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Designing prospective clinical pharmacogenomic (PG) trials: meeting report on drug development strategies to enhance therapeutic decision making

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Introduction

For some drugs, measurement of expression of an obvious molecular drug target will provide a reasonably accurate basis for pharmacogenomic selection of patients. Herceptin for the treatment of breast cancer is one such example.[1] For many drugs, however, there may be no such *a priori* measurement that results in accurate identification of the appropriate patient population. For example, immunohistochemical measurement of *EGFR* expression does not accurately predict response of lung tumors to Iressa.[2,3] In such cases, a pharmacogenomic profile can be used to identify patients who are either responsive to treatment or free of serious adverse events when treated. Derivation of such profiles requires a process of screening large numbers of potential markers. Identification of such marker sets can be achieved through various methodologies. Example are: a genome-wide expression profile as measured by DNA microarray analysis of the mRNA transcripts collected from diseased cells, single nucleotide polymorphisms (SNPs) in candidate genes related to metabolic processes or the mechanism of action of the drug, or indeed SNPs identified through 'hypothesis free' whole genome scanning.

During the development of a pharmacogenomic profile, individual markers are evaluated, and those correlated with the end point (i.e. the defined phenotype) are selected. The selected markers that are identified as having potential predictive value are then combined into a pharmacogenomic profile that is, a 'composite biomarker' having an association with a specified phenotype or clinical end point. It is important to note that the pharmacogenomic profile or composite biomarker may comprise one or more individual markers. For pharmacogenomic targeting with regard to a composite biomarker, it is not necessary that the individual markers be correlated with the clinical end point, but rather that the composite biomarker itself is evaluated and validated. The ultimate goal is to show that the pharmacogenomic profile can be used during clinical development to select, deselect, or stratify patients for treatment or following drug approval to manage patient treatment options in a manner which improves patient outcomes. If this cannot be accomplished, then one does not have a well-defined pharmacogenomic profile against which drug-related claims can be made.

With regard to any diagnostic or 'test' that is used to characterize a phrmacogenomic profile, what is required in terms of its performance or validation needs to be considered. This will depend on what the composite biomarker or pharmacogenomic profile is designed to predict.[4] For example, a pharmacogenomic profile must be highly sensitive (limited false negatives) in identifying patients susceptible to a life-threatening adverse event whereas a less sensitive pharmacogenomic profile that accurately predicts efficacy, albeit in a smaller subset of those patients for which the medicine is effective, may also have considerable value. FDA in its Guidance to Industry regarding Genomic Submissions has defined various levels of 'biomarkers' and their 'validity' within the drug development process and regulatory decision making.[5] The FDA along with industry groups such as PHRMA, DIA and PWG has also sponsored several workshops to educate and explore the issues surrounding incorporation and validation of biomarkers, particularly pharmacogenomic markers, into the drug development process [6,7]

It should also be noted that not all pharmacogenomic profiles may result in a test being developed as, for example, where the data are generated and used as an adjunct to facilitate

decision making in early drug development or data interpretation. In this instance, the goal is not necessarily to define a diagnostic pharmacogenomic profile for use in the marketplace.[8]

In those instances where ultimately a pharmacogenomic test is required, there are many aspects to consider, including the establishment of clinical utility and determining clinical and analytical validity (reliability: precision and accuracy). Each of the components of a composite biomarker need not be individually validated as noted previously. It is only required that the composite biomarker perform usefully in selecting patients for treatment.

Although there is a large literature on prognostic factors for disease, prognostic factors that are not therapeutically relevant are rarely used. Pharmacogenomic biomarkers are prognostic factors that are therapeutically relevant. Lack of clarity on whether it is the pharmacogenomic composite biomarker that is being validated or whether the interest is in using the composite biomarker to evaluate a new drug for a given population results in confusion about the proper design of studies that utilize pharmacogenomic biomarkers. One fact that is widely recognized, however, is that the data used to develop a composite biomarker must be distinct from the data generated and used to evaluate the actual drug response within patient subsets having a specific pharmacogenomic profile. This distinction is particularly important in cases where large numbers of markers are screened for inclusion in the 'composite biomarker'.[9,10] Separating the development of the composite biomarker from its use in drug evaluation based on a patient's pharmacogenomic profile means that the development process should result in a single, completely defined composite biomarker that subsequently allows patients to be stratified based on their pharmacogenomic profile.

