# PERSONALIZED MEDICINE IN ONCOLOGY AND THE IMPLICATION FOR CLINICAL DEVELOPMENT

*Dr. Jamal Gasmi, Senior Director of Hematology and Oncology at Medpace, discusses personalized medicine in oncology and implications for clinical research.*

The notable success of imatinib for the treatment of chronic myeloid leukemia and trastuzumab for the management of HER2-positive breast cancer patients has generated great enthusiasm for the delivery of more effective and safer treatment to patients based on the genetic anomalies harbored by their cancer.[1] Subsequently, the identification of driver mutations and cancer genome sequencing have facilitated the development of novel targeted anticancer agents. Unfortunately, the attempt to replicate the success of imatinib and trastuzumab have been far less successful.

Many challenges remain in developing effective and efficient new targeted therapy agents, identifying the biomarker tests that indicate which patients will be responsive to them, and implementing them in clinical practice.

## CHALLENGES IN THE PERSONALIZED ONCOLOGY ERA

The advances on our understanding of biologic and molecular cancer profiles has led to the fragmentation of cancer into a variety of disease subsets. Each of these subsets are now less common than cancer diagnosed by histology alone, which likely benefits from a unique treatment approach. The need for efficiency through the discovery and the use of new biomarkers becomes blatantly obvious for the development of more efficient

molecularly-targeted agents. However, time, cost, and effectiveness are seemingly in competition to validate biomarkers throughout the clinical research process.

Even with the giant leap of bringing targeted therapies from concept to reality, using biomarkers successfully in clinical practice remains very challenging. Identifying biomarkers is only the first hurdle. What follows is a drastically difficult and time consuming series of steps to prove them clinically relevant.

Demonstrating that the biomarker is indeed, a surrogate for the clinical benefit, is a major undertaking, and the practical complexity of developing analytically valid diagnostic tests for the biomarker are grossly underestimated. The availability and accessibility of adequate tissue samples and reference laboratories, as well as the ability to reproduce and validate assays are arduous.

Additional issues regarding the study conduct and execution should be taken into consideration. Patient enrollment in clinical trials might be difficult due to several barriers including the protocol complexity, a long list of eligibility criteria required by molecularly driven trials, a lack of investigator interest and time, insufficient patient awareness, regulatory burden and ethical considerations. Other complications include the need for samples or tissue required to assess the biomarker for trial eligibility, which may require a large number of patients to be screened if the biomarker is of low prevalence in the tumor type under study which may impact the study duration.[2-3]

Prospective clinical trials should be the gold standard in validating a predictive biomarker, however with few exceptions, they can be time consuming, costly, and not even optimally informative. In such situations, an optional approach is to perform retrospective biomarker testing from previous randomized trials comparing therapies for which the marker is conjectured to be predictive. To illustrate how advances have been made and how clinical development must evolve to better individualize patient care, we will review the development of two major targeted therapy agents in advanced non-small cell cancer. A retrospective approach has been used for EGFR –TKI and a prospective approach for ALK+ inhibitor using enrichment design.

# THE EVOLVING PERSONALIZED THERAPY FOR ADVANCED NON-SMALL LUNG CANCER

Lung cancer is the most commonly diagnosed cancer, and is the leading cause of cancer deaths worldwide. Although the peak of the lung cancer epidemic seems to have passed in western countries, Asia will face a major epidemic in the future. Non-small cell lung cancer is the most major histological type, accounting of more than 85% of cases. Moreover, at diagnosis the majority of patients have advanced disease requiring palliative treatment with the objective of extending survival and improving the patient's quality of life.

Platinum based chemotherapy was considered the standard of care for patients with a good performance status. However platinum in combination with different compounds such as vinorelbine, gemcitabine or taxanes have shown similar efficacy, indicating that the ceiling with chemotherapy had been reached in efficacy and new treatment is needed.[4]

## 1. Epidermal Growth Factor Receptor (EGFR) –Tyrosine kinase inhibitors.

The Epidermal growth factor receptor was the first tyrosine kinase receptor to be identified. Defects in the EGFR pathway have been implicated in several cancer types including NSCLC. The first EGFR tyrosine kinase inhibitors ( TKI) gefitinib and erlotinib have shown an interesting response rate and symptom improvement in heavily pretreated patients with advanced NSCLC,[5-6] which led to the implementation of large phase III trials in first-line setting comparing TKI in combination with standard chemotherapy to placebo with standard chemotherapy. No significant advantage was demonstrated by the addition of erlotinb or gefitinib to chemotherapy over placebo with chemotherapy.[7-8] This disappointing clinical data initiated further investigations to identify a subgroup of patients that may be more likely to benefit from EGFR-TKI. Analysis of biospecimens from clinical trials identified a subgroup of patients that were most likely to respond to EGFR-TKI: Asian female patients, never smokers and with adenocarcinoma subtype. Further investigations have identified that patients harboring mutations in the EGFR tyrosine kinase domain are the most likely to benefit from EGFR-TKI therapy approach.[9-10]

Based on these findings, a large randomized trial has been conducted in East Asia comparing gefitinib, to chemotherapy using paclitaxel and carboplatin in first-line setting in advanced non-small lung cancer. Eligibility criteria requires female patients with adenocarcinoma subtype and a never or light smoker inclusion criteria.

