According to Dr. Antonia, monoclonal antibodies targeting programmed death-ligand (PD-1/PD-L1) interaction are the most advanced in clinical development. The next step, he says, is combining the immune checkpoint inhibitors with other treatment modalities to “treat the other 80 percent of patients.” He notes that the future of immunotherapy for lung cancer will be to include using other drugs in combination with antibodies such as anti-PD-1 and anti-CTLA4.

Non-small cell lung cancer trials
According to Ben Creelan, MD, findings on immune checkpoint inhibitors and the subsequent use of the immune system to eliminate lung cancer represent a great step forward. He is the lead investigator (PI) on Moffitt trial 17736 for patients with advanced non-small cell lung cancer (NSCLC). It is a phase I, open-label, multicenter study to assess the safety and preliminary antitumor activity of gefitinib (Iressa) in combination with MEDI4736 (an anti-PD-L antibody).

“The key is to reverse the immune suppression caused by tumors,” explains Dr. Creelan. “We have seen durable remissions of 20 percent.” He expects that many of the immune-based trials at Moffitt for patients with lung cancer will “yield dramatic impact” and notes that immunotherapy is receiving increased interest because of both the benefit-risk ratio and durable activity.

“The mainstay of systemic therapy has been to stop tumor growth with chemotherapy,” he notes. “Relapse or progression was accepted as inevitable. By contrast, the advent of immune therapies holds the potential to raise the tail of the survival curve.”
Moffitt’s Clinical Trials for Lung Cancer
(continued from front page)

Another immunotherapeutic clinical trial currently underway is Moffitt trial 17608, a phase Ib open-label study to evaluate the safety and tolerability of MEDI4736 in combination with tremelimumab in patients with advanced NSCLC. Patients enrolled do not have to have the PD-L1 mutation.

Dr. Creelan is also the PI on Moffitt trial 17643 for patients with advanced NSCLC. This trial studies a new oral therapeutic compound developed in Moffitt labs using plant saponins, called “triterpenoids.” Biologically active natural triterpenoids include those in peas, teas and oats.

“Based on immunology work carried out at Moffitt, this synthetic compound is believed to shrink tumors by restoring host immune function,” explains Dr. Creelan. “It is a once-a-day pill.”

Screening is based on laboratory results, and patient eligibility criteria includes under age 75; relatively normal liver, heart and kidney function; and measurable NSCLC with progression after one or more lines of any systemic therapy.

“The goal of this study is to reduce oxidation caused by tumors and is aimed at reversing tumor-induced immune suppression,” says Dr. Creelan. “The trial has been ongoing since January and with no severe adverse events related to the study.”

KRAS-EGFR mutation

Dr. Creelan is also the PI on Moffitt trial 17176, a combination phase I trial to evaluate the safety and tolerability of the irreversible epidermal growth factor receptor (EGFR) inhibitor afatinib in combination with the SRC kinase inhibitor dasatinib for patients with NSCLC. An example of “personalized medicine,” this trial profiles patients for the EGFR mutation.

Another trial in “personalized medicine” is Moffitt trial 17361, for which Jhanelle Gray, MD, faculty lead of clinical research in the Department of Thoracic Oncology, is the PI. It is a phase I/Ib trial of MEK162 in combination with erlotinib for patients harboring either the KRAS or EGFR mutation. It is a single institution, investigator-initiated study.

“EGFR mutant as well as KRAS mutant lung cancers may greatly benefit from

EGFR

Activation of the epidermal growth factor receptor (EGFR) protein stimulates protein tyrosine kinase, which leads to activation of signaling pathways associated with cell growth and survival. Both EGFR over-expression and activating mutations in the tyrosine kinase domain of the EGFR gene lead to tumor growth and progression. Consequently, EGFR has become a target for anticancer drug therapy. Erlotinib and gefitinib are examples of EGFR tyrosine kinase inhibitors (TKIs) that can prevent activation of the signaling pathways and improve response rates in selected NSCLC patients.

KRAS

The KRAS protein stimulates signaling pathways downstream from EGFR. KRAS mutations lead to activation of the KRAS protein that continually stimulates these downstream pathways. Although EGFR TKIs can block EGFR activation, they cannot block the activity of the mutated KRAS protein. Patients with KRAS mutations tend to be resistant to erlotinib and gefitinib. KRAS mutations are more likely found in adenocarcinomas in patients who are smokers.

