Department of Investigational Cancer Therapeutics

Phase I Clinical Trials

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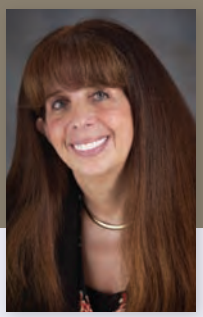
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

FROM THE CHAIR



Razelle Kurzrock, MD
Chair, Department of Investigational Cancer Therapeutics

Equipoise Lost

Regulations were put in place with good intentions, that is, to protect patients and data accuracy. However, there is accumulating concern that equipoise has been lost, and that there needs to be scrutiny of regulations to determine which are beneficial and which are harmful. For instance, the 12-14 years it now takes to get a drug approved by the FDA is much longer than just a decade ago. Considering that cancer is now the number one killer of Americans, many people feel there should be a greater sense of urgency.

Many patients have complained that the study calendar in clinical trials disrupts their lives. These disruptions detract from their quality of life. In addition, sometimes adhering precisely to the study calendar does not improve medical care. Another related concern is that the results of clinical trials ultimately may not reflect how the drug will behave in practice, when physicians and patients will adjust the calendar of administration and monitoring of the drug.

There is also evidence that the United States is losing many trials to other countries because of the inefficiencies of our system. Recent published reports claim that in some European countries, trials can be activated in half the time it takes in US institutes. Dr. David Dilts, a prominent researcher on the processes involved in clinical research, has documented the multitude of steps needed to activate a clinical trial and the fact that it may take years to do so. As a result, the USA could be in danger of losing its leading edge in clinical trials research.

Finally, these factors may dramatically escalate drug development costs. This, in turn, increases health care costs. We must recognize that resources are not unlimited.

Bench to Bedside & Back

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Equipoise—The Balance between Risks and Benefits—Has Been Lost to Dysregulation of Cancer Clinical Research:

Why We Must Assume Responsibility Now to Restore the Balance and Halt the Needless Loss of Human Lives

No reasonable person disagrees that some degree of regulation is needed to protect cancer patients from harm when they are enrolled in clinical trials. However, is there a point at which the regulations become so burdensome—and clinical trial design so out of sync with current scientific knowledge—that the development of new, potentially lifesaving, therapies becomes painfully slow, yet with no significant improvement in safety? Not only do Drs. David Stewart, left, Simon Whitney, and Razelle Kurzrock answer that question with a resounding "yes" in their article published in Journal of Clinical Oncology (June 10, 2010), they describe the many signs that time has arrived now and propose solutions. They also demonstrate how hundreds of thousands of cancer patients lose their lives every year as a result by calculating a life-years lost formula that throws the disturbing impact of dysregulation into stark relief. They make a strong case for deeming unethical the striking imbalance between potential life-years lost and lives saved.

Smart Regulations Needed to Free Up Research Superhighway

Dr. Stewart likens the current clinical trials regulatory process to speed bumps on the research superhighway that slow a Ferrari capable of going 200 mph to 5 mph, when traveling 55 mph would keep most drivers reasonably safe. "Every piece of information that must be collected, and every step that must be taken from drug discovery to final approval, is a speed bump slowing the pace of progress while increasing costs and decreasing the number of ideas that can be tested," he lamented. "If we can free up the research superhighway, then the funding dollars become very valuable because we can put them to valuable use. Now they are not very valuable because they are all stuck in traffic jams." He and others advocate replacing rigid regulation, and over-emphasis on regulations that actually do little or nothing to improve safety, with smart regulations based on considering safety and efficacy together—on having the right regulations while allowing enough speed to get where we need to go. "If you just focus on safety, that doesn't get you where you want to go," he noted. "We need to identify a few smart regulations and leave the rest to clinical judgment."

