

## Review Article

# Personalized therapy for pancreatic cancer: Myth or reality in 2010?

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### Introduction

Modern anti-cancer therapies using specific kinase inhibitors are directed towards critical molecular targets that are involved in tumor progression and resistance towards cytotoxic agents. These therapies have led to modest incremental benefit for unselected cancer patients over that offered by the traditional cytotoxic agents. Significant benefit from these novel kinase inhibitors is limited to a select few patients who may have activating mutations related to the target kinases. Oncologists and clinical investigators have long been aware of the inter-individual differences in prognosis and therapeutic outcome of similar cancer histologies. These differences are attributable to the genetic and epigenetic heterogeneity of cancer. There has therefore been a recent emphasis on a more personalized treatment approach based on the underlying genetic profile (1). Personalized therapies, wherein underlying genetic or pathway aberrations are matched with specific therapeutic agents, are likely to change the existing treatment paradigms and lead to exponential clinical gains.

The opportunities for targeted therapeutics in cancer at the current time are considerable. However, there are also a number of challenges in this field. The success of a personalized approach depends upon the identification of the underlying molecular abnormality using a reliable biomarker. Clinical trials of personalized therapy for cancer

using standard randomized trial designs are not inexpensive, and the current regulatory standards for drug approval do not sufficiently address the personalized therapy paradigm. Furthermore, there are ethical issues involved in the design of randomized clinical trials for a specific, targeted patient population. Pancreatic cancer is one of the most genetically heterogeneous of human cancers and may be particularly suited for personalized therapy.

### Success in personalized cancer therapies

Personalized medical care in oncology is currently a reality for a select group of cancers. With improved knowledge of tumor biology and the advent of novel technologies allowing identification of molecular targets, it has become possible to develop therapies against different subsets of cancers. Specific examples are discussed below.

- The recognition of biologic and molecular subtypes of breast cancer that have differential responses to therapeutic agents has had a major impact in the treatment of this disease (2). For instance, breast cancers that express endocrine receptors, in particular the estrogen receptor, derive benefit from endocrine therapy and may be more responsive to pre-operative chemotherapy (3-5). About 20-25% of the breast cancers overexpress the human epidermal growth factor receptor (HER2). Tumor HER2 status predicts resistance to chemotherapeutic and hormonal agents and is associated with aggressive tumor biology (6). Moreover, tumors that express high levels of HER2 benefit from the HER2-targeted agents, trastuzumab and lapatinib (7).
- The development of imatinib mesylate has revolutionized the treatment of BCR-ABL-positive chronic myelogenous leukemia (CML). Targeting the phosphorylation of the BCR-ABL fusion protein, which is critical to CML cell growth and survival, this highly effective multi-tyrosine

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kinase inhibitor is offered as initial therapy to all patients presenting with CML, inducing durable complete cytogenetic response in up to 80-85% of patients. Since its introduction in 2001, imatinib has replaced interferon based therapies and decreased the need for the highly morbid procedure of allogeneic stem cell transplantation, which are now reserved for nonresponders to imatinib or for those with intolerable side effects(8). Similarly, the success of imatinib has also been mirrored for gastrointestinal stromal tumors, in which the median survival of these patients has been increased from approximately 20 to 60 months(9).

- In non-small cell lung cancer, the tyrosine kinase inhibitors, erlotinib and gefitinib, have demonstrated efficacy by blocking the gene encoding epidermal growth factor receptor (EGFR) and resulted in clinical benefit in certain subgroups of patients. Each agent has increased response rates and progression free survival in patients harboring activating EGFR tyrosine kinase domain mutations (10, 11). Moreover, a recent large phase III randomized controlled trial demonstrated the superiority of first-line gefitinib therapy compared to combination chemotherapy in a clinically selected population consisting of Asian patients, women with adenocarcinoma and a light smoking history (12).

The success of these examples demonstrates that patient outcomes can be improved by use of therapies that are rationally selected against molecular targets. In each example, knowledge of the molecular profile of the tumor guided the selection of therapy for the patient.

