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Current Perspective

New science-based endpoints to accelerate oncology drug development

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Abstract

Although several new oncology drugs have reached the market, more than 80% of drugs for all indications entering clinical development do not get marketing approval, with many failing late in development often in Phase III trials, because of unexpected safety issues or difficulty determining efficacy, including confounded outcomes. These factors contribute to the high costs of oncology drug development and clearly show the need for faster, more cost-effective strategies for evaluating oncology drugs and better definition of patients who will benefit from treatment. Remarkable advances in the understanding of neoplastic progression at the cellular and molecular levels have spurred the discovery of molecularly targeted drugs. This progress along with advances in imaging and bioassay technologies are the basis for describing and evaluating new biomarker endpoints as well as for defining other biomarkers for identifying patient populations, potential toxicity, and providing evidence of drug effect and efficacy. Definitions and classifications of these biomarkers for use in oncology drug development are presented in this paper. Science-based and practical criteria for validating biomarkers have been developed including considerations of mechanistic plausibility, available methods and technology, and clinical feasibility. New promising tools for measuring biomarkers have also been developed and are based on genomics and proteomics, direct visualisation by microscopy (e.g., confocal microscopy and computer-assisted image analysis of cellular features), nanotechnologies, and direct and remote imaging (e.g., fluorescence endoscopy and anatomical, functional and molecular imaging techniques). The identification and evaluation of potential surrogate endpoints and other biomarkers require access to and analysis of large amounts of data, new technologies and extensive research resources. Further, there is a requirement for a convergence of research, regulatory and drug developer thinking – an effort that will not be accomplished by individual scientists or research institutions. Research collaborations are needed to foster development of these new endpoints and other biomarkers and, in the United States (US), include ongoing efforts among the Food and Drug Administration (FDA), National Cancer Institute (NCI), academia, and industry.

Keywords: Drug development; Oncology; Surrogate endpoint; Biomarker; Genomics; Proteomics; Functional imaging; Molecular imaging

1. Introduction

Over the past decade, new oncology drugs have been developed that prolong survival, induce remission, provide better quality of life in cancer patients, and promise to prevent cancers in populations at risk. Particularly noteworthy are molecularly targeted drugs such as the anti-Her2/*neu* antibody trastuzumab for treatment of ErbB2-expressing breast cancers [1], the aromatase inhibitor letrozole for adjuvant treatment of breast cancers [2], the kinase inhibitor imatinib mesylate for treatment of chronic myelogenous leukaemia and

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gastrointestinal stromal tumours [3], the proteasome inhibitor bortezomib for treatment of multiple myeloma [4], and epidermal growth factor receptor (EGFR) inhibitors, such as the small molecule gefitinib which is approved for treatment of lung cancers [5], and the antibody cetuximab which is approved for treatment of advanced colorectal cancer [6,7]. However, these drugs treat only a few cancers (hence, relatively few patients), and the resources (time, money and patients) required to bring them to market have been enormous, making the research and development effort prohibitive and the cost to patients potentially unbearable. The United States (US) Food and Drug Administration (FDA) has stated that more than 80% of drugs entering clinical development (i.e., as Investigational New Drugs) fail to get marketing approval, and the failure rate in Phase III trials is estimated at approximately 50% [8–11]. The cost of bringing a new drug to market from discovery through Phase III clinical trials is estimated at US $0.8–1.7 billion and requires 8–10 years [10]. These high development costs are translated into increasing costs to patients receiving the new drugs. For example, treating colorectal cancer with the recently approved anti-vascular endothelial growth factor antibody bevacizumab has been estimated at more than $40 000 ($4400 per month for 10 months) [12–14]. Moreover, despite its promise in treating cancer, it appears to have significant cardiotoxicity and may not be used in many patients who would otherwise benefit. These factors clearly show the need for faster, more cost-effective development of cancer therapeutics and reflect the need for better definition of patients who will benefit from treatment.