Inform Patients to Set Own Level of Acceptable Risk

That means that the level of acceptable risk should be substantially higher for clinical research in fatal, incurable disease such as metastatic malignancies than for benign or potentially curable conditions. Based on their experience with patients with advanced cancer on Phase I clinical trials, as well as data published in the literature, they disagree with the assumption that these patients should be considered a vulnerable, exploitable population unable to make informed, voluntary decisions. Instead, conscientious oncologists too often find themselves spending dozens of hours on

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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 nearly $200 million annually.
- We have 13 specialized Programs of Research Excellence (SPORE) awards from the National Institutes of Health, more than any other institution in the country.
- We see 105,219 cancer patients per year, 32,380 of them new patients.
- Nearly 10,000 patients are on therapeutic clinical trials.

Response Highlights

Triple Drug Combination Poses Triple Threat to Rare Dendritic Sarcoma

What seemed like a simple cold to Jacqueline Fenton, (photo, middle) and then a goiter to her primary care physician, turned out to be a rare follicular dendritic cell sarcoma, when her doctor sent a biopsy in 1995 to MD Anderson Cancer Center for confirmation of pathology findings that were suspicious for a malignancy. She traveled from her home in Center, Texas to undergo a standard therapeutic regimen of surgery, chemotherapy, and radiation under the care of Dr. Alma Rodriguez, which put her in remission for eight and a half years. Then a routine annual check-up at MD Anderson in 2004 revealed that the cancer had returned, and Fenton had five surgeries by Dr. Ehab Hanna in the Head and Neck Center, but the cancer kept recurring year after year. Fenton tried erlotinib in December 2006, as her sarcoma was EGFR positive, then two cycles of RICE (rituximab, ifosfamide, carboplatin, etoposide), but her disease was non-responsive to these therapeutic regimens. In 2008, Fenton had an episode of acute respiratory distress syndrome and had to be transported by life flight to a hospital in Tyler, where she was on life support for more than three weeks—an interval she doesn't remember at all.

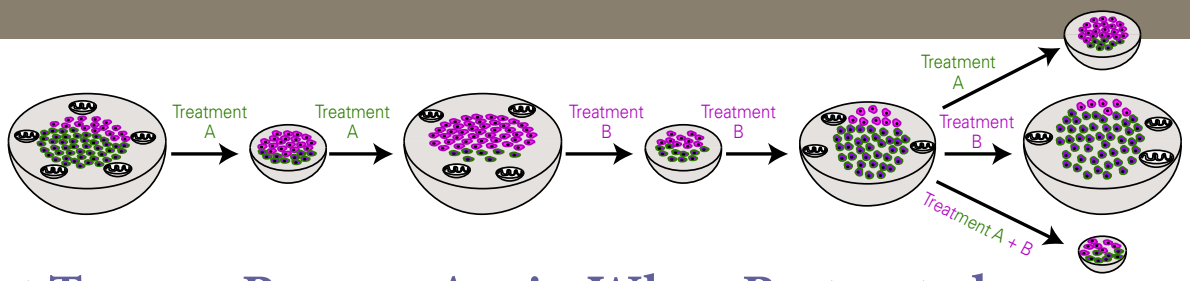
When too much scar tissue precluded additional surgery, Dr. Hanna referred Fenton to Dr. David Hong (photo, far right) in Investigational Cancer Therapeutics in 2009, where she started on a Phase I trial of a novel therapy. "The first one worked for awhile, then quit," Fenton commented. When her disease began progressing again, she had no qualms about trying another investigational treatment. "I thought, if it helps me, it might help others," Fenton said. She was switched to her current triplet regimen in February 2010 of dasatinib, a Src inhibitor; bevacizumab, an anti-VEGF antibody that has an anti-angiogenic effect; and metronomic paclitaxel—low-dose cytotoxic therapy that exerts additional anti-angiogenesis. The study coordinator is Hala Abdulkadir (photo, left). "We assumed that this combination could be an active anti-cancer treatment targeting angiogenesis, invasion, migration, proliferation, apoptosis, and resistance to chemotherapy," said Dr. Filip Janku, a clinical research fellow in the Department of Investigational Cancer Therapeutics who designed the protocol. "This patient was already doing well after her first eight weeks of treatment." Fenton had primarily subclavical disease, mostly on the right side, to the extent that her trachea was narrowed and pushed to the left. Dr. Janku reported that she showed substantial improvement on the new protocol, and her trachea was not as narrow. "I feel good today. I do have my bad days, but I generally feel good on this treatment," said Fenton in August. "All of my doctors here have been wonderful. And not just the doctors, the nurses, too—everyone." Dr. Janku noted that Fenton's disease remains well-controlled based on her CT scans from June and August, with a nice partial response. "While it is still too early to say how she will do long term, this early response is gratifying because this type of cancer generally does not respond to therapy," said Dr. Razelle Kurzrock, chair of the department and principal investigator of the study. "It will be important to watch her over time, and to treat other patients with this rare cancer and see whether or not they respond, too."

