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THE
# CLINICAL CANCER LETTER
*Cancer research news for clinicians*

*Lung Cancer:*

## NCI Lung Cancer Mutation Consortium: Screening For Mutations Can Focus Therapy

Screening tumor samples for cancer-causing genetic mutations can help tailor treatment to specifically target those mutations in patients with advanced lung cancer.

A study detected one of ten such mutations in 54 percent of 516 lung cancer patients tested at diagnosis. The results enabled doctors to select the most appropriate drug designed to block the identified mutation and choose other treatment options for those patients whose tumors did not have a mutation.

The results of the multicenter study were presented at the ASCO annual meeting by the study's lead author, Mark Kris, chief of the Thoracic Oncology Service at Memorial Sloan-Kettering Cancer Center,

"The key to treating men and women with lung cancer lies in

(Continued to page 2)

*Advanced Melanoma:*

## Two Trials Presented at ASCO Demonstrate Drop in Death Risk, Increased Survival

Two separate trials presented data at ASCO's annual meeting showing great clinical benefit for patients with advanced melanoma.

An international, multicenter, phase III trial evaluating PLX4032 (vemurafenib) demonstrated a 63 percent decrease in risk of death compared to the dacarbazine, the standard chemotherapy. Vemurafenib treatment also resulted in significant tumor shrinkage in 48 percent of patients (n=675). Vemurafenib is a daily oral medication that targets and blocks the BRAF mutated gene. This gene has been associated with half of melanomas.

The agent is sponsored by Plexxicon and Hoffmann-LaRoche.

A second study evaluated the immunotherapy ipilimumab (Yervoy) as first-line treatment. It was approved by the FDA in March 2011.

The double-blind, randomized trial compared dacarbazine to dacarbazine plus ipilimumab. Patients that received both therapies lived approximately two months longer than those on chemotherapy alone, and approximately twice as many of these patients survived two to three years after treatment began. Yervoy is sponsored by Bristol-Myers Squibb.

"By temporarily blocking this brake, ipilimumab allows the immune system to become more robustly activated than it otherwise would and, therefore, in some people causes the production of antibodies and T-cells that can recognize melanoma leading to control of the disease," said Jedd Wolchok, of Memorial Sloan-Kettering Cancer Center.





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## One Mutation Accounted For 54 Percent of Tested Tumors

(Continued from page 1)

understanding the genetic makeup of each person's tumor," Kris said. "Pinpointing specific mutations known to play a role in one-third of lung cancers can help maximize the chance of treatment success with personalized medicine."

Fourteen institutions are participating in this ongoing study, which has tested 1,000 patients who have been newly diagnosed with stage IV lung cancer that has returned after initial treatment with surgery, chemotherapy, and/or radiation. All 14 are members of NCI's Lung Cancer Mutation Consortium, an initiative created to identify the frequencies and characteristics of genetic mutations found specifically in lung cancer and research treatments that target them.

Study researchers are screening lung tumors using multiplexed assays for mutations in KRAS, EGFR, HER2, BRAF, PIK3CA, AKT1, MEK1 and NRAS, and are using flourescence in situ hybridization for ALK rearrangements and MET amplifications. The most common mutations found so far have been KRAS (23 percent) and EGFR (17 percent).

Patients whose tumors are found to have the driver mutation EGFR-1 are treated with the targeted drug Tarceva (erlotinib). Patients whose tumors exhibit one of the nine other mutations avoid being treated with erlotinib—which would not likely benefit them—and are offered participation in one of several LCMC-linked clinical trials investigating new medicines that target these specific genetic defects. For example, patients who have the EML-4ALK mutation may enroll in a clinical trial studying the experimental drug crizotinib, which is currently under FDA review for the treatment of lung cancers that have that mutation.

According to Kris, the next step is to expand this concept of customizing treatment based on a patient's unique genetic tumor profile to all lung cancers and all stages of lung cancer. "In fact, this process can work for any cancer, and our assay panel already includes important mutations in colorectal cancer (KRAS) and melanoma (BRAF)," Kris said in a statement.

"As additional mutations are discovered by efforts like the Cancer Genome Atlas, these mutations can be quickly included in the routine molecular analyses. At the same time, our investigators will continue researching new therapies that target these genetic abnormalities, providing hope for the 220,000 people diagnosed with lung cancer each year."

