the prediction of trabectedin sensitivity. Although this was a small retrospective study, it showed that DNA repair gene expression patterns can predict the sensitivity of sarcoma patients to trabectedin.

A potential design for a pivotal phase II trial for a given drug in a particular tumour type based on a molecular signature is described in Fig. 1.

CONCLUSION: The identification of molecular signatures correlating with tumour vulnerability to anticancer agents is instrumental in the era of molecular medicine. Such molecular signatures are expected to be trans-tumoural and thus applicable for predicting sensitivity to a given drug in a set of other malignancies. This approach could have a positive influence on development time and costs, pharmacoeconomics, success rates in pivotal studies, the pharmaceutical industry's business models, and—most important—the well-being of cancer patients. Implementing such a framework would require a close interaction of academia, regulatory agencies, patient organizations and industry.

CONFLICT OF INTEREST STATEMENT: Dr. Jose Jimeno is an employee of Pharma Mar S.A. and owns stock of Zeltia (Holding Company) and it can be confirmed that there is no conflict of interest involved in this paper, nor in his participation in this entire event.

References:

1. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *New Engl J Med* 2005;**353**(2):123–32.
2. Petrylak DP, Tangen CM, Hussain MA, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *New Engl J Med* 2004;**351**:1513–20.
3. Ramirez JL, Rosell R, Taron M, et al. 14-3-3σ methylation in pretreatment serum circulating DNA of cisplatin-plus-gemcitabine-treated advanced non-small-cell lung cancer patients predicts survival: the Spanish Lung Cancer Group. *J Clin Oncol* 2005;**23**:9105–12.
4. Jimeno J, Maki R, Casali P, Faircloth G, Martinez N, Nieto A, et al. Therapeutic impact of ET-743 (Yondelis®, Trabectedin) a new marine derived compound in sarcoma. *Curr Opin Orthop* 2003;**14**:419–28.
5. Committee for medicinal products for human use summary of positive opinion for Yondelis, Doc. Ref. EMEA/CHMP/316962/2007, London,19 July 2007. http://www/emea.europa.eu/pdfs/human/press/pr/43140707en.pdf http://www.emea.europa.eu/humandocs/Humans/EPAR/yondelis/yondelis.htm.
6. D'Incalci M, Jimeno J. Preclinical and clinical results with the marine natural product trabectedin (Yondelis, Ecteinascidin-743, ET-743). *Expert Opin Inv Drugs* 2003;**12**:1843–53.
7. Le Cesne A, Blay JY, Judson I, van Oosterom A, Verweij J, Radford J, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: An EORTC soft tissue and bone sarcoma group trial. *J Clin Oncol* 2005;**23**:576–84.
8. Morgan JA, Le Cesne A, Chawla S, von Mehren M, Schuetze S, Casali PG, et al. Yondelis Sarcoma Study Group, Randomized phase II study of trabectedin in patients with liposarcoma and leiomyosarcoma (L-sarcomas) after failure of prior anthracylines (A) and ifosfamide (I). Journal of Clinical Oncology. ASCO Annual Meeting Proceedings Part I, Vol 25, No. 18S (June 20 Supplement); 2007. p 10060.
9. Grosso F, Jones RL, Demetri GD, Judson IR, Blay JY, Le Cesne A, et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. *Lancet Oncol* 2007;**8**(7):595–602.
10. Grosso F, Sanfilippo R, Dileo P, Coco P, Fumagalli E, Montani E, et al. Breaking down tumor responses by their dimensional entity in advanced STS (Non-mixoid / round cell liposarcoma) treated with trabectedin may predict progression free survival. 12th Annual CTOS Meeting November 2–4, 2006, Venice, Italy. Procc. Book, pp 58 [Abs 716].
11. Schöffski P, Grosso F, Taron M, Casali P, Sciot R, Judson I, et al. DNA repair functionality as a molecular signature for sensitivity(S)/resistance(R) in sarcoma patients (pts) treated with trabectedin (ET-743, Yondelis). Presented at the AACR annual meeting; 2007 [abstr 144].

doi:10.1016/j.ejcsup.2007.09.024

ADAPTIVE TRIAL DESIGN AND ITS ROLE IN ONCOLOGY: AN EMEA PERSPECTIVE

E. Skovlund. *Committee for Medicinal Products for Human Use, Norwegian Medicines Agency, Sven Oftedals vei 8, 0950 Oslo, Norway*

E-mail address: Eva.Skovlund@noma.no

Much can be gained through innovative thinking and methods during the early phases (I and II) of drug development, which are largely exploratory in nature. Phase III, however, should be confirmatory.

There are several potential problems associated with adaptive or flexible designs that can pose risk to the integrity and credibility of a trial. For example, breaking the blind early can lead to problems with dissemination of study results and the study population might change between the early and late stages of drug testing. Regulators tend to be wary if the scientific question is not clear which will lead to difficulties with interpreting the outcome results. The overarching problem, from a regulatory point of view, is overemphasis on statistical significance rather than on clinical relevance. Maintaining integrity is critical.

Adaptive trial designs are often less statistically efficient than fixed plans. To protect against all eventualities, statistical inference must consider the worst-case inflation of type I error. Investigators must be cautious about basing study design changes on unreliable interim efficacy estimates. Such designs can also risk sacrificing the flexibility to use emerging results from external sources to alter key design features.

Regulators are very disturbed by changing scientific hypotheses. Both the treatment and the indication must be identified. Some methods allow changes in target population, primary end-point and secondary end-points, while protecting against

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.

doi:10.1016/j.ejcsup.2007.09.025

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.