Department of Investigational Cancer Therapeutics

# Phase I Clinical Trials

VOLUME 8, NO. 1 • WINTER/SPRING 2012

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

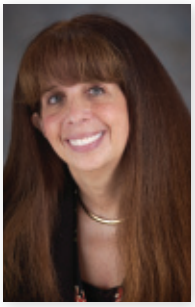
Making Cancer History®

# Is It About Time. . .

## to Move Molecular Profiling and New Targeted Therapies Earlier in the Disease Course?

## Lessons Learned from Chronic Myelogenous Leukemia Success Story

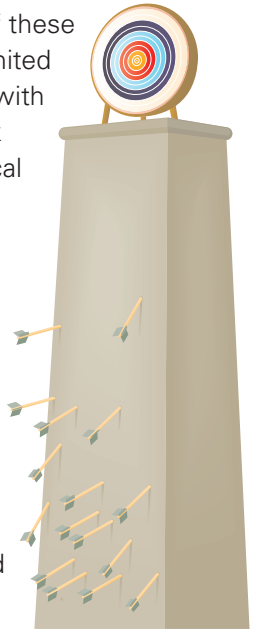
## FROM THE CHAIR



**Razelle Kurzrock, MD**
Chair, Department of Investigational Cancer Therapeutics

Moving imatinib and later generations of BCR-ABL inhibitors to newly diagnosed disease has transformed the outcome of chronic myelogenous leukemia (CML) from a death sentence within four years to an estimated average survival of more than 20 to 25 years. "Can similar success stories be attained with solid tumors by moving novel targeted therapies from advanced metastatic disease to earlier disease?" ask Razelle Kurzrock, MD, chair of Investigational Cancer Therapeutics, and Jason Westin, MD, instructor in Lymphoma /Myeloma. Comparing the blast crisis phase of CML to metastatic disease in solid tumors, Dr. Kurzrock points out the dramatic increase in complete response from approximately 15 to 90 percent when imatinib was moved from treating patients with advanced CML, who were in blast crisis, to patients in the earlier chronic phase of the disease. She noted that the difference likely reflects the multitude of complex new chromosomal aberrations as malignancies progress. "We need to figure out how to move targeted therapy earlier because metastases are often too genetically complex to eradicate," Dr. Kurzrock said.

Despite the development of several drugs inhibiting specific critical drivers of solid cancers, most targeted therapies have shown modest effects, and the dramatic disease regression seen in some patients does not usually translate to complete remissions or cures. As the use of most of these targeted therapies has been limited to heavily pre-treated patients with advanced disease, Dr. Kurzrock surmises that the missing critical element for more enduring outcomes may be simply timing: moving novel targeted therapies to molecularly simpler early-stage disease, when there are fewer key molecular drivers to target. "We take our best drugs and wait to give them to patients when it's too late," said Dr. Westin. "Now targeted therapy is used at a stage where it's likely to fail."



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WHY MD Anderson?

- We are ranked #1 nationwide in cancer care by U.S. News & World Report.
- We lead the way nationally in National Cancer Institute grant awards dollars, receiving more than $236 million annually.
- We have 12 specialized Programs of Research Excellence (SPORE) awards from the National Institutes of Health, more than any other institution in the country.
- We see more than 108,000 cancer patients per year, 35,000 of them new patients.
- Nearly 10,000 patients are on therapeutic clinical trials.

Bench to Bedside & Back

## Chronic Myelogenous Leukemia Success Story - continued from page 1

Drs. Kurzrock and Westin caution, however, that the parallel between CML, primarily advanced by a single driving mutation, is not directly comparable to solid tumors, as they are usually molecularly more complex, and there may be more than one driver for even an early-stage malignancy. Effective treatment will require a rational combination of several targeted drugs hitting key mutations to "take out the critical nodes." Dr. Westin draws an analogy to airline networks. Taking out one key airport hub such as Houston would have little effect on Continental Airline's operations because they could simply reroute the flights, but removing three key airports could take out the airline. Similarly, to get an adequate response to treatment for cancer, "We must attack several nodes at the same time. Some nodes may have 50 connections, but if we identify and take out the most critical nodes simultaneously, we can have a dramatic exponential effect. We've identified 15 driving mutations but we don't know how they play together, so we have to take out several key ones that are driving a particular malignancy." But, importantly, the number of critical hubs is likely to be much fewer in early disease than in advanced metastatic disease.

**Jason Westin, MD**

In addition to the need to move effective drugs earlier, the other reason for calling a paper they submitted for publication "It's about Time" is the urgency of this need; "It's about time we did this," said Dr. Westin, "We shouldn't wait any longer. Let's just do it." One barrier to "just doing it" that must be overcome first, however, may be the reluctance of oncologists to forego the use of long-established, standard therapies that produce some remissions and cures. This must be done in a thoughtful way so that patients who can be cured or achieve long-term survival with classic therapies do not have their chances for a good outcome diminished.

Drs. Kurzrock and Westin recommend introducing the early targeted approach by initially using it with patients who, perhaps due to co-morbidities or age, will not tolerate harsh chemotherapy, radiation therapy, or surgery. Alternatives may include giving these therapies to patients after surgery, particularly if they are at very high risk of relapse. Also, some rarer cancers may not have FDA approved therapies that are known to be effective, and in these tumors, targeted treatments could be introduced earlier.

"Quickly moving promising targeted therapies to the treatment of the earliest phases of biomarker-defined solid tumors has the potential to dramatically improve patient outcomes, and ultimately prove that imatinib in CML is not an anomaly, but a paradigm," Dr. Kurzrock concluded. Dr. Westin added, "The era of not looking before treating is over. We need to do molecular profiling of fresh biopsies, then act quickly against the key drivers. It is important not to miss the window of time when there are five drivers to target instead of 50 or 100."

# Response Highlights

## Patient with Metastatic Renal Cell Cancer Responds Rapidly to First-in-Human PI3K Inhibitor

After only eight weeks on a Phase I clinical trial of a first-in-human, oral, small-molecule inhibitor of the PI3 kinase family of proteins, Carl Klimitchek and his treatment team led by Gerald Falchook, MD, assistant professor, and principal investigator Razelle Kurzrock, MD, chair, Department of Investigational Cancer Therapeutics, were encouraged by the rapid shrinkage of his lung tumors associated with metastatic renal cell carcinoma. Furthermore, Klimitchek continues to respond to this drug more than two years later.

