

PROSPECTIVE

# Parallel Anticancer Drug Development and Molecular Stratification to Qualify Predictive Biomarkers: Dealing with Obstacles Hindering Progress

Victor Moreno Garcia<sup>1</sup>, Philippe A. Cassier<sup>2</sup>, and Johann de Bono<sup>1,2</sup>

**Summary:** Current anticancer drug development still largely follows the classic designs developed for chemotherapeutic agents over the past 4 to 5 decades, remaining slow, costly, and inefficient, with continuing high risks of costly late drug attrition. A Pharmacologic Audit Trail has been described to decrease these risks, incorporating pharmacokinetic, pharmacodynamic, intermediate efficacy endpoints, as well as patient stratification molecular biomarkers. Molecular biomarker-based patient selection in hypothesis-testing early clinical trials is critical to clinically qualify putative predictive biomarkers for rationally designed, molecularly targeted drugs as early as possible. Nevertheless, major concerns have been raised about the impact of using such biomarkers in early trials, in view of the costs and time involved to develop multiple certified assays for clinical use. The rapid evolution of novel technologies of utility to this field, such as next-generation sequencing and circulating tumor-cell isolation, makes these valid concerns of critical importance. We therefore propose a more efficient parallel predictive biomarker and clinical anticancer drug development process to deal with the obstacles hindering progress. *Cancer Discovery*; 1(3); 207-12. ©2011 AACR.

## THE PROBLEM

The cost of developing an anticancer drug to reach approval currently approaches >1 billion U.S. dollars, with many agents taking >10 years to move from concept to generalized use as anticancer therapeutics (1). These figures are affected by the high rate of late clinical trial failure, often following the conduct of multiple phase III trials. An example of such late failures was the recent discontinuation of the

clinical development of figitumumab, a human monoclonal antibody targeting the insulin growth factor-1 receptor (2). The development of analytically validated biomarkers early in the creation of rationally designed, molecularly targeted drugs has been advocated by both the scientific community and regulatory agencies as a means of reducing both risks and costs. The early identification of a subgroup of patients with high likelihood of benefit could indeed reduce the possibility of late failure, reduce the number of patients needed to show statistical significance, and lower the costs of drug development while maximizing patient benefit and decreasing the numbers of patients exposed to inactive drugs.

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## PREDICTIVE BIOMARKERS: KEY TO THE SOLUTION?

The use of predictive biomarkers has been shown to be both technically feasible and financially worthwhile

**Table 1. Examples of predictive biomarkers**

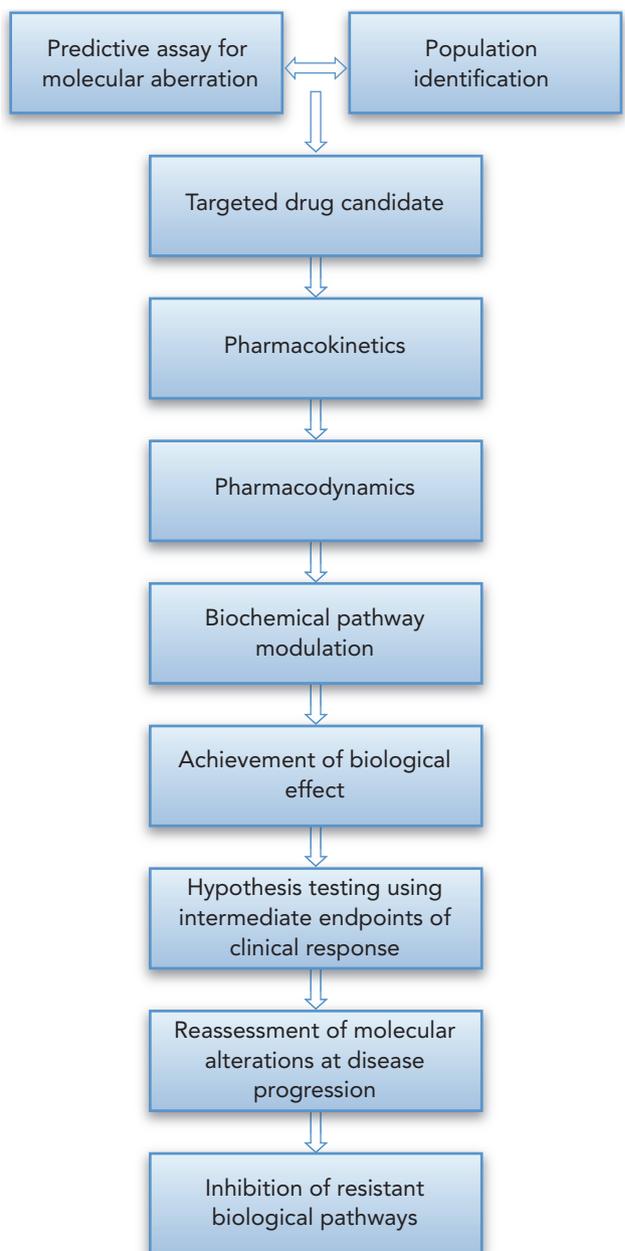
Target	Drugs	Biomarker	PPV/RR (%)
ER $\alpha$	Tamoxifen, Als	ER expression on IHC	20-30
HER2	Trastuzumab, lapatinib	HER2 expression on IHC, HER2 amplification, and FISH	24 (FISH)
KIT	Imatinib	KIT mutation (exon 11 vs exon 9)	70/50
EGFR	Cetuximab, panitumumab	KRAS mutation	12
BRAF	PLX4032	BRAF V600E mutation	75
ALK	Crizotinib	EML4-ALK translocation	57
PARP	Olaparib, iniparib, veliparib	BRCA1/2 mutation	33-41