For cancer preventive drugs, the trend and need are similar. Promising drugs include the anti-oestrogen tamoxifen which has been approved by the FDA for reducing risk of breast cancer [15] and the cyclo-oxygenase-2 (COX-2) selective anti-inflammatory drug celecoxib which has been approved for treating colorectal adenomas in familial adenomatous polyposis (FAP) [16,17]. Besides the large investment in time and subjects required to demonstrate cancer preventive activity and clinical benefit in Phase III clinical trials, the long-term administration required for these drugs poses significant safety issues, even for drugs already evaluated for safety in and approved for other chronic use indications as tamoxifen and celecoxib both are for adjuvant treatment of breast cancers and treatment of inflammatory symptoms like those found in patients with arthritis, respectively. As a pointed example, another COX-2 selective inhibitor rofecoxib was recently withdrawn from the market based on an increased incidence of cardiovascular adverse events appearing in subjects enrolled in a study of preventive activity against colorectal adenomas (hence, against colorectal cancer) seen after only 18 months of treatment. Indeed, safety is potentially a more challenging issue than efficacy for cancer preventive drugs. Despite the large savings in life and morbidity that can be envisioned by preventing cancer and neoplastic progression, unexpected toxicities of long-term treatment could negate the expected benefit and could make the risks of developing a cancer preventive indication economically unfeasible. The exceptions to this caveat are the highly promising drugs already having well established markets for other indications, and known safety and dose-response profiles. Even such apparently well-characterised drugs may run into late stage development problems if the effects of long-term exposure have not been expected or analysed and optimal doses have not been defined, as they apparently were not for rofecoxib. Clearly, the use of biomarkers to define subjects at risk for toxicity is as important as the use of biomarkers to evaluate efficacy. In addition to characterising these specific features of the drug, the use of biomarkers to provide more robust quantification of a high-risk individual's probability for developing invasive disease if untreated (e.g., those with high-grade intraepithelial neoplasia (IEN) in any of a number of target organs [18] and those having highly penetrant germline lesions such as FAP or *BRCA1*) would tip the balance to favourable development of a drug, especially if alternative modes of effective treatment are not available or result in significant morbidity.

2. Why are development costs prohibitive? Well-defined measurable endpoints and patient populations are needed

The requirement for every new drug approval is demonstration of net clinical benefit, and so identification of the endpoints and settings that define clinical benefit is at the core of accelerating drug development. In fact, lack of clearly defined and measurable endpoints and populations benefiting from treatment have been cited by both the FDA and industry as the major factors in the rising costs and late-stage failures in drug development [8,9]. Remarkable advances in the understanding of neoplastic progression at the cellular and molecular levels have spurred the discovery of molecularly targeted drugs. This progress along with advances in imaging and bioassay technologies are the basis for describing and evaluating such new endpoints as well as for identifying patient populations. Recognition of the need for new definitions of clinical benefit has led to individual efforts by and collaborations among the FDA, the US National Cancer Institute (NCI), and international academic and pharmaceutical/biotechnology industry scientists to develop strategies and guidance addressing these definitions [9,18–26]. A critical aspect of this effort in the US has been the recent systematic deliberations in the oncology community on endpoints in specific clinical settings and results that describe clinical benefit in these settings. This effort involves the FDA, NCI, the Ameri-

can Society of Clinical Oncology and the American Association of Cancer Research. To date, the treatment of cancer precursors (IEN) has been considered in various cancer target organs [18], particularly the prevention of colorectal adenomas as a surrogate for prevention of colorectal cancer [27,21]. The scientists have also considered disease-free survival (DFS) as an endpoint in trials of lung cancer therapy, DFS and time to progression (TTP) as endpoints for treatments of colorectal cancer, and prostate-specific antigen (PSA)-derived and imaging-derived endpoints in prostate cancer. The following provides perspectives on the deliberations of these scientists and the recommendations going forward.

3. What are surrogate endpoint biomarkers? Can use of these and other biomarkers address the need for better endpoints and well-defined patient populations?

For cancer therapeutics, overall survival (OS) has long been considered the standard endpoint for determining clinical benefit, and reliance on OS is a major contributor to the rising costs of oncology drug development. Since it is not disease, drug or patient specific, OS results in requirements for large, long trials with potentially confounded outcomes. Likewise, time and money are inadequate for developing cancer preventive drugs against cancer incidence as the standard measure of clinical benefit. Even in well-defined high-risk populations, cancer incidence is usually low, latency is long, and so trials require large cohorts and many years to complete. Thus, the oncology drug development community has recently been focusing on clinical trial strategies using biomarker endpoints based on strong scientific rationales as surrogates for survival and cancer incidence, with the expectation that these biomarkers potentially will provide definitive estimates of clinical benefit in shorter timeframes.