### ***Pancreatic cancer is heterogeneous***

Pancreatic cancer is genetically and biologically heterogeneous. There is extensive inter-tumor genetic variability from individual to individual, resulting in multiple combinations of genetic mutations. For instance, it has been demonstrated that the pancreatic cancer genome is highly complex, with an average of 63 somatic alterations in each cancer, the majority of which are point mutations (13). Underlying these large numbers of functional genetic alterations, however, is the deregulation of 12 core biological regulatory processes or pathways in the majority of pancreatic tumors (13). This genetic heterogeneity can be considered in terms of three main molecular events: mutational oncogenic activation, tumor suppressor gene inactivation, and inactivation of genome maintenance genes involved in repair mechanisms (14).

Oncogenic k-ras mutations occur in 30% of early precursor lesions and 90% of advanced pancreatic adenocarcinomas and represent the most frequently encountered genetic variation

in pancreatic cancer (15). Mouse model studies indicate that k-ras mutations are an initiating step in pathogenesis of pancreatic oncogenesis (16), and the prevalence of k-ras mutations increases with increasing dysplasia in precursor lesions (17). K-ras is a member of the ras family of GTP-binding proteins that mediate a wide variety of cellular functions including differentiation, proliferation and survival (18). Multiple effector pathways and mediators (RAF-mitogen-activated kinase, phosphoinositide-3-kinase, Ral GDS pathways and NFκB) are engaged by k-ras activation, accelerate oncogenesis and represent potential downstream therapeutic targets (19). At the current time, we have not successfully targeted the k-ras activating mutations. However, its downstream effector molecules have been targeted with success.

The majority of pancreatic tumors have inactivation of the tumor suppressor genes p16, p53 and SMAD4, leading to loss of function (20). Inherited p16 mutations have been implicated in the etiology of the Familial Multiple Mole Melanoma (FAMMM) syndrome, which carries an increased risk of developing pancreatic cancer. Alteration of the p53 tumor suppressor gene, by missense alterations of the DNA-binding domain, occurs in >50% of pancreatic adenocarcinomas and disrupt regulation of cellular proliferation and apoptosis in response to DNA damage (20). Elevated levels of the calcium-binding protein S100A2, a potent modulator of p53 transcriptional activity may correlate with the metastatic phenotype of pancreatic cancer and a poor outcome following pancreatectomy (21, 22). Approximately 60% of pancreatic cancers have inactivation of the SMAD4 gene by processes of homozygous deletion and intragenic mutation, which are important in the intracellular mediation of the TGF beta intracellular signaling pathway. SMAD4 gene mutational status has been shown to significantly correlate with patient outcome, as pancreatic cancer patients with loss of SMAD4 expression have a greater propensity to metastasize and a poorer prognosis (23). As the SMAD4 protein can be detected by immunohistochemical staining, SMAD4 mutational status may be useful as a molecular prognostic marker as well as predictor for TGF beta-directed therapies.

Another tumor suppressor gene of interest is BRCA2, as inherited loss of function mutations of this gene are thought to be associated with an increased predisposition to developing pancreatic cancer and promotion of the malignant progression of pancreatic neoplasms (24). Estimated to occur in approximately 10% of pancreatic cancers, germline inactivation of the BRCA2 gene renders the homologous recombination repair of DNA cross-linking damage deficient and consequently causes genomic instability (25). *In vivo*, BRCA2 deficient xenografts demonstrate hypersensitivity to DNA crosslinking agents

**Table 1 Characteristics of prevalent genetic mutations in pancreatic adenocarcinoma**

Gene	Variation	Prevalence in pancreatic cancers	Sporadic/ Inherited	Phenotype/ Clinical behavior
<i>K-RAS</i>	Activating mutation	30-100% (20)	Sporadic	More aggressive
<i>p16</i>	Inactivating mutation	95% (70)	Inherited	Association with development of FAMM Syndrome, predisposition to pancreatic cancer
<i>SMAD4</i>	Inactivating intragenic mutation	60% (71)	Sporadic Inherited	Decreased survival
<i>p53</i>	Mutation by missense alteration	50% (72)	Sporadic	---
<i>BRCA2</i>	Germline mutation	10-17% (25, 73)	Inherited	Significant risk for development of pancreatic cancer
<i>MLH1</i> <i>MSH2</i> <i>MSH6</i>	Inactivating mutation Epigenetic changes	---	Sporadic	Possible favorable prognosis Associated with HNPCC

FAMM: Familial multiple mole melanoma syndrome; HNPCC: Hereditary non-polyposis colon cancer syndrome

including cisplatin (26).