Klimitchek's physician in Victoria referred him to MD Anderson after spotting a lesion on his lung following left nephrectomy for a 12 cm mass with left pleural involvement. His renal cell cancer had been diagnosed in 2005 while he was only in his 40's and the father of three children. Nizar Tannir, MD, associate professor in Genitourinary Medical Oncology, found metastases to the lung and bone, and began Klimitcheck on a clinical trial of sorafenib. His cancer progressed, so he was switched to sunitinib, followed by wedge resection of the lung metastases. His disease continued to progress rapidly in 2009 despite treatment with everolimus, then two cycles of gemcitabine combined with capecitabine, and a pleural catheter was placed to drain fluid from growing pleural effusions in August 2009.

Klimitchek was then referred to the Clinical Center for Targeted Therapy in September 2009, where he started on a Phase I clinical trial of bevacizumab with bortezomib, under the care of Gerald Falchook, MD, and Susan Tse, RN, (photo, left) research nurse supervisor. After four cycles on this regimen, his cancer again progressed. When clinicians told him they wanted to stabilize his cancer, Klimitcheck replied, "That's not what I want. I want to cure it. I want to be the first to cure kidney cancer. I'll be the guinea pig."

The next clinical trial with a PI3 kinase inhibitor proved to be much more successful; he had an immediate and enduring response. "He had such a fast response that everyone was shocked," said his wife Candy. "I decided to try an experimental drug because my cancer kept spreading and was not responding to other treatment," said Klimitchek. "They monitor you closely so you are not at risk." Klimitchek began the drug in December 2009, and by February 2010, his pleural effusions had resolved and stopped draining, which enabled removal of the pleural catheter. At that time, Klimitchek's restaging scans revealed that he had achieved more than a 50 percent reduction in the size of his tumors. Subsequent scans demonstrated continued decrease in the size of his tumors, which are in near remission as of March 2012. Klimitcheck's performance status has remained excellent, and he has been able to continue to work full-time. "I had no side effects from this drug," said Klimitchek. "I felt the same way I did when I was first diagnosed; I felt no symptoms. Other treatments made me very sick."

"The treatment team has been great," said Mrs. Klimitcheck. "They included me and treated us like part of the family."

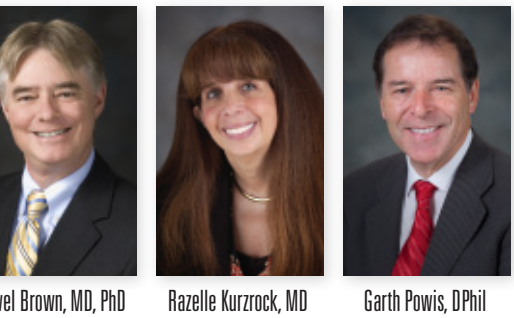
Klimitcheck said his experience with cancer has inspired his daughter, a student at Texas A&M in the biological sciences, to seek a future career doing cancer research.

# Lessons Learned from a Molecularly Targeted Early Clinical Trials Workshop:

## How Can We Apply New Target Discovery to Prevention and Early-Stage Disease?

A multidisciplinary team of oncologists and scientists from subspecialty areas of Molecular Medicine, Medical Oncology, Experimental Therapeutics, Personalized Medicine, New Drug Discovery, Clinical Cancer Prevention, Epidemiology, Pathology, and Surgery, all came together November 5, 2011 to tackle a burning question:

**How and when should we introduce molecularly targeted therapies earlier in the course of a patient's malignancy, before it becomes too advanced to generate a lasting response or cure?**



Powel Brown, MD, PhD



Razelle Kurzrock, MD



Garth Powis, DPhil

The joint workshop was sponsored by the Cancer Center Support Grant (CCSG) Targeted Therapy and Cancer Prevention Programs and was co-chaired by Garth Powis, DPhil, chair of Experimental Therapeutics, Razelle Kurzrock, MD, chair of Investigational Cancer Therapeutics, and Powel Brown, MD, PhD, chair of Clinical Cancer Prevention. President Ronald DePinho, MD attended the conference and stressed the importance of putting our energy into research that is transformative.

Dr. Powis launched the workshop with an overview of targeted molecular research resources available at MD Anderson. Noting that pharmaceutical industries tend to focus on therapeutics for the major four cancers, leaving more than 100 underserved cancers, he pointed out that numerous agents are under development at MD Anderson. His Pharmaceutical Development Center aims to provide resources to investigators to propel drugs much more quickly into the clinic than the typical 15 years, and at a markedly lower cost. Within a few years, 21 drugs are in clinical trials and several are moving toward FDA approval.

# Can We Molecularly Target Cancer Prevention?

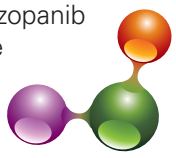
Ernest Hawk, MD, professor and vice president for Cancer Prevention, discussed the results of the premalignant cancer genome project co-led by Xifeng Wu, MD, chair of Epidemiology, and Lupa Mishra, MD, chair of Gastroenterology, Hepatology, and Nutrition. They have one of eight programs that participate on the Premalignant Genome Atlas. The three components consist of a BioBank of premalignant lesions, cohorts of patients with premalignancies such as colon polyps, and technology platforms. A primary goal is to determine the differences between high-risk patients who develop cancers and low risk patients who do not.

Powel Brown, MD, PhD, presented on 10 cancer prevention clinical trials conducted at 14 sites through the Phase I and II Chemoprevention Consortium started by Scott Lippman, MD, currently chair of Thoracic/Head and Neck Medical Oncology. The inhaled steroid budesonide was studied in former and current smokers with lung nodules but there was no difference in nodule shrinkage compared with patients who did not receive budesonide. Another study aims to modify arachidonic acid metabolism by chemopreventive agents in smokers accrued through Craig's list; the statin Zilentin is administered to block leukotriene pathways along with celecoxib. A new multi-center Phase II trial of a PARP inhibitor led by Banu Arun, MD, professor in Breast Medical Oncology, and Dr. Brown will be conducted with more than 800 triple negative breast cancer survivors. "Phase I and cancer prevention investigators need to get together to identify premalignant drivers to target," Dr. Brown advised. "We should take what we learn from advanced cancers to early cancers and to prevention, then choose the right genes to target," Dr. Kurzrock added.