The regulator's definition of a surrogate endpoint biomarker 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 on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint'' [28].

Recent thinking by regulators and clinical trialists has expanded the description of surrogate endpoint and other relevant biomarkers to reflect their scientific bases and utility in early drug development, cohort selection, and patient management, as well as in determining clinical benefit. Note that the resulting categories of biomarkers, as described following, are not mutually exclusive – a given biomarker may belong to different categories depending upon the specific setting in which it is used.

3.1. Clinical correlates

Clinical correlates are those endpoint biomarkers currently useful for obtaining drug approvals (Table 1); historical data has shown their relevance to clinical benefit [29]. These are tumour response (objective response (OR) and response rate (RR)), DFS, PFS, and TTP; quality of life (QOL) measurements may also be used to substantiate drug approvals. However, none of these are ideal surrogate endpoint biomarkers yet, since all require measurement of the treated cancer, and these measurements are difficult to make accurately and reproducibly because of the heterogeneity and multifocality of the disease. Anatomical imaging (computerised tomography (CT) and magnetic resonance imaging (MRI)) is used most frequently, but even with the advent of standardised criteria for interpretation (the World Health Organisation criteria [30] and response evaluation criteria in solid tumours (RECIST) [31]), imaging results are often inadequate for evaluating early or subtle changes signalling disease progression, or characterising the effects of molecularly targeted drugs that do not necessarily shrink tumours. As described below, new technology, particularly functional and molecular imaging, may soon improve the reliability of these endpoints.

3.2. Prognostic biomarkers

Prognostic biomarkers are also correlated with clinical outcome (Table 2). Examples are biological progression biomarkers and risk biomarkers.

Biological progression markers, as measures of tumour burden, are often modulated by drug intervention, but may not be on the causal pathway or implicated in mechanisms of neoplastic progression. They are cellular proteins associated with tumour appearance or progression, e.g., carcinoembryonic antigen (CEA), ∀-fetoprotein (∀FP), prostate-specific antigen (PSA), CA-125 [32]. Often these biomarkers are used to monitor the effects of chemotherapy or other treatment. They have high potential as surrogate endpoint biomarkers, since they are typically easily measured in target tissue or in blood, and numerous studies show their correlation to cancer biology [32,33]. The FDA has not based marketing approval solely on the basis of changes in biological progression markers, although they have been accepted as part of composite endpoints – for example, CA-125 has been included with CT measurements in a composite endpoint for disease progression in patients with advanced refractory ovarian cancer [22,29,34].

Neoplastic progression may not be a linear function of biomarker concentration, but may be described by more complex relationships. Thus, the use of biological progression markers as surrogate endpoint biomarkers may depend on careful modelling to develop algorithms

Table 1
Clinical correlates: surrogate endpoint biomarkers used for evaluation of oncologic drug and biological products[a,b]

Surrogate Endpoint	Definition
OR and RR	Disappearance of the cancer lesion and its manifestations, encompassing CR and PR Based on tumour measurements from anatomical imaging for solid tumours Response criteria (e.g., % reduction in tumour size and duration of response) are defined for CR and PR and are disease-dependent RR is the likelihood that a tumour will either shrink or disappear after a specific treatment based on observations in a significant group of patients (e.g., in a clinical trial)
TTP	Time from randomisation to documented progressive disease Currently based on tumour measurements from anatomical imaging (and not on biological progression markers)
DFS or time to recurrence	Mathematical curve estimating the percentage (%) of patients who will both survive *and* be without evidence of disease at various periods of time after initial treatment DFS is basis for drug approval for cancers with high rates of recurrence or where DFS correlates strongly to overall survival
PFS	Mathematical curve estimating the percentage (%) of patients who will both survive *and* be without evidence of disease progression at various periods of time after initial treatment
QOL, symptom improvement, composite endpoints	Relief of tumour-related symptoms (e.g., pain, morbidity) May be used alone or in conjunction with OR and TTP to support drug approvals
IEN	IEN are precancers that are treated by drug therapy or surgical removal Regression of existing or prevention of new IEN have been considered for supporting approval of drugs to prevent cancers or to treat precancers