Abbreviations: AI, aromatase inhibitor; IHC, immunohistochemistry; PPV, positive predictive value; RR, response rate.

(examples are shown in Table 1). Paradoxically, however, the codvelopment of biomarkers together with a drug (companion diagnostics) may hinder the development process: Like a novel anticancer drug, novel biomarkers require extensive preclinical evaluation, analytical validation, and clinical qualification. Indeed, clinical qualification of biomarkers (clinical utility) has been, in most cases, assessed retrospectively and late in the related drug's development [phase III trials or postmarketing, e.g., *KRAS* mutations predicting nonresponse to epidermal growth factor receptor (EGFR)-directed antibodies]. Finally, quality issues in biomarker development have been the subject of numerous reviews highlighting inconsistencies between reports, probably as a result of the unvalidated methodologies utilized. Nevertheless, it is critical that putative predictive or patient enrichment biomarkers are developed as early as possible in the drug development process, and ideally evaluated in the setting of new drug phase 1 trials.

### CHALLENGES TO DELIVERING THE PHARMACOLOGICAL AUDIT TRAIL: FIT-FOR-PURPOSE BIOMARKERS

The integration of pharmacokinetic and pharmacodynamic data has introduced scientifically measurable early drug development endpoints. The pharmacologic audit trail (PhAT) is a rational framework that provides a stepwise assessment of the failure risk of a novel compound during its development (Fig. 1; ref. 3). However, concerns about PhAT delivery stem from a lack of availability of fully validated assays that can be conducted in appropriately certified laboratories operating according to Clinical Laboratory Improvement Amendments (CLIA) or Good Clinical Laboratory Practice (GCLP) standards. This concern is valid, as an increasingly large number of both uniplex and multiplex putative biomarkers are being described using increasingly sophisticated technologies. To prevent the stifling of innovative clinical and translational research, clearer guidelines are now needed to support the use of what is best described as biomarkers that are “fit for the intended purpose.” We recommend that biomarker development needs be parallel to drug development but that degrees of stringency in biomarker conduct be variable contingent on how the biomarker is being used in the clinical trial in question. This point is particularly important with regard to patient molecular stratification in phase I clinical trials. We recommend that in phase I trials, in which patient selection is usually according to “best guess,” pharmacodynamic biomarkers must be used to the most stringent standards because these pertain to the primary endpoint of the trial but predictive biomarkers for selecting patients in dose escalation and expanded cohorts can be used according to less exacting standards outside more costly CLIA or GCLP-certified laboratories (Table 2). This recommendation is feasible because these are exploratory tertiary trial endpoints and would be more cost-effective. We advise that resources for more costly predictive biomarker assays run in certified laboratories are then focused on later-stage trials, with resources being activated for selected assays for which preliminary clinical data exist from



**Figure 1.** The pharmacologic audit trail.

phase I trials, to support investment in their clinical utility in efficacy studies.