Mutations or epigenetic changes of DNA mismatch repair (MMR) genes such as *MLH1*, *MSH2*, *MSH3*, *MSH6*, *PMS1*, and *PMS2*, which play a role in the correction of DNA replication errors also contribute to the pathogenesis of pancreatic cancer (27). Microsatellite instability (MSI), resulting from inactivation of a DNA MMR gene, is more prevalent in a histologically and molecularly distinct subset of pancreatic carcinomas (28). Consistent with previous reports that the prognosis of patients with MSI positive tumors was better than that of patients with MSI negative tumors in colorectal cancer (29), gastric cancer (30), and cancer of the papilla of Vater (31), MSI positivity in pancreatic cancer may also portend a more favorable prognosis (32). Moreover, the possibility of a germline mutation and presence of hereditary non-polyposis colorectal cancer syndrome (HNPCC), or Lynch syndrome, correlates with presence of defective MMR and increased susceptibility to developing other gastrointestinal malignancies. MSI-H colorectal cancers derive benefit from irinotecan therapy; whether this is also the case with pancreatic cancer remains to be determined (33). These unique molecular features of pancreatic cancer have potential utility of being developed into molecular prognostic indicators of outcome and as therapeutic targets while establishing an individualized treatment plan for a patient. These genetic abnormalities and their incidence are represented in Table 1. At MD Anderson Cancer Center, we are investigating the role of pharmacogenetics in the individualization of therapies for

pancreatic cancer.

#### Pharmacogenetics

To personalize therapy, it must be recognized that considerable inter-individual variability in therapeutic outcome arises at least partly from the underlying genetic profile which can impact on drug pharmacokinetics and toxicity profile (referred to as pharmacogenetics) (34). Modern technologies can allow the investigator to interrogate the pathway impacted by the study agent (candidate gene approach) or more recently, the whole genome (genome wide association studies). Implications of pharmacogenetics are manifold and include a shift away from current paradigm of offering a standard therapy to all patients with a similar disease phenotype to an individualized treatment plan that accounts for pharmacogenetic profile. However, the ethical, legal, and economic impact resulting from rapid advances in this field is yet to be determined. Table 2 depicts previously described genetic variations of commonly used anti-cancer agents that are presently available for clinical management.

We have investigated the variations of genes involved in the metabolism of gemcitabine, the most commonly utilized agent for pancreatic cancer.

#### Advanced pancreatic cancer - SNP data – gemcitabine

Despite its role as the backbone of pancreatic cancer therapy, gemcitabine demonstrates only a modest response at the expense of hematologic toxicity which can result in treatment

**Table 2 Examples of functional genetic polymorphisms and effect on chemotherapy toxicity**

Enzyme	Variation	Drug	Effect
Glucuronosyl transferase (UGT1A1)	SNP*	Irinotecan	Neutropenia Diarrhea
Dihydropyrimidine dehydrogenase (DPD)	Point mutation Aberrant splicing	5-fluorouracil	Neurotoxicity Myelosuppression Diarrhea
Thiopurine methyltransferase (TPMT)	Non synonymous SNP	Mercaptopurine Azathioprine Thioguanine	Myelosuppression Secondary tumors
Methylene tetrahydrofolate reductase (MTHFR)	Point Mutation	Methotrexate	Mucositis

\*SNP: single nucleotide polymorphism

delays and dose decreases. Many gemcitabine resistance mechanisms including altered levels of its activation enzyme, decreased intracellular drug transport, increased drug metabolism, and increased expression of DNA repair enzymes have been proposed as contributing to the failure of gemcitabine therapy (35-38). Evidence published in early 2009 from the RTOG9704 trial confirmed that increased intra-tumoral expression of human equilibrative nucleoside transporter (hENT1), the major protein believed to be responsible for transporting gemcitabine into cells, was associated with an improved overall and disease-free survival in patients with resected pancreatic cancer treated with gemcitabine as compared with those receiving 5-fluorouracil (39). Preclinical evaluation in lung cancer has demonstrated that overexpression of ribonucleotide reductase regulatory subunit M1 (RRM1), a DNA repair enzyme, may also be a marker of poor response to gemcitabine therapy (40). Previous clinical studies have suggested that gemcitabine therapy has less efficacy in patients with advanced tumors expressing high levels of RRM1 (41, 42). Further immunohistochemical study of RRM1 correlates overexpression of protein levels with a worse overall survival and disease control than those patients with RRM1-negative tumors (43).