Breakout session IV addressed the development and use of pharmacogenomic biomarkers in prospective clinical trials. If during the Phase I and II development process of a new drug, it becomes apparent that efficacy is limited to a subset of patients that can be identified based on a pharmacogenomic profile, then the efficiency of the Phase III trials can be vastly improved by selecting patients based on this pharmacogenomic profile, that is, an 'enriched' population.[11] This can result in positive small-sized Phase III trials conducted in a targeted patient population rather than large negative 'nontargeted' Phase III trials where patients are enrolled irrespective of their pharmacogenomic profile. However, in this scenario, it still needs to be ascertained what data would be required for the 'nonenriched' population, particularly with regard to the size and constituents of the safety database. Clearly, the development and utilization of pharmacogenomic profiles creates new demands on the Phase I/II development process.

Although a pharmacogenomic profile that correlates with drug response may be identified during Phase I/II development, it may not be clear whether the pharmacogenomic profile is sufficiently accurate to serve as a basis for excluding patients in Phase III trials. In such a case, the pharmacogenomic profile could be used to stratify Phase III patients, with the new drug evaluated in both subsets of patients (i.e. those with and those without the specified pharmacogenomic profile).

Breakout session IV used two case studies to explore aspects of the development of pharmacogenomic profiles during Phase I/II development, and prospective use of such pharmacogenomic profiles in pivotal Phase III trials. Case 1 was designed to identify late clinical development study designs using a PG classifier to select a subgroup of patients or to perform a predefined subset analysis. Case 2 was designed to identify early clinical development study designs that facilitate Phase III studies. The objectives of the workshop were to identify points of agreement or disagreement regarding: the requirements for prospective Phase I–III study designs, implications of these designs for product labeling, 'validation/qualification' requirements for prospective PG classifier use, and possible paths forward.

Case study 1 and discussion: prospective use of genetic markers in phase III

A monoclonal antibody CURESIT is the standard of care for Tumeroma, an uncommon ($\sim$100 000 cases/year) malignant disease of adults. CURESIT treatment is associated with response rates (RRs) of 60–70% with statistically significant evidence of progression-free survival (PFS) and a significant survival advantage in the adult population. CURESIT infusion results in an increase in serious (Grade III/IV) cytokine release syndrome in 40–50% of patients.

Preclinical studies

Laboratory studies have shown that the affinity of CURESIT for Tumeroma cell surface receptor binding is influenced by polymorphic DNA variations in the receptor binding site resulting in amino-acid substitution at that site. Tumeroma cells with the homozygous GG genotype receptor have the tightest CURESIT binding and demonstrate the greatest ($>$80%) *in vitro* cell killing. Tumeroma cell kill with the heterozygous GT genotype is similar while homozygous TT receptor genotype cells have only about a 40–50% tumor cell kill *in vitro*. Studies of the effector cell genotype in the general population indicate that the frequency of GG genotype is 30%, the GT genotype is 40%, and the TT genotype is 30%.

Further laboratory work has indicated that a new monoclonal antibody, BETERMAN, which also targets Tumeroma cells, can more effectively kill Tumeroma cells *in vitro*. Head to head laboratory comparisons indicate that BETERMAN binds to the Tumeroma cell surface receptor better than CURESIT and demonstrates greater cell kill *in vitro* with the GG and GT cell receptor genotype (100 versus 80%).

Clinical development CURESIT

When the data from three small clinical studies of CURESIT therapy in Tumeroma patients were examined retrospectively, a correlation was ob-

served between response (RR) and/or PFS and effector cell receptor genotype. Looking at the CURESIT data, the GG genotype is associated with the best response and longest PFS (RR, 80%, median PFS, 1 year), GT slightly less (RR, 70%, median PFS, 11.5 months), and TT with a poor response (RR, 20%, median PFS, 4 months).

Clinical development of BETERMAN

Phase I studies of BETERMAN have been conducted in Tumeroma patients. A dose/schedule have been determined which is safe. Samples were collected for genotypic analysis but have not been analyzed. In the expanded cohort of 12 patients at the dose selected for further study, a 100% RR has been observed. After a median of 6 months follow-up, none of the 12 have relapsed. The question is: What is the best course of development for BETERMAN in Phase II? Should the company analyze the genotypic data and begin to target a specific subpopulation? Would data from a small Phase I study warrant such a decision?

