Elizabeth A. Eisenhauer and Christopher Twelves, editors, 2015, 356 pages, Cambridge University Press, $69.95
Review by Norman M. Goldfarb


The following table provides an example of the book’s practical approach. It presents variations in Phase I study conduct that are permissible if the protocol is written to provide these options. Otherwise, protocol amendments are required.

<table>
<thead>
<tr>
<th>When the Unexpected Happens</th>
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<tbody>
<tr>
<td><strong>If this happens:</strong></td>
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<tr>
<td>Although the patient has a grade 3 toxicity (fatigue), it is not clear if this is due to drug or disease.</td>
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<td>Two of six patients have a grade 3 event, which qualifies as DLT, but they are not the same event, (e.g., one is myelosuppression, the other is nausea).</td>
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<td>Preclinical toxicology suggested that myelosuppression will be dose-limiting, and the DLT definition is based on this. However, another grade 3 organ toxicity has been seen.</td>
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| In a weekly intravenous phase I study, the protocol calls for holding the dose if DLT criteria are met (grade 4 neutropenia for 7 days). A patient has grade 3 neutropenia on day 15: although the protocol does not specify exactly when to hold the dose, the patient is not doing well. | Patient safety concerns should take precedence over protocol direction, particularly if, as in this case, the way the protocol was written did not seem to take this type of problem into account. In weekly schedules of myelosuppressive agents, it is often the case that the treatment-day dose has to be reduced or held for degrees of toxicity that are less that what would be called a DLT. In fact, some would advise including as one of the definitions of DLT the need to hold or reduce}
not require holding the dose, the investigator is uncomfortable giving treatment.

treatment. In any event, the investigator should hold treatment in this case, and parties to this protocol should discuss how to amend the dose-reduction section.

<table>
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<tr>
<th>A dose level is found to meet criteria for MTD: two of three patients had DLT. The next-lower dose level is expanded, and no toxicity more than grade 1 is seen.</th>
<th>Treat a new cohort of patients at a dose level intermediate to the two dose levels described. Protocol design section should be written so as to allow this; otherwise an amendment will need to be made.</th>
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<tbody>
<tr>
<td>A dose level is found to produce DLT in two of six patients, making it the MTD, BUT the other four patients at that dose experienced no more than grade 2 toxicity.</td>
<td>It may be that your drug is affecting different patient risk groups differently. Look at the entire trial database to see if there is an obvious difference in those that get toxicity versus those that do not, e.g., prior treatment, performance status, renal or hepatic function. If there is an obvious cause, consider amending the protocol to continue escalation in the low-risk group. If no obvious patient risk group is found, choices are to proceed to lower dose as per protocol or to cautiously add one to two more patients to the current dose level to further assess it, provided protocol language is permissive enough to allow this.</td>
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The book consists of 12 chapters by 23 authors:

- Introduction
- Preclinical Data and Requirements
- Phase 0 Clinical Trials
- Basics of Phase I Design: First-in-Human Studies
- Ethical Issues in First-in-Human Phase I Cancer Trials
- Phase I Trials in Special Populations and Circumstances
- Phase I Trials of Immunotherapeutics
- Statistical Designs for First-in-Man Phase I Cancer Trials
- Writing the Protocol
- Practical Aspects of Pharmacokinetics and Pharmacodynamics
- Process, Pitfalls and Logistics of Phase I Trials
- Reporting and Interpreting Results

The book is available in bookstores.

Reviewer

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