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*Ovarian Cancer:*

## OCEANS Study: Avastin Shows Tumor Shrinkage in 79 Percent

Genentech announced results from OCEANS, a phase III study evaluating Avastin (bevacizumab) in combination with chemotherapy (gemcitabine and carboplatin) in women with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer.

OCEANS was a randomized, double-blind, placebo-controlled trial in 484 women, who had received no more than one treatment regimen prior to enrollment in the trial.

The primary endpoint of the study was progression free survival. The secondary endpoints of the study included overall survival, objective response, duration of response and safety profile.

Women recieving Avastin experienced a 52 percent reduction in the risk of their disease progressing (HR=0.48, $p<0.0001$) compared to women who received chemotherapy alone. They had a median progression-free survival of 12.4 months, compared to 8.4 months in women who received chemotherapy alone. Tumor shrinkage occured in 79 percent of the women, compared to 57 percent who received chemotherapy alone.

The drug arm received Avastin (15 mg/kg every three weeks) in combination with carboplatin and gemcitabine chemotherapy, followed by Avastin as a single agent until disease progression or unacceptable

toxicity; the control arm received placebo in combination with carboplatin and gemcitabine chemotherapy, followed by placebo alone.

Adverse events were consistent with those seen in previous trials of Avastin across tumor types. Grade 3-5 adverse events occcuring more often in the Avastin arm were hypertension (17 percent vs. <1 percent), proteinuria (9 percent vs. 1 percent) and bleeding that does not occur in the central nervous system (6 percent vs. 1 percent). There were no gastrointestinal perforations seen during the safety reporting period of this study.

Avastin is a biologic antibody designed to bind to VEGF. Avastin interferes with the tumor blood supply by directly binding to the VEGF protein to prevent interactions with receptors on blood vessel cells.

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The primary endpoint of the study was PFS. The secondary endpoints of the study included overall survival, objective response, duration of response and safety profile.

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## *Non-Small Cell Lung Cancer:*
## Cetuximab Plus Chemoradiation Boosts Survival in Phase II Study

A phase II study evaluating the combination of cetuximab with chemotherapy resulted in longer median and overall survival in patients with non-small cell lung cancer.

The study, "Phase II Study of Cetuximab (C225) in Combination with Chemoradiation (CRT) in Patients with Stage IIIA and IIIB NSCLC (RTOG 0324)", said that patient survival was greater than treatments in previous Radiation Therapy Oncology Group lung cancer clinical trials. It was published June 10 in the Journal of Clinical Oncology.

The study enrolled 93 participants from 42 RTOG centers; data from 87 of the participants were eligible for the study analysis. The median survival time was 22.7 months and the two-year survival rate was 49.3 percent, with a response rate of 62 percent (n=54).

A ROTG press release said that these results corroborate several large randomized clinical trials that have validated the efficacy of cetuximab in combination with either chemotherapy or radiation therapy in both NSCLC and squamous cell carcinoma of the head and neck.

"Results from this trial demonstrate that cetuximab in combination with chemoradiation is well tolerated by patients with inoperable Stage III NSCLC," said George Blumenschein, the paper's lead author. "The rate of severe side effects experienced by the study participants was commensurate with what has been widely reported for patients treated with the same chemoradiotherapy regimen alone."

A subsequent phase III trial has been planned, RTOG 0617. The randomized study will also explore the potential benefits of adding cetuximab to CRT in a similar target population—over 90 percent of the planned 500 study participants have been enrolled.

Cetuximab is a chimerized monoclonal antibody that targets and binds to the epidermal growth factor receptor.

*Non-Small Cell Lung Cancer:*

## First-Line Tarceva Nearly Doubles PFS in EGFR-Activated Tumors

Genentech and Astellas Pharma US Inc. announced results from EURTAC, a phase III study evaluating Tarceva (erlotinib) in patients with advanced non-small cell lung cancer with EGFR-activating mutations.

The study showed that first-line Tarceva nearly doubled progression-free survival compared to chemotherapy alone, from 5.2 months to 9.7 months, meeting its primary endpoint.

Tarceva reduced the risk of progression by 63 percent, compared with platinum-based chemotherapy (HR=0.37, $p<0.0001$). The safety profile for Tarceva was consistent with previous studies in NSCLC.

The genetically distinct type of lung cancer studied in EURTAC (European Randomised Trial of Tarceva vs. Chemotherapy) occurs in approximately 10 percent of lung cancer patients in the Western population and approximately 30 percent of Asian patients.