Recently, the clinical significance of single nucleotide polymorphisms (SNP) of gemcitabine metabolic genes was evaluated in pancreatic cancer by our group (44). Okazaki et al examined 17 SNPs of eight genes in 154 patients with potentially resectable pancreatic adenocarcinoma treated with neoadjuvant concurrent gemcitabine and radiation therapy with or without cisplatin. Though none of the SNPs was significantly associated with overall survival (OS) individually, a combined genotype effect was observed, in which the risk of death was increased for patients with variant gemcitabine metabolic genes. Moreover, hematologic toxicity

due to gemcitabine was associated with polymorphisms of the cytidine deaminase and deoxycytidine kinase genes. This study suggests that the clinical outcome of pancreatic cancer patients treated with gemcitabine-based chemotherapy results, in part, from variations in genes responsible for gemcitabine metabolism and elimination. The results of this study support the investigation of pharmacogenetic profiling to individualize gemcitabine-based therapy for pancreatic cancer. An effort is being made to expand pharmacogenetic profiling for other agents that are considered effective in pancreatic cancer.

Although gemcitabine has been the mainstay of chemotherapy for pancreatic cancer for the past decade, the beneficial effects from gemcitabine are mostly palliative and survival gains from this agent are limited. Developmental efforts have focused on the addition of other chemotherapeutic agents to gemcitabine and thus far the only phase III study that resulted in survival benefit was the National Cancer Institute of Canada-Clinical Trials Group PA.3 (NCIC-CTG PA.3) study which showed that the addition of erlotinib to gemcitabine resulted in a modestly improved survival as compared with gemcitabine alone (45). A recent phase III study presented at the American Society of Clinical Oncology (ASCO) meeting in 2010, investigated the combination of 5-fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX) vs. gemcitabine for the treatment of patients with advanced pancreatic cancer (46). In this study, 342 patients were enrolled; at a preplanned interim analysis, the median overall survival in the FOLFIRINOX arm was significantly longer than that in the gemcitabine arm (10.5 vs. 6.9 months,  $p < 0.0001$ ) at the cost of higher toxicities including diarrhea, emesis and neutropenia in the study arm. While the toxicities associated with this regimen are concerning, there is now an alternative to gemcitabine chemotherapy for pancreatic cancer patients. As discussed

below, there are promising biomarkers that correlate with gemcitabine resistance and the availability of a valid alternative regimen that excludes gemcitabine opens avenues for biomarker-driven cytotoxic chemotherapy in pancreatic cancer.

#### *Limitations of tissue acquisition in pancreatic cancer*

An important limitation in case of biomarkers to study pancreatic cancer is that tissue procurement is limited in this disease. A dense fibrotic stroma surrounds the tumor and most biopsies are obtained via fine needle aspiration. These aspirates are paucicellular and this limits biomarker assessment. On the other hand, core needle biopsies are feasible from metastatic sites such as liver and often yield adequate tissue for biomarkers. This however, limits the stage of cancers for study and introduces a selection bias. Better technologies to examine biomarkers in the peripheral blood or from fine needle aspirates are required.

#### *Cancer biomarkers: better indicators of 'non-responsiveness'*

Despite advances in biomarker technology, the currently available biomarkers are more effective in identifying patients who will not respond to targeted agents rather than identify those who will benefit. For instance k-ras mutation or HER2 neu status of the tumors have thus far been more effective as a negative predictive markers for cetuximab or herceptin therapy for colorectal and breast cancers than as predictors of response. For instance, the response rate for patients treated with panitumumab in the phase III trial of panitumumab versus supportive care (BSC) was 10%, but the retrospective analysis of patients with wild-type k-ras tumors from that trial demonstrated a response rate to panitumumab of 17% (47, 48). These results are comparable with those from the phase III trial of cetuximab versus BSC, with response rates of 8% for those patients receiving cetuximab and 12.8% for patients with wild-type k-ras tumors receiving cetuximab (49). Thus, the response rates in the k-ras wild type tumors is very modest and the positive predictive value of this mutation is low; on the other hand the negative predictive value is higher with no responses in the mutated phenotype. Cross-talk between signaling pathways and tumor genetic heterogeneity may account for these results; tumors that have drug-sensitizing mutations may have simultaneous activation of down-stream drug-resistance pathways or mutations. Despite these limitations, biomarker-driven clinical trials are likely to be associated with stronger efficacy signals and lead to cost-effective health care. Specific examples as applicable to pancreatic

cancer are discussed below.