### PATIENT ENRICHMENT BIOMARKERS

Overall, we therefore envision parallel drug and predictive biomarker development from the very first in human evaluation of a novel agent, with the level of stringency required for putative enrichment or predictive biomarker assay conduct depending on the specific trial in question, with less costly

**Table 2. Biomarkers and proposed level of stringency of the assay during drug development**

Phase	Endpoint	Certification
I	Primary	
	Toxicity	CLIA/GCLP
	Secondary	
	RR	CLIA/GCLP
	Pharmacokinetics	CLIA/GCLP
	Pharmacodynamics	CLIA/GCLP
IB/II	Exploratory	
	Enrichment biomarkers	No <sup>a</sup>
IB/II	Primary	
	RR/Survival	CLIA/GCLP
	Secondary	
	Predictive biomarker relationship with primary endpoint	CLIA/GCLP
	Exploratory	
	New candidate biomarkers	No <sup>a</sup>
III	Primary	
	Biomarker-selected survival	CLIA/GCLP
	Secondary	
	New proposed biomarkers in phase II	CLIA/GCLP

<sup>a</sup>Local standards apply.

and non-CLIA/GCLP laboratories being used in the more exploratory analyses conducted in phase I trials, while still including rigorous analytically validated and reproducible assays. These putative predictive biomarkers in phase I trials can be described as patient enrichment with “fit-for-purpose” biomarkers, which may also be better termed enrichment biomarkers (Fig. 2).

## PARALLEL DRUG AND PREDICTIVE BIOMARKER DEVELOPMENT

We propose that biomarker development comprises several key phases.

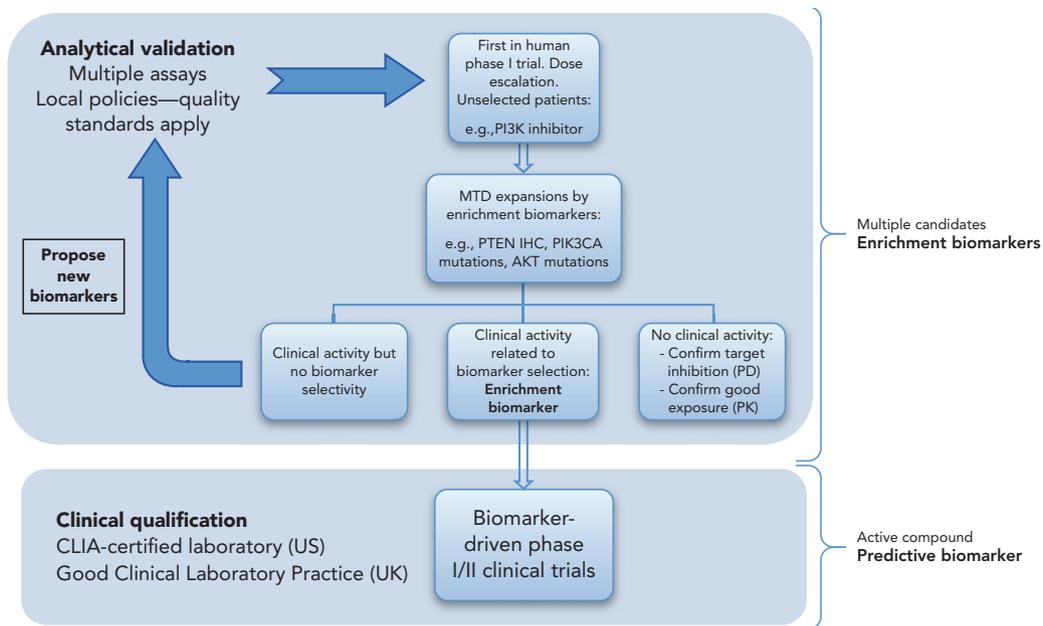
### Preclinical Discovery and Assay Analytical Validation

Preclinical discovery and assay analytical validation should be the focus of preclinical drug development and should be conducted, as much as possible, in the early drug discovery phase. Biomarker discovery will ultimately require some degree of understanding of how the drug kills tumor cells and will require evaluation in both *in vitro* and *in vivo* models. Rigorous analytical validation relating to both predictive and pharmacodynamic assay reproducibility will need to be established very early on in these studies to allow biomarker preclinical utilization. Estimates of how much, and for how long, target blockade is needed to generate

antitumor activity in models with the molecular background of interest should be set forth as a goal for biomarker-driven early clinical trials.