Dr. Banu Arun noted that chemoprevention significantly reduces the risk of breast cancer, yet less than 20 percent of patients take selective estrogen receptor modulators (SERMs) to reduce their risk because they don't want the side effects. "What if there were no side effects?" she challenged, as she discussed new agents with less toxicity, many effective against estrogen receptor negative cancer as well. For example, treatment with celecoxib was found to be a favorable modulator of insulin growth factor binding protein-1 (IGFBP-1) in high-risk patients. She recommends future breast cancer prevention trials of agents targeting inflammatory pathways. Another alternative to SERMs her research team is studying is aromatase inhibitors such as anastrazole. Arun and colleagues found that anastrozole significantly modulated IGFBP-1 levels in women at increased risk of developing cancer in contralateral breast tissue, results which support using IGFBP-1 as a surrogate endpoint biomarker in prospective chemoprevention studies. Anastrozole is currently being studied for chemoprevention in a large Phase III trial. A prevention study of the anti-inflammatory statin atorvastatin is being conducted in women at increased risk for breast cancer. The endpoints are modulation of proliferation, apoptosis and inflammatory markers, as well as evaluation of its metabolites in plasma and tissue.

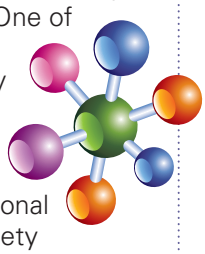
Theresa Bevers, MD, professor in Clinical Cancer Prevention, summarized the findings of some prominent Phase III cancer prevention trials. Her longitudinal STAR study comparing tamoxifen and raloxifene in the prevention of breast cancer found an overall reduction on raloxifene of adverse effects such as endometrial cancer and thromboembolic events and equal reduction of invasive breast cancer but with about 77 percent of tamoxifen's overall benefit over nearly seven years. Her statin polyp prevention trial in patients with resected colon cancer aims to determine the effect of rosuvastatin administered postoperatively for five years on the occurrence of adenomatous polyps of the colon or rectum, metachronous colorectal carcinoma, or colon cancer recurrence. Based on previous studies, she estimates a 45 percent decrease in the odds of recurrence, independent of the effect of aspirin.

Presenting on cancer therapy as a continuum, Scott Lippman, MD, professor and chair of Thoracic/Head and Neck Medical Oncology, noted that one problem with prevention of lung cancer is that we don't have a good risk model for never smokers. Genome-wide association scan studies at several institutions including MD Anderson have identified SNPS that are the most significantly associated with lung cancer risk for current or former smokers. Several drugs targeting the epidermal growth factor receptor (EGFR), analplastic lymphoma kinase (ALK), and vascular endothelial growth factor (VEGF) have been approved for the treatment of advanced non-small cell lung cancer, are better tolerated than conventional chemotherapy, and exhibit dramatic efficacy with careful selection of patients who are likely to respond, but which agents should be moved up to treat early-stage NSCLC remains uncertain. John Heymach, MD, PhD's team has been using cytokine and angiogenic factors successfully to predict tumor response in patients with early-stage, non-small cell lung cancer (NSCLC). Working with investigators from Cornell University, his team found that a CAF signature of hepatocyte growth factor (HGF) and interleukin-12 was associated with tumor response to the oral angiogenesis inhibitor pazopanib, identifying responding patients with 81 percent accuracy. An international, multi-center Phase III trial of pazopanib in Stage I NSCLC is now underway under the leadership of investigators in France.



## How Can We Use Lessons Learned from Advanced Cancer to Target Earlier Stages?

"We can learn a lot from clinical trials treating advanced cancer to inform preventive and early trials," commented Dr. Kurzrock. "We need not only new drugs but also new approaches. We need to ensure that more drugs that enter phase I trials eventually get approved." She added that the FDA approved drugs we have now are not doing so well, often raising overall survival by only a couple of months, with a typical response rate from two percent to around 20 percent. "We have the tools and technology now to do better than this," she said. The Phase I Program is target-based rather than diagnosis-based. Unlike many programs of its kind, however, there is much more emphasis on proof of principal and response than on dose finding. Her program has demonstrated that molecular testing makes a difference in early clinical trials even though Phase I patients typically have already had an average of four pretreatment cycles. "One of the problems is in the way we are classifying cancers," she noted. "Response rates are very high—35 to 77 percent—when treatment is by molecular matching." A successful example is our histology-independent PREDICT trial in the Department of Investigational Cancer Therapeutics; 1200 patients with a variety of advanced cancers were analyzed for multiple molecular aberrations and matched whenever feasible to drugs targeting those aberrations. Outcomes were significantly better in matched than unmatched patients. The study has important shortcomings, including the fact that it was not randomized, but the results nevertheless suggest that matching patients with targeted drugs based on their molecular profile can be associated with higher than anticipated response rates, even in heavily pretreated patients receiving Phase I drugs.



For more successful cancer treatment in the future, Dr. Kurzrock sees a need to combine the right drugs for dual inhibition of key cell signaling pathways, and to move such targeted treatment earlier in the disease course when it can be more effective. To accomplish this on a large scale, she noted, we need advanced multi-assay technology so we don't run out of tissue, and careful analysis of host factors is necessary to prevent toxicity. Cost and coverage assessment must be considered to avoid giving expensive drugs that won't really benefit patients.

Dr. DePinho commented on the critical importance of preclinical research. "We need to exploit model systems in preclinical studies to better inform which agents work with each other," Dr. DePinho noted.

## Are We Making Good on the Promise of Personalized Cancer Treatment for All?

Presenting on behalf of the Institute for Personalized Cancer Therapy, Michael Davies, MD, used melanoma as an example. The BRAF inhibitor vemurafenib proved highly successful when given to patients who had the BRAF V600E mutation; most patients with the BRAF mutation responded, while patients who had wild-type BRAF did not respond. "Vemurafenib was the shortest Phase III clinical trial ever," he commented. The trial was closed less than one month after the last patient was enrolled because outcomes were clearly much better than for standard treatment. He cautioned, however, that selective BRAF inhibitors may actually cause harm if given to the wrong patients. Four out of five patients with wild-type BRAF, for example, had progressive disease on vemurafenib because it stimulated tumor growth in these patients by re-activating the MAPK pathway or activating another major survival pathway such as PI3K. He noted that complete inhibition of the target pathway is necessary for a drug to be effective and shut down the pathway. Not only must we give the right drug to the right patient, we also must give the right dose, he stressed, asking, "What degree of inhibition is needed to get clinical benefit?" He added that our greatest challenge is how to address the development of drug resistance because most patients will eventually relapse. An example is a patient who achieves a nearly complete response, but three months later, all the tumors come back.

