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Qualification of imaging biomarkers for oncology drug development

John C. Waterton [a,c,*], Liisa Pylkkanen [b,c]

[a] *AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*
[b] *EORTC Headquarters, Avenue E. Mounier 83/11, 1200 Brussels, Belgium*

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Abstract Although many imaging biomarkers have been described for cancer research, few are sufficiently robust, reliable and well-characterised to be used as routine tools in clinical cancer research. In particular, biomarkers which show that investigational therapies have reduced tumour cell proliferation, or induced necrotic or apoptotic cell death are not commonly used to support decision-making in drug development, even though such pharmacodynamic effects are common goals of many classes of investigational drugs. Moreover we lack well-qualified biomarkers of propensity to metastasise. The qualification and technical validation of imaging biomarkers poses unique challenges not always encountered when validating biospecimen biomarkers. These include standardisation of acquisition and analysis, imaging-pathology correlation, cross-sectional clinical–biomarker correlations and correlation with outcome. Such work is ideally suited to precompetitive research and public–private partnerships, and this has been recognised within the Innovative Medicines Initiative (IMI), a Joint Undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations, which has initiated projects in the areas of drug safety, drug efficacy, knowledge management and training.

1. Biomarkers in oncology drug development

Recent developments and discoveries in cancer biology have substantially increased our understanding of cancer at the molecular and cellular levels. The challenge for drug-developers is not only to translate this knowledge into safe and effective therapies for cancer patients, but to do so in a rapid and cost-effective way.

There is a growing need to modernise the drug development process by incorporating new techniques that can predict the safety and efficacy of new drugs better, quicker and at lower cost. One tool is the use of biomarkers, which are of immense importance in oncology drug development. While the ultimate goal for a drug developer is always to show the benefit of the drug in

* *Corresponding author:* Tel.: +44 (0) 1625 513633.
E-mail address: john.waterton@astrazeneca.com (J.C. Waterton).
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clinical end-points (i.e. how a patient survives, feels and functions), most oncology drug development would be impossible without biomarkers. Following Atkinson et al.,[1] a biomarker is, in contradistinction to a clinical end-point, 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'. Using this inclusive definition of biomarkers, even very well established measurements, such as objective tumour response,[2] are properly described as biomarkers, not clinical end-points. Biomarkers can be used to predict response to specific therapies, predict response regardless of therapy, or to monitor response once a therapy has begun.

The biomarkers available to the drug developer fall into two broad technological categories. Firstly, there are molecular markers, which are obtained by removing a sample from a patient, and detecting an analyte, usually remotely from the patient. Examples of these *biospecimen* biomarkers are genetic, genomic and protein analytes detected e.g. from biofluids or tissue samples. Biomarker technologies in the second category remove no material from the patient, but rather detect and analyse an electromagnetic or acoustic *biosignal* emitted by the patient. This class includes electrophysiological and imaging biomarkers (IBs). IBs have unique benefits, but raise unique scientific, technical and regulatory challenges not always encountered with molecular markers.

Biomarkers are essential also in accelerating the identification and adoption of new therapies, but at present there are many barriers for their use in drug development and clinical practice. The AACR-FDA-NCI Cancer Biomarkers Collaborative consensus focused mainly on biospecimen rather than biosignal/imaging biomarkers, but identified critical areas in their recommendations[3] to advance biomarker development in cancer drug development, including standardisation and harmonisation, collaboration and data sharing, regulations, stakeholder education and communication and science policy, which are equally relevant to imaging. In this report we discuss the opportunity to introduce imaging biomarkers (IBs) which show that investigational therapies have reduced tumour cell proliferation, or induced necrotic or apoptotic cell death, together with qualification and technical validation in the context of imaging, the need for standardisation of acquisition and analysis, imaging-pathology correlation, cross-sectional clinical–biomarker correlations and correlation with outcome.

2. Benefits and challenges of imaging biomarkers

IBs exhibit important attributes not often shared by biospecimen biomarkers, in that they can interrogate a large extent (or even all) of the pathological tissue in the body, and also normal tissues, in a single, relatively non-invasive, examination; they can promptly detect small and early focal responses which may predict subsequent benefit or harm and they can often be followed up frequently. However the use of imaging measurements as biomarkers also raises challenges not commonly encountered using biospecimen biomarkers. With biospecimen biomarkers, a defined analyte is commonly quantitated using an *in vitro* diagnostic device, a process quite separate from collection of the sample from the patient. With imaging, however, the quality and validity of the imaging measurement as a biomarker often depends crucially on the use of a diagnostic imaging device, in the presence of the patient, in a manner for which the device (a) was not designed, (b) has not received regulatory approval and (c) is unfamiliar to the user in the trial site. Moreover, for many IBs, the identification of the 'objectively measured characteristic[1]' with a quantifiable concentration of a specified analyte, may be quite impossible.