[a] See text for discussion and references.
[b] Abbreviations: CR, complete response; DFS, disease-free survival; IEN, intraepithelial neoplasia; OR, objective response; PFS, progression-free survival; PR, partial response; QOL, quality of life; RR, response rate; TTP, time to progression.

relating their expression to clinical endpoints. To this end, significant progress has been made in defining measures of CA-125 response as a surrogate endpoint biomarker measuring DFS from ovarian tumours [22,35,36]. Similarly, post-treatment PSA doubling time (PSA-DT) appears to predict survival in prostate cancer patients with rising PSA following local treatment, and PSA velocity appears to be a very good measure of tumour progression [23,37,38].

Risk biomarkers are prognostic markers that are not often modulated by drug intervention, but are implicated in mechanisms of causality or neoplastic progression. They describe risks of cancer or cancer progression and include carcinogen exposure, genetic predisposition [39–41], pharmacogenomic parameters [41], previous disease or precursor lesions [18,42,43], and multifactorial risk models (such as the Gail model for breast cancer risk) [44]. Risk biomarkers are commonly used in oncology drug development to identify clinical cohorts for intervention (e.g., women with high Gail risk scores) and those study populations likely to be responsive to a given drug treatment – e.g., patients with tumours overexpressing HER-2/*neu* for successful intervention with trastuzumab [45,46]. Molecular diagnosis, such as the signature gene expression patterns found by Staudt that identify patients with B-cell lymphoma who are likely to respond to standard therapy [47], represents another type of risk biomarker potentially useful in describing populations in which a therapy may be successful.

3.3. Predictive biomarkers

Predictive biomarkers measure the effects of drug or other intervention, are pharmacodynamic biomarkers and include cellular, histopathological, and imaging biomarkers when they are modulated by treatment intervention (Table 2).

Drug effect biomarkers are biological effects produced by a drug that may or may not be directly related to the neoplastic process, but that correlate to biological and clinical effects on cancer. Some of these biomarkers are measured in blood, saliva or urine; many are not meaningful unless measured in the drug's target tissue(s).While some of these biomarkers may be applied to many mechanistically distinct drug classes, most reflect anti-cancer activity of only a few classes. Quite often, these biomarkers are measures of reduced expression or activity of a molecular target in a mechanism-based therapy, for example, EGFR tyrosine kinase activity of EGFR inhibitors. Predictive biomarkers of drug-specific toxicities, such as induction of cytochromes P-450 are also important for early drug development and patient safety during treatment as are those of drug resistance, such as MDR-1 [41,48]. Although drug effect biomarkers are extremely useful endpoints for preclinical and early clinical pharmacology studies and in correlating cancer preventive and therapeutic activity to drug administration, they are not usually adequate surrogate endpoints. Nevertheless,

Table 2
Prognostic and predictive biomarkers used in oncology drug development[a,b]

Name	Definition	Examples
Prognostic biomarkers		
Biological progression markers	Measurements of cellular proteins associated with tumour appearance or progression Measures of tumour burden	CEA, ∀FP, CA-125 (Rustin response criteria), hCG, PSA (e.g., PSA-DT)
Risk markers	Describe risks of cancer occurrence or cancer progression	Somatic mutation, amplification and overexpression of oncogenes and tumour suppressor genes (e.g., *PTEN*, *BCR-ABL*, HER-2/*neu*, *RAS*, *AKT*) Aneuploidy Genetic predisposition (e.g., *APC*, *BRCA1/2*, *MLH1*, *MSH2*, Li-Fraumeni syndrome, ataxia telangiectasia) Genetic polymorphisms (e.g., *CYP1A1*, *GSTM1*, *GSTP1*, *SRD5A2*) DNA methylation Environmental and lifestyle (e.g., HPV or HBV infection, tobacco use) Multifactorial risk model (e.g., Gail model for breast cancer risk)
Predictive biomarkers		
Drug effect/pharmacodynamic markers	Biological effects produced by a drug that may or may not be directly related to neoplastic process	Effect on molecular target (e.g., EGFR inhibition, RAS farnesylation inhibition) Induction of enzyme activity relevant to drug toxicity (e.g., *CYP1A1*, *CYP1A2*) Functional (and molecular) imaging of drug interaction at target tissue
Cellular, histopathological, and imaging markers	Biological effects occurring during neoplastic progression (causally related to cancer)	Quantitative pathology or cytology of cancers, precancers, high-risk tissue Anatomical imaging (e.g., MRI, CT) Functional imaging (e.g., FDG-PET) Genomic and proteomic expression profiles Proliferation biomarkers (e.g., PCNA, Ki-67) Apoptosis biomarkers (e.g., BCL-2 expression, TUNEL) Differentiation biomarkers (e.g., cytokeratins)