In the study, 1,275 patients were screened for EGFR activating mutations and 174 patients were randomly assigned to receive Tarceva or platinum-based chemotherapy. Secondary endpoints included response, overall survival and toxicity profiles.

Grade 3 or 4 adverse events that occurred more often in Tarceva patients were rash, diarrhea and liver enzyme elevation. One related death was reported for a patient who received Tarceva.

EURTAC was designed and sponsored by the Spanish Lung Cancer Group and conducted together with investigators from France and Italy in cooperation with Roche.

"We are pleased with the results from the EURTAC study, which is promising for patients with this genetically distinct type of NSCLC," said Steve Ryder, president of Astellas Pharma Global Development. "The data from the EURTAC study reinforces the role that Tarceva may have in NSCLC patients with a once-a-day oral pill and a known toleration profile."

*Stomach Cancer:*

## Telatinib Demonstrates Positive Results in First-Line Treatment

A phase II study evaluating telatinib first-line treatment, in combination with chemotherapy, for patients with metastatic stomach cancer showed positive results.

The addition of telatinib, an oral antiangiogenic agent, to chemotherapy resulted in rapid and sustained tumor regression in two-thirds of evaluable patients with inoperable metastatic stomach cancer, regardless of the tumor location or whether it had already spread to the liver.

Among 39 evaluable patients treated with telatinib, 64 percent showed partial response and one patient had a complete response, and 26 percent achieved stable disease.

The median progression-free survival was 140 days and the combination was well tolerated at the full recommended dose. The most common telatinib-related side effects, such as hypertension and fatigue, were manageable and reversible. In general, the side effects experienced by the clinical trial patients were consistent with side effects related to chemotherapy.

"Antiangiogenic agents are an important class of drugs for the treatment of gastrointestinal cancers. Telatinib's high response rate coupled with a lack of overlapping side effects with chemotherapy suggest that telatinib may be an important combination therapy candidate for patients with stomach cancer," said Jaffer Ajani, professor of medicine at the MD Anderson Cancer Center.

"These phase II data build on our previous telatinib results in gastrointestinal cancers. The promising response rates and exceptional tolerability in combination with chemotherapy in a difficult-to-treat patient population is beyond what has been seen previously with other oral antiangiogenic agents," said Lori Kunkel, chief medical officer of ACT Biotech.

*Esophageal Cancer:*

## Barret's Less of a Risk Factor For Cancer of the Esophagus

The results of a study published in JNCI suggest patients with Barrett's esophagus have a lower risk of esophageal cancer than previously reported.

Researchers prospectively followed 8,522 patients in the Northern Ireland Barrett's Esophagus Registry. After an average follow-up time of seven years, 79 patients were diagnosed with esophageal cancer, 16 with cancer of the gastric cardia, and 36 with high-grade dysplasia.

In the entire group, the incidence of these three conditions combined was 0.22 percent per year. Previous studies have reported an incidence of cancer among BE patients between 0.58 percent and 3 percent per year.

The study also recorded the incidence of cancer and high-grade dysplasia in different subgroups of patients. Men were statistically significantly more likely

to progress to malignancy than women, and people age 60-69 had a higher risk than those under age 50 or over age 80. The highest rates of progression were among patients with low-grade dysplasia (1.40 percent) or specialized intestinal metaplasia (0.38 percent) at their initial endoscopy and biopsy.

*Prostate Cancer:*

## New Abiraterone Acetate Results Show Greater Benefit Than Before

Final survival results from a study evaluating abiraterone acetate (Zytiga) demonstrated greater median survival than previously reported.

The drug was recently approved by FDA for men with metastatic prostate cancer when chemotherapy is not effective.

The randomized, double blind, placebo-controlled trial included 1,195 men with metastatic prostate cancer whose disease had progressed after docetaxel-based chemotherapy. Patients were randomized to receive prednisone with either abiraterone acetate or placebo.

After following up with patients after 20.2 months of treatment, overall survival for the abiraterone acetate group was 15.8 months, versus 11.2 months for the placebo group.

Interim results of the trial published May 26 in The New England Journal of Medicine found that, in patients followed for a little more than 12 months, overall survival for the abiraterone acetate group was 14.8 months versus 10.9 months for the placebo plus prednisone group.

In this final analysis, presented at ASCO's annual meeting, the difference in median overall survival between the two groups improved from 3.9 to 4.6 months.