ALK

Rearrangements of the gene encoding the anaplastic lymphoma kinase (ALK) protein have been linked to abnormal cell proliferation and NSCLC. The most common ALK rearrangement in NSCLC is EML4-ALK. Patients with ALK rearrangements are younger than most and do not benefit from EGFR-specific TKI therapy but may be considered for therapy targeting the activated receptor TKI that results from EML4-ALK and other ALK fusions. Crizotinib is the first FDA-approved ALK TKI. It is indicated for treatment of locally advanced or metastatic NSCLC in patients whose tumors are positive for ALK.
dual inhibition of both pathways,” explains Dr. Gray. “Our aim is to further classify these tumors through biomarker evaluation and to establish safety, tolerability and efficacy of the combination.”

The trial has four cohorts, and patients will receive oral MEK (15 mg) either daily or twice daily (15-45 mg) and erlotinib (100-150 mg) daily.

**ELM4-ALK rearrangement**

In addition to lung cancer immunotherapy-based clinical trials, clinical trials that target specific mutations associated with lung cancer continue to be conducted and with good response from patients. For example, Moffitt trial 17340 investigates the HSP90 inhibitor AT13387 alone and in combination with crizotinib for patients with stage IV NSCLC. The target of the study, headed by Moffitt medical oncologist Alberto Chiappori, MD, is the anaplastic lymphoma receptor tyrosine kinase (ALK) translocation.

“The patients who will benefit from the trial are those who have the ALK translocation, which is susceptible to drugs that inhibit ALK,” explains Dr. Chiappori. “Crizotinib is a first-generation ALK inhibitor.”

About 5 to 8 percent of patients with NSCLC are estimated to have this chromosomal rearrangement that contributes to carcinogenesis. The patients with the rearrangement are often younger and nonsmokers.

According to Dr. Chiappori, testing for the ALK mutation is becoming a more routine process and more trials are available.

**Small cell lung cancer**

Another study on which Dr. Chiappori is the PI is Moffitt trial 17778, a randomized, double-blind, placebo-controlled phase II clinical trial of alisertib (MLN8237) in combination with paclitaxel vs. placebo in combination with paclitaxel as a second-line therapy for small cell lung cancer. Alisertib shows a greater than 200-fold higher selectivity for Aurora A kinase than does the structurally related Aurora B kinase, without any significant activity against 205 other kinases. It has been shown to significantly reduce tumor burden with tumor growth inhibition in preclinical studies.

Because of the high rates of mortality for patients with small cell lung cancer, treatment through clinical trials need not be a “last resort” but rather a consideration for newly diagnosed patients before they start traditional treatments, notes Dr. Chiappori.

“If a patient is in the middle of treatment, that patient is not a candidate for a clinical trial,” he emphasizes. “Being on a study is a treatment. So the time to ask about the availability of a clinical trial is when options are being weighed at diagnosis.”

It makes good sense, says Dr. Chiappori, to take advantage of a treatment that might not otherwise be available for years to come.

**Back to vaccines**

According to Dr. Antonia, it is time to “resurrect” tumor vaccines and use them in combination with therapeutic approaches directed at the tumor microenvironment.

“People became pessimistic about tumor vaccines because they often did not produce clinical responses, although they were able to induce anti-T-cell tumor responses,” explains Dr. Antonia.
The vaccines they’ve developed, such as GM.CD40L, are now being used in a Moffitt trial (16439) in combination with CCL21. Dr. Gray is the PI.

Dr. Antonia and his colleagues are also laying the groundwork for clinical trials with adoptive T-cell therapy using tumor-infiltrating lymphocytes — TIL therapy — now being used for melanoma but soon to expand into lung cancer therapeutics.

The new wave of therapy will combine drugs that target the tumor microenvironment with agents directed at the immunosuppressive lymphoid compartment.

**Lung cancer CT screening trial aims to improve screening infrastructure**

Treating lung cancer is about to take another step forward with an improved ability to screen patients. In July, Moffitt received a $1.6 million Infrastructure Grant from the James and Esther King Biomedical Research Program titled “Expansion of Enduring Infrastructure to Support Lung Cancer Screening Research.” The program is a three-year lung cancer screening clinical trial with impetus coming from the U.S. Preventative Services Task Force (2014) approving guidelines recommending low-dose CT scans annually for older smokers. Research will focus on lung CT scans and on radiomics, proteogenomics, epidemiology and smoking cessation.

“Each year in Florida, more than 17,000 new cases of lung and bronchus cancer are diagnosed, and there are over 12,000 lung and bronchus cancer-related deaths,” cites Dr. Antonia, the PI on the grant. “Given the large number of poor outcomes, early screening and detection can have great impact on patient survival. Statewide screening could reduce mortality by 20 percent.”