[a] See text for references.
[b] Abbreviations: APC, adenomatous polyposis coli; CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; CT, computerised tomography; CYP, cytochrome P450; EGFR, epidermal growth factor receptor; FDG-PET, F-18-deoxyglucose positron emission tomography; ∀FP, ∀-fetoprotein; GST, glutathione-*S*-transferase; HBV, Hepatitis B virus; hCG, human chorionic gonadotropin; HPV, human papilloma virus; MRI, magnetic resonance imaging; PCNA, proliferating cell nuclear antigen; PSA, prostate specific antigen; PSA-DT, PSA doubling time; SRD5A2, 5α-steroid reductase; TUNEL, terminal deoxynucleotidyl transferase biotin-dUTP nick end labelling (apoptosis assay).

newer techniques for tissue-based pharmacodynamic measurements, including molecular and functional imaging will allow the development of biomarkers that are better models of drug effect and that will be very useful in preclinical and early clinical phases of oncological drug development – for example, to select the drug dose and dose regimen, duration of treatment, identify possible toxicities, and to compare potencies of several drug candidates [41,48]. Moreover, these pharmacodynamic biomarkers will facilitate selection of patient populations likely to benefit from a given treatment.

Cellular, histopathological, and imaging biomarkers are biological alterations occurring during neoplastic progression [18,49,50] These biomarkers may be histological changes in tissue measured by imaging techniques; cellular biomarkers, such as those of increased proliferation/reduced apoptosis, altered differentiation, gene mutations; or altered gene expression (including expression patterns observed by genomic and proteomic analysis). If modulated by drug treatment, these biomarkers have high potential as surrogate endpoints in early cancer drug development, and with validation against clinical correlates, as endpoints for pivotal clinical studies. As noted above, these biomarkers are also risk markers for disease incidence and progression.

4. What are the criteria for a good surrogate endpoint biomarker? Validation and feasibility

Drug development scientists have formulated science-based and practical criteria for validating biomarkers as

Table 3
Summary criteria for a surrogate endpoint biomarker[a]

Fits biological mechanism(s) of neoplastic progression
• Specific for cancer or precancer (e.g., differential expression, level or activity of biomarker in normal *vs.* at-risk and diseased tissue)
• Frequently found during cancer development, at least for an identifiable cohort (e.g., those with specific genetic lesion or other risk marker)
• Associated with clinical risk identification or diagnosis/prognosis
• Modulation correlates with decreased neoplastic progression and/or clinical benefit
• Is responsive to treatment (a dose-related response may be anticipated)
Biomarker and its assay provide acceptable sensitivity, specificity, and accuracy
• Intra- and interobserver variability is minimal
• Assay is standardised and validated using archival clinical samples, preclinical models, etc.
• Assay is adequately quantitative (e.g., statistically significant difference between treatment and control groups can be demonstrated)
• Biomarker stability can be maintained during preparation, storage and assay
Biomarker measurement is clinically feasible
• Measurement can be obtained by non-invasive or minimally invasive techniques
• Possibility of sampling bias is minimal or is taken into account by sampling procedure
• Serial monitoring is possible
• Biomarker has short latency compared with clinical neoplastic progression

[a] See text for discussion and references.

surrogate endpoints, e.g., [19,33,49,51,52]; these criteria are summarised in Table 3 and include considerations of mechanistic plausibility, available methods and technology, and clinical feasibility.