"In addition to demonstrating that abiraterone acetate prolongs lives, this treatment also offers men with metastatic castration resistant disease after docetaxel chemotherapy a new treatment option at a point in the illness where hormonal agents are typically not considered," said Howard Scher, chief of the Genitourinary Oncology Service at Memorial Sloan-Kettering.

"The survival benefit demonstrated that these tumors are not uniformly resistant to hormonal therapy."

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*Glioblastoma:*

## MGMT Gene Can Determine Disease Aggressiveness

A prospective international phase III clinical trial sponsored by Radiation Therapy Oncology Group suggests that testing the MGMT gene in glioblastoma patients can distinguish between forms of the disease that can be more or less aggressive.

The study, RTOG 0525, examined tumors removed from 833 glioblastoma patients, and showed that when the gene promoter is altered by a chemical change called methylation, patients respond better to treatment.

"We show that MGMT methylation represents a new genetic test that can predict clinical outcomes in glioblastoma patients who have been treated with radiation combined with the chemotherapeutic drug temozolomide," said co-author Arnab Chakravarti, chair and professor of Radiation Oncology and co-director of the brain tumor program at the Ohio State University Comprehensive Cancer Center.

An indication that MGMT methylation status might have prognostic importance emerged from an earlier study sponsored by the European Organisation for Research and Treatment of Cancer.

Patients with tumors carrying the methylated gene had an overall survival of 21 months versus 14 months for those with the unmethylated gene. The difference in progression-free survival was 8.7 months and 5.7 months for methylated versus unmethylated tumors respectively. The narrow difference, Chakravarti noted, indicates that patients with the methylated gene had slower growing tumors.

"Patients with the methylated gene could receive the standard treatment, radiation therapy plus the chemotherapeutic drug temozolomide," Chakravarti says. "Those with an unmethylated gene might receive an experimental treatment through a clinical trial."

According to Chakravarti, research is now needed to learn whether MGMT contributes directly to tumor aggressiveness, or whether it is just an indicator of other changes that cause tumor aggressiveness.

"Our study confirms the prognostic significance of MGMT gene methylation and demonstrates the feasibility of prospective tumor-tissue collection, molecular stratification and collection of patient outcomes in a large transatlantic intergroup trial," said principal investigator Mark Gilbert, professor of neuro-oncology at MD Anderson Cancer Center.

*Lymphatic Mapping:*

## Phase III Study: Lymphoseek Superior to Vital Blue Dye

The results of a phase III study demonstrated that Lymphoseek was superior to vital blue dye at identifying nodes that drain the primary site of the tumor during the intraoperative lymphatic mapping procedure.

The study's primary endpoint was the Lymphoseek concordance rate, or the number of nodes stained by VBD that were also identified by Lymphoseek.

Lymphoseek achieved a 100 percent concordance rate (95% CI 0.9840-1.0000, $p<0.0001$) among all blue nodes (N=229). Lymphoseek also achieved a 100 percent concordance rate (95% CI 0.9726-1.0000, $p<0.0001$) when looking at the total patients evaluated (N=133). Lymphoseek detected all of the nodes stained by VBD in all of the patients.

All phase III Lymphoseek concordance data were statistically significant ($p<0.0001$). Breast cancer and melanoma occurrence was approximately 50/50 among all nodes stained by VBD in the study.

The study also analyzed the reverse concordance rate of VBD and superiority between the two diagnostic agents. The number of Lymphoseek-detected nodes that were also VBD-stained was 61 percent (95% CI 0.5546-0.6554, p=1.0000) among all 378 nodes detected by Lymphoseek in the study. Among all patients (N=152), only a reverse concordance rate of 50 percent (95% CI 0.4179-0.5821, p=1.0000) was observed with VBD.

The reverse concordance rate for VBD on both phase III studies was not statistically significant (p=1.0000) from either the node or patient perspective. VBD was in fact inferior to Lymphoseek in these phase III studies on this measure of lymph node detection. Lymphoseek was found to be superior to VBD on a per node basis through statistical analysis ($p<0.0001$).

Lymphoseek had 100 percent sensitivity (95% CI 0.9119-1.0000), identifying all tumorous nodes confirmed by pathology. This resulted in a zero percent (95% CI 0.0000-0.0881) false detection rate.

A meta-analysis that included 71 studies and 25,240 total melanoma patients concluded that the overall FDR rate for lymphatic mapping was 12.5 percent (95% CI, 11% to 14.2%), which is significantly higher than the Lymphoseek observation. On the other hand, a sensitivity of only 75 percent (95% CI 0.5880-0.8731) was observed with VBD, which resulted in a 25 percent (95% CI 0.1269-0.4120) FDR.

