Published in final edited form as:

Stat Biopharm Res. 2015 ; 7(4): 357–358. doi:10.1080/19466315.2015.1094407.

Comment

A Ivanova¹, K M Anderson², Gary L. Rosner³, and E. Rubin⁴

¹Department of Biostatistics, University of North Carolina at Chapel Hill, NC, USA

²Clinical Biostatistics and Research Decision Sciences, Merck Research Laboratories, North Wales, PA 19454-2505, USA

³Oncology Biostatistics & Bioinformatics, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

⁴Oncology Clinical Research, Merck Research Laboratories, North Wales, PA 19454-2505, USA

Abstract

We congratulate the authors on their comments on innovative approaches to drug development that fall out of the traditional mold and may result in more quickly bringing safe and effective treatments to patients. Changes in the overall clinical develop approach are most relevant to “breakthrough” therapies, which have generally yielded exceptional efficacy data in early clinical studies, motivating exploration of accelerated development and regulatory approaches, as well as a potential ethical need for crossover upon progression in randomized controlled studies (Horning et al., 2015). As is clear from the manuscript, it will be important to develop an understanding of what works well and where the pitfalls in new approaches are. We comment briefly on the four topics mentioned by the authors, combining comments on items 2 and 3: 1) non-proportional hazards, 2) interpretability of extended Phase I trials, 3) single-arm trials as a basis for approval, and 4) recent innovations in trial design.

Non-proportional hazards

Comments on sample size assuming non-proportional hazards are certainly worthwhile. While alternate analyses and modeling are suggested to evaluate treatment effect in non-proportional hazards scenarios, they seem to be suggested only as supportive to the classic logrank test. It may be time to consider alternate primary analysis methods such as those provided in the authors’ references.

Treatment switching to the experimental treatment is a likely result of randomized trials following early approval in single arm trials. As noted, this creates difficulties in achieving statistically significant or even interpretable effects of treatment on overall survival. Preferred methods for this seem to be evolving with time. While definitive survival results will normally become challenging, ensuring some level of safety with respect to mortality is critical at a minimum. Modeling putative treatment effects had treatment switching not been available are important from a payor perspective.

The stem cell transplant as follow-on therapy is certainly an interesting example. One perspective is that a transplant enabled by a therapy is at least indirectly attributable to the

drug given as is the resulting OS benefit. This should be among the perspectives considered for such a treatment as it is only dependent of very transparent assumptions compared to modeling approaches. The non-Hodgkin's lymphoma example of the strategy of induction plus maintenance therapy is arguably common to many cases where drugs are given for more than a short duration. Optimal treatment duration is a difficult issue to address and is perhaps best addressed in post-marketing studies after a treatment regime including induction and maintenance has been shown to be safe and efficacious.

Interpretability of extended Phase I trials and single arm trials as a basis for approval

Ivanova et al. (2016) in a recent review of published phase 2 trials reported that if a trial provided a clear description of the statistical design and analysis a recommendation for future investigation was less likely than a trial that did not include this information. For trials including the design the percentage of recommendation for further study was only 68%. For trials not including the design it was 89%. This has the clear danger of taking forward programs based on *post hoc* results. An example of how to make an 'expanded Phase I trial' reasonably rigorous is to generate hypotheses during the trial and then confirm them. This requires a certainly amount of flexibility written into the protocol or substantial amendment(s), but these may be a more efficient way to quickly develop a new therapy than the traditional Phase I, II, III paradigm. Note that these uncontrolled studies are being followed by randomized trials for this compound to confirm very positive early findings. This ensures both early access for patients in great need, but also careful confirmation of benefit in randomized comparisons versus standard therapy. This option is not mentioned by the authors, but certainly has been expected by regulators.

Recent innovations in trial design

As noted by the authors, master protocols and/or basket trials are increasingly being used in an effort to accelerate oncology drug development. One aspect that deserves additional comment is the issue of rapidly developing companion diagnostics along with a therapeutic, assuming that such diagnostics may be needed to yield the large effect sizes characteristic of "breakthrough" therapies, and how such approaches are facilitating this co-development. The "basket" imatinib B2225 study described by the authors was initially an enrichment design and only enrolled patients with tumor characteristics expected to yield high sensitivity to treatment with imatinib: these characteristics were identified by local lab tests for KIT, PDGFRA, and PDGFRB protein expression. Ultimately imatinib was approved for multiple additional indications based on this study, but without the need for co-approval of companion diagnostic tests for expression of these proteins. This is not typical, and since development of highly predictive companion diagnostics often requires relatively large, mature data sets, co-development of companion diagnostics sufficient to meet current regulatory standards has the potential to delay development of "breakthrough" therapies. Lung MAP, I-SPY2, and the adaptive signature design^{3,4} all represent innovative strategies to increase the efficiency of co-development of companion diagnostics.

Summary and conclusions

As Dr. Sridhara and colleagues point out, the lines between the traditional phases of drug development have been blurring. We do not see seamless designs as a bad thing. In fact, it may well be time to reassess the goals of each phase of drug development in the new era of oncology drug development. We view this change as an opportunity for statisticians to contribute new and more efficient designs and methods of analysis to help get more effective treatments to patients and oncologists as soon as we have enough evidence that the clinical benefit outweighs any risks.

References

1. Horning SJ, Haber DA, Selig WK, Ivy SP, Roberts SA, Allen JD, Sigal EV, Sawyers CL. Developing standards for breakthrough therapy designation in oncology. *Clinical Cancer Research*. 2013; 19:4297–4304. DOI: 10.1158/1078-0432 [PubMed: 23719260]
2. Ivanova A, Paul B, Marchenko O, Song G, Patel N, Moschos SJ. Nine-year change in statistical design, profile, and success rates of phase II oncology trials. *Journal of Biopharmaceutical Statistics*. 2016; 26 in press.
3. Freidlin B, Simon R. Adaptive signature design: an adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients. *Clinical Cancer Research*. 2005; 11:7872–7878. [PubMed: 16278411]
4. Scher HI, Nasso SF, Rubin EH, Simon R. Adaptive clinical trial designs for simultaneous testing of matched diagnostics and therapeutics. *Clinical Cancer Research*. 2011; 17:6634–6640. [PubMed: 22046024]