#### *Biomarkers for erlotinib*

Several promising biomarkers of therapeutic interest have been described in patients with non-small cell lung cancer treated with gefitinib or erlotinib. These include activating mutations of EGFR and tumor k-ras mutation status. These biomarkers have yet to be prospectively validated in the case of pancreatic cancer. Although the NCIC-CTG PA.3 study did perform a post-hoc analysis of available pancreatic tumor biopsy tissue for k-ras mutations and EGFR amplification, it failed to establish a significant link between either of these markers and outcome with a trend favoring erlotinib observed only in patients with the wild-type k-ras (50, 51). Epithelial to mesenchymal transformation (EMT) has also been correlated with the efficacy of erlotinib therapy in lung cancer (better response noted with the epithelial phenotype) and is a common feature of pancreatic cancers as well. The degree of EMT is measured by the relative levels of molecular epithelial (vimetin, integrin-alpha 5) versus mesenchymal (desmoplakin, keratin-19, cadherin 1) markers (52). The mesenchymal phenotype, morphologically distinguished by the irregularity of its cells, lack of organized structure and weak intracellular adhesions is more aggressive and carries a poor prognosis (53). Further investigation of the predictive value of k-ras mutation status and EMT in pancreatic cancer is needed. Recent data from Ratain et al, indicate the association between polymorphisms of the multidrug ABCG2 transporter and erlotinib pharmacokinetic profile and EGFR polymorphisms and diarrhea (54). Incorporation of these biomarkers can help reduce the toxicity resulting from erlotinib therapy.

#### *Nanoparticle albumin-bound (Nab) paclitaxel*

Nab-paclitaxel is a solvent-free, albumin-bound 130-nm particle form of paclitaxel (Abraxane, Abraxis Bioscience, CA, USA), which was developed to avoid toxicities associated with the Cremophor vehicle used in solvent-based paclitaxel. This agent takes advantage of the increased delivery of albumin to tumors through receptor-mediated transport. SPARC (secreted protein, acidic and rich in cysteine) is selectively secreted by pancreatic cancer cells and binds to albumin-bound paclitaxel with the resultant release of paclitaxel in the vicinity of tumor cells. Together, the absence of solvents and the receptor-mediated delivery result in decreased toxicity and increased antitumor activity of nab-paclitaxel compared with solvent-based paclitaxel. A phase I study of gemcitabine and nab-paclitaxel has demonstrated impressive response rates and progression-free survival; in this study responses

and progression-free survival correlated with SPARC expression (55). In the future, the investigational plans are to administer this agent only for the tumors that have SPARC expression.

### **Targeting DNA repair to exploit synthetic lethality**

Another potential strategy toward development of effective novel therapy for pancreatic cancer is exploiting the concept of synthetic lethality, a genetic interaction in which the combination of mutations in two or more genes leads to cell death. Cells typically have the ability to repair therapy-induced single strand (SS) and double strand (DS) DNA breaks by the conserved mechanisms of base excision repair (BER) and homologous recombination (HR) repair, respectively (56). Since 10% of patients with pancreatic cancer harbor germline inactivation of the BRCA2 gene, leading to deficient HR, these individuals are susceptible to genomic instability after incurring a second insult to BER (23). Moreover, sporadic pancreatic cancers harbor similar repair pathway defects resulting from other genetic mutations or DNA repair and damage response pathways and share this susceptibility "profile of BRCAness" (57).

Defective DNA damage and repair pathways are targets for inhibition of poly (ADP-ribose) polymerase I (PARP-1), a critical enzyme of DNA repair. PARP-1 is required for the BER of chemotherapy and radiation-induced DNA single strand breaks (58). When PARP-1 is inhibited in the presence of defective HR repair (as in BRCA2 mutations or in cancers exhibiting properties of "BRCAness"), the resultant DNA damage can be lethal (synthetic lethality) (56, 58). Thus, PARP inhibition might be a useful therapeutic strategy in the treatment of certain pancreatic cancers and is currently under investigation. However, the identification of aberrant DNA repair in cancer tissue is far from ideal at this point. Promising leads have been published recently to identify aberrant homologous recombination in body fluids such as ascites; these need to be validated in pancreatic cancer (59).