On a per patient basis, 55 patients were identified to have lymph nodes containing pathology-confirmed tumor across both NEO3-05 and NEO3-09 studies. Lymphoseek did not miss any of the 55 total patients, while VBD missed four patients (two with breast cancer and two with melanoma) for a FDR of 7.3 percent ($p<0.044$). Lymphoseek also identified two patients with lymphoma that were not identified by VBD.

No clinically significant drug-related adverse events or morbidity issues have been observed. In phase III trials, the only drug-related adverse event, anaphylactic hypotension, was experienced with VBD treatment.

Lymphoseek aided in upstaging four melanoma and breast cancer patients, which will help the patients receive the appropriate treatment. This means that Lymphoseek helped determine that some patients were at a later disease stage (i.e. stage III vs. stage II) than the stage diagnosed by the doctor. No patients were upstaged by VBD.

*Radiation Therapy:*

## Intensity Modulated Therapy Safer Than Three-Dimensional Radiation

According to a study published in the International Journal of Radiation Oncology·Biology·Physics, intensity modulated radiation therapy causes fewer gastrointestinal side effects when combined with hormone therapy than using three-dimensional radiation therapy.

Three-dimensional radiation therapy combined with hormone therapy has been proven very effective at treating men with intermediate to high-risk prostate cancer. But these treatments can cause very uncomfortable gastrointestinal side effects due to exposure of the rectum to radiation during treatment.

Researchers at Fox Chase Cancer Center conducted a study to see if IMRT, which allows doctors to better concentrate radiation in the prostate and limit rectal exposure, reduces the side effects while continuing to deliver the necessary radiation to successfully treat the cancer.

The study followed 293 patients; 170 received 3D-CRT and 123 received IMRT. With a mean follow-up of 86 months, a multivariate analysis shows that patients treated with 3D-CRT were more than twice as likely to develop gastrointestinal toxicity compared to patients treated with IMRT.

"The use of IMRT significantly reduces the risk of late GI toxicity in men undergoing concurrent radiation therapy and hormone therapy for prostate cancer," Mark Buyyounounski, a radiation oncologist at Fox Chase, said in a statement. "I encourage men with prostate

cancer receiving hormone therapy and radiation therapy to talk their doctors about whether IMRT has advantages over other types of radiation therapy."

*Smoking Cessation:*

## Smokers Quitlines Found Effective Regardless of Recruitment Method

A study published online in JNCI said that proactive telephone counseling helps smokers quit regardless of how they are recruited to a telephone quitline.

Smokers who use telephone counseling quitlines may do so in response to active recruitment methods, such as physician referral or direct mail or phone calls, or passive methods, such as posters or television ads.

In the study, Flora Tzelepis, of University of Newcastle, Australia, and colleagues analyzed 24 previous studies of proactive telephone counseling to see whether the method of recruitment made a difference in quit rates.

They looked at both point prevalence abstinence—the number of smokers who had not smoked for at least a day or a week before the interview—and at prolonged or continuous abstinence over a period of months.

The researchers found that proactive counseling helped increase long-term smoking cessation regardless of how the smokers were recruited. Quitlines had a statistically significantly positive effect on prolonged and continuous abstinence after 6-9 months and after 12-18 months. Their effect on point prevalence abstinence was also statistically significant at 6-9 months, but not at the longer-term follow-up.

"In general," the authors wrote, "our findings have strengthened the support for proactive telephone counseling for smoking cessation." They noted, however, that few active-recruitment trials are available to evaluate the impact of the recruitment channel on prolonged/continuous abstinence, particularly in the midterm, and that additional data are urgently needed.

In an accompanying editorial, Damon Vidrine and Jennifer Irvin Vidrine, of MD Anderson Cancer Center, note that smokers in this study who responded to advertisements and other passive recruitment efforts were more willing to set a quit date in the next month compared to actively-recruited smokers. This suggests they were more highly motivated to quit.

The fact that active recruitment methods, they wrote, resulted in quit rates almost as high as passive recruitment has "enormous implications for the public health impact of quitline-delivered cessation treatment."

*Basal Cell Carcinoma:*

## Study: Vismodegib Effective Where Surgery is Inappropriate

Genentech said a phase II study with vismodegib showed positive results in people with advanced basal cell carcinoma for whom surgery is considered inappropriate.