The overall progression-free survival as the main endpoint was in favor of gefitinib. A planned retrospective analysis of EGFR on the available sample tissue has shown that patients with EGFR mutation has a significantly better PFS with gefitinib whereas patients with wild type has a better PFS with chemotherapy.[11]

Subsequent studies using EGFR-activating mutations as the selection process, confirmed that first-line therapy with an EGFR TKI was better for progression-free survival, although in most of the studies, this did not translate to overall survival.[12-13] This data supports that EGFR status is the driver for treatment decision.

## 2. Anaplastic Lymphoma Kinase (ALK) inhibitor

ALK activating mutation or translocation have been identified in several types of cancer, however, it was only recently that the EML4-ALK fusion gene was discovered to be a potent oncogenic driver in non-small cell lung cancer. Patients with the ALK fusion gene, or ALK-positive non-small cell lung cancer, may, therefore, represent a unique patient population that is susceptible to targeted ALK inhibition. Crizotinib is a potent and selective ATP competitive oral inhibitor of the ALK and MET tyrosine kinases that inhibits tyrosine phosphorylation.[14]

Of note, ALK translocation occurs only in approximately 5% of all NSCLC patients, moreover ALK rearrangements and EGFR mutations seems to be mutually exclusive while mainly occurring in patients with the same clinical feature; younger patients never or light smokers and adenocarcinoma subtype.[15]

The clinical development of crizotinib started with the first-in-human study conducted in two parts. The first part was to assess the safety and tolerability, and determined a maximum tolerated dose of crizotinib in any solid tumor refractory to standard therapy. The second part was an expanded prospectively enriched molecular cohort to explore the activity of crizotinib dosed at the MTD in NSCLC patients with ALK positive.

Overall, in this heavily ALK+ pre-treated non-small cell lung cancer population, the confirmed overall response rate at eight weeks was 57%. Response also potentially appears to be independent of the number of previous treatment regimens. The updated results of this expanded ALK+ cohort confirm that the majority of patients responded to crizotinib with the overall response rate of 60.8% and the PFS closer to 10 months.[16] The clinical data of the second global single arm phase II trial was consistent with what has been reported.[17] Based on this data , FDA granted accelerated approval to crizotinib for the treatment of patients with locally advanced or metastatic NSCLC with ALK positive as detected by a concurrently FDA approved diagnostic test, only four years after the first report of ALK rearrangement in NSCLC. Subsequently the PROFILE 1007 phase III trial comparing crizotinib to chemotherapy in previously pre-treated NSCLC patients with ALK+ confirms similar outcomes reported in the phase II trials, leading to the approval of crizotinib by European Medicine agency[18].

Although theses targeted therapies have brought significant improvements, all patients eventually develop resistance.[19-20] Multiple resistance mechanisms have been identified, such as secondary mutations preventing inhibitor binding. The development of second and third generation EGFR and ALK inhibitors to overcome these resistances was successful. Indeed osimertinib with activity against EGFR T790M and ceritinib and alectinib against the L11986M ALK mutation that confers resistance to crizotinib, have demonstrated efficacy in resistant patient population[21-23] leading to the FDA approval for these three agents.

## IMPLICATIONS FOR CLINICAL DEVELOPMENT

The example on the progress of personalized medicine in NSCLC provides evidence of the increasing importance of genetic profiling of cancers. As a consequence, the clinical trial structure has to evolve and tailored to genomic information. New trial designs have been proposed to much the right drug to the right patient at the right dose and at the right time.[24-25] These novel trial designs using the latest techniques in molecular profiling are now used in early drug development, with the aim to provide more informative therapeutic choice for patients. Two major categories of studies follow this design:

1. Basket trials evaluate the effect of specific therapeutic agents on a defined molecular target regardless of the underlying cancer type. This design allows a particular targeted therapeutic strategy across multiple cancer type cohorts. Examples are NCI's Molecular Analysis for Therapeutic Choice (MATCH) and the Molecular Profiling-based Assignment of Cancer Therapeutics trials (MPACT). This design permits the flexibility to continually open and close arms of the study. Each of these cohorts of a cancer type is analyzed separately but in in a single clinical trial. If there is a signal of efficacy in particular cohort, the cohort can be expanded to enroll more patients of that particular tumor type. In contrast, cohorts that do not demonstrate efficacy can be closed while the study continues with other tumor types. A basket trial design is especially advantageous when the mutation or cancer type is rare. The aim of basket trials can be either exploratory or for registration purposes in some cases.

2. Umbrella trials evaluate multiple targeted therapeutic strategies in a single cancer type. These studies utilize an individualized treatment plan after analysis of the molecular profile of each patient's tumor. Examples are Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And molecular Analysis 2 (I-SPYTRIAL2), and the phase II adaptive randomization design Biomarker-integrated Approaches of Targeted therapy for Lung Cancer Elimination (BATTLE), and the lung-MAP trial.

However, there are also certain challenges to genomic-based clinical trials; the rarity of certain molecular subtypes, statistical approaches on the study design and the uncertainty to discern and to prioritize the best drug are the main issues. Collaboration between research institutions, differences on regulation across countries, and collaboration with different sponsors are another hurdle.

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