### Phase I Trial Clinical Qualification

*Phase I trial clinical qualification* relates to the clinical utility of the biomarker. Once it has been discovered, and can reliably be measured, the question is, then, does it provide useful information in the clinic? Does it properly identify patients likely to respond to the drug we are testing? Phase I expansion cohorts are the place to start this process, which will likely extend to early phase II trials. Simple questions can be answered in the expansion part of phase I trials, for example, by treating 10 patients selected on the basis of an enrichment biomarker. In the United States, the need for CLIA certification of the laboratory performing the biomarker assays is also required. This certification was implemented in 1988 to ensure reproducibility and a standard of high quality for clinical laboratory tests throughout the U.S. territory. Although laudable, this process is not practical in the context of early drug development and may be responsible for a significant increase in development cost and time consumption. Indeed, although the need for biomarker assays to be performed in CLIA-certified laboratories for phase III seems reasonable, the use of such laboratories should not be mandatory for the conduct of enrichment biomarkers in phase I/early phase II trials in



**Figure 2.** Proposed roadmap for biomarker-driven drug development. Abbreviations: MTD, maximum tolerated dose; PD, pharmacodynamic; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetic.

which repeat modification of the biomarker/assay based on both clinical and preclinical inputs may be critical to the development process.

### Phase II Trial Clinical Qualification

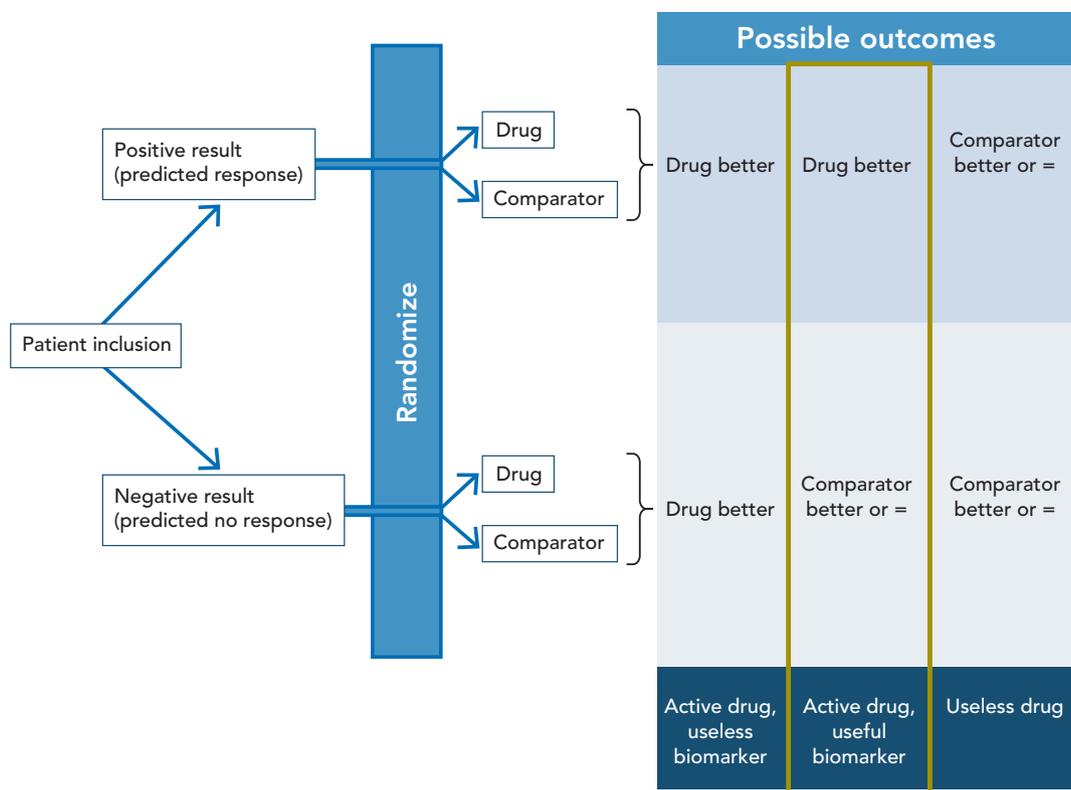
Once evidence exists that the biomarker is an enrichment biomarker (i.e., in late phase I, early phase II drug trial) efforts should be made to qualify the assay before reaching the phase III trial, so that both the drug and the assay can be evaluated in clinical trials concurrently. This step should further ensure assay reproducibility, validity, and variability by the testing of multiple baseline samples. This process should deliver evidence of the drug activity and of a clinically qualified predictive biomarker. Assessing the drug and biomarkers in phase II trials will require different designs, depending on the predictive values (both positive and negative) of the biomarker and previously acquired data. In cases such as that of crizotinib and *ALK-EML4* fusion, the need for a phase II study in this context is not obvious, as >80 patients have been treated in the phase I expansion cohort (the sample size of a phase II study); the biomarker assay relies on FISH, which is a relatively well validated technique and seems to have a high positive predictive value (4). However, the negative predictive value is unknown. A major issue before going to phase III will nevertheless be the technical validity of the assay: intra- and interpatient reproducibility, as well as interobserver reproducibility.