Vismodegib is an investigational, oral medicine designed to selectively inhibit signaling in the Hedgehog pathway, which is implicated in more than 90 percent of BCC cases.

The international, single-arm, multicenter trial showed vismodegib substantially shrank tumors or healed visible lesions in 43 percent of patients with locally advanced BCC and 30 percent of patients with metastatic BCC, as assessed by independent review.

The study enrolled 104 patients with advanced BCC, including laBCC (71) and mBCC (33).

The primary endpoint of the trial showed an overall response rate of 43 percent in the laBCC cohort, and 30 percent in mBCC, as assessed by independent review. Study investigators assessed the overall response rate for laBCC and mBCC at 60 percent and 46 percent, respectively. The median duration of progression-free survival by independent review for both metastatic and locally advanced BCC patients was 9.5 months.

laBCC patients had lesions that were inappropriate for surgery (inoperable, or for whom surgery would result in substantial deformity) and for which radiotherapy was unsuccessful or contraindicated. Study participants received 150mg vismodegib orally, once daily until disease progression or intolerable toxicity.

The most common drug-related adverse events were muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite and diarrhea.

"Vismodegib is an example of our commitment to understanding and developing medicines that target the biologic cause of a particular disease," said Hal Barron, chief medical officer and head of Global Product Development.

"Our goal is to provide a medicine to people with this rare and disfiguring form of advanced skin cancer as soon as possible, and we are discussing these results with global regulatory authorities."

Serious adverse events were observed in 26 patients, or 25 percent. Four patients had events that were considered to be related to vismodegib, including one case each of: blocked bile flow from the liver, dehydration with loss of consciousness, pneumonia

accompanied by cardiac failure, and pulmonary embolism.

Fatal events were reported in seven patients (7 percent); none were considered by investigators to be related to vismodegib. In all cases, patients had other pre-existing diseases or symptoms that were related to their presumed cause of death.

## NCI-Approved Clinical Trials For The Month of June

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigator listed.

**Phase I**

8799: A Phase 1 Study of the Mitogen Activated Protein Kinase (MEK) 1 Inhibitor AZD6244 Hydrogen Sulfate (Selumetinib Sulfate) in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN). National Cancer Institute Pediatric Oncology Branch; Widemann, Brigitte C. (301) 496-7387

8808: An Early Phase 1 Study of ABT-888 in Combination with Carboplatin and Paclitaxel in Patients with Hepatic or Renal Dysfunction and Solid Tumors. University of Pittsburgh Cancer Institute; Tawbi, Hussein Abdul-Hassan. (412) 692-2600

8810: Phase I Study of the Combination of the VEGFR Inhibitor, AZD2171, and MEK Inhibitor, AZD6244, in the Treatment of Solid Malignancies. Mayo Clinic; Haluska, Paul. (507) 284-2511

8976: Phase I Study of the Hsp90 Inhibitor, PU-H71, in Patients with Refractory Solid Tumors and Low-Grade Non-Hodgkin's Lymphomas. National Cancer Institute Developmental Therapeutics Clinic; Kummar, Shivaani. (301) 435-5402

**Phase I/II**

8811: Phase I Followed by Phase II Randomized, Placebo-controlled Study of ABT-888 Added to Chemoradiotherapy with Carboplatin and Paclitaxel for Unresectable Stage III Non-Small Cell Lung Cancer. City of Hope; Argiris, Athanassios. (412) 623-4083

E1A10: A Randomized Phase I/II Study of Bortezomib, Rituximab, Dexamethasone and Temsirolimus in Patients with Untreated or Relapsed Waldenstrom`s Macroglobulinemia or Relapsed Mantle Cell Lymphoma or Follicular Lymphoma. Eastern Cooperative Oncology Group; Heffner, Leonard Thompson. (404) 778-5871

N1087: Phase I/II Study of the Combination of Bendamustine, Rituximab and MK-2206 in the Treatment of Relapsed Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma. North Central Cancer Treatment Group; Ding, Wei. (507) 284-2176

**Phase II**

S1001: A Phase II Trial of PET-Directed Therapy for Limited Stage Diffuse Large B-Cell Lymphoma (DLBCL). Southwest Oncology Group; Persky, Daniel O. (520) 626-2218