As molecular biology is leading to new treatment options with reduced normal tissue toxicity, imaging should have a role in objectively evaluating new treatments. New imaging procedures, however, need to be characterised for their effectiveness under realistic clinical trial conditions to ensure that they can reliably identify the best drug at the optimal dose for the right patient group.

3. Current imaging biomarkers and unmet needs

Imaging (and other) biomarkers can be used to predict prognosis; to personalise, i.e. to predict which treatment is optimal for each patient; to monitor treatment in order to detect when change is necessary and to determine whether drugs, doses and schedules elicit a desired or undesired biological effect in certain patients (Box 1).

BOX 1: Biomarker Inference

Consider observations made at three time-points, t:

$t = b$ (baseline)
$t = f$ (follow-up)
optionally $t = i$ (interim: $f>i>b$).

C_t is some clinical measurement of a patient's quality of life: how s/he feels or functions, or perhaps whether s/he has survived, made at time t. ΔC_i is the change in the clinical measurement between b and i.

B_t is a biomarker measurement made at time t. ΔB_i is the change in the biomarker measurement between b and i.

M_1, M_2 are medical interventions[i]:
M_1 is initiated later than b but earlier than i or f
M_2 is introduced or adjusted following M_1, and is initiated later than i but earlier than f

$F|(p)$ is a forecast of C_f, made given prior information p

E is the absolute forecast error: $E|(p) = \left| C_f - F|(p) \right|$

We can identify four categories of Biomarker Inference:

Inference	Formal definition	Representative Imaging Biomarkers (examples)
prognostic[ii]	$E\|(C_b, B_b) < E\|(C_b)$	TNM stage (CT, MRI etc.)
predictive	$E\|(C_b, B_b, M_1) < E\|(C_b, M_1)$	Radiolabelled antibody biodistribution (SPECT) TNM stage (CT, MRI etc.)[iii]
monitoring	$E\|(\Delta C_i, \Delta B_i, M_1, M_2) < E\|(\Delta C_i, M_1, M_2)$	Cardiotoxicity (echocardiography) Recurrence (FDG PET SUV)
response	$E\|(\Delta C_i, \Delta B_i, M_1) < E\|(\Delta C_i, M_1)$	Tumour response, PFS, (CT, MRI RECIST) Warburg effect (FDG PET SUV) Perfusion / permeability (DCEMRI k^{trans})

Abbreviations: TNM, Tumour-Node-Metastasis staging; CT, X-ray computed tomography; MRI, Magnetic Resonance Imaging; SPECT, Single Photon Emission Computed Tomography (also scintigraphy); FDG, fludeoxyglucose; PET, Positron Emission Tomography; SUV, Standardised Uptake Value; RECIST, Response Evaluation Criteria in Solid Tumours; DCEMRI, Dynamic Contrast-Enhanced MRI; k^{trans}, transfer coefficient for contrast agent into tumour.

[i] e.g. drug/dose given, altered or withdrawn; surgery; radiotherapy; active surveillance; palliative care.
[ii] Diagnostic biomarkers are, with rare exceptions such as diagnosis post-mortem, generally also prognostic.
[iii] Many anticancer drugs have regulatory approval for treatment of specified cancers with specific TNM stage: logically, therefore, TNM is a predictive biomarker derived largely or entirely from imaging

Indeed some of the biomarkers exemplified in Box 1 are so familiar that they are sometimes not thought of as biomarkers at all. Unfortunately, though, in this era of anti-cancer therapies targeted against Hanahan and Weinberg's 'eleven hallmarks of cancer[4]', our palette of reasonably well understood IBs has major gaps. For