"The IPCT delivers the promise of personalized cancer medicine," Dr. Davies said. "To improve outcomes, we must analyze every patient to identify targets for treatment." The aim is for all 30,000 patients per year to have tumor biopsies to determine whether the patient has a druggable aberration. But we also have to know what to do with the sixty percent of patients with no target identified. We need to understand these aberrations and what treatment is effective. An unusual responder program is planned to further investigate patients with marked responses on clinical trials. Their tumors will be biopsied and undergo candidate gene analysis to determine whether expected biomarkers are present, which will then be subjected to clinical validation. When expected biomarkers are not present, deep characterization sequencing, then high throughput biological validation investigations will be conducted. A clearinghouse study will enroll new patients in Sequenom studies, then in deeper characterization studies if a mutation isn't found.

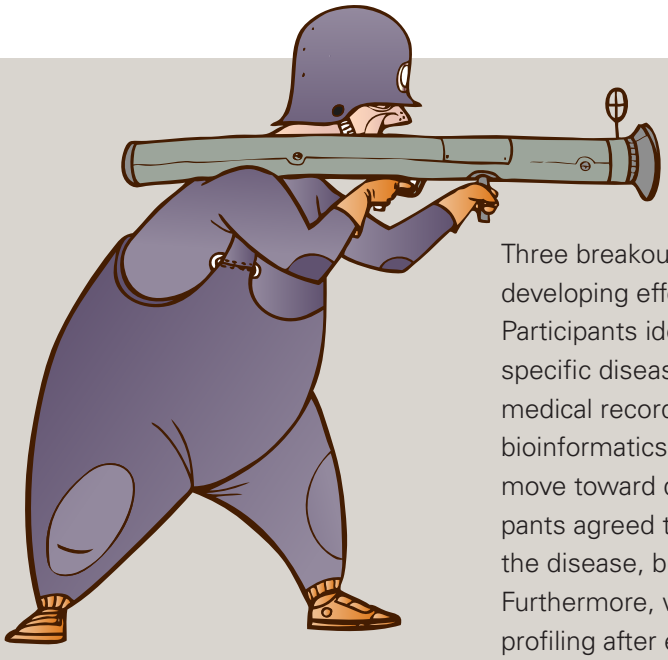
## How Early to Start Targeted Therapy?

If oncologists across MD Anderson agree that molecularly targeted treatment is likely to be more effective if moved to earlier stages of disease, or even to the prevention stage, then why aren't we treating early stage disease in that way?

Elias Jabbour, MD, professor in Leukemia, explained how treating newly diagnosed disease with a targeted therapy transformed chronic myelogenous leukemia (CML). After the development of tyrosine kinase inhibitors, ten-year survival rose to 80 to 90 percent of patients with CML by moving imatinib, nilotinib and dasatinib to frontline treatment. Most of these patients will now have a normal life span. However, he noted that patients need to achieve an optimal response early, between six and 12 months, to have a good outcome.

Lajos Pusztai, MD, DPhil, professor in Breast Medical Oncology, discussed issues surrounding how early targeted therapy should be introduced in breast cancer. He noted that more than 80 percent of patients with Stage I and II breast cancers are cured with current drugs, but at the other end of the spectrum, Stage IV is incurable with current drugs. Can drugs with a modest life-prolonging effect in metastatic breast cancer increase cure rates in early disease? We don't want to compromise patients with disease that is curable with current treatments. We need to identify those patients who are not likely to be cured with current therapeutic modalities. However, "We don't want to try to cure the same patient five times." Individualizing cancer treatment strategies starts with using a genomic predictor of response and survival following standard chemotherapy for invasive breast cancer. Patients who don't get an excellent response to preoperative chemotherapy tend to have progressive disease, and nearly one-third of these patients are dead within three years. Immune signatures have predictive value only for high risk breast cancers, such as triple negative or extensive residual disease after standard treatment. Thus, he contends that ethical and feasibility issues prevail for moving clinical trials of new targeted therapies to early stage breast cancer.

Chris Holsinger, MD, associate professor, Head and Neck Surgery, examined the treatment of early-stage cancer from the surgeon's point of view. "Surgery is the first targeted therapy," he said. He emphasized that current techniques are minimally invasive and endoscopic, with a high rate of preservation of the larynx. Robotics are used for hard to reach places; an entire tumor can be removed using robotic resection. Using improvements in surgery and biopsy capabilities, new targeted molecular therapy can be used to treat early stage head and neck cancer with no alteration in speaking, swallowing, or breathing.



## Challenges and Solutions

Three breakout sessions identified and offered solutions to challenges in developing effective early targeted therapies and cancer prevention strategies. Participants identified an urgent need for a searchable clinical database for specific disease outcomes, which is not currently available in Clinic Station medical records. Participants recommended providing specific support to bioinformatics experts to collaborate with specific programs and centers as we move toward data-dense whole genome studies. First and foremost, participants agreed that we must bring novel drugs to patients earlier in the course of the disease, before it becomes too complicated (see "From the Chair," on pg. 1). Furthermore, we need to have the capability of doing biopsies for molecular profiling after each relapse, as well as at the time of diagnosis. It was felt that we need better access to new drugs, more well-annotated preclinical models to inform clinical studies, and access to advanced multi-assay CLIA approved molecular profiling technology.

## Department of Investigational Cancer Therapeutics


**Razelle Kurzrock, MD, FACP**
Chair, Dept of Investigational Cancer Therapeutics
Chair, Phase I Working Group
Phone: (713) 794-1226 • Pager: (713) 404-2397
E-mail: rkurzroc@mdanderson.org

**Toni L. Abbasi, RN, MBA**
Clinical Administrative Director
Lymphoma/Myeloma Center
Phone: (713) 792-5612 • Pager: (713) 404-2012
E-mail: tabbasi@mdanderson.org

**Christie Carver-Fryer, RN, BSN**
Manager, Clinical Protocol Administration
Clinical Center for Targeted Therapy
Phone: (713) 562-3699 • Pager: (713) 606-3631
E-mail: cpcarver@mdanderson.org

**Gerald Falchook, MD,** Assistant Professor
Dept. of Investigational Cancer Therapeutics
Phone: (713) 792-9669 Pager : (713) 606-0345
E-mail: gfalchoo @mdanderson.org

**Siqing Fu, MD, PhD,** Associate Professor
Dept. of Investigational Cancer Therapeutics
Phone: (713) 792-9669 • Pager: (713) 606-0942
E-mail: SiqingFu@mdanderson.org