The research has four aims:

- to develop sustainable processes in screening, education and promotion;
- to expand and improve existing lung cancer screening infrastructure by collecting and managing screening data, including outcomes and biospecimens;
- to create a high-throughput imaging pipeline to extract radiological image features; and
- to develop smoking cessation interventions for lung cancer screening participants.

According to Dr. Gray, a study published in the *New England Journal of Medicine* in 2011 showed a decrease in mortality with CT scanning for lung cancer. Past studies had never shown a benefit when compared to X-ray screening. As part of this project, Moffitt aims to establish a lung cancer screening registry.

“We want to be able to collate images, look at nodules and determine which features have higher risks,” explains Dr. Gray. “The program will also be linked to Moffitt’s smoking cessation program.”

Those interested in lung cancer screening should contact: **1-888-MOFFITT.**

### The Lung Cancer Mutation Consortium Protocol

Moffitt Cancer Center was one of 14 sites participating in *The Lung Cancer Mutation Consortium Protocol*, a federally funded study coordinated by researchers at the University of Colorado. The nationwide study offered advanced lung cancer patients screenings of their tumors for genetic mutations. Some of those mutations might be targets for treatment with experimental or existing therapies.

“There are drugs that can attack those abnormal genes, and when we match drugs to these genes, we can have results that are dramatic,” says Moffitt study principle investigator Eric Haura, MD, director of the Lung Cancer Center of Excellence and program leader of Chemical Biology and Molecular Medicine at Moffitt. He adds that identifying mutations in malignant lung tumors will help in understanding the “frequency of each mutation, its association with clinical features and outcome, and its association with other mutations.

This type of clinical study fits in with Moffitt’s goals for personalized medicine. “We are developing expertise and momentum in proteomics, involving the application of innovative advanced technology, such as the ‘next generation’ of the genome, to the problems related to cancer,” says Dr. Haura.

### Moffitt Plays Pivotal Role in FDA Approval Of New Anti-PD-1 Inhibitor Keytruda for Metastatic Melanoma

On Sept. 4, 2014, the U.S. Food and Drug Administration (FDA) announced the approval of a new cancer immunotherapy to treat patients with metastatic melanoma, Keytruda (pembrolizumab) by Merck & Co.

The approval of Keytruda addresses an unmet medical need for patients with advanced melanoma whose cancer has progressed on prior therapies.

Jeffrey S. Weber, MD, PhD, director of the Donald A. Adam Comprehensive Melanoma Research Center of Excellence at Moffitt Cancer Center, was one of the lead investigators of the PD-1 clinical trial that led to the drug receiving breakthrough status from the FDA.

“Pembrolizumab is the first PD-1 drug to be approved by the FDA, and it is a clearly effective drug that will prolong survival for many patients with metastatic melanoma,” Dr. Weber said. “This approval is a real advance and a major milestone in the treatment of the disease.”
NON-SMALL CELL LUNG CANCER MUTATION-SPECIFIC TRIALS

EGFR MUTATION
MCC#17176: A phase I trial evaluating safety and tolerability of the irreversible epidermal growth factor receptor inhibitor BIBW 2992 in combination with the SRC kinase inhibitor dasatinib for patients with non-small cell lung cancer (NSCLC).
Contact: Amanda Carpenter, 813-745-3905.

MCC#17736: A phase I, open-label, multicenter study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of gefitinib in combination with MEDI4736 (anti-PD-L1) in subjects with NSCLC.
Contact: Kara Rogers, 813-745-1457.

KRAS-EGFR
MCC#17361: A phase I/ib trial of MEK162 in combination with erlotinib in NSCLC harboring KRAS or EGFR mutation.
Contact: Milijana Ugrenovic, 813-745-2010.

ELM4-ALK REARRANGEMENT
MCC#17340: A study of HSP90 inhibitor AT13387 alone and in combination with crizotinib in NSCLC.
Contact: Germaine Gonzalez Vasquez, 813-745-8350.

MCC#17652: A phase II, multicenter, single-arm study of oral AP26113 in patients with ALK-positive, locally advanced or metastatic NSCLC who have previously been treated with crizotinib.
Contact: Diana Lima, 813-745-7363.

NON-SMALL CELL LUNG CANCER
MCC#16088: Lung Cancer Mutation Consortium Protocol.
Contact: Karen Johnson, 813-745-6176

MCC#17681: A randomized, double-blind, placebo-controlled multicenter trial of bavituximab plus docetaxel versus docetaxel alone as second-line therapy in patients with stage IIb/IV non-squamous NSCLC.
Contact: Milijana Ugrenovic, 813-745-2010.