FROM THE CHAIR - continued from page 1

These problems are not unresolvable. The following potential solutions have been suggested by Dr. Stewart as well as by others.

- In order to activate clinical trials, perform processes in parallel, not serially. Currently, there are numerous steps and in many organizations, each step cannot be performed until numerous other functions are complete, often resulting in long feedback loops or gridlock.
- Limit the number of reviews a protocol can undergo to those by no more than two or three regulatory bodies.
- Encourage rather than discourage flexibility in clinical trials that enhances patient safety and emulates the clinical practice situation. This will also reduce the chance that the drug will not perform well in practice because patients that would not have been eligible for enrollment in the study are treated, or calendar adjustments are made in practice. To maintain data integrity, report what was actually done.
- Increase emphasis on ensuring that patients are fully and honestly informed. Presume that adults who are fully informed can make decisions for themselves, or should at least be able to opt to do so.
- Patients need to know about the side effects of all drugs, not just experimental ones. Provide online access to the side effect profile of experimental drugs, just as it is available for approved drugs. A password-protected site might be necessary, with the option for patients to request print-outs if they do not have computer access. This online access should include up-to-date information about response to the drug, since this is what most patients are interested in; current consents do not address response rates despite numerous pages on side effects. Such online access and a centralized information source would reduce the inefficiencies of the system, including redoing the consent numerous times, re-consenting patients over and over, and extensive paperwork for adverse events.

We are standing on the threshold of a new era in cancer therapy. We largely understand the biology of tumors and have powerful new targeted drugs, some of which are producing remarkable responses. We need to do everything we can to get new effective therapies to patients with life-threatening or terminal cancer as quickly and safely as possible.



Can Resistant Tumors Regress Again When Re-treated with Failed Drugs? Investigators Say Yes and Explain How

When a patient's tumor begins progressing after initially responding to a drug regimen, the prevailing assumption in oncology is that the patient's cancer has become resistant to that drug and that re-administering the drug later will still be ineffective. "The failed drug is typically withdrawn and a different drug started," said Razelle Kurzrock, MD, chair, Investigational Cancer Therapeutics. But that's not always the case, explained Aung Naing, MD, assistant professor, and Dr. Kurzrock in a recently published article [Clinical Colorectal Cancer 2010;9(2):E1-4]. Several patients enrolled in their Phase I Clinical Trials Program have demonstrated renewed response of their cancers when given these "old drugs" again. Why does this happen? They hypothesize that re-challenging these cancers with previously failed drugs can renew tumor regression, even after the development of resistance, because "responsive clones that have not been completely eradicated can re-emerge when a therapeutic regimen is changed," using other agents in combination with the old drug may create a different synergy, and/or epigenetic changes driving resistance reverse after a drug holiday. In addition, adding a new drug that blocks the molecular pathways involved in resistance to chemotherapy can restore sensitivity to the original chemotherapy, when combined with the new drug. The following two case reports demonstrate successful re-treatment with presumed failed drugs.

A 63-year-old man received FOLFOX for four months when his colorectal cancer relapsed two years after surgery, then infused 5-FU and radiation, followed by FOLFIRI with bevacizumab for 11 months. His CEA level began climbing, so he went on a therapeutic regimen of the cytotoxin irinotecan, the anti-angiogenic agent bevacizumab, and the epidermal growth factor receptor antibody cetuximab, which partially decreased his tumor size and CEA levels for six months to the point of poor tolerance. At that time, he switched to a short interval of capecitabine, again until losing tolerance, then returned to the previous triplet for several months of stable disease. When radiographic progression again occurred, along with bowel obstruction requiring surgical intervention, this regimen was again discontinued. Finally, the same therapy with irinotecan, bevacizumab, and cetuximab was restarted, despite previous progressions on this combination, and this time, the patient experienced disease stabilization for 11 months before progression re-occurred.