**Phase III**

ACCL0934: A Randomized Trial of Levoflaxacin to Prevent Bacteremia in Children Being Treated for Acute Leukemia (AL) or Undergoing Hematopoietic Stem Cell Transplantation (HSCT). Children's Oncology Group; Alexander, Sarah Weeks. (416) 813-7654 ext. 4068

N107C: A Phase III Trial of Post-Surgical Stereotactic Radiosurgery (SRS) Compared with Whole Brain Radiotherapy (WBRT) for Resected Metastatic Brain Disease. North Central Cancer Treatment Group; Brown, Paul D. (713) 563-2415

RTOG-0924: Androgen Deprivation Therapy and High Dose Radiotherapy with or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial. Radiation Therapy Oncology Group; Roach, Mack. (415) 353-7181

RTOG-1005: A Phase III Trial of Accelerated Whole Breast Irradiation with Hypofractionation Plus Concurrent Boost Versus Standard Whole Breast

Irradiation Plus Sequential Boost for Early-Stage Breast Cancer. Radiation Therapy Oncology Group; Vicini, Frank A. (248) 551-1219

**Other Phases**

9122: Pharmacokinetics of the Chimeric Anti-GD2 Antibody, ch14.18, in Children with High-Risk Neuroblastoma. Children's Hospital of Philadelphia; Balis, Frank M. (267) 426-5414

AEWS11B1: INI-1 Deletions in Ewing Sarcoma. Children's Oncology Group; Schiffman, Joshua David (801) 587-4745

AHOD11B1: Investigation to Evaluate the Levels of Human Germinal-center-Associated Lymphoma (HGAL) Protein in Pediatric Hodgkin Lymphoma and Correlate with Early Response. Children's Oncology Group; Keller, Frank G. (404) 785-0908

ANBL11B2: ROR1 as a Novel Target for Neuroblastoma. Children's Oncology Group; Dave, Hema Kishore. (301) 451-7386

ANBL11B3: Expression of Ubiquitin Carboxyl-Terminal Hydrolase 1 (UCHL1) in Neuroblastoma Cancer Stem Cells and Its relationship to Patient Prognosis. Children's Oncology Group; Sugalski, Aaron. (210) 638-1529

ANHL11B1: Expression of T Immunoregulatory Proteins in ALK+ Anaplastic Large Cell Lymphoma (ALCL). Children's Oncology Group; Lim, Megan So-Young (734) 936-1874

AREN11B2: Investigation of DICER1 in Cystic Nephroma and Cystic Partially Differentiated Nephroblastoma. Children's Oncology Group; Hill, Dana Ashley. (202) 476-2815

ARST11B4: A Study to Assess and Quantify Surface Insulin-like Growth Factor I Receptor (IGF-IR) in Rhabdomyosarcoma (RMS) Tumor Tissue. Children's Oncology Group; Malempati, Suman. (503) 494-1543

GOG-0273: Chemotherapy Toxicity in Elderly Women with Ovarian, Primary Peritoneal or Fallopian Tube Cancer. Gynecologic Oncology Group; von Gruenigen, Vivian E. (330) 379-3514

NSABP-C07-CS1: A Laboratory Study of Relationships Between Genomic Tumor Expression Profiles and the Likelihood of Recurrence and Clinical Benefit with Adjuvant 5-FU/LV and Oxaliplatin in Patients with Resected Stage II and Stage III Colon Cancer. National Surgical Adjuvant Breast and Bowel Project; Wolmark, Norman. (412) 330-4600

S0106A: Proteomic Signatures Associated with Complete Response (CR) and Complete Continuous Response at One Year (CCR1) Following Cytarabine-Based Induction Chemotherapy in Younger Adult Patients (18-60 Years of Age) with a Newly Diagnosed Non-M3 AML. Southwest Oncology Group; Radich, Jerald Patrick. (206) 667-4118

**Pilot Phase**

8868: Pilot Study of the Combination of MK-2206, an AKT Inhibitor, and AZD6244, a MEK Inhibitor, in Patients with Advanced Colorectal Carcinoma. National Cancer Institute Developmental Therapeutics Clinic; Kummar, Shivaani. (301) 435-5402

*FDA News:*

## FDA: Silicone Breast Implants Safe, But Not "Lifetime Device"

FDA released a report updating the clinical and scientific information for silicone gel-filled breast implants.

The report confirms that silicone gel-filled breast implants are safe and effective when used as intended, but warns that women should fully understand the risks prior to considering implants for breast augmentation or reconstruction.