**David Hong, MD,** Assistant Professor
Dept of Investigational Cancer Therapeutics
Medical Director
Clinical Center for Targeted Therapy
Phone: (713) 792-2740 • Pager: (713) 404-0560
E-mail: dhong@mdanderson.org

**Filip Janku, MD, PhD,** Assistant Professor
Dept. of Investigational Cancer Therapeutics
Phone: (713) 563-2632 • Pager: (713) 606-4593
E-mail: FJanku@mdanderson.org

**Stacy Moulder, MD,** Associate Professor
Depts. of Investigational Cancer Therapeutics
and Breast Medical Oncology
Phone: (713) 792-2817 • Pager: (713) 606-3721
E-mail: smoulder@mdanderson.org

**Aung Naing, MD,** Assistant Professor
Dept. of Investigational Cancer Therapeutics
Phone: (713)792-2950 • Pager: (713) 404-2400
E-mail: anaing@mdanderson.org

**Ollieta Nicholas, MBA**
Associate Director, Research Planning and Development
Dept. of Investigational Cancer Therapeutics
Phone: (713)792-4397 • Pager: (713) 606-3690
E-mail: onicholas@mdanderson.org

**Janet Norton, MBA,** Department Administrator
Dept. of Investigational Cancer Therapeutics
Phone: (713) 745-6789 • Pager: 713/404-4742
E-mail: jenorton@mdanderson.org

**Sarina Piha-Paul, MD,** Assistant Professor
Dept. of Investigational Cancer Therapeutics
Phone: (713)794-4225 • Pager: (713) 404-1209
E-mail: spihapau@mdanderson.org

**Susan R. Pilat, RN, BSN,** Research Nurse Manager
Dept. of Investigational Cancer Therapeutics
Phone: (713) 745-3296 • Pager: (713) 404-2822
E-mail: spilat@mdanderson.org

**Apostolia Maria Tsimberidou, MD, PhD**
Associate Professor
Dept. of Investigational Cancer Therapeutics
Phone: 713/792-4259 • Pager: (713)404-1870
E-mail: atsimber@mdanderson.org

**Jennifer Wheler,** MD, Assistant Professor
Dept. of Investigational Cancer Therapeutics
Phone: (713)745-9246 • Pager: (713)404-1201
E-mail: jjwheler@mdanderson.org

**Ralph Zinner, MD,** Associate Professor
Dept. of Investigational Cancer Therapeutics
Phone: (713)795-6601 • Pager: (713)404-2724
E-mail: rzinner@mdanderson.org



NEWSLETTER PRODUCTION:

**Carol A. Howland, MS**
Editor & Program Manager, DoCM Publications

Graphic Design:
MD Anderson Medical Graphics & Photography


For patient referrals, contact:
Christie Carver-Fryer, RN, BSN


The University of Texas
MD Anderson Cancer Center
Department of Investigational
Cancer Therapeutics – Unit 455
1515 Holcombe Boulevard
Houston, Texas 77030-4009



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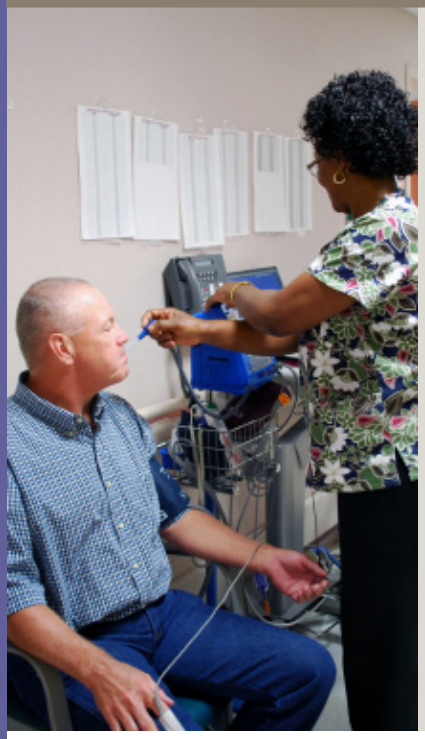

## Did You Know That in Fiscal Year 2011...

- There were 128 Phase I clinical trials on the program's priority list?
- 1,366 patients were enrolled in Phase I trials?
- The Clinical Center for Targeted Therapy had 12,313 patient visits?
- The department received more than $15 million in peer-reviewed and sponsored research?
- This became the largest program in the world expediting the development of early phase clinical trials of new cancer therapeutic agents?

## The goals for Phase I trials in the next couple years are to:

- Move the program toward personalized therapy, fingerprinting patients to predict potential response, and identify preliminary subsets of responsive patients to use as a foundation for Phase II studies.
- Enhance the capacity of Phase I studies to serve as a conduit to Phase II efficacy studies, especially for uncommon tumors, so that early evidence of response can be quickly translated into new treatment.
- Have a large number of high-impact studies, aiming to investigate "the best molecules in the nation."
- Emphasize strongly the quality of patient care, keeping in mind that the patient must always come first, not the study.
- Continue to foster team work and a collaborative atmosphere both within the program and in its interactions with other investigators throughout the institution, so that the ultimate goal of bringing new therapies to cancer patients can be met.
- Further develop the Phase I infrastructure, from faculty to research nurses, coordinators and other personnel, in order to maximize program growth and excellence.