anti-angiogenic or anti-vascular approaches, the drug developer is reasonably well furnished with useful biomarkers utilising magnetic resonance imaging (MRI),[5,6] computed tomography (CT), ultrasound or positron emission tomography (PET). For drugs affecting the deregulated cellular energetics of the Warburg effect, PET using [^{18}F]-2-fluoro-2-deoxy-D-glucose (INN: fludeoxyglucose F 18; abbreviation: FDG[7]) offers an obvious assessment. However the drug developer is poorly served by IBs for drugs which are intended to elicit an antiproliferative or pro-apoptotic effect or to cause tumour cells to die. Nor do we have good markers for activation of invasion and appearance of metastasis before these events become macroscopically evident. Naturally most effective classical anti-cancer drugs, such as chemotherapeutic agents should reduce the tumour size, or at least prevent progression, and drug developers have good tools to measure this in Phase III studies using conventional morphologic[2] CT or MRI measurements. These conventional radiological measurements usually need quite large patient numbers followed for several cycles of therapy and are unsuitable for early drug development phase when the drug developer needs pharmacodynamic measurements to help establish dose, schedule, patient population and perhaps identify suitable candidates for drug combinations.

In comparison to classical chemotherapeutic agents, the response evaluation after e.g. novel targeted therapies is more complex, as targeted agents are often more cytostatic than cytotoxic, and response evaluation with conventional radiological measurements is difficult; in some occasions the measurable cancer lesions may even grow in size (e.g. due to necrosis), while the patient is responding to the therapy. Fortunately ingenious imaging scientists have devised a wide variety of tracers, contrast agents, imaging devices and analysis algorithms to help fill the gaps and provide an armamentarium of IBs to serve the full range of targeted therapies envisaged by cancer drug developers. Imaging biomarkers have distinct advantages over those that require a biopsy sample in that they are 'non-invasive' and can be monitored longitudinally at multiple time points in the same patient. However, very few IBs are widely considered adequate to provide unambiguous support for decisions to stop or proceed in drug development projects: in other words they are not qualified for this purpose.

4. A roadmap for qualifying imaging biomarkers

It may be helpful to distinguish the terms 'Qualification' and 'Validation'. Biomarker Qualification has been described as a 'graded, fit-for-purpose evidentiary process linking a biomarker with biological processes and clinical end-points, dependent on the intended application[8]'. Qualification is thus the assembly of data to aid the interpretation of biomarker measurements, and support decisions which rely on those interpretations. These decisions can include internal business decisions by drug developers (e.g. 'does this molecule sufficiently demonstrate the anticipated biological activity at a tolerated dose to support further Phase II/III trials?'); regulatory decisions ('will the public health benefits from marketing of this drug in this indication outweigh any harms?'); or patient care decisions ('should this patient receive this treatment or that?'). Technical validation, however, merely assesses the technical performance characteristics of the devices and procedures for measuring the biomarker. It would be quite possible, therefore, to have a biomarker which could be measured reliably (technically valid) anywhere in the world, but was completely uninterpretable (not qualified); equally possible would be a well-qualified biomarker whose interpretation and clinical implications were completely secure, but which could only be measured reliably in a single specialised academic laboratory.

Qualification explores the potential confounds from the measurement, and attempts to understand the risk of detecting a false negative or false positive. Most biomarkers are not surrogate end-points, and probably never will be: we cannot ignore the risk of false positive or false negative, but we can manage and minimise the risk. However, since an IB depends ultimately on the detection and analysis of a signal emitted by the patient during a scanning event inside an imaging device, the processes of qualification differ somewhat from the more familiar path taken by *in vitro* diagnostics seeking the precise and accurate quantification of a defined molecular analyte. In drug development the qualification of IBs is a significant challenge, and is driven perhaps more by the risk that the drug developer will confuse a true negative with a false negative, than by the understandable desire to detect an expected positive biological effect.

Qualification of IBs involves a number of activities including the initial introduction of robust and standardised procedures, correlation with pathology, cross-sectional correlations, correlation with outcome and estimation of effect size, reproducibility and optimal timing of observation to permit successful clinical trials of new investigational therapies with adequate design and sufficient statistical power.

4.1. Robust and standardised procedures

Following first description of a new IB in the academic literature, the image acquisition and analysis must be standardised at least to an extent permitting further qualification activities. We need to understand how a biomarker measurement made in one patient, in one centre, should be compared with the measurement made by a different device elsewhere. We need to have regulatory approvals for the manufacture and use of tracers and contrast agents, imaging devices and software. We

need to ensure that the procedure is ethical and acceptable to patients, practical in multiple centres (ideally not just specialist cancer centres), and we need to be sure that the costs are manageable within the context of an overall drug development programme. It is often valuable to ensure the deployment of IBs in early clinical development to increase the possibility of clear positive or negative signals obtained from the trial, and reduce the number of patients needed to recruit. Response biomarkers are therefore ideally used first in Phase I drug development with cancer patients who are failing to benefit from existing therapies, which creates a challenge for a drug developer, as the response to treatment may be modest in patients who already developed resistance to therapeutic agents. Lung and liver metastases are common in this patient group, so IBs need to be robust in this setting, minimising problems from motion artefact, from confounding liver metabolism of certain PET tracers, and from magnetic susceptibility artefacts which can confound MRI.