As suggested by these criteria, ideal surrogate endpoints look and act like the true clinical endpoint they represent. *Clinical correlates*, which are direct measurements of the tumour are potentially good surrogate endpoints on this basis. Single molecular and cellular biomarkers are more likely to fail as surrogate endpoints in that they may not adequately describe a cancer, but represent isolated events that may or may not be on the causal pathway or otherwise specifically associated with neoplastic progression. However, because they reflect the biology of cells and tissue that are cancerous or are undergoing neoplastic progression, complex panels of cellular markers, such as those measured by genomics and proteomics, are expected to have high potential utility as surrogate endpoints. Similarly, biomarker endpoints derived from individual parameters, but based on careful characterisation of their pattern of expression during neoplastic progression, are also very promising. An example, already cited above, is PSA kinetic parameters, such as the PSA-doubling time (PSA-DT) [23,37,38].

The heterogeneity of cancers adds more complexity to the definition of valid surrogate endpoints. For example, anatomical imaging and other simple measures of size may not be adequate for capturing changes occurring in different parts of a single tumour or among multiple metastatic foci. Functional and molecular imaging may improve this situation, allowing different processes in different parts of the tumour or different tumours to be visualised, as well as guiding sampling for further analysis by, for example, microarray analysis.

Several rigorous mathematical definitions of valid surrogate endpoints have incorporated these considerations, with the primary concept for validation being attributable portion – that is, the higher the percentage of the disease outcome that can be attributed to the biomarker, the better this biomarker is expected to perform as a surrogate endpoint [53,54] The recent work by D'Amico and his colleagues on PSA-DT cited above shows that, even in the best cases, validation by attributable portion is only nearly possible. Nonetheless, every measurement of a biomarker or clinical endpoint will have error that abrogates the ability to fully attribute the cancer to the surrogate endpoint. Problems with the 'gold standard' clinical endpoint, OS, are noted above. Practically, surrogates should not be held to higher medical standards than this clinical endpoint as a measure of clinical benefit.

New technologies and specific assays that adequately detect biomarkers are also important [49,55,56]. It is highly desirable to measure modulation of biomarkers quantitatively as the difference between the biomarker value at the end of treatment (and during treatment) and baseline. Thus, baseline biopsies or other baseline measurements are critical; the capability for serial sampling is also important. Many biomarker assays are complex because of multiple steps, stringent specifications for obtaining and processing samples and/or large numbers of data-points (e.g., DNA microarray and proteomic analyses, quantitative pathology). Training, data calibration or normalisation, and adjudication procedures (particularly for pathology readings) may be required to minimise intra- and inter-observer variability. Diligence in obtaining such high quality data is critical to improve the efficiency and cost-effectiveness of biomarker studies. For example, quality standards for technical validation of clinical laboratory and pathology assays need to be applied to assays for cancer biomarkers [41,57–59]. In some cases, these assays can potentially be standardised and validated retrospectively

using archival clinical samples or prospectively using animal or other preclinical models [41,49]. Of equal importance, demographic data on archival tissue samples are often insufficient for reconstructing the clinical status of the patients. The need for standardisation has been recognised and progress has been made to develop a national biospecimen network [26] in the US that will require drug developers (sponsors and investigators) to agree on a set of defining data for tissue samples that will be banked for future research. These efforts will be invaluable for the future validation of surrogate endpoints and other biomarkers.

Ultimately, biomarker assay parameters will be used to rigorously define surrogate endpoints. The guidelines developed by the working group on RECIST for measuring tumour response in clinical trials of chemotherapeutic drugs are an example of defining and developing other surrogate endpoint biomarker assessments [31]. These guidelines include definitions of measurable and non-measurable tumours, units of measurement, applicability of various methods of measurement (particularly, CT and MRI), criteria for study populations for trials with tumour response endpoints, baseline and endpoint evaluations (both frequency and measurements done). However, the applicability of the current RECIST criteria is controversial, largely because the criteria are based on one-dimensional measurements of tumours and somewhat arbitrary descriptions of significant tumour masses. It is expected that these criteria will be revised in the future to encompass three-dimensional tumour measurements, and that functional and molecular imaging techniques will allow better identification of tumour masses relevant to neoplastic progression (and regression).