# Active Phase I Program Protocols

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

| Protocol | Principal Investigator | Drug Mechanisms | Diseases | Comment |
|---|---|---|---|---|
| * BAY 73-4506 | George Blumenschein, Jr., MD | Multi-kinase (raf, VEGFR, PDGFR) inhibitor | Advanced cancer | |
| GSK1120212 and<br>1) docetaxel<br>2) erlotinib<br>3) pemetrexed<br>4) pemetrexed and carboplatin or<br>5) nab-paclitaxel | George Blumenschein, Jr., MD | MEK inhibitor combined with chemotherapy | Solid tumors | Allows CNS metastases |
| *Azacytidine and valproic acid + carboplatin | Gerald Falchook, MD | Histone deacetylase inhibitor, hypomethylating agent, and chemotherapeutic agent | | Ovarian cancer |
| Bevacizumab and bortezomib | Gerald Falchook, MD | Anti-angiogenic agent and proteasome inhibitor | Advanced cancer | Allows children any age and CNS metastases |
| Bevacizumab and<br>1) sunitinib<br>2) sorafenib<br>3) erlotinib and cetuximab<br>4) trastuzumab and lapatinib | Gerald Falchook, MD | Anti-angiogenic agent and multi-kinase inhibitor, EGFR inhibitor, HER2 inhibitor | Advanced cancer | Allows children any age and CNS metastases |
| GSK 2118436 | Gerald Falchook, MD | BRAF inhibitor | Solid tumors | |
| MLN8237 | Gerald Falchook, MD | Aurora kinase inhibitor | Solid tumors | Allows CNS metastases |
| MLN8237 (enteric coated tablet) | Gerald Falchook, MD | Aurora kinase inhibitor | Solid tumors | Allows CNS metastases |
| EMD1214063 | Gerald Falchook, MD | cMET inhibitor | Advanced cancer | Allows CNS metastases |
| GSK 1120212 | Gerald Falchook, MD | MEK inhibitor | Advanced cancer | Allows CNS metastases |
| MLN8237 and paclitaxel | Gerald Falchook, MD | Aurora kinase inhibitor | Solid tumors | Allows CNS metastases |
| EMD1204831 | Gerald Falchook, MD | c-MET inhibitor | Solid tumors | Allows CNS metastases |
| GSK2118436 and GSK1120212 | Gerald Falchook, MD | MEK and BRAF inhibitors | Solid tumors | Allows CNS metastases |
| GSK2118436 or GSK2118436/GSK1120212 BRAF or BRAF/MEK rollover | Gerald Falchook, MD | MEK and BRAF inhibitors | Solid tumors | Allows CNS metastases |
| Doxil, gemcitabine, and Velcade | Gerald Falchook, MD | Chemotherapy with proteosome inhibitor | Advanced cancer | Allows children any age and CNS metastases |
| Trientine and carboplatin | Siqing Fu, MD, PhD | Chelating agent and alkylating agent | Advanced cancer | Allows children any age and CNS metastases |
| *CUDC-101 | Siqing Fu, MD, PhD | HDAC/EGFR/Her2 inhibitor | Solid tumors | Allows CNS metastases |
| Hepatic arterial infusion with abraxane | Siqing Fu, MD | Anti-microtubule agent | Solid tumors | |
| Pazopanib and vorinostat | Siqing Fu, MD, PhD | Angiogenesis inhibitor and HDAC inhibitor | Advanced cancer | Allows brain primary and CNS metastases |
| Nano-curcumin | Siqing Fu, MD, PhD | Natural plant-derived NFκB inhibitor | Advanced cancer | Allows children age 13 and older and CNS metastases |
| *ABI-009 | Ana Gonzalez-Angulo, MD | Albumin-tagged mTOR inhibitor | Solid tumors | |
| MK-2206 and paclitaxel | Ana Gonzalez-Angulo, MD | AKT inhibitor combined with microtubule inhibitor | Advanced cancer | Allows brain primary and CNS metastases |
| BYL719 | Ana Gonzalez-Angulo, MD | PI3K inhibitor | Advanced cancer | |
| *Tipifarnib and sorafenib | David Hong, MD | Combines farnesyltransferase inhibitor (tipifarnib) with Raf kinase/ VEGFR inhibitor (sorafenib) | Advanced cancer | |
| *E7080 | David Hong, MD | Angiogenesis inhibitor | Advanced cancer | |
| *Gemcitabine and dasatinib | David Hong, MD | Src inhibitor and anti-metabolite | Solid tumors | Allows CNS metastases |
| *AZD2171 and bevacizumab | David Hong, MD | VEGF Inhibitor | Advanced cancer | Allows CNS metastases |
| AMG655 rollover | David Hong, MD | Activating peptide against death receptor (DR5) | Advanced cancer | |
| AMG 208 | David Hong, MD | c-MET inhibitor | Solid tumors | |
| MABp1 | David Hong, MD | IL-1α inhibitor (human monoclonal antibody) | Advanced cancer | Allows CNS metastases |
| Nab-paclitaxel, gemcitabine, bevacizumab | David Hong, MD | Recombinant monoclonal antibody, nanoparticle albumin-bound paclitaxel, chemotherapy agent | Advanced cancer | Allows children any age and CNS metastases |

* Closed to new patient entry

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## TREATMENT PLANNING CONFERENCE

Referring physicians and nurses who want to present patients for possible phase I clinical trial inclusion are invited to attend the weekly treatment planning conference held every Wednesday from 9:00 a.m. to 9:30 a.m. in the Rotary House, first floor conference rooms A/B/C.

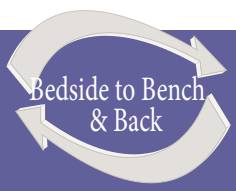
Emailing the patient's name and record number to Kristie Lawhorn, RN, research nurse supervisor, by noon Tuesday is recommended, but not mandatory, to add a case to the meeting agenda.