A case of a young woman with Ewing's sarcoma illustrates the probable co-existence of two different clones in her tumors. This patient was featured in the fall/winter 2007 of this newsletter because, after failing four previous clinical trials, her metastatic disease had such a dramatic sustained response to a monoclonal antibody that targets the insulin-like growth factor-1 receptor (IGF-1R). She continued on this drug successfully with no disease progression for nearly three years until October 2009, when a tumor in her lung began to re-grow. Dr. Kurzrock suspects that inoperable microscopic residual disease in the lung that does not respond to IGFR-1R inhibition continued to grow slowly while the IGF-1R inhibitor kept the other tumors in check. Therefore, she decided to switch the patient in November to a clinical trial that still had an IGF inhibitor, but combined it with the mTOR inhibitor temsirolimus. This combination proved to work synergistically, and the patient's tumors regressed completely until there was no evidence of disease. The patient continues to do well on this regimen as of September 28, 2010. "Withdrawing the IGFR-1R inhibitor would likely have resulted in rapid re-growth of this patient's tumors that were responding to this agent," Dr. Kurzrock commented.

Keeping this young woman on her previous drug while adding a new one to address new progression averted the scenario depicted in the figure above, in which a tumor harbors two clones. Clone A (green) is sensitive only to treatment A and clone B (purple) only to treatment B. The tumor initially responds to treatment A, but as clone B continues to grow, there is eventually new tumor growth on treatment. If treatment B is then administered without also continuing treatment A, the tumor will shrink as clone B regresses, but eventually, there will again be tumor growth as clone A continues to grow. Combined therapy with both treatments A and B could maximize tumor shrinkage, as it did in the sarcoma patient's case when she continued on treatment A, the IGF-1R inhibitor, with the addition of a new drug, temsirolimus, to target clone B.

Results from a recent, large, longitudinal, observational study conducted in France also confirm the published findings of Drs. Naing and Kurzrock. Patients with breast cancer whose cancer initially responded to trastuzumab but then progressed had considerably better outcomes when trastuzumab was continued while they were on new therapy to treat the progressive cancer, compared with patients who had discontinued trastuzumab [see Extra et al, The Oncologist 2010;15:799-809].

Dr. Naing is currently conducting a prospective study of 20 to 25 re-treated patients to determine their best response. A molecular analysis will be done on all patients' tumors. "We want to study how these patients develop resistance," he said. Future plans involve combining re-treatment drugs with new drugs to elicit the best tumor response possible.

EQUIPOISE—THE BALANCE BETWEEN RISKS AND BENEFITS - continued from page 1

the phone with pharmaceutical representatives, or personnel representing regulatory bodies, trying to persuade someone to allow their consenting cancer patient access to a potentially beneficial trial when that patient has only weeks to live unless a beneficial therapy is found. Often a patient is excluded from a trial based on inconsequential minor differences in continuous data measures. Dr. Stewart gives the example of platelet count, which can range from nearly undetectable to over a million, yet The FDA and IRB could set the cutoff point for allowing a patient on the trial to 100 and act as though 99 is highly dangerous and exclude the patient from a potentially beneficial trial, when the two numbers are exactly the same. It would be the same as if the speed limit on a roadway were 35, and the same major fine was levied, whether you went 36 miles per hour or 136 miles hour. "The key emphasis should be on ensuring that patients are fully informed of the risks, rather than assuming for them what risks they should be allowed to take," said Dr. Stewart and colleagues. Also, they deem it inappropriate to use the same structures and mechanisms to regulate the investigation of skin lotions and anti-cancer drugs.