### **IgF1R as a target in pancreatic cancer**

Genetic variations in the insulin-like growth factor (IGF)-axis may also play a role in the development and progression of pancreatic cancer. It has been previously demonstrated that the protein products of these pathway genes (IGF1 receptor, IGF2 receptor, IGF binding protein family, and insulin-receptor substrate family) are involved in maintenance and regulation of tissue homeostasis and regulation of growth, differentiation and migration (60, 61). In a meta-analysis of 96 studies, circulating levels of IGF1, IGFBP3 (IGF binding protein), and IGFBP3 A-202C genotype were shown to

be important in carcinogenesis and potentially serve as biomarkers for cancer growth in various human malignancies through genotype-phenotype correlation analyses (62).

In pancreatic cancer, IGF1 may function as a growth factor (63). IGF1 is upregulated in human pancreatic cancer tissue, with serum levels elevated in pancreatic cancer patients (64, 65). We recently noted that genetic variations in the IGF axis pathway are prognostic in advanced pancreatic cancer (66). After genotyping 41 SNPs from 10 IGF-axis genes in over 700 advanced pancreatic cancer patients, we noted that SNP of the IGF1R, IGF2R, and IRS1 gene were significantly associated with survival. In a current study that includes an IGF1R-directed antibody, MK-0646 we have noted a correlation between IGF1/IGFBP3 ratio and response. These findings will be confirmed in a wider cohort of patients and a prospective, biomarker-driven study is planned (67).

### **Biomarker validation**

Biomarker-driven therapeutic clinical trials can include the co-development of the biomarker and the study agent, particularly when the biomarker is relatively novel.

The goal is to have appropriate validation before the marker can reach clinical applications; but validation is a cumbersome process for which standards are not clearly established. Critical issues that need to be addressed for the validation studies include the specificity and reproducibility of the marker. In the case of pancreatic cancer, this is further complicated by inter-patient heterogeneity and difficulty in obtaining representative sampling from the primary tumor site (pancreas). Regulatory guidance in this regard will be imperative in the development of biomarker driven targeted therapies for pancreatic cancer.

### **Clinical trial design for targeted agents**

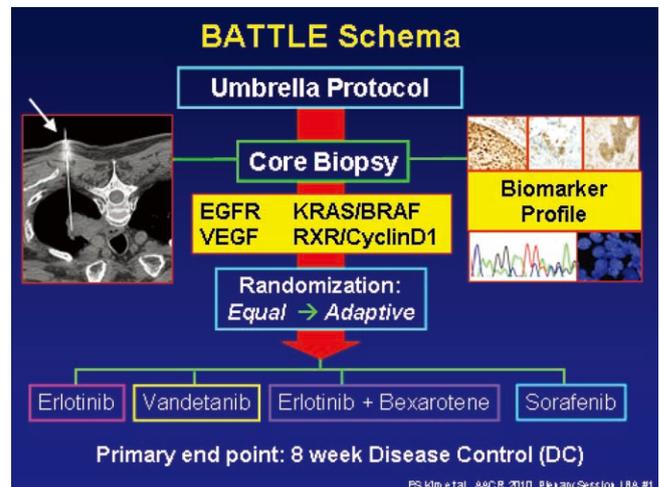
The use of a panel of biomarkers as potential predictive tools for the enrollment of patients on clinical trials with targeted agents requires innovative clinical trial design beyond the traditional simple randomization. These traditional trial designs are based on the 'frequentist' principles. Frequentist trial designs are based on the probability of observing results as being disparate from the expected or the 'null hypothesis'. In these frequentist designs, a p value is defined as the probability that the observed results are sufficiently disparate from the controls and a p value of <0.05 is generally considered as significant. The advantage of the traditional randomized trials is that these are relatively easy to implement and they are scientifically robust and focused. However, the latter is also a potential disadvantage as these trial designs are inflexible, limiting innovation or modification as the trial

proceeds. Furthermore, traditional randomized trials tend to be large and expensive wherein some patients are needlessly exposed to inferior therapies. Recent examples of these types of trials which are with erlotinib for advanced pancreatic cancer and herceptin in gastric cancer which enrolled >500 patients each and proved that these targeted agents were of some benefit. On the other hand, a sample size of 600 patients was also required to prove that bevacizumab was ineffective in pancreatic cancer despite the use of stopping rules in the trial.

