the experimental type I error. When modifying scientific hypotheses during a trial, one is essentially testing the global hypothesis that at least one of the treatment regimens tested affects at least one of the proposed clinical outcomes in at least one of the identified target populations. This could lead to severe problems both in estimating efficacy and defining the actual indication. Also the idea of 'seamless' phase II/III trials was discussed. Although such designs might seem advantageous, phase II studies must not be slighted in dose finding and other aspects. In some cases, regulators may already be requiring too little work in phase II. Furthermore, many phase II/III trials are not truly adaptive; rather, they are designed as phase III trials in settings where adequate information on biological activity is lacking.

It is mainly the early phases of drug development, being inherently more exploratory than confirmatory, which could benefit from flexibility in trial design. Adaptive designs are not often used, although requests for scientific advice about them is rather frequent.

CONFLICT OF INTEREST STATEMENT: Dr. Eva Skovlund is an official of The Norwegian Medicines Agency and the University of Oslo and it can be confirmed that there is no conflict of interest involved in this paper, nor in her participation in this entire event.

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CLINICAL SURROGATE END-POINTS

Sergio Palmeri. *Medical Oncology, University of Palermo, via del Vespro, 129, 90127 Palermo, Italy*

E-mail address: sergiopalmeri@alice.it

This presentation reflected a personal opinion about the role of surrogates as clinical end-points. According to the Biomarkers Definitions Working Group, a surrogate is 'a biomarker that is intended to substitute for a clinical end-point and is expected to predict clinical benefit (or harm or lack of clinical benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence'.[1] Although overall survival is the gold standard recognised by both the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) as a basis for conditional (EMEA) or accelerated (FDA) approval of new anticancer agents, surrogate end-points are often considered to be reasonably likely to predict clinical benefit.

WHAT IS REQUIRED FOR DRUG REGISTRATION OR APPROVAL?: The European Union's legal requirements for approval of a new agent were highlighted. First, it must demonstrate a positive benefit–risk ratio. Second, whenever possible, the agent should be compared in a randomised, controlled clinical trial to a placebo or an established treatment (as appropriate). Measures must be taken to minimise bias and uncertainty. Authorisation will be refused, however, if the agent's efficacy is not substantiated or is lacking, or if the agent is shown to be harmful.

The FDA's International Conference on Harmonisation generated two general considerations for clinical trials that are relevant to the use of surrogates as end-points.[2,3] Confirmatory (phase III) trials should demonstrate clinical benefit, and the primary end-point should provide the most clinically relevant and convincing evidence of effect based on a valid and reliable measure indicative of treatment benefit.

Clinical end-points for approval or registration of anticancer agents include overall, disease-free or progression-free survival (PFS).[8] PFS has generally relied on imaging or the onset or worsening of disease-related symptoms. Response, if the effect is dramatic, may also be a basis for approval. Tumour response is most often based on imaging results or Response Evaluation Criteria in Solid Tumours (RECIST),[5] a set of standard parameters used to document and report tumour response. Protection against toxicity and reduction in the risk of disease can also be acceptable bases for approval or registration. In general, patient benefit is difficult to use as a clinical end-point because of the lack of reliable, reproducible instruments for measuring such factors as palliation or improvement of symptoms. Quality-of-life assessments are not presently considered as a basis for approval.

The EMEA's experience shows that it has been quite flexible in accepting end-points other than overall survival and PFS for approval. Indeed, almost half of approvals are based on response rate (Table 1). Response rate is only used as a basis for approval when the anticancer agent demonstrates 'dramatic activity' in the EMEA guideline or in situations where no established alternatives exist and the prognosis is relatively homogeneous (e.g. imatinib mesylate, Glivec®) for chronic myeloid leukaemia after failure of interferon). Overall, response rate has been an end-point in 22 trials (47%), PFS in 16 (34%), and overall survival in 9 (19%). The experience of the FDA with end-points other than overall survival was also discussed. Table 2 shows the proportions of

Table 1 – EMEA experience with various end-points used in drug-registration trials

Indication	N = 47	End-points
Hematologic	13 (28%)	PFS, RR
Breast	13 (28%)	OS, PFS, RR
Sarcoma	5 (11%)	RR
Lung cancer	5 (11%)	OS
Colorectal	3 (6%)	OS, RR
Brain cancer	3 (6%)	OS, PFS, RR
Ovarian	3 (6%)	PFS, RR
Head and neck	1 (2%)	RR
Prostate	1 (2%)	OS

PFS, progression-free survival; RR, response rate; OS, overall survival.

Table 2 – FDA experience with various end-points used in clinical trials in support of accelerated or regular approval

	Accelerated (%)	Regular (%)
Response rate	93	53
Time to progression	7	20
Symptom benefit	0	12
Other	7	32

Columns do not total 100% due to multiple end-points.

clinical studies that relied upon various end-points to support accelerated or regular approval.

CONFLICT OF INTEREST STATEMENT: Professor Sergio Palmeri is an ex official of The EMEA and now holds the Chair of Medical Oncology at the University of Palermo, Italy, and it can be confirmed that there is no conflict of interest involved in this paper, nor in his participation in this entire event.

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