| Protocol | Principal Investigator | Drug Mechanisms | Diseases | Comment |
|---|---|---|---|---|
| LY2606368 | David Hong, MD | CHK1 inhibitor | Advanced cancer | |
| ABT 348 monotherapy or ABT 348 and 1) carboplatin and gemcitabine or 2) docetaxel<br>ABT 348 BID dosing | David Hong, MD | Aurora kinase inhibitor and VEGF inhibitor combined with alkylating agent/chemotherapy or antimitotic agent | Advanced cancer | |
| Pazopanib and lapatinib or trastuzumab | David Hong, MD | VEGFR/PDGFR/Raf inhibitor and mTOR inhibitor and HER2 inhibitor | Advanced cancer | Allows children and CNS metastases |
| Sirolimus and cetuximab | Filip Janku, MD, PhD | mTOR inhibitor, anti-EGFR monoclonal antibody | Advanced cancer | Allows children and CNS metastases |
| Sirolimus and vorinostat | Filip Janku, MD, PhD | mTOR inhibitor combined with histone deacetylase inhibitor | Advanced cancer | Allows children any age and CNS |
| Docetaxel and sirolimus | Filip Janku, MD, PhD | Antimitotic agent and mTOR inhibitor | Advanced cancer | Allows children any age and CNS metastases |
| Lapatinib and 1) sirolimus or 2) metformin | Filip Janku, MD, PhD | Tyrosine kinase inhibitor combined with mTOR inhibitor or antihyperglycemic agent | Advanced cancer | Allows children any age and CNS metastases |
| Dasatinib, bevacizumab, paclitaxel | Filip Janku, MD, PhD | Src inhibitor and anti-VEGF monoclonal antibody and microtubule inhibitor | Advanced cancer | Allows children any age and CNS metastases |
| Hydroxychloroquine and 1) sirolimus or 2) vorinostat | Filip Janku, MD, PhD | Autophagy, mTOR, and HDAC inhibitors | Advanced cancer | Allows CNS metastases |
| BEZ235 and MEK162 | Filip Janku, MD, PhD | PI3K inhibitor and MEK inhibitor | Advanced cancers | Allows CNS metastases |
| *R7112 | Razelle Kurzrock, MD | MDM2 antagonist | Advanced cancer | |
| *PRO 1762 (TRAIL) | Razelle Kurzrock, MD | Tumor necrosis-related, apoptosis-inducing ligand | Solid tumors, non-Hodgkins lymphoma | |
| CNTO 328 rollover | Razelle Kurzrock, MD | Antibody against interleukin-6 | Castleman's disease, lymphoid tumors, myeloma | No CNS metastases |
| Doxil, bevacizumab, temsirolimus | Razelle Kurzrock, MD | Anthracycline antibiotic, monoclonal antibody, and mTOR inhibitor | Advanced cancer | Allows children and CNS metastases |
| Temsirolimus, topotecan, and bortezomib | Razelle Kurzrock, MD | mTOR inhibitor, combined with topoisomerase and proteosome inhibitors | Advanced cancer | Allows children and CNS metastases |
| Torisel and PI3 kinase mutations | Razelle Kurzrock, MD | mTOR inhibitor | Advanced cancer | |
| XL-184 randomized discontinuation | Razelle Kurzrock, MD | MET/RET/VEGFR inhibitor | Advanced cancer | |
| *GSK 2126458 | Razelle Kurzrock, MD | PI3K inhibitor | Advanced cancer | Allows CNS metastases |
| BKM120 and GSK1120212 | Razelle Kurzrock, MD | PI3K and MEK inhibitors | Advanced cancer | Allows CNS metastases |
| GSK1120212 and GSK2141795 | Razelle Kurzrock, MD | MEK and AKT inhibitors | Solid tumor | Allows CNS metastases |
| Temsirolimus in patients with PTEN loss or PIK3CA mutations | Razelle Kurzrock, MD | mTOR inhibitor | Advanced cancer | Allows brain primary and CNS metastases |
| MK-4827 and temozolomide | Razelle Kurzrock, MD | PARP inhibitor and alkylating agent | Advanced cancer | Allows brain primary and CNS metastases |
| MK-8669 and MK-2206 or MK-0752 | Razelle Kurzrock, MD | mTOR and AKT inhibitors or mTOR and notch inhibitor | Advanced cancer | Allows brain primary and CNS metastases |
| Pazopanib and GSK1120212 | Razelle Kurzrock, MD | VEGFR/PDGFR/Raf and MEK inhibitors | Advanced cancer | Allows CNS metastases |
| Olanzapine | Aung Naing, MD | Atypical neuroleptic | Advanced cancer with cachexia | |
| *KX2-391 | Aung Naing, MD | Src kinase inhibitor | Advanced cancer | Allows CNS metastases |
| Valproic acid and 1) sorafenib 2) sutent 3) dasatinib 4) erlotinib 5) lapatinib or 6) lenalidomide | Aung Naing, MD | HDAC inhibitor combined with targeted agents | Solid tumors | |
| *TAS106 and carboplatin | Aung Naing, MD | RNA polymerase inhibitor | Solid tumors | |
| *IMC-A12 and CCI-779 | Aung Naing, MD | IGF-1R and mTOR inhibitors | Advanced cancer | Allows children age 16 or older and CNS metastases |
| MSC1936369B and temsirolimus | Aung Naing, MD | MEK and mTOR inhibitors | Advanced cancer | Allows brain primary and CNS metastases |
| Bevacizumab and temsirolimus | Sarina Piha-Paul, MD | Monoclonal antibody and mTOR inhibitor | Advanced cancer | Allows children any age |
| *GDC-0449 | Sarina Piha-Paul, MD | Hedgehog pathway inhibitor /drug interaction study | Advanced cancer | |
| IP oxaliplatin and paclitaxel plus IV paclitaxel and bevacizumab | Apostolia Tsimberidou, MD, PhD | Regional (intraperitoneal) therapy | Advanced cancer | Allows children any age and CNS metastases |
| Hepatic arterial infusion of cisplatinum with IV Doxil | Apostolia Tsimberidou, MD, PhD | Cytotoxic, combined regional and systemic chemotherapy | Advanced cancer | Liver predominant disease. Allows children any age and CNS metastases |