Responsibility to Act Now

Recognition of dysregulation and its attendant detrimental consequences to cancer patients isn't new. For example, Drs. Stewart and Kurzrock gave voice to a rising chorus against the current research regulatory climate, describing the mounting roadblocks to moving beneficial drugs more rapidly from the lab to the clinic, in a 2009 article in the same journal (Cancer: The Road to Amiens. Journal of Clinical Oncology 2009;27:328-33), which we also discussed in the winter/spring 2009 issue of this newsletter. The first article identifies the problem while the second article identifies the costs associated with the problem and proposes solutions, Dr. Stewart explains. However, he also goes a step further to exhort oncologists, investigators, and advocacy groups alike that not only do we have the ability to solve these problems, we have a responsibility to do so. "Investigators claim, 'the IRB said we can't do this, the FDA said we can't do that.' That's a cop out. We can't continue to have the problems we're having," Dr. Stewart entreats. "They result from apathy and complicity. Change takes the courage, the resolve, and the commitment to try. We do have the ability to

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EQUIPOISE—THE BALANCE BETWEEN RISKS AND BENEFITS - continued from page 3

change things, but only if we are willing to try." To bring home his message, Dr. Stewart quotes the timeless words of Sir Winston Churchill, "It's not enough that we do our best; sometimes we have to do what's required."

Proposed Solutions Easily Enacted

But what is required? Dr. Stewart and colleagues propose numerous solutions, which they summarize in a convenient table in their article. When asked to select a few of the solutions that could be implemented the most readily and right now, Dr. Stewart replied, "All could be easily implemented immediately if people just decide this is the best way to do things." Examples of other solutions that address some of the most obstructive barriers to conducting clinical cancer research are highlighted next.

In addition to reform of regulatory oversight, Stewart and colleagues advocate reforms to preclinical requirements and the study activation process. Dr. Kurzrock and colleagues in ICT successfully established a "Zero Delay" project which, by tackling administrative processes in parallel with industry sponsors instead of sequentially, among other reforms, were able to activate a trial and enroll the first patient within 46 days of completing the study protocol, and 48 hours after the FDA had approved the Investigational New Drug (IND) application. This reduced the overall timeline by three months [see their article in Journal of Clinical Oncology 2009;27: 4433-40].

Dr. Stewart and colleagues advise several ways to reform study conduct that would expedite the clinical trial process. They advise avoiding duplication of reporting serious adverse events, instead, for example, making SAE reports available online to patients, physicians, and IRBs and eliminating the requirement to report SAEs from other institutions involved in the study if all local patients are off the therapy. "The marked excess of time and resources devoted to dealing with outside SAE reports is counterproductive because the few potentially important events are buried in an avalanche of unimportant ones, minor variations on ones that are already well-known, or ones that are more likely to be due to the underlying cancer or to comorbidities than to the therapy," commented Dr. Stewart and co-workers. They also believe patients who are off a therapy should not be required to sign a new consent if new toxicities are observed, nor should a study be delayed while a consent form is modified and awaiting re-approval. They recommend permitting the principal investigator to do selected types of protocol modifications that do not impact the safety of the patient or the integrity of the data without IRB and FDA approval, as long as what was actually done is reported. Indeed, many of these types of modifications are performed to enhance individual patient outcome.

To optimize the chances of identifying the most effective drugs and the subsets of patients they are most likely to benefit, Dr. Stewart and colleagues say it's imperative to look for agents that are active against tumors containing particular molecular targets, rather than looking for what appears to be the most effective drug in unselected patient populations. "A drug successfully hitting an uncommon target may be missed and discarded unless thousands of unselected patients are treated," they lament. "Conduct small studies aiming for large gains, not large studies aiming for small gains." Careful patient selection should begin with the earliest phase I and II trials, they suggest, assessing molecular markers that correlate with response and restricting phase III trials to patients possessing favorable molecular markers. Biomarkers correlating with progression-free survival should be chosen over those correlating with overall survival, as the latter are likely to be confounded by comorbidities and subsequent therapy. In case the drug could also benefit other subsets of patients, later studies could investigate outcomes in other types of patients.

