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Editorial: Fast track clinical development for treatments for cancer

Every one agrees that cancer, especially inoperable and metastatic disease, constitutes an area of high, unmet medical need. Put another way, it is a lethal condition. Because of this, the Food and Drug Administration (FDA) will consider so-called fast track applications for marketing approval. Thus, many emerging biopharmaceutical companies see an opportunity to get a treatment to the US market quickly (a similar system does not yet exist in Europe).

The fast track guidance from the FDA specifically says that it can 'approve a marketing application . . . upon a determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit'. The guidance goes on to point out that 'where an accelerated approval is based upon a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, post-marketing studies are ordinarily required 'to verify and describe the drug's clinical benefit and to resolve remaining uncertainty as to the relation of the surrogate endpoint upon which approval was based to clinical benefit, or the observed clinical benefit to ultimate outcome'. This definition was written in 1992. As in everything else, 10 years is a long time in science and medicine.

The guidance also goes on to point out that a fast track application can be considered for a life-threatening disease or life-threatening aspect of a disease for which there is no other treatment. If there is a treatment already approved, then the new treatment being considered for fast track application must have greatly enhanced

efficacy or safety over its predecessor. Additionally, if a competing product is approved while a sponsor's treatment is in development, then the fast track designation may be lost or that sponsor may be required to show additional benefit over the newly approved product. An interesting conundrum that the guidance does not address (maybe it was not an issue when it was written) is what to do when the indications for a cancer drug are expanded and generally accepted by academic trials that are never followed up with a change in the official labelling of the drug.

At no stage does the guidance encourage sponsors to believe that a single clinical trial is sufficient for fast track approval of a new entity. This concept belongs more appropriately to compounds given orphan drug status. Now, many cancers, because of their rarity, do, in fact, qualify for such status but the approval is limited to that indication and the market opportunity is narrow. The major killers in the cancer world are, unfortunately, not all that rare and therefore do not qualify. In addition, the guidance does not suggest that randomised, controlled studies may be replaced by open label, uncontrolled trials.

The particulars of what the guidance means are also important and have changed over time as evidence has accumulated about the validity of surrogate end-points. In cancer, two surrogate end-points have been used to attempt to predict overall survival. These are the so-called tumour response rate and the time to disease progression. A tumour response is, crudely, defined as the tumour or tumours getting smaller or a tumour marker level measured in blood decreasing or vanishing altogether.

This may seem straightforward but the devil, as usual, is in the detail. Unless a tumour is in the skin, so that it can be seen and measured with a tape measure, it has to be visualised by one of several imaging technologies. The standard at the moment is computed tomography (CT) scanning, which visualises internal tumour masses that may then be measured. However, masses that lie next to other, especially bony, structures are difficult to measure because their edges may lie behind the structure and they therefore cannot be seen. Very small masses may also not show up on images and may be missed (this is important, for example, in ovarian cancer). Furthermore, if there are several masses, they may not all respond in the same way to a given treatment. There are obvious difficulties in assessing tumour 'responses' when some masses are getting larger or not changing, while other masses are getting smaller in the same patient.

There was a time when tumour markers were believed to offer an alternative solution. These are molecules that are shed from the surface of the tumour and appear in the blood. If the molecule is characteristic of the tumour, then it can be followed prospectively. In general it is true that rising levels of tumour marker observed in blood indicate tumour progression, even when enlarging tumours cannot be visualised on CT scanning. However, the converse turns out not to be true in all cases – low levels of tumour markers in blood do not always indicate a response. This is because the tumours, as they become more aggressive and uncontrolled, may cease to produce their tumour markers, which therefore do not appear in blood. Because of this, a false impression of success may be created just at a time when the tumour takes a decisive turn for the worse.

Time to disease progression has proved equally fraught in practice. Put generally, what it means is the time that it takes for disease that has responded or is not getting worse to start growing again. CT scanning and tumour markers have both been used to try to provide objective data. Both have distinct limitations. CT scans are time

consuming and, although they are not individually overwhelmingly expensive, the costs of repeated scans mount up. Being X-rays, they also are a potential radiation hazard to the patient if used too often. The standard of care would be to repeat these scans every three months. A lot can happen in three months and, therefore, time to disease progression tends to be an imprecise measure at best, especially when a treatment may increase the time to disease progression by only a few weeks. There are also difficulties in interpretation of the scans, as for disease responses, if some masses behave differently from others in the same patient.

Likewise, tumour markers may prove to be unreliable for the same reasons as those given for the indication of the response. As the tumour becomes more undifferentiated, it ceases to shed its tumour markers and therefore progresses undetected.

Because of these uncertainties, and especially in late stage cancer where overall survival is measured in months, the distinct trend now is to require overall survival studies for registration. This is true both for the FDA and for the European authorities. If companies want to try to use studies of tumour response rates or time to progression to decide whether to launch larger well-controlled studies for registration, that is their decision. However, these studies are now not considered to be sufficient for registration unless they are spectacularly successful and would doubtless have to be followed by further confirmatory studies, as the Fast Track Guidance points out. In cancer, it is clear that these confirmatory studies would have to show an increase in overall survival.

These circumstances are not obvious if you look at the recent history of cancer drug approvals. Review of either the FDA Summary Basis of Approval or the Committee for Proprietary Medicinal Products (CPMP) European Public Assessment Report (EPAR) documents for products such as paclitaxel or temazolamide, suggests that their sponsors did not have to provide overall survival data for their initial registration packages.

Frequently, the package also included only one randomised controlled trial. However, times have changed and the prevailing view is to require survival data, especially since these trials can generally be completed in two to three years. In the case of irinotecan, survival data were available even in the first New Drug Application (NDA) in its accelerated approval process. In addition, the standard of two well-controlled trials is being reinforced. This is not only because the standard surrogate markers have been shown to be difficult to interpret and to have little relationship, in some cases, with overall survival, but also because there are more useful therapies available now than there were previously.

For biotechnology there may be even one more added complication. The notion of the response rate really arose from an era when the treatment of cancer was either by cytotoxic or radiation therapy, the aim of which was to eradicate disease. While nobody disputes that eradication of cancer is the best solution, everyone also agrees that, in many cases, it simply is not possible. The oncology community and the pharmaceutical industry are coming around to the view that it may be more important to contain cancer, especially metastatic disease, than to try to cure it. If this is the case, response rates and time to disease progression become meaningless concepts and overall survival and quality of life are the only useful end-points. This notion applies to many areas of treatment, be they immunotherapies, anti-angiogenesis therapies, potentially gene therapies and numerous others.

So survival studies are in and the

standard two well-controlled studies are in. Is it possible to get fast track approval based on open label, uncontrolled data? The issue is this. If you study only your own compound and do not compare it with something else, then it is impossible to set it into the context of the bigger picture. The use of retrospective comparators is a minefield and is considered to be pointless. The Fast Track Guidance explicitly says that a fast track development must be able to demonstrate improvements in safety and/or efficacy over existing treatments (and there are vanishingly few cancers for which there is no treatment – they may not be great, but they are there). Therefore, it is obvious that an uncontrolled trial is unlikely to succeed. A further complication arises when a new compound is used in conjunction with an existing therapy that also exercises a therapeutic effect. In this instance, the only way to demonstrate the benefit of that new compound is in a randomised, placebo-controlled trial.

The way forward is clear. The fast track development does offer companies the opportunity to have their data reviewed on an expedited basis. However, it does presuppose that the product offers significant benefits over other established therapies and it does demand that the data are sound.

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