MCC#17643: An open-label, multicenter, dose-escalation, phase I study of the safety, tolerability, pharmacodynamics and pharmacokinetics of RTA 408 in the treatment of patients with advanced solid tumors.
Contact: Kara Rogers, 813-745-1457.

SMALL CELL LUNG CANCER
MCC#17778: A randomized, double-blind, placebo-controlled, phase II clinical trial of alisertib (MLN8237) in combination with paclitaxel versus placebo in combination with paclitaxel as second-line therapy for small cell lung cancer.
Contact: Angela Akar, 813-745-4625.

IMMUNOTHERAPY
MCC#17148: A phase I study to evaluate the safety, tolerability and pharmacokinetics of MEDI4736 in subjects with advanced solid tumors.
Contact: Diana Lima, 813-745-7363.

MCC#17608: A phase Ib open-label study to evaluate the safety and tolerability of MEDI4736 in combination with tremelimumab in subjects with advanced NSCLC.
Contact: Amanda Carpenter, 813-745-3905.

MCC#17765: A phase II non-comparative, open-label, multicenter, international study of MEDI4736 in patients with locally advanced or metastatic NSCLC (stage IIIB-IV) who have received at least two prior systemic treatment regimens, including one platinum-based chemotherapy regimen (Atlantic).
Contact: Germaine Gonzalez Vasquez, 813-745-8350.

MCC#17738: An open-label, randomized, phase III trial of nivolumab versus investigator’s choice chemotherapy as first-line therapy for stage IV or recurrent PD-L1+ NSCLC.
Contact: Milijana Ugrenovic, 813-745-2010.

For a complete listing of clinical trials, please visit www.moffitt.org/clinicaltrials.

Phase I Clinical Trial Consortium
To Further Personalized Cancer Care
Moffitt Cancer Center is one of three facilities collaborating with Princess Margaret Cancer Centre in the Princess Margaret Phase I Consortium. The consortium is a result of a five-year UMI grant from the National Cancer Institute. UMI grants support large-scale collaborative research activities, such as clinical trial networks.

Working as a team, the consortium will have more access to patients who may qualify for these phase I studies and improve the potential for larger phase II and phase III studies.

The consortium will be overseen by Princess Margaret’s Lillian L Siu, MD, FRCP. Daniel Sullivan, MD, will serve as Moffitt’s principal investigator with collaboration from Richard Lush, PhD, and Amit Mahipal, MD. The two other facilities participating in the consortium are Juravinski Cancer Centre and British Columbia Cancer Agency.

“This is an innovative collaboration that will further personalized cancer care,” said Dr. Sullivan. “Patients participating in our early phase studies will undergo genomic screening that will help us identify drivers of drug sensitivity or resistance. We can then use that information to help identify and correlate gene markers with clinical outcome.”

Select Thoracic Oncology Clinical Trials at Moffitt Cancer Center
SAVE THE DATE

JOIN IN ON CONTINUING MEDICAL EDUCATION & PEER-TO-PEER INTERACTION

• Cutaneous Lymphoma Symposium
  October 16, 5:00 pm–9:00 pm
  Oystercatchers, Tampa, FL
  Register: www.moffitt.org/cutaneous2014

• Advances in Cancer Immunotherapy™
  December 5, 8:00 am–4:00 pm
  Marriott Waterside Hotel & Marina, Tampa, FL
  Contact Katie at Kkoerner@sitcancer.org or
  www.sitcancer.org/sitc-meetings/acit2014/fl

• Moffitt Mingles, A Holiday Networking Event
  December 4, 5:30 pm–8:00 pm
  Moffitt Cancer Center at International Plaza
  RSVP to Terra.Dawson@Moffitt.org

• Women’s Health Issues: Breast, Thyroid, Gyn
  October 23, 5:30 pm–8:15 pm
  Moffitt Cancer Center at International Plaza
  To register, RSVP to CME.RSVP@Moffitt.org

SPECIAL EVENT (Non-CME)

• Moffitt Mingles, A Holiday Networking Event
  December 4, 5:30 pm–8:00 pm
  Moffitt Cancer Center at International Plaza
  RSVP to Terra.Dawson@Moffitt.org

Most sessions are open to all physicians interested in the field and topic. Contact us at 813-745-4988 for details.

For more information on upcoming conferences, visit MOFFITT.org/conferences.