4.2. Correlation with pathology

In the absence of a well defined analyte, the interpretation of the change in an IB, and the imputation of underlying pathological change, can pose considerable difficulties. The aim is to minimise false positives (change in the IB without the desired pathological change), and false negatives (pathological change not evident in the IB). It is often difficult to obtain specimens for imaging–pathology correlation in patients: such specimens as are available may be of variable quality, and not representative of the entire tumour. It is also challenging to correlate the imaging biomarker with variable pathological characteristics within one disease entity, e.g. with different histological subtypes and with different tumour grades. Of course, it is never possible to obtain a complete pathological specimen both before and after treatment, since the tumour can only be resected once, but stringent qualitative measures can be in place to ensure successful correlation of IBs and tissue pathology. However, given the difficulty in definitive imaging-pathology correlation in humans, studies in animal tumour models, with different interventions eliciting different degrees of response, are extremely illuminating in defining the circumstances in which an IB change truly represents the desired biology, and when it does not. In particular, for a novel pharmacology that has never been tested in man, the only way to explore the relationship between imaging change and pathologic change following treatment is in a well-designed animal study.

4.3. Effect size, reproducibility and timing

Clinical trials cannot be designed without sufficient information for power calculations. If data on the effect size and optimal timing of measurement are not available from previous clinical studies using similar agents, the careful translation of findings from suitable animal models is the best alternative. Specifically the relationship between the dose of the investigational agent and the histopathologic response, the IB response and tumour growth retardation in animals can help interpret positive and negative IB findings in patients. Since statistical power depends on both effect size and reproducibility, the control of variability is essential. However, unlike an *in vitro* diagnostic device, an imaging study includes many sources of variability, not all of which can easily be controlled. These include differences in patient preparation, differences between different manufacturers and models of scanner, and differences in region-of-interest definition. Another important variable is the homogeneity of the study material, within a single lesion, between lesions in the same patient and between patients. Although homogeneity could be guaranteed by careful selection of suitable patients earlier in the course of their disease for clinical trials, this is not often practical in Phase I drug development. However in later phases of drug development IBs have a potential to reduce the numbers of patients needed to test e.g. the effects of novel targeted agents by predicting or identifying non-response early-on (i.e. as predictive trial-of-therapy biomarkers, Box 1) and thus enriching the clinical trial population with patients more likely to respond.

4.4. Cross-sectional correlations

Since IBs are never used in isolation but are interpreted together with other biomarker data and clinical changes, it is essential to establish whether IBs correlate with other biomarkers in the same patient. An IB of proliferation or apoptosis should correlate with other prognostic and predictive biomarkers of the same pathology; however a perfect correlation between an expensive imaging biomarker, and an inexpensive blood-borne biomarker, would make the imaging biomarker redundant.

4.5. Correlation with outcome

There are two roles for molecular characterisation of disease. Molecular imaging biomarkers before therapy help predict the aggressiveness of disease (prognostic biomarkers, Box 1) and identify therapeutic targets, and therefore help to select the optimal therapy for each individual (predictive biomarkers, Box 1). Measurements of specific biochemical or pathophysiologic processes made during or after therapy may be sensitive measures of tumour response (response biomarkers, Box 1). The ultimate goal for an IB, or indeed any biomarker, must be to understand its predictivity so well that it can become a surrogate for clinical benefit. It is, however, a sobering observation that even the familiar RECIST[2] tumour size assessment, universally

employed in oncology drug development, is not widely accepted as a surrogate for survival. Surrogacy can only be reliably established with large number of adequately powered clinical studies using a variety of interventions, and with the aid of meta-analyses. This is a daunting goal which constitutes the very last step in biomarker qualification.

