Biomarker-Driven Clinical Trials: Challenges Overcome One-By-One

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High screening failure rates. Slow patient accrual. Slow sample turn-around time. Tissue sample heterogeneity. Data platform incompatibility. Tissue type variability. “Site fatigue.” Those conducting clinical trials driven by biomarkers have been plagued by problems such as these, but Moffitt researchers are overcoming them and are confident and optimistic that ultimately their efforts will be worthwhile and patients will benefit.

For Robert M. Wenham, MD, director of Moffitt's Total Cancer Care® program, among the first hurdles are determining what a biomarker is and then validating it.

“Last year the Institute of Medicine issued a report describing what a valid biomarker is,” says Dr. Wenham. “In the past what some thought were valid biomarkers turned out not to be.”

The 274-page report, “Evolution of Translational Omics: Lessons Learned and the Path Forward,” said in its introduction that: (Biomarkers are different) from other medical technologies, including a different regulatory oversight process, the difficulty in defining the biological rationale behind a test based on multiple individual biomarkers, the complexity of data sharing with other scientists, and the high degree of hope placed in the promise of omics-enabled technologies and medical care. Omics-based tests, and indeed all clinical laboratory tests, are subject to a different regulatory framework than drugs.

New Emphasis In Clinical Trials

Daniel Sullivan, MD, executive vice president and associate center director, Clinical Investigations, says that Moffitt is now focusing its clinical trials on higher-risk patients with later-stage and metastatic disease. “Conducting clinical trials driven by biomarkers are among that effort. And, to make them more successful, Moffitt is partnering with new sites and working closely with pharmaceutical companies,” says Dr. Sullivan.

“We've learned a lot along the way,” says Eric B. Haura, MD, director of Moffitt's Lung Cancer Center of Excellence and Lung SPORE. Since July 2012, Dr. Haura has been running a biomarker-driven phase I trial testing the tumor response rate of dasatinib, which is already FDA-approved for treating leukemia. This trial investigates the clinical activity of dasatinib and tumor response rate for patients with squamous cell lung cancer. Patients eligible must have the DDR2 kinase gene mutation or an inactivating B-RAF mutation.
Biomarker-Driven  Continued from front

“Only two to five percent of patients with squamous cell lung cancer have the DDR2 mutation,” says Dr. Haura. “If our trial is successful, the drug could be of great benefit to thousands of patients.”

Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancers, and approximately 25% of those diagnosed with NSCLC are of the squamous cell variety. Targeted therapy for squamous cell lung cancer has lagged behind adenocarcinoma, the most common kind of NSCLC. Yet, with the introduction of molecular profiling that can identify driver mutations, molecularly targeted therapy has been highly effective for well-defined varieties of lung cancer.

According to Dr. Haura, biomarker-driven clinical trials offer promise of great success, but the hurdles in finding the right trial patients are many. First among the hurdles is making sure that the biobanked patient tissue samples are the right kind for biomarker analysis.

“We need tumor material to do DNA sequencing for screening, but patients may have inadequate tissue material and may need additional biopsies,” he explains. “Another challenge is found in sending the tissue sample out for analysis, then getting it back in a timely way. Many of our clinical trials participants have a limited life expectancy, so there is no time to waste.”

Now, making a critical difference in reducing the time spent conducting biomarker-driven trials is Moffitt’s new Precision Molecular Diagnostics Laboratory, established in July of 2012 and directed by Anthony M. Magliocco, MD.

The laboratory is an esoteric, CLIA-certified lab conforming to the Clinical Laboratory Improvement Amendments of 1988 and capable of running tests that are beyond the capability of ordinary labs. Dr. Magliocco and his staff are assisting in the identification of biomarkers through molecular analysis and also running the variety of sophisticated tests needed by principal investigators (PIs) to conduct biomarker-driven trials. Therefore, tissue samples will no longer have to be sent out for analysis.

“Using the latest technologies, we will be working with M2Gen to match patients to clinical trials by sequencing the M2Gen biorepository of tissue samples and immediately assigning people to existing clinical trials or clinical trials yet to be developed,” says Dr. Magliocco. “We can do a thousand tests on a tissue specimen and look for gene mutations that indicate which clinical trial might be right for an individual patient.”

Challenges With Biosamples

Absolutely the new possibilities presented by the new CLIA-certified lab will be of great help, says PI Jhanelle Gray, MD, a medical oncologist in Moffitt’s Department of Thoracic Oncology and Experimental Therapeutics Program. Dr. Gray, with the help of her colleagues, has run a biomarker-driven phase I trial for patients with advanced colon or ovarian cancer. She knows first-hand some of the challenges in turning around tissue samples to see which patients are really qualified for a trial and to speed up patient accrual.