In Bayesian designs, uncertainty is measured as a probability. Unknown parameters are given a probability distribution while what is known is taken as a given. However, once the results of the study become more evident, these are no longer probabilities and are taken as a given. Thus these trial designs are inherently adaptive and allow the investigator to modify trials mid course based on current data. Thus, Bayesian adaptive designs allow for changes to the clinical trial based on ongoing progress and allow enrichment based on the results. These designs are especially suitable for the development of biomarker-directed targeted therapy. For instance, the prior distribution of a biomarker profile may not be known with a great deal of certainty; this can therefore be hypothesized and refined as the trial develops. A pharmaceutical company can tie in the decision rules within the Bayesian trial design to determine the pathway for drug development. Bayesian designs are extensively being utilized at MD Anderson Cancer Center, wherein over a hundred clinical trials are ongoing using these principles. A detailed review of this trial design is described elsewhere. The disadvantages of this design is that it is computationally intensive, restricted to a limited number of centers with expertise and is not yet widely recognized by regulatory agencies as an efficient and economical pathway towards drug development. While these issues appear to be complex, successful implementation is possible and requires a multi-disciplinary effort. One such an example is an ongoing study in non-small cell lung cancer at our institution.

### *Battle trial for non small-cell lung cancer*

The recently concluded BATTLE 1 (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) phase II clinical trial conducted at MD Anderson Cancer Center illustrates the potential of Bayesian adaptive randomization as a study design for evaluating novel targeted therapies in cancer using personalized biomarker profiles to guide treatment allocations (Fig 1). First, 97 patients with stage IV non small-cell lung cancer who had received at least one prior chemotherapy were each assigned to receive one of four possible drugs (Erlotinib, Vandetanib,



**Figure 1** Scheme for Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE): Phase II clinical trial models the potential of prospectively integrating patient tumor biomarkers to guide the assignment of and assess the effect of new experimental therapeutics in non-small cell lung cancer. (Slide courtesy Edward Kim MD.)

Erlotinib + Bexarotene, or Sorafenib) by traditional simple randomization. Core biopsies of the lung were obtained from this initial subset of patients and profiled for four biomarkers (EGFR, KRAS/BRAF, VEGFR-2 and RXR/Cyclin D1). The primary study endpoint was progression-free survival at 8 weeks. Interim analysis was conducted to determine the specific biomarker profiles that predicted a favorable clinical response in each of the four study arms. These interim results were used to 'adapt' the randomization for the next 158 patients who entered the study. That is, each patient in this latter subset was assigned to that treatment likely to be most effective given the biomarker characteristics of the patient's tumor. Preliminary results indicate increased survival for the patients treated in this trial as compared with historical controls from the same institution who received 'unselected' therapy. The National Cancer Institute has recently underscored the value of bringing innovative methodologies to the design of biomarker-driven pancreatic cancer clinical trials, and the focus on personalizing management through the integration of biomarker correlates prospectively into BATTLE 1 is one such groundbreaking paradigm that can certainly be applied to pancreatic cancer (68).

### **Summary**

The lack of significant gains in the therapy of pancreatic cancer is at least partly attributable to its genetic heterogeneity. Even the current knowledge of these genetic variations opens several possible avenues for biomarker-

driven targeted therapy trials. These trials require the existence or co-development of biomarkers, innovation in design, implementation and regulatory guidance.

Recently, the Washington D.C. based 'think-tank', the Brookings Institution sponsored a workshop on clinical cancer research (69). This workshop included senior clinical investigators, scientists and representation from pharmaceutical companies and regulatory agencies. The challenges of targeted cancer approval process were recognized and the panel emphasized the need for a pathway for development and early approval of targeted therapies in a narrowly defined population, which would be expanded as subsequent studies merit. The panel's recommendations included principles for more efficient development of targeted cancer therapies with companion diagnostic tests. If trial results indicated that the therapy was safe and effective in the sub-population identified by an analytically valid diagnostic test, one way to accelerate availability of a promising candidate while further research is conducted would be to grant a "targeted approval" of the diagnostic (for the identification of the patient subgroup studied in the trial) and drug (for use in the subpopulation identified by the test). Full approval of the strategy would be granted upon completion of confirmatory Phase III trials and post-marketing studies.

Such a strategy, if implemented, is likely to accelerate the development of targeted therapies for subpopulations of pancreatic cancer.

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