5. The role of public–private partnerships

In recent years drug developers and investigators in the private and public sector have appreciated the massive investments needed to establish biomarkers and other drug development tools. The strategies described by EMA[9] and FDA[10] are particularly eloquent. In many cases it is clear that the precompetitive resources required will be best harnessed through consortia and public–private partnerships. The Innovative Medicines Initiative (IMI)[11] aims to accelerate the development of better and safer medicines and is Europe's largest public–private initiative. IMI is a Joint Undertaking between the European Union and European Federation of Pharmaceutical Industries and Associations (EFPIA), whose research agenda is built to overcome the principal causes of delay in pharmaceutical R&D by focusing on four areas, predicting safety, predicting efficacy, knowledge management and education and training. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

6. Oncology imaging biomarker qualification under the IMI

The QuIC-ConCePT (Quantitative Imaging in Oncology: Connecting Cellular Processes to Therapy) consortium has been created in response to these challenges of IB qualification. Initially it has two main objectives. The first objective is to qualify three specific IBs of tumour cell proliferation, apoptosis and necrosis, to allow the drug developer to demonstrate reliably the modulation of these pathologic processes in tumours in patients in future trials. Our vision is that drug developers can incorporate these biomarkers for decision-making in Phase I trials of investigational therapies, confident that the biomarkers are technically valid, that a measured change in the biomarker faithfully reflects the desired change in the underlying tumour pathology, and that the IBs can be readily deployed in multiple cancer centres in a robust, consistent, ethical and cost-effective way that is acceptable to the patients with cancer who will volunteer for our trials. The second objective uses a number of approaches to devise, evaluate and introduce IBs of invasion and metastasis.

The biomarkers of tumour cell proliferation and necrosis will be developed from 3′-deoxy-3′-[^{18}F]fluorothymidine (FLT)[12,13] PET. Accumulation of FLT in cells has been linked to the proliferation rate of the underlying cells,[14] and this IB and its application in the QuIC-ConCePT project will be explained further in the article[15] by Soloviev et al. appearing in this journal.

Apparent self-diffusion coefficient (ADC) of water protons measured by MRI depends on the water interaction with cellular, subcellular and macromolecular entities that impede water movement and provide a unique IB of the fraction of the tumour occupied by viable cells.[16,17] ADC is described in the article[18] by Sinkus et al.

Both ADC and FLT are already familiar in clinical cancer research. A search of the U.S. National Institutes of Health ClinicalTrials.gov registry (accessed 27th October 2011) reports 75 oncology trials, enrolling 6071 patients, using ADC as a biomarker, and 42 oncology trials, enrolling 1922 patients, using FLT as a biomarker. Despite this, there remains significant validation challenges in implementing these in multicentre Phase 1 protocols, and significant qualification challenges in understanding, for example, whether a negative finding is a true-negative (no biological effect) or a false-negative caused perhaps by unsuitable timing of observation or suboptimal analysis. In contrast, apoptosis imaging in oncology is less mature, and QuIC-ConCePT will take a more innovative approach, with the novel isatin-5 sulfonamide PET apoptosis tracer, [^{18}F]ICMT-11 introduced in the article[19] by Nguyen et al. This radiotracer has subnanomolar affinity for caspase-3, and has been shown to bind with high specificity to cells and mouse tumours treated to induce apoptosis.

Finally, a paper by Lambin et al. will discuss the potential of Radiomics[20] to predict invasive potential and outcome through extracting information from clinical cancer images using advanced feature analysis.

The project will be delivered using a comprehensive portfolio of animal studies, human studies, image analysis and regulatory work assessing reproducibility, effects of intervention, timing, dose-response and imaging-histopathology correlation. It will seek to qualify these IBs for use in Phase I drug development, in particular in patients with lung and liver metastases. Although focused on the Phase I setting it is recognised that the knowledge created will directly benefit cancer imaging in many other settings, and hopefully will be ultimately used to evaluate prognosis and response in cancer patients in clinical practice.

Conflict of interest statement

None declared.

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Appendix A

QuIC-ConCePT Consortium participants include: AstraZeneca, European Organisation for Research and Treatment of Cancer (EORTC), Cancer Research UK, University of Manchester, Westfälische Wilhelms-Universität Münster, Radboud University Nijmegen Medical Center, Institut National de la Santé et de la Recherche Médical, Stichting Maastricht Radiation Oncology 'Maastro Clinic', VUmc Amsterdam, King's College London, Universitair Ziekenhuis Antwerpen, Institute of Cancer Research – Royal Cancer Hospital, Erasmus Universitair Medisch Centrum Rotterdam, Imperial College of Science Technology and Medicine, Keosys S.A.S., Eidgenössische Technische Hochschule Zürich, Amgen NV, Eli Lilly and Company Ltd., GlaxoSmithKline Research & Development Limited, Merck KGa, Pfizer Limited, F. Hoffmann – La Roche Ltd., Sanofi–Aventis Research and Development.

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