After consideration of a number of scenarios, the company decides to study all Tumeroma patients in Phase II and collect more samples for future retrospective analysis. Upon completion of Phase II, retrospective analysis of the Phase II data shows that in the GG and GT genotypes, a 90% RR persists with the median PFS not reached. In the TT subtype the RR is reported as 20% with a median PFS of 4.5 months. It is time to plan the pivotal studies. Consider the sponsors decisions based on whether the genotypic test kit was validated or was not validated at the time of study start. The questions discussed by the workshop participants were:

1. What kind of Phase III study to run?

- A randomized study of BETERMAN against CURESIT in all Tumeroma patients, without collection of genotype information
- A randomized trial of BETERMAN versus CURESIT with randomization stratified on genotype.
- A randomized study of BETERMAN against CURESIT in all Tumeroma patients, but with collection of DNA samples for genotypic analysis to be performed at a later date.
- A randomized study of BETERMAN against CURESIT enrolling only patients with GG and GT genotypes.
- A noninferiority trial of BETERMAN in the GG and GT populations with CURESIT as the comparator arm to determine if BETTERMAN is no less effective than CURESIT but with a lower incidence of serious toxicity.

Case 1 discussion

With regards to study design, the majority of the participants agreed with the company's approach to just collect samples in Phase II for retrospective genotyping analysis. It was felt that there would not be sufficient validated data from a small Phase I study to warrant targeting a specific subpopulation in Phase II. Further, the audience was also in agreement that if a diagnostic test was to be considered for Phase III, then Phase II study designs would need to reflect and support this approach. Notably, analytical and clinical validation test parameters must be considered. For example, even if the test data will only be retrospectively analyzed in Phase II, consideration of Phase II sample size may be important in order to clinically validate any findings prior to use in Phase III. In addition, following the retrospective Phase II analysis, a follow-on Phase IIb study may be required to further validate the biomarker findings. While not noted specifically by the audience, it also needs to be recognized that such a subsequent evaluation may result in data being generated that indicates that the classifier needs to be revised; therefore, a costly iterative cycle may emerge.

Moving to Phase III study designs, participants tended to agree that prospective use of a marker in a Phase III setting required a clear analysis plan in place prior to study start. In addition, there was consensus that the classifier should be set prior to and not be changed during Phase III. In the case that a classifier is changed during Phase III, this would constitute a new exploratory data analysis, and another Phase III study would be needed to validate this changed classifier.

The strategic decision as to which type of study design to select for Phase III was met with a variety of opinions and no clear consensus. There was a good deal of support for a two-stage approach in which the study would be designed as a randomized trial to compare treatments overall for all cases and if the overall treatment difference did not meet prespecified objectives then a subpopulation analysis would be considered. The levels for declaring statistical significance would be established to preserve the type I error rate for the overall study at 5%.[12]

Interestingly, it was noted that the selection of a study design approach should reflect business decisions on the part of the company, and should be discussed early in the development process. For example, the level of so-called 'market fragmentation' that is deemed feasible from a business perspective needs to be factored in.

The ethical implications in terms of whether to evaluate the drug in test-negative patients versus only in test-positive patients were also recognized as important points to consider prior to moving forward. The audience concurred that a biomarker's value can be best assessed in terms of impacting the risk/benefit equation. Some questioned the ethics of excluding patients from a study if a test was not highly accurate or if clinical response was observed in a particular genetic subtype, albeit perhaps a low-level response. Would it be medically responsible to not develop the drug in that subtype?

With regards to the development of a diagnostic test for the medical management of patients there was some debate regarding whether results from drug treatment in a test-negative population would be required for validation of the clinical utility of the test. Noted was the need to recognize the regulatory complexity surrounding study designs in test-negative versus test-positive patients. In some cases, it is possible that sufficient information may exist before study of a drug diagnostic combination to make study

in test-negative patients unnecessary. Also mentioned was the possibility of a postapproval commitment to study alternative populations for which clinical data were not available preapproval (as in the case of the Erbitux drug/*EGFR* test approval). In general, exact requirements for establishing clinical performance of the test associated with the drug would have to be determined on a case-by-case basis depending on the disease and the treatment available, test claim, and specific set of circumstances.

Reimbursement for diagnostics was briefly mentioned, and there was agreement that this area needs greater focus and clarity.

