EJC SUPPLEMENTS 5 (2007) 37–40

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

# How can biomarkers become surrogate endpoints?

B. Berns[a], P. Démolis[b], M.E. Scheulen[c,*]

[a]Clinical Haematology & Oncology, Centocor Ltd., 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, UK
[b]Assesment Anticancer Drugs, AFSSaPS, Saint Denis 143, 147 Boulevard Anatole France, F-93285 Saint-Denis Cedex, Paris, France
[c]Innere Klinik und Poliklinik (Tumorforschung), Westdeutsches Tumorzentrum, Universitätsklinikum Essen, Hufelandstraße 55, D-45122 Essen, Germany

ARTICLE INFO

*Keywords*:
Biomarker
Drug approval
Drug registration
Endpoint
Surrogate
Targeted agents

ABSTRACT

As there is an urgent need for careful planning of development schemes for new classes of molecularly targeted anticancer therapies, the use of biomarkers as surrogate endpoints in therapeutic trials was discussed by BDA delegates, representing the pharmaceutical industry, regulatory agencies, academia, and patient advocacy groups in a breakout session. The aim was the clarification of the role of surrogates in the conduct of clinical trials that serve as a basis for drug licensure or registration, especially in the setting of accelerated or conditional approval. The discussions focused on three questions: (a) how to validate biomarkers, (b) how biomarkers might be used as surrogate endpoints in small clinical trials, and (c) how a biomarker might be used in studies of agents other than the one for which it was validated. The deliberations of the group are discussed herein.



## 1. Biomarkers as regulatory tools

As there is an urgent need for careful planning of development schemes for new classes of molecularly targeted anticancer therapies, the use of biomarkers as surrogate endpoints in therapeutic trials was discussed by BDA delegates, representing the pharmaceutical industry, regulatory agencies, academia, and patient advocacy groups in a breakout session. The aim was the clarification of the role of surrogates in the conduct of clinical trials that serve as a basis for drug licensure or registration, especially in the setting of accelerated or conditional approval.

Biomarkers are characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1,2] Biomarkers have assumed an increasingly important role as surrogate endpoints in the development and approval of new molecularly targeted anticancer agents. Biomarkers have been the impetus in the shift away from the 'one size fits all' and toward 'the right drug at the right dose in the right patient' approach for molecularly targeted anticancer therapies.[3] Hence, biomarkers play an important role for scientists and industry in drug development and also for regulators in the licensure or registration process who expect changes induced in a surrogate endpoint by a therapy to reflect changes in a clinically meaningful endpoint, such as survival.

In the context of clinical trials, biomarkers are usually pharmacologic markers that can serve as a surrogate marker or surrogate endpoint., According to Robert Temple of the U.S. Food and Drug Administration, 'a surrogate endpoint of a clinical trial is a laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Changes induced by a therapy are expected to reflect changes of a clinically meaningful endpoint.[4]

Use of surrogates entails certain advantages and disadvantages. Generally speaking, clinical trials that rely on surrogate endpoints can be faster, cheaper, and more efficient than those with clinical endpoints, but it is critical to bear in mind that surrogates are not a measure of the endpoint of real interest. An additional drawback is that reliance on a

* *Corresponding author.*
E-mail address: max.scheulen@uk-essen.de (M.E. Scheulen).
1359-6349/$ - see front matter 
doi:10.1016/j.ejcsup.2007.09.003

surrogate endpoint results in a much smaller amount of controlled safety data than would be obtained from a trial with a clinically relevant endpoint.[5]

Regulators in the United States and the European Union emphasise that if biomarkers are to be used as regulatory tools, they must be validated, be consistent with the pathophysiology of the disease, and have some biological plausibility. Regulators give credence to epidemiologic evidence that a biomarker is a risk factor for the disease under study as well as confirmation that it is on the intervention pathway. Effects of treatment on the biomarker should explain or be associated with the effects of treatment on the clinical endpoint. Establishing that a biomarker possesses such characteristics bolsters the case for relying on it for accelerated (United States) or conditional (European Union) approval.