5. How are biomarkers measured? Are biomarker measurements clinically feasible? What new tools are available?

Feasibility is another important aspect of developing and defining surrogate endpoint biomarkers [41,49,56]. In this regard, ideal biomarkers are easily accessible and are amenable to serial monitoring – i.e., they can be obtained by non-invasive or minimally-invasive techniques and have limited potential for sampling error (a particular problem in tissues that are not directly visualised). Often direct sampling of involved tissue is not satisfactory or practical, e.g., sampling is difficult, requires repeated biopsy with possible associated morbidity, and/or interferes with serial monitoring by depleting available tissue (without being curative) or by introducing new biology (such as inflammation). In these cases, remote sampling can be achieved by using surrogate tissues (e.g., easily accessed oral epithelial tissue, which has been used to evaluate cancer risk biomarkers for other parts of the upper aerodigestive tract [60]), by sampling circulating cells (e.g., tumour epithelial cells which have been used to characterise breast and prostate cancers [61,62]; and circulating endothelial progenitor cells, which appear to be a biomarker for solid tumour angiogenesis [63,64]), or by using functional and molecular imaging and nanotechnology-based methodologies which are highly promising as minimally invasive measurements with good sampling potential.

Some of the most promising tools for measuring biomarkers are based on genomics and proteomics. For example, many different commercial gene chip (DNA microarray) packages are now made, and the capability for making customised gene chips is widely available. Besides evaluating changes in tissues undergoing neoplastic progression, microarrays may be designed to evaluate subjects at risk, e.g., those carrying specific germline mutations and genetic polymorphisms, and those likely to respond to a given therapy. Staudt's elegant work to identify patients with B-cell lymphoma who are likely responders to standard therapy cited above [47] and applications in breast [65–68] are among many relevant examples of applying microarray-derived biomarkers in clinical evaluation. Similarly to gene microarray analysis, the development of protein expression profiles (proteomics), to evaluate risk/prognosis, cancer stage, and treatment effects also shows high promise [48]. Most proteomics assays involve mass spectrometer analysis of protein patterns (e.g., matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (MALDI-TOF) and surface-enhanced laser desorption/ionisation mass spectrometry (SELDI-TOF) measurements). Developing reliable endpoints based on these techniques is the subject of intensive applied research efforts. Sampling, instrument calibration, and protein assay conditions are among the parameters that are being addressed. Many elegant techniques for improving sampling have been developed to allow exploration of whole tumours and tissues surrounding tumours, particularly in organs not easily visualised such as prostate and ovary. One example is laser microdissection which has been used in creating proteome profiles of prostate cancers [69]. A joint NCI-FDA research project has been dedicated to evaluating proteomic patterns in major cancers and developing these assay methods. Ovarian, breast and prostate cancers have been the initial subjects of this collaboration [70–78].

Improvements in tools for tissue visualisation include confocal microscopy [79], digital mammography [80], lung imaging fluorescence endoscopy (LIFE) for evaluating bronchial tissue [18], and the magnifying endoscope for colorectal monitoring [81]. Tools such as the "camera in a capsule" which has already been used in a clinical trial setting for monitoring gastrointestinal tissue [82]; and some of the promising nanotechnologies such as nanotubes, nanowires and microcantilevers [26] that will allow *in situ* detection of genomic and

proteomic changes in cells will also be highly useful for adequate visualisation and monitoring of tissue. Further, higher resolution than is achieved in normal anatomical imaging of tumours may be needed to detect diffuse lesions or microlesions. Although applied to date only in animal studies, near infrared fluorescence (NIRF) imaging may hold promise for detecting such lesions [83]. Similarly computer-assisted image analysis provides quantitative assessments of multiple histopathological features at the cellular level [18]. Phenotypic biomarkers of neoplastic progression can be measured by anatomical and functional imaging techniques. For example, functional imaging by F-18-deoxyglucose positron emission tomography (FDG-PET) is particularly promising because it is an accepted and widely used clinical imaging tool in cancer [84–86]. Its utility is based on its ability to track the dependence of cancer cell function on glycolysis, and it is routinely used for staging, restaging, and evaluating the progression of certain cancers. It is also used for monitoring therapeutic response (e.g., in locally advanced and metastatic breast cancers), and the body of available data show that indications of therapeutic response by FDG-PET imaging are correlated with outcomes in several cancers.

