable in an era when few biologically based candidate cancer treatments existed, has led to a plethora of negative phase III trials for patients with extensive-stage small-cell lung cancer. Prompted by the negative results, our goal (1,2) was to identify a strategy that would improve the ability to introduce new agents into treatment regimens. With the discovery of numerous molecular targets and chemical entities, it will become increasingly important to better use more of the information from exploratory phase II trials to determine if investigators should continue the development of a particular regimen.

The model we introduced provided a framework for computing the expected power for a phase III trial based on the observed phase II survival result (2). This model is in contrast with current practice, which calculates power based on the hypothetical "wished for" treatment effects. The retrospective data from our analyses showed that several of the phase II trials were themselves too small or the median survival too short to take the same regimen onto a phase III

trial. Consequently, we believe that the use of this type of model may be useful when applied prospectively.

By contrast with the assertion by Buyse et al., there is no difficulty in obtaining relevant survival data for standard treatment arms for use with our approach. Such data are available from phase III trials of cooperative oncology groups, and the variability in the survival outcome of different phase III trials of the standard regimens can be incorporated in our model to reflect the uncertainty in predicting the outcome for the standard treatment. We also cannot agree with the apparent preference of Buyse et al. for using no data rather than nonrandomized data in planning phase III trials.

Buyse et al. suggests that similar results could have been obtained by modeling phase III expected power using phase II response rates. However, many cytostatic drugs yet to be developed may not produce tumor shrinkage. We also believe that response rates are generally more subjective and more variable endpoints. In addition, response rates are more influenced by patient factors. Perhaps more important, we are not proposing that response rates should not be used in selecting regimens for phase III trials, but that survival endpoints should also be used. Survival information from phase II trials is typically available when phase III trials are planned.

The current database that we have been able to put together for extensive-stage small-cell lung cancer is inadequate to definitively compare the relative usefulness of the two endpoints in models, such as the one we have proposed. As we stated (2), prospective evaluations of our model are needed. We believe that the type of model we introduced is an additional tool for deciding whether to use a regimen tested in a phase II study in a candidate phase III trial. Our model is potentially of great value, and the initial results, although limited, are sufficiently promising to warrant further evaluation of the approach using phase II trial survival data.

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## NOTES

*Editor's note:* Dr. Pazdur declined to respond to the correspondence of Buyse et al.

The views and opinions expressed herein are those of the authors and are not to be construed as the official opinion of the United States Navy or the Department of Defense.

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