## 2. Questions that must be considered

The BDA has a strong interest in the identification and use of surrogates in improving the cancer drug development process. Exploration using biomarkers has several aims. They allow the drug to be followed until it reaches the target and enable its effects at the tumour site to be identified. Such markers can also help define subpopulations of patients who would be most likely to benefit from a particular therapy, thereby minimising the numbers of patients exposed to the risk of treatment with little likelihood of clinical benefit.[6] Therefore, investigators, industry, and regulators must find common ground when designing safety and efficacy trials of molecularly targeted agents, in order to conduct trials in the most expeditious way to deliver effective therapies to market as quickly as possible.

Questions remain, however, about the use of biomarkers as surrogates in clinical trials. The BDA delegates discussed three in particular during the breakout session:

1. Are there situations when novel, unvalidated biomarkers can be considered as primary supportive evidence (e.g., surrogate endpoints) for regulatory approval?
2. Following validation of a biomarker based on a traditional endpoint (e.g., survival), could a biomarker be used as an endpoint for registration (conditional/accelerated) for another compound, most likely in the same tumour type and setting? [The original version used 'initial proof of correlation' rather than 'validation', but the participants seemed to agree that 'validation' was better.]
3. Could a biomarker be used as an endpoint for conditional registration (EU) or accelerated approval (US) in the case of a rare indication where clinical benefit cannot be demonstrated formally in a randomised, controlled trial?

The above questions served as a framework for the BDA delegates' discussion of surrogates, discussed in the sections that follow.

## 3. Exploring a role for unvalidated biomarkers in regulatory approval

From the current regulatory perspective, unvalidated biomarkers have little or no role in the approval process. However, complete validation is not always realistic or possible. Under such circumstances, extrapolation would be required with acceptance of some degree of uncertainty. Depending on the setting, similarity of background evidence, robustness and size of the results, such data could be used as supportive evidence for a regulatory filing.

## 4. Using a surrogate in studies of other compounds

If, for example, a surrogate endpoint (validated biomarker) were used as a basis for approving a particular tyrosine kinase inhibitor for treating chronic myelocytic leukaemia, would regulators accept that same surrogate for approving a novel tyrosine kinase inhibitor to be used for the same indication?

The regulatory view holds that correlation is not the same as validation. Correlation would not be considered a sufficient criterion for establishing a biomarker as a surrogate for clinical benefit, usually defined as overall survival. Initial proof of correlation, however, could be the first step in validation, but validation of a biomarker is critical to regulators considering accelerated or conditional approval of an anticancer agent.

Biomarkers could be used to support the case for approval even if they are not formally validated; for example, some surrogates are actually part of the disease definition and contribute directly to the clinical outcomes of those patients. Nevertheless, caution must be exercised because biomarkers do not always correlate with clinical benefit.

One challenge arises because pinpointing when everyone would agree that a biomarker is valid and could then use it confidently is not possible. Although it would be useful to be able to define the point when a drug might receive conditional/accelerated approval based on a surrogate validated for another therapy, the situation is unfortunately not so clear. The price for early approval based on surrogates is greater uncertainty. Consider the hypothetical example of a biologically plausible marker used as a surrogate endpoint in several studies with different compounds. The surrogate endpoint correlated well with the outcomes in each trial. In such a case, no one could object to using the biomarker again. On the other hand, if only one or two studies have been done using a biomarker as the surrogate endpoint, and it showed some, but not compelling, correspondence with clinical outcomes, chances are the regulatory authority would not accept that biomarker as a surrogate endpoint for another agent. The level of uncertainty that would be acceptable depends on a number of factors. For example, why rely on progression-free survival (a surrogate) if death (a clinical outcome) occurs a few weeks after disease progression. In this situation, regulators would have no reason to accept progression-free survival as a basis for approval of the agent.

Mode of action is another important consideration that could make it difficult to use even a validated biomarker as a basis for approval of another compound. For example, consider the reliance upon blood cholesterol as a surrogate for cardiovascular risk. Hormone replacement therapy reduces cholesterol, but it does not reduce cardiovascular risk; in fact, it appears to increase risk. Another example would be gastrointestinal stromal tumour (GIST) with hepatic metastases that, treated with imatinib (Gleevec®/Glivec®), demonstrate