6. What are the prospects for validating a surrogate endpoint?

It is apparent from published guidelines that validation of a surrogate biomarker for clinical benefit must of necessity be defined in probabilistic terms, since validation in absolute terms (per the Prentice criteria [53]) is most often not feasible. However, it is quite possible and beneficial to ensure that the putative surrogate endpoint biomarker meets scientific and medical criteria reasonably expected to represent clinical benefit. The most promising leads for potential surrogate biomarkers are provided by clinical data obtained in trials with known outcomes, observational epidemiological data from treated patients, preclinical efficacy studies correlating biomarkers with cancer outcomes and, finally, a strong mechanistic rationale relating the surrogate biomarker to clinical benefit.

Therefore, there are many strategies to move forward in acquiring data for validation of candidate surrogate biomarkers. FDA has strongly encouraged the incorporation of surrogate endpoint evaluation into the overall clinical development plan for a new oncological drug or indication [87]. One likely successful strategy is the use of a surrogate endpoint in interim analysis of a pivotal study. Another appealing strategy for evaluation of surrogate endpoints has been proposed – the re-analysis of drugs of known clinical benefit in prospective clinical trials or retrospective archival tissue studies to evaluate their effects on potential surrogate endpoint biomarkers using new technologies [25]. A strong mechanistic rationale is another promising approach. For example, the compelling rationale for colorectal adenomas (colon IEN) as a surrogate endpoint for colorectal cancer is based on histopathology and elucidation of genetic progression in the adenoma–carcinoma sequence, as well as clinical studies showing that removal of adenomas lowered colorectal cancer incidence [21,49].

7. The future of science-based surrogate endpoints in oncology drug development

The need is clear for developing more efficient and effective development paths for oncology drugs, and the increasing knowledge of the molecular, cellular and tissue processes that characterise neoplastic progression suggest that surrogate endpoints provide opportunities to address this need. It is apparent from the foregoing discussion that the identification and evaluation of potential surrogate endpoints require access to and analysis of large amounts of data, new technologies and extensive research resources. Further, there is a requirement for convergence of research, regulatory and drug developers thinking – an effort that will not be accomplished by individual scientists or research institutions. Research collaborations are needed to foster the development of these new endpoints. Examples of on-going efforts in this regard among the FDA, NCI, academic oncologists, and the pharmaceutical industry were cited earlier in this paper. Other such efforts exist and provide the basis for repositories to facilitate access to both novel technologies as they become available (e.g., genomic, proteomic, functional and molecular imaging technologies, nanotechnologies.) and clinical trial samples (e.g., serum, biopsy tissue, DNA, imaging data, etc.). These efforts could leverage existing technology, clinical networks, and translational research programmes. The NCI supports several programmes that contribute [26]. For example, the NCI's Specialized Programs of Research Excellence (SPORE) programme has fostered multidisciplinary teams to address biomarker identification and validation. The NCI's Cancer Bioinformatics Informatics Grid (caBIG) project is creating a bioinformatics system to aid in the collection and sharing of key data elements (e.g., outcome, demographic, etc.) across cancer research institutes. Tissue banks and other real or virtual tissue repositories are being developed under specific NCI initiatives and under collaborative physician networks (e.g., Oncology Cooperative Groups). Finally, the repositories could also draw from other successful local, national, and international collaborations that support translational research and biomarker development, such as those of the European Organisa-

tion for Research and Treatment of Cancer (EORTC) and the UK's National Cancer Research Institute [25].

The extensive resources required for current drug development efforts have been discussed. Science-based biomarkers used to select patients most likely to benefit (potential responders and those at high risk for neoplastic progression), identify safety risks, and predict efficacy in preclinical and early clinical development have the potential for significantly reducing the required resources and time to drug approvals. The FDA has estimated that 10% improvement in predicting toxicity or efficacy prior to Phase III could save the US $100 million in development costs [9,10]. The relatively large effect of this small improvement is indicative of the high promise of surrogate endpoints and other biomarkers in accelerating cancer drug development.

Conflict of interest statement

None declared.

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