Case study 2 and discussion: prospective use of biomarkers during early development

Preclinical background

A novel small molecule, DIA0001, has been developed that inhibits cdk4/6 cell cycling. Toxicology assessment of DIA0001 has been performed and indicates the compound may cause dose-dependent bone marrow suppression in rats and dogs. Preclinical efficacy assessment included tumor xenograft models showing activity against Colo 205, a colon cancer cell line. Preclinical microarray-based pharmacogenomics identified a set of genes with a statistically significant fold change in expression between responsive and nonresponsive tumor cell lines. The gene set ($n = 66$) primarily contained genes associated with cell proliferation, representing Gene Ontology categories that included cell cycling, DNA replication and repair, and mitosis. One particular gene, GOOFY1, had a higher level of expression in the sensitive cell lines and a remarkable reduction in expression post-treatment compared to pretreatment. The reduction in expression level was greater for higher doses. GOOFY levels were further measured by both qRT-PCR and ELISA assays, which corroborated the data derived from the microarray studies. It was not clear whether GOOFY1 was downstream in a pathway of the protein target of DIA001. In reviewing the literature as well as internal and external microarray databases, it appears that GOOFY1 levels are highly expressed in normal human testis and thymus, and in a variety of cancers including colon adenocarcinoma, breast adenocarcinoma, and both squamous and adenocarcinoma of the lung. The compound has received management approval to proceed into clinical development.

Clinical development: phase I

The clinical development plan includes several Phase I studies including an open histology, dose escalation study of DIA0001 alone and a Phase I study of patients with metastatic adenocarcinoma of the colon in conjunction with 5-FU, LV, CPT-11 and Avastin.

A pharmacogenomic assessment will be conducted during the Phase I trials. How should GOOFY1 be measured?

a. Measurement of GOOFY1 levels in tumors before and after treatment by qRT-PCR or ELISA?
b. Global microarray expression profiling of patients during Phase I trials?

The two planned Phase I clinical trials were performed with full expression profiling on the patients. The MTD for solo therapy of DIA0001 was determined to be 400 mg qD $\times$ 5 days every 4th week. The MTD for combination therapy for colon cancer was lower at 200 mg qD $\times$ 5 days every 4th week. The DLT was bone marrow suppression in both Phase I clinical trials. Expression profiling from both groups was performed. In those patients with elevated GOOFY1 levels prior to therapy, GOOFY1 levels did decrease over the course of therapy. Additionally, several additional genes were identified that decreased in a dose-dependent manner, including GOOFY2 and GOOFY3. Screening against the same internal and external databases shows elevations in GOOFY1, GOOFY2 and GOOFY3 levels in the same types of cancers: breast, colon and lung adenocarcinoma and squamous cell carcinoma of the lung. Interestingly, virtually complete inhibition of GOOFY1, 2 and 3 occurred at dose levels substantially lower than MTD (100 mg qD $\times$ 5 days q4 weeks for solo therapy and 50 mg qD $\times$ 5 days q4 weeks for combination therapy in patients with colon therapy).

Clinical development: phase II

The decision to move to Phase II has been tentatively approved.

a. In which cancer subtypes would you conduct Phase II clinical trials? Would this decision be based on levels of GOOFY gene expression?
b. What dose(s) would you select for patients with colon cancer given the data on GOOFY $^{1-3}$ pathway inhibition from the Phase Ib?

A Phase II program was approved based upon Phase I data and the incidence of the proposed biomarker in colon cancer. The Phase II colon cancer trial included three dosing arms (200, 50 and 0 mg) of DIA001 in addition to baseline standard chemotherapy. Complete pharmacogenomic assessment, including pretreatment tumor measurement of GOOFY levels and pretreatment microarray expression profiling, is performed on patients on all three arms.

Future use of GOOFY during later clinical development

RRs for patients with colon cancer (PR + CR) are 35, 30 and 20% (200 versus 50 mg versus control) based on approximately 25 patients per arm. Using the 16 responders among the 50 patients treated with DIA001 a composite biomarker (referred to as GOOFY4) was developed that appeared to identify those patients who responded to DIA001 plus chemotherapy. GOOFY4 was composed of a novel set of genes not restricted to GOOFY1, GOOFY2 and GOOFY3. Using cross-validation on the analysis set of 50 patients, the estimated probability of responding to treatment was 70% for patients with positive values of the composite biomarker, but only 20% for other patients.

What would the next set of studies in patients with colon cancer be?

(1) No further studies, there was insufficient response.

(2) A standard Phase III program.
(3) A follow-up Phase II trial in colon cancer to test the accuracy of GOOFY4 and to refine the composite biomarker.
(4) A GOOFY 4-stratified Phase III program powered sufficiently to show a difference between the chemotherapy alone versus chemotherapy plus DIA001 separately for the two strata.
(5) A Phase III clinical trial comparing chemotherapy alone versus chemotherapy plus DIA001 with entry restricted to GOOFY4-positive patients.