“Tissue sample heterogeneity, tumor biopsy yield and tissue preparation variability have posed problems,” she says. “Although initial evaluations may suggest that a patient has the desired biomarker, when the sample is sent to a vendor lab for analysis, the initial findings cannot be confirmed.”

“Because fine-needle aspiration biopsy is unlikely to yield the amount or kind of information needed for biomarker analysis, the recent move from fresh frozen to formalin-fixed paraffin-embedded samples will help to reduce screening failure rates and, consequently, speed up patient accrual through better sample correlation,” says Dr. Sullivan. “It has often taken six to eight months to get a biomarker-driven trial up and running.” Everyone agrees - that is too long.
Challenges In Biomarker-Driven Clinical Trials

- Identification of biomarker-positive patients
- Tumor banks with primary surgical samples, from early-stage disease
- Tissue type variability (fresh frozen vs. formalin-fixed, paraffin-embedded)
- Screening failure rates
- Slow accrual
- “Site fatigue”
- Timely assay results
- Lab turn-around times, shipping and return
- Patients who have positive markers but are clinically ineligible
- Incompatible databases; lack of correlation across platforms

But discovering a sample positive for a biomarker is just the first step.

“Once we have a biomarker-positive sample and the corresponding potential patient located, then resources are directed to recontacting and educating the patient and their primary physician on the specifics of the clinical trial of interest as well as prescreening for trial eligibility,” says Dr. Gray. “It is truly necessary to have a collaborative team environment between Moffitt, M2Gen/Total Cancer Care and the pharmaceutical company for successful completion of all these steps.”

Tumor heterogeneity can be a huge issue. Why?

“Because we are dealing with cancer (abnormal cells out of control, with no uniformity) and variable biomarker frequencies, at times large numbers of patients have to be screened,” Dr. Gray says. “We may screen 20 to find one, or hundreds to find a few. But we are more willing to accept a high screening failure rate if we find that one person for whom the drug has a great chance of working.”

Data Challenges

The PIs running biomarker-driven trials are quick to note the assistance from M2Gen® in identifying those patients with the biomarkers of interest. Searching the Total Cancer Care® data warehouse for patients appropriate for a given biomarker-driven trial has been made more efficient with a Health Research Information platform built on an Oracle database with a user interface called Transmed. This allows the PIs to search for an initial cohort of patients using a program called “Cohort Explorer.”

Even with these tools, it takes time to screen and identify those patients, then follow up with a cohort refinement questionnaire to further evaluate the patient’s suitability for a trial. Once that information is available, the principal investigator is notified, and the clinical trial PI can contact a Moffitt consortium site PI or the patient’s physician to discuss the eligibility of that patient for a clinical trial.

Even before the newest data analysis tools were on the scene, some of the thinking and data collection carried out through Total Cancer Care® had to be re-thought and retooled for biomarker-driven trials,” says Dr. Wenham.

“Collecting the right kind of data to run these kinds of trials proved to be more difficult than we had originally thought,” reflects Dr. Wenham. “To answer future questions, one needs to have an idea about what those future questions might be. When we started working with biomarker-driven protocols, we found that a lot of the information we needed was difficult to get to, not there or not in the form we needed. Dumping data together did not give us what we needed.”

Now, after retooling the Total Cancer Care® data collection process, working with Oracle and Deloitte, and refining data platforms and the data management function at M2Gen®, the processes are running more smoothly.

For example, Shilpa Gupta, MD, a medical oncologist in Moffitt’s Genitourinary Oncology Program, is conducting a phase I biomarker-driven parallel trial for breast cancer and prostate cancer based on gene signatures, and has found that initial matching with the help of M2Gen® was critical.

“With the help of data managers at M2Gen, and using the Total Cancer Care data warehouse, we searched for the marker of interest in patients with advanced prostate or breast cancer. Then we generated a questionnaire to find out if the patient was still alive, PSA level for prostate cancer patients, whether currently receiving hormone or chemotherapy, and if the patient had documented metastatic disease,” says Dr. Gupta. “It was a big list to start with, and some patients may have had surgery many years ago, but we needed to check study criteria, such as PSA or loss of PTEN for post-surgical prostate cancer patients, for example, because we could assume that the marker, which indicates poor outcomes, is driving prostate cancer. Then we could target using the trial drugs.”
Dr. Gupta’s trials are testing ridaforolimus (MK-8669) plus MK-2206 or MK-8669 plus MK-0752 in doublets to explore dose-limiting toxicities and maximum tolerated dose for both prostate and breast cancer patients with metastatic or locally advanced solid tumors. The breast cancer patients must have a low RAS gene signature score and a high Ki67 label index if they were estrogen-receptor positive.

“Ours was a case of successful trial matching,” says Dr. Gupta. “It’s been an exciting journey. The prostate cancer arm is closed, and the one patient on the trial is doing quite well. The breast cancer arm is still open.”

She also says that challenges still exist, but close teamwork has helped overcome them.

