tumors and in mesothelioma. Furthermore, anatomical changes in the tumor as described by RECIST may be detected later than functional changes in some circumstances, as for example in gastro-intestinal stromal tumors treated with Imatinib. Even though Response Rate may not be anymore the systematic reference endpoint in phase II studies screening new anticancer agents there is still a need to quantify tumor lesions to assess rigorously disease stabilization and progression. The findings of this review together with experience acquired thus far and the results of some ongoing research projects pave the way for a revised version of the criteria. This new version will clarify a number of issues of the previous version which have been addressed by the RECIST working group over the last five years through questions received from those applying RECIST in real situations and answers that were posted on the RECIST website. More data on the use of tumor markers (and references to other published criteria) will be integrated as well as specific criteria for particular tumor types. In collaboration with our colleagues' radiologists more attention will also be given to recommendations for the use of sophisticated imaging techniques and the utilization of contrast products. Finally, issues such as the need for confirmation of response and the minimum number of target lesions needed to make a correct tumor assessment are being investigated in large data sets from recently completed large trials using RECIST.

**11** INVITED

**Functional imaging in drug development – a primary or secondary endpoint in cancer clinical trials**

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Investigators in drug development need in vivo assays to tell them whether a given patient has the appropriate molecular phenotype to benefit from a targeted therapy, to indicate whether the drug has hit its molecular target, to determine whether the drug has been given in the optimal biologic dose, and to ascertain whether the tumor is responding.
In vivo molecular imaging is a form of in vivo assay. Such assays cannot provide the degree of genomic and proteomic information that can be obtained from in vitro assays on biopsied tissue or body fluids. However, in vivo imaging has at least three important advantages that complement in vitro tests. First, imaging provides spatially localized information over large volumes of tissue, whereas in vitro tests are usually performed on a very small volume of tissue. Second, in vivo imaging can give dynamic information by being obtained serially or continuously. In vitro assays provide information from a single point in time. Third, in vivo imaging depicts information from a tumor in its usual milieu or microenvironment. In vitro assays will reflect the changes in gene expression patterns that occur very quickly after tissue is removed by biopsy.
Increasingly, endpoints such as objective response, time-to-progression, disease-free survival and progression-free survival are used in drug trials, and imaging is a major component of such endpoints. Important among these tools are molecular imaging methods. Unlike anatomic imaging, molecular imaging methods display biochemical and physiologic abnormalities underlying the cancer rather than the structural consequences of these abnormalities.
Imaging-based biomarkers have many potential uses in all phases of the drug development process. Imaging end points can be employed to define, stratify, and enrich study groups, e.g., the use of F-18-labeled estradiol PET scans to identify patients for aromatase inhibitor trials. Second, some clinical imaging methods have potential to facilitate early clinical pharmacokinetic/pharmacodynamic assessments, e.g., dynamic-contrast-enhanced magnetic resonance imaging (DCE MRI) as a measure of the exposure-dependent effects of drugs targeting the tumor vasculature (e.g., anti-angiogenesis) occurring prior to tumor shrinkage. Third, imaging-based biomarkers have potential to replace or supplement histological analyses in clinical testing, e.g., several optical technologies, sometimes referred to collectively as "optical biopsy". Finally, as biomarkers of tumor response, imaging end-points can also serve as early surrogates of therapy success. For example, FDG-PET can provide an early indication of therapeutic response that correlates well with clinical outcome.

**12** INVITED

**Regulatory acceptance of novel endpoints in oncology trials**

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The European Medicines Agency (EMEA) has recently published a new guideline on the clinical development of new anticancer agents. This is a major revision of its former anticancer guideline adopted in 1996 and revised in 2001 and 2003, reflecting the drug development issues that are relevant for the new classes of anticancer drugs.
For non-cytotoxic drugs, the early stages of clinical drug development are more complex and have to be tailored according to the assumed pharmacology of the individual compound as defined in non-clinical studies. The assessment of biomarkers might be needed early in order to define dose and schedule. For the exploratory trials (phase II) of cytostatic agents, time to progression (TTP) more appropriately reflects the anti-tumour activity but the interpretation of TTP data without an internal control (i.e., a randomized study) can be problematic. Alternative endpoints may also be used to demonstrate antitumor activity, e.g., functional imaging and assessment of pharmacodynamic endpoints in the tumour. Concerning cytotoxic agents, objective response rate (ORR) remains a useful measure of activity.
For confirmatory trials (phase III), the primary endpoints of choice are progression-free survival (PFS), disease free survival (DFS) and overall survival (OS), regardless of the type of agent. For studies with PFS or DFS as primary endpoint, adherence to protocol-defined schedules for tumour assessments is essential. Independent review and confirmation of best tumour response and progression should generally be undertaken if PFS is the primary endpoint.
In patients with tumour-related symptoms at base line, symptom control, if related to anti-tumour effects may serve as primary endpoint in late line therapy studies, provided that the study can be conducted under proper double-blind conditions. Time to symptomatic tumour progression or tumour response-related activities, e.g. limb-saving surgery, may also be adequate primary measure of patient benefit. In double-blind studies and especially in the palliative setting, health-related quality of life using generally accepted instruments might be a valuable secondary endpoint. Tumour markers convincingly demonstrated to reflect tumour burden can be used, in combination with other measures of tumour burden, to define tumour response and progression, an example being multiple myeloma and the M-component. For new classes of compounds, however, it has to be demonstrated that the marker is a valid measure of tumour burden and that no bias in the assessment is introduced, e.g. through differential suppression of the tumour marker.

**13** INVITED

**Phase zero clinical trials in oncology: a new paradigm for early drug development?**

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The growth in number of new and novel targeted anticancer therapies in clinical development requires new paradigms to optimize the drug development process. Because many new agents have specific molecular targets, obtaining early proof of concept data in first in human clinical studies has grown in importance. Often diverse biochemical and molecular endpoint assessments are grafted onto conventional Phase I clinical trials that retain the traditional primary goals of defining toxicity profiles and determining the maximally tolerated dose. A new strategy, endorsed by the US FDA and other organizations, is to perform first in human proof of concept clinical trials called Phase Zero studies prior to conventional Phase I dose escalation studies. Although a uniform definition for Phase Zero trials has not been established, it frequently refers to low dose studies performed without any therapeutic intent. Such trials may be single or multidose studies conducted in normal volunteers or in cancer patients. Potential examples in oncology include microdosing of single or multiple agents for pharmacokinetic evaluation, or pharmacodynamic studies assessing novel biochemical or molecular biomarker endpoints. By definition, such trials would not include dosing to the maximally tolerated levels and therapeutic benefit would not be an endpoint. Such studies would be performed under a special exploratory Investigational New Drug (IND) application, which would require less extensive manufacturing and preclinical toxicity testing than a conventional IND. These guidelines may be particularly attractive for academic cancer researchers interested in developmental therapeutics. Potential disadvantages include the need to conduct conventional Phase I studies in later clinical trials and the ethical problem of using non-therapeutic drug doses in cancer patients. Other problems include the lack of ability to extrapolate microdose pharmacokinetic and pharmacodynamic findings to higher pharmacological doses. Examples of the possible incorporation of this strategy into comprehensive drug development programs in oncology will be discussed.