They summarize the extent of the problem as "not one or two large impediments to progress, but rather the collective effects of hundreds of small impediments" and recommend the careful scrutiny of regulations and processes governing clinical cancer research, discarding or changing those that do not demonstrate the addition of significant benefit. They conclude that in a new era based on immense progress in understanding the biology of cancer and on our ability to identify molecular profiles of tumors, "slowing progress in a regulatory traffic jam, abandoning good drugs that work in specific subsets of patients, and approving drugs in unselected populations whose survival benefit is measured in days to weeks can no longer be justified." Dr. Stewart concludes that current clinical trial regulatory systems are zero tolerance systems, and they are not working, nor do they reflect medical practice. He sees training junior investigators to be comfortable making decisions based on judgment, rather than just following all the rules exactly, as a solution that will help streamline processes, provide better care, and in addition, produce results that are likely to be similar to those found once the drug reaches community practice, where physicians use judgment, rather than follow strict protocols.

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	
*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 1) sunitinib 2) sorafenib 3) erlotinib and cituximab 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
*PX-478	Gerald Falchook, MD	HIF-1 alpha 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
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
ABI-009	Ana Gonzalez-Angulo, MD	Albumin-tagged mTOR inhibitor	Solid tumors	
*AMG655	Roy Herbst, MD, PhD	Activating peptide against death receptor (DR5)	Advanced cancer	No CNS metastases
*PRO 1762 (TRAIL)	Roy Herbst, MD	Tumor necrosis-related, apoptosis-inducing ligand	Solid tumors, non-Hodgkins lymphoma	
*AMG 386 with: 1) AMG 706 2) bevacizumab 3) sorafenib or 4) sunitinib	David Hong, MD	Combines 2 anti-angiogenic agents	Solid tumors	Allows CNS metastases
*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
PBI-05204	David Hong, M. D.	Cytotoxic agent	Advanced cancer	
BIIB028	David Hong, MD	Hsp90 inhibitor	Solid tumors	
AMG 208	David Hong, MD	c-MET inhibitor	Solid tumors	
PX866	David Hong, MD	PI3K 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
LY2606368	David Hong, MD	CHK1 inhibitor	Advanced cancer	
ABT 348 monotherapy or ABT 348 and 1) carboplatin and gemcitabine or 2) docetaxel	David Hong, MD	Aurora kinase inhibitor and VEGF inhibitor combined with alkylating agent/chemotherapy or antimitotic agent	Advanced cancer	
Olanzapine	Razelle Kurzrock, MD	Atypical neuroleptic	Advanced cancer with cachexia	
R7112	Razelle Kurzrock, MD	MDM2 antagonist	Advanced cancer	

* Closed to new patient entry • Continued on reverse side

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.