Khaledoun Almhanna, MD, medical oncologist in Moffitt’s Gastrointestinal Oncology Program, is conducting a phase I dose-escalation study of intravenous infusion of MLN0264 for patients with advanced gastrointestinal malignancies expressing guanylyl cyclase C, expressed in different percentages in GI malignancies. The trial assesses the safety profile and dose-limiting toxicities of the drug and the maximum tolerated dose.

“This trial has been open since July 2012 and is being conducted at Moffitt as well as at centers in Colorado, Massachusetts and Spain,” says Dr. Almhanna. “We are planning an expansion phase of this trial in which we hope to enroll 12 or more patients. During that trial phase, we expect to benefit from M2Gen’s resources for quickly finding patients with eligible biomarkers and then use the Moffitt CLIA lab to repeat tests.”

“Quickly” was the operative word for Dr. Almhanna.

“In biomarker-driven trials, the life expectancy of patients is often less than one year,” explains Dr. Haura. “Many of our patients are diagnosed outside of Moffitt and come here for treatment. Getting tumor material from outside of Moffitt can be a challenge, especially if their initial biopsy was a fine-needle aspiration biopsy.”

According to Dr. Haura, they need a good amount of tumor tissue to perform a DNA analysis, so patients who might be trial candidates may need additional biopsies.

“If someone has a life expectancy of six months, we can’t wait six months to get data back,” he says. “This is where the Moffitt CLIA lab is so critical.”

“Site fatigue” is another issue. It can come with the complications of the large task of identifying patients with biomarkers, screening them, discovering high rates of screening failure, or having long waits for samples to be found or returned from a lab, or patients who are not responding to treatment. When things are not working well, says Dr. Gray, enthusiasm can wane and site fatigue can set in.

“A successful future of biomarker-driven trials is also a population issue,” says Dr. Wenham.

“Having 90,000 patients in the database is not enough,” he says. “Hundreds of thousands are not enough. We need millions of patients to take our drug discovery program to the next level. In the future we won’t be screening hundreds to find a few. I think we will have to be able to screen millions to find thousands and, when we do, we can give something back to them.”

Biomarker-Driven Clinical Trials Open To Accrual

**MCC#16718**: An open-label, dose-escalation, phase I, first in human study of MLN0264 in adult patients with advanced gastrointestinal malignancies expressing guanylyl cyclase C.

**Objectives**: To assess the safety profile, including dose-limiting toxicities of MLN0264 administered as an intravenous (IV) infusion to patients with advanced gastrointestinal malignancies expressing guanylyl cyclase C. To determine the maximum tolerated dose in every 3-week dosing schedule of MLN0264. To describe the pharmacokinetic profile of MLN0264, total antibody (conjugated and unconjugated), and monomethyl auristatin E in blood. PI: Khaledoun Almhanna, MD.

**Contact**: Jennifer Cooksey, 813-745-4740.

**MCC#16968**: Phase II trial of dasatinib in subjects with advanced cancers harboring DDR2 mutation or inactivating B-RAF mutation.

**Primary Objective**: To assess the clinical activity of dasatinib, defined as tumor response rate, by stratum, in subjects with cancer harboring a DDR2 mutation or inactivating B-RAF mutation. 

**Secondary Objectives**: 1. To describe duration of response in responding subjects with cancer harboring a DDR2 mutation or an inactivating B-RAF mutation, by stratum. 2. To estimate progression-free survival (PFS) rate at 12 weeks of treatment (assessed at week 13) and overall PFS distribution in subjects with cancer having a DDR2 mutation or an inactivating B-RAF mutation, by stratum. 3. To estimate overall survival in subjects with malignancy harboring a DDR2 mutation or an inactivating B-RAF mutation, by stratum. 4. To describe the safety and tolerability of dasatinib in this setting. PI: Eric Haura, MD.

**Contact**: Angela Akar, 813-745-4625.

**MCC#17028**: Phase I parallel protocol of MK-8669 (ridaforolimus) + MK-2206 and MK-8669 (ridaforolimus) + MK-0752 doublets (MKMK) in patients with advanced cancer.

**Objectives**: To define the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of MK-MK doublets (ridaforolimus + MK-2206 and ridaforolimus + MK-0752) administered to adult patients with solid tumors. To determine the effect of MK-0752 on the exposure to ridaforolimus following concomitant administration of ridaforolimus and MK-0752. To explore the antitumor activity of MK-MK doublets in the Part B expansion cohorts in patients with solid tumors. To assess the pharmacokinetic profile of MK-MK doublets in patients with solid tumors. PI: Shilpa Gupta, MD.

**Contact**: Jennifer Cooksey, 813-745-4740.
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To schedule a lung screening exam, call the New Patient Appointment Center at 1-888-860-2778.

Robert M. Wenham, MD
Director, Clinical Investigations

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