Case 2 discussion

Audience members generally were uncomfortable basing the dose for Phase II development on inhibition of the GOOFY gene products because of the lack of biological credentials of the genes. Consequently, Phase II development utilized a randomized design with three dose levels. Some in the audience questioned, however, whether such a design with only 25 patients per arm was sufficient for dose selection.

The biological credentials of the GOOFY genes were also generally considered too weak to use comfortably for determining which tumor types to develop in Phase II. In oncology, many drugs have been broadly developed in phase II. Preclinical information on the mechanism of action of the drug can be used to focus phase II development. Most participants considered that PG markers should be developed preclinically whenever possible so that they can be used in early development programs. Furthermore, association of the marker with the pathophysiology of the disease under investigation and/or the mechanism of action or efficacy of the investigational drug would increase confidence in the biomarker and enhance the likelihood of its adoption during development. However, an observational classifier may still have utility during drug development. Trying to decipher mechanism of action may take a very long time, and if a classifier is available, a company might consider using it even though mechanistic relation to the disease or drug action may be unknown. There was a suggestion to go after mechanistic data in parallel to running Phase II, and not delay the Phase II because of the lack of it.

During Phase II it was generally felt that greater emphasis should be placed on developing classifiers for use in identifying responsive patients than on documenting the effect of treatment on candidate biomarkers. Consequently, for DIA001 Phase II trials, most felt that the emphasis should be on pretreatment specimen sampling and characterization. Determining the effect of treatment on gene expression levels in Phase I studies requires tumor sampling before and after drug administration. The potential benefit of such information should be balanced with logistic and ethical considerations. Most participants believed that tumor expression profiles should be analyzed quickly in Phase II, not banked, so that results could potentially be used in the design of Phase III trials.

There was also a general consensus that more time should be spent at Phase II developing the biomarker, before going to Phase III. Ideally, a classifier for use in Phase III should be developed and qualified during Phase II. However, it was pointed out that in the current drug development paradigm, achieving confidence in the classifier may be difficult at the end of Phase II due to small sample sizes and lack of comparator arms. It was therefore proposed that if a classifier is discovered in Phase II, a confirmatory Phase IIB study may be useful to confirm the classifier before designing a Phase III study. Further, while not specifically addressed by the audience, there also needs to be the recognition that convergence of clinical utility and regulatory decision-making drivers, such that there is agreement that a drug-test focus is warranted, may occur at many different points along the drug development continuum. Clearly, this poses challenges for timely completion of appropriate clinical studies the later this convergence occurs.

It was generally agreed that a biomarker with strong biological credentials based on the therapeutic target and pathophysiology of the disease might be used to restrict entry in Phase III. A biomarker or classifier developed empirically during Phase I/II without compelling biological credentials is more likely to be used to stratify patients in Phase III trials or to define *a priori* subset analyses than for restricting eligibility. There was support, however, for using such classifiers for enriching Phase III trials with patients likely to be responsive. Such enrichment procedures, however, must be accommodated in the statistical analysis plan.

Conclusions

Two sessions to Track IV were held, both attended by over 150 people from industry, regulatory agencies, and academics to address the issues involved in designing prospective pharmacogenomic clinical trials. Cases were presented that focused on two oncology indications. Although many of the issues and possible solutions discussed are applicable outside of oncology, it is noted that the risk–benefit assessment will differ compared to nononcology indications. A general summary of the discussion from the two sessions indicates that there were a number of general points of agreement. First, there was universal agreement that the intended use of a PG biomarker needs to be defined early in the development program. The target population must be defined early, the biomarker should optimize the risk/benefit profile, and the study designs must be program specific – there are no 'one size fits all' answers. Second, the probability of success for development/use of a PG classifier is low in the context of our current clinical development paradigm. Therefore, drug developers need to rethink basic premises of how clinical trials are conducted. Retrospective Phase II analyses of test data with a follow-on Phase IIb study and/or larger Phase II studies may be required to further refine and validate the biomarker findings. Also, adaptive study designs may need to be considered. Third, a

well-defined analysis plan must be in place by the time one gets to Phase III. Fourth, the precise requirements for 'validation/qualification' remain a stumbling block and regulatory authorities can assist in developing guidelines in this area. Finally, there was a general consensus that evidenced-based medicine is the future for drug development; therefore, samples for PG biomarker discovery and validation should be routinely collected over the course of the development program to enable PG studies.

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