Active Protocols continued

Protocol	Principal Investigator	Drug Mechanisms	Diseases	Comment
NPI-0052	Razelle Kurzrock, MD	Proteosome inhibitor	Advanced cancer	No CNS metastases
Doxil, gemcitabine, and velcade	Razelle Kurzrock, MD	Chemotherapy with proteosome inhibitor	Advanced cancer	Allows children any age and CNS metastases
CNTO 328	Razelle Kurzrock, MD	Antibody against interleukin-6	Castleman's disease, lymphoid tumors, myeloma	No CNS metastases
Curcumin	Razelle Kurzrock, MD	Plant-derived NFκB inhibitor	Pancreatic cancer	Phase II
AZD8330	Razelle Kurzrock, MD	MEK inhibitor	Advanced cancer	Allows CNS metastases
Hepatic arterial infusion with abraxane	Razelle Kurzrock, MD	Anti-microtubule agent	Solid tumors	
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
CNTO328	Razelle Kurzrock, MD	IL-6 monoclonal antibody	Solid tumors	
Torisel and PI3 kinase mutations	Razelle Kurzrock, MD	mTOR inhibitor	Advanced cancer	
OPB-31121	Razelle Kurzrock, MD	STAT3 inhibitor	Solid tumors	
Sirolimus and cetuximab	Razelle Kurzrock, MD	mTOR inhibitor, anti-EGFR monoclonal antibody	Advanced cancer	Allows children and CNS metastases
XL-184 randomized discontinuation	Razelle Kurzrock, MD	MET/RET/VEGFR kinase inhibitor	Advanced cancer	
GSK 2126458	Razelle Kurzrock, MD	PI3K inhibitor	Advanced cancer	Allows CNS metastases
Dasatinib, bevacizumab, paclitaxel	Razelle Kurzrock, MD	Src inhibitor combined with anti-VEGF monoclonal antibody and microtubule inhibitor	Advanced cancer	Liver predominant disease. Allows children any age and CNS metastases
Docetaxel and sirolimus	Razelle Kurzrock, MD	Antimitotic agent and mTOR inhibitor	Advanced cancer	Allows children any age and CNS metastases
Sirolimus and vorinostat	Razelle Kurzrock, MD	mTOR inhibitor combined with histone deacetylase inhibitor	Advanced cancer	Allows children any age and CNS metastases
Lapatinib and 1) sirolimus or 2) metformin	Razelle Kurzrock, MD	Tyrosine kinase inhibitor combined with mTOR inhibitor or antihyperglycemic agent	Advanced cancer	Allows children any age and CNS metastases
GSK1120212 and GSK2141795	Razelle Kurzrock, MD	MEK and AKT inhibitors	Solid tumor	Allows CNS metastases
Effect of temsirolimus	Razelle Kurzrock, MD	mTOR inhibitor	Advanced cancer	Allows brain primary and CNS metastases
Bevacizumab and temsirolimus and 1) carboplatin 2) paclitaxel or 3) sorafenib	Razelle Kurzrock, 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
*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
*AZD 8055	Aung Naing, MD	mTOR inhibitor	Advanced cancer	
Bevacizumab and temsirolimus	Sarina Piha-Paul, MD	Monoclonal antibody and mTOR inhibitor	Advanced cancer	Allows children any age
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
Hepatic arterial infusion of oxaliplatin and 1) hepatic arterial infusion of fluorouracil with bevacizumab 2) systemic fluorouracil, leucovorin, bevacizumab, and cetuximab 3) bevacizumab or 4) bevacizumab and cetuximab	Apostolia Tsimberidou, MD, PhD	Regional (hepatic) chemotherapy with Avastin	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 irinotecan and 1) bevacizumab 2) bevacizumab and oxaliplatin 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 **1) bevacizumab** **2) sorafenib** **3) temsirolimus or** **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 **1) capecitabine and bevacizumab or** **2) capecitabine**	**Apostolia Tsimberidou, MD, PhD**	Regional (hepatic) chemotherapy with DNA synthesis inhibitor, with or without VEGF inhibitor	Advanced cancer	Liver predominant disease
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	Advanced cancer	
***R4733**	**Jennifer Wheler, MD**	Gamma secretase	Solid tumors	
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 **1) bevacizumab** **2) everolimus** **3) sorafenib or** **4) erlotinib**	**Jennifer Wheler, MD**	Hormone blocker	Advanced cancer	Allows children any age 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
GSK1120212 and 1) Docetaxel 2) erlotinib 3) pemetrexed 4) pemetrexed and carboplatin or 5) nab-paclitaxel	George Blumenschein, Jr., MD	MEK inhibitor combined with chemotherapy	Solid tumors	Allows CNS metastases
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 shitake mushroom	Advanced cancer	Allows children any age and CNS metastases
Nano-curcumin and/or resveratrol	Siqing Fu, MD, PhD	Natural plant-derived NFκB inhibitor and anticancer agent	Advanced cancer	Allows children any age and CNS metastases
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	
BKM120 and GSK1120212	Razelle Kurzrock, MD	PI3K and MEK inhibitors	Advanced cancer	Allows CNS metastases
Hydroxychloroquine and 1) sirolimus or 2) vorinostat	Razelle Kurzrock, MD	Autophagy, mTOR, and HDAC inhibitors	Advanced cancer	Allows CNS metastases
AZD8055 (intermittent dosing)	Aung Naing, MD	mTOR inhibitor	Advanced cancer	
GDC-0449	Sarina Piha-Paul, MD	Hedgehog pathway inhibitor drug/drug interaction study	Advanced cancer	

Did You Know That in Fiscal Year 2010...

- There were 118 phase I clinical trials on the program's priority list?
- 1,182 patients were enrolled in Phase I trials?
- The Clinical Center for Targeted Therapy had 13,677 patient visits—4,991 more than in 2009?
- The department received more than $10 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.