* Closed to new patient entry

| Protocol | Principal Investigator | Drug Mechanisms | Diseases | Comment |
|---|---|---|---|---|
| Hepatic arterial infusion of oxaliplatin and<br>1) hepatic arterial infusion of fluorouracil with bevacizumab<br>2) systemic fluorouracil, leucovorin, bevacizumab, and cetuximab<br>3) bevacizumab or<br>4) bevacizumab and cetuximab | Apostolia Tsimberidou, MD, PhD | Regional (hepatic) chemotherapy with Avastin | Advanced cancer | Liver predominant disease. Allow s children any age and CNS metastases |
| Hepatic arterial infusion of irinotecan and<br>1) bevacizumab<br>2) bevacizumab and oxaliplatin<br>3) bevacizumab and cetuximab | Apostolia Tsimberidou, MD, PhD | Regional (hepatic) and systemic chemotherapy | Advanced cancer | Liver predominant disease. Allows children any age and CNS metastases |
| 5-azacytidine and oxaliplatin | Apostolia Tsimberidou, MD, PhD | Hypomethylating agent (azacytidine) and platinum compound (oxaliplatin) | Advanced cancer | |
| Hepatic arterial infusion of abraxane and IV gemcitabine and bevacizumab | Apostolia Tsimberidou, MD, PhD | Antimicrotubule agent with a nucleoside analog and anti-VEGF monoclonal antibody | Advanced cancer | Liver predominant disease. Allows CNS metastases |
| Bendamustine and bevacizumab | Apostolia Tsimberidou, MD, PhD | Cytotoxic alkylating agent, anti-VEGF monoclonal antibody | Advanced cancer | Allows children age 13 or older and CNS metastases |
| Lenalidomide with<br>1) bevacizumab<br>2) sorafenib<br>3) temsirolimus or<br>4) FOLFOX | Apostolia Tsimberidou, MD, PhD | Antiangiogenic agent, VEGF or tyrosine kinase or mTOR inhibitors or chemotherapy regimen | Advanced cancer | Allows CNS metastases |
| Hepatic arterial infusion of oxaliplatin with<br>1) capecitabine and bevacizumab or<br>2) capecitabine | Apostolia Tsimberidou, MD, PhD | Regional (hepatic) chemotherapy with DNA synthesis inhibitor, with or without VEGF inhibitor | Advanced cancer | Liver predominant disease |
| Bevacizumab and temsirolimus and<br>1) carboplatin<br>2) paclitaxel or<br>3) sorafenib | Shannon Westin, MD | anti-VEGF monoclonal antibody and mTOR inhibitor combined with alkylating agent, mitotic inhibitor, or RAF kinase/VEGFR inhibitor | Advanced cancer | Allows children any age and CNS metastases |
| Valproic acid and bevacizumab | Jennifer Wheler, MD | Oral histone deacetylase inhibitor combined with monoclonal antibody against VEGF | Advanced cancer | Allows children any age |
| *PCI-24781 | Jennifer Wheler, MD | HDAC inhibitor | Advanced cancer | Allows CNS metastases |
| *MGCD265 | Jennifer Wheler, MD | VEGFR 1, 2, 3/cMET/tie/ron inhibitor | Advanced cancer | |
| XL147 + Taxol/carboplatin | Jennifer Wheler, MD | PI3K inhibitor with chemotherapy regimen | Advanced cancer | |
| EGFR mutation (umbrella protocol) | Jennifer Wheler, MD | Screening for EGFR mutations | Advanced cancer | |
| Erlotinib + cetuximab (companion to EGFR mutation umbrella protocol) | Jennifer Wheler, MD | EGFR inhibitor and monoclonal antibody | Advanced cancer | |
| Erlotinib + bortezomib (companion to EGFR mutation umbrella protocol) | Jennifer Wheler, MD | EGFR inhibitor and proteasome inhibitor | Advanced cancer | |
| Erlotinib + dasatinib (companion to EGFR mutation umbrella protocol) | Jennifer Wheler, MD | EGFR inhibitor and anti-metabolite | Advanced cancer | |
| QBI-139 | Jennifer Wheler, MD | ribonuclease protein antagonist | Solid tumors | |
| *GSK2141795 | Jennifer Wheler, MD | AKT inhibitor | Advanced cancer | Allows CNS metastases |
| Anastrozole monotherapy or anastrozole and<br>1) bevacizumab<br>2) everolimus<br>3) sorafenib or<br>4) erlotinib | Jennifer Wheler, MD | Hormone blocker | Advanced cancer | Allows children any age and CNS metastases |
| BAY80-6946 and paclitaxel | Jennifer Wheler, MD | PI3K and microtubule inhibitors | Advanced cancer | |
| Pazopanib and everolimus | Jennifer Wheler, MD | Angiogenesis and PI3K inhibitors | Advanced cancer | Allows brain primary and CNS metastases |

* Closed to new patient entry

# Upcoming Phase I Program Protocols

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

| Protocol | Principal Investigator | Drug Mechanisms | Diseases | Comment |
|---|---|---|---|---|
| Bay 94-9343 | George Blumenschein, MD | Anti-mesothelin antibody drug conjugate | Advanced cancer | |
| GSK 1120212 rollover | Gerald Falchook, MD | MEK inhibitor | Advanced cancer | Allows CNS metastases |
| MEDI0639 | Gerald Falchook, MD | Notch inhibitor | Advanced cancer | |
| VGX-100 and bevacizumab | Gerald Falchook, MD | VEGF monoclonal antibody | Advanced cancer | |
| Curcumin, vorinostat, and sorafenib | Siqing Fu, MD, PhD | Natural plant-derived NFκB inhibitor, histone deacetylase inhibitor and VEGF inhibitor | Advanced cancer | Allows CNS metastases |
| Azacytidine, lenalidomide, grifola frondosa | Siqing Fu, MD, PhD | Hypomethylating agent, antiangiogenesis, and maitake mushroom | Advanced cancer | Allows children any age and CNS metastases |
| Perifosine | Siging Fu, MD, PhD | AKT inhibitor | Advanced cancer | Allows CNS metastases |
| ISIS 481464 | David Hong, MD | STAT3 inhibitor | Advanced cancer | |
| Anakinra with denosumab or everolimus | Filip Janku, MD, PhD | IL-1R antagonist or anti-RANKL monoclonal antibody combined with mTOR inhibitor | Advanced cancer | Allows children and CNS metastases |
| Venurafenib + sorafenib | Filip Janku, MD, PhD | BRAF + CRAF, BRAF, KIT, RET, VEGFR, PDGFR inhibitor | Advanced cancer | Allows children and CNS metastases |
| Cetuximab and SIR-spheres | Razelle Kurzrock, MD | EGFR inhibitor and Yttrium microspheres | Advanced cancer | Allows children any age, brain primary and CNS metastases |
| Vandetanib and everolimus | Razelle Kurzrock, MD | EGFR/VEGFR/RET and mTOR inhibitors | Advanced cancer | Allows children any age, brain primary and CNS metastases |
| XL184 rollover | Razelle Kurzrock, MD | MET/RET/VEGFR kinase inhibitor | Advanced cancer | |
| IL-2 aerosol | Aung Naing, MD | Anti-interleukin-2 aerosol | Advanced cancer with pulmonary metastases | Allows children any age, brain primary and CNS metastases |
| Temsirolimus and metformin | Aung Naing, MD | mTOR inhibitors | Advanced cancer | Allows children age 14 or older and CNS metastases |
| OSI-906 and AZD6244 | Sarina Piha-Paul, MD | IGF-1R and RAS/RAF/MEK/ERK inhibitors | Advanced cancer | Allows children any age and CNS metastases |
| LDOS47 | Sarina Piha-Paul, MD | Immunoconjugate for CEA | Solid tumors | |
| MK-8242 | Apostolia Tsimberidou, MD, PhD | HDM2 inhibitor | Advanced cancer | |
| Brentuximab vedotin | Jennifer Wheler, MD | CD-30 antibody | Solid tumors | Allows CNS metastases |
| MGCD265 and<br>1) erlotinib or<br>2) docetaxel | Jennifer Wheler, MD | VEGF/MET and EGFR inhibitors or VEGF/MET inhibitor and antimitotic agent | Advanced cancer | |
| Erlotinib and pralatrexate | Jennifer Wheler, MD | EGFR inhibitor and dihydrofolate reductase (DHFR) inhibitor | Advanced cancer | Allows children any age and CNS metastases |