In other cases in which the (positive or negative) predictive value is not very high, and therefore the clinical utility of the

biomarker is not obvious, a phase II trial will be needed to assess both the new drug and the corresponding biomarker. These trials will need to be randomized (new drug versus placebo) and stratified according to the biomarker, to further clarify its frequency and predictive/clinical value so that the phase III design may be planned. Response rate represents an acceptable endpoint for this type of trial and usually requires a smaller sample size than does progression-free survival, and therefore represents a more cost-effective option. Alternative designs such as randomized discontinuation—in which patients with stable disease, after a run-in period on the drug, are randomized to drug or placebo—have been proposed to detect treatment impact when the targeted agent shows a low response rate and a high potential for disease stabilization. This design acknowledges our lack of understanding of the antitumor effect and accepts minimal increments in progression-free survival, often in days or weeks, as acceptable outcomes. However, concern remains about whether this standard is high enough to result in significant survival benefit in registration phase III trials. In fact, upfront randomization has shown greater statistical power when the treatment effect is large (5).

### Phase III Trial Clinical Qualification

Phase III is critical, as the final context of biomarker use will be determined by this stage of development. This last phase will provide definitive evidence that the drug is active and the biomarker can select patients most likely to benefit. Only a well-controlled randomized trial can prove



**Figure 3.** Example of randomized phase III trial designs for biomarker-driven clinical trials: a proposed example to confirm predictive value of the biomarker and clinical efficacy of the anticancer drug simultaneously. The comparator in both arms will allow demonstration that the biomarker is really predictive and not a prognostic factor. Although this design initially may seem to require a much larger number of patients, if the biomarker has enough positive predictive value to select patients likely to respond, it could reach statistical significance with a lower total number than in a classic phase III trial in unselected patients. Early stopping rules can be applied to both arms of this study.

this level of evidence. Although phase III trials are usually tumor specific, we envision the development of biomarker-specific trials in which patients could be selected by means of the predefined biomarker. However, this design will be feasible only when the biomarker has shown high predictive value to select patients likely to benefit in previous stages of the development process (as was mentioned earlier for the *ALK-EML4* translocation and crizotinib or *BRCA* mutations and PARP inhibitors). A different approach when less previous evidence of biomarker–drug activity is available will be a randomized trial in which patients are randomized to drug or comparator (placebo or best available treatment), stratified by the potential biomarker. Although these trials require a larger number of patients because of the 4-arm comparisons, they are able to show definitive evidence of drug activity and at the same time to confirm the validity of the predictive biomarker (Fig. 3).

### IMPLICATIONS FOR FUTURE ANTICANCER DRUG DEVELOPMENT

The future of cancer medicine relies on the codevelopment of new anticancer drugs, together with predictive biomarkers, with the aim of avoiding unnecessary treatment of patients

unlikely to benefit and reducing costs overall by reducing the failure rate of anticancer drug development. There is a shift in the paradigm of drug development, as it is no longer viable to develop targeted drugs without a reliable indicator of potential benefit derived from them. However, tighter regulations for early drug development can endanger companion diagnostics, such as the recently released oversight of the U.S. Food and Drug Administration on laboratory-developed tests. We envision that although premarketing regulations must be clear to ensure patient safety and reliability of the diagnostic test, the regulations for early phase I clinical trials should be loosened for hypothesis fit-for-purpose enrichment biomarker testing. This pragmatic approach is critical because it will be very difficult and costly for the community to prioritize the conduct of all putative enrichment biomarkers in certified laboratories.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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# CANCER DISCOVERY

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