Based on the report, women considering silicone gel-filled implants should understand:

• Breast implants are not lifetime devices. The longer a woman has silicone gel-filled breast implants, the more likely she is to experience complications. One in five patients who received implants for breast augmentation will need them removed within 10 years of implantation. For patients who received implants for breast reconstruction, as many as one in two will require removal 10 years after implantation.

• The most frequently observed complications and outcomes are capsular contracture (hardening of the area around the implant), additional surgeries and implant removal. Other common complications include implant rupture, wrinkling, asymmetry, scarring, pain, and infection.

• The complications that existed for women receiving breast implants at the time of approval are similar to the complications observed today.

Preliminary data do not indicate that silicone gel-

filled breast implants cause breast cancer, reproductive problems or connective tissue disease. However, in order to rule out these and other rare complications, studies would need to enroll more women and be longer than those conducted thus far.

The report includes preliminary safety data from post-approval studies conducted by each of the two breast implant manufacturers (Allergan and Mentor), a summary and analysis of adverse events received over the years by the FDA, and a comprehensive review and analysis of recent scientific publications that discuss the safety and effectiveness of silicone gel-filled breast implants. It can be found at: http://1.usa.gov/1ErO5v.

FDA approved silicone gel-filled breast implants in November 2006 for breast augmentation in women over age 22 and for breast reconstruction in all women. As a condition of the approval, the FDA required each of the two companies to conduct six post-approval studies to characterize the long-term performance and safety of the devices.

"The FDA will continue to monitor and collect safety and performance information on silicone gel-filled breast implants, but it is important that women with breast implants see their health care providers if they experience any symptoms," Jeffrey Shuren, director of FDA's Center for Devices and Radiological Health.

"Women who have enrolled in studies should continue to participate so that we may better understand the long-term performance of these implants and identify any potential problems."

Sidney Wolfe, director of Public Citizen's Health Research Group, said that FDA should not return silicone gel-filled breast implants back to the market, and that professional plastic surgeon associations have instructed their members to downplay the cancer risks that come with receiving implants--specifically anaplastic large cell lymphoma.

"The agency's newer information about the risk of implant-associated lymphoma and the previously known risks are serious enough to warrant advising women against having these implanted," said Wolfe in a statement.

"Although there are many excellent and ethical plastic surgeons, the fact that many have been informed by their own organizations to downplay the risks of breast implants is incompatible with adequate informed consent for too many women," he said. "The FDA's acknowledged inadequacy of implant company safety studies makes their continued use resemble an experiment on women, rather than a product with 'a reasonable assurance of safety.'"

*FDA News:*

## FDA Updates Safety Labeling Of 5-Alpha Reductase Inhibitors

FDA changed the label of 5-alpha reductase inhibitors to include safety information about the increased risk of being diagnosed with high-grade prostate cancer.

The June 9 warning applies to the drugs finasteride and dutasteride, which have similar molecular structures and are approved for the treatment of benign prostatic hyperplasia.

Finasteride, sponsored by Merck, is also approved for male pattern baldness, and dutasteride, sponsored by GlaxoSmithKline, is often used for this indication off-label.

The warning is consistent with the Dec. 1, 2010, vote of the FDA Oncologic Drugs Advisory Committee, which set a high bar for approval of drugs that are given to asymptomatic and presumably healthy people (The Cancer Letter, Dec. 3, 2010).

The warning is also consistent with the agency's review of two large, randomized controlled trials—the Prostate Cancer Prevention Trial, and the Reduction by Dutasteride of Prostate Cancer Events trial.

*The agency's recommendation reads:*

FDA is informing healthcare professionals that the Warnings and Precautions section of the labels for the 5-alpha reductase inhibitor (5-ARI) class of drugs has been revised to include new safety information about the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer). This risk appears to be low, but healthcare professionals should be aware of this safety information, and weigh the known benefits against the potential risks when deciding to start or continue treatment with 5-ARIs in men.

The new safety information is based on FDA's review of two large, randomized controlled trials—the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial—which evaluated daily use of finasteride 5 mg versus placebo for 7 years and daily use of dutasteride 0.5 mg versus placebo for 4 years, respectively, for the reduction in the risk of prostate cancer in men at least 50 years of age. The trials demonstrated an overall reduction in prostate cancer diagnoses with finasteride 5 mg and dutasteride treatment. This overall reduction was due to a decreased incidence of lower risk forms of prostate cancer. However, both trials showed an increased incidence of high-grade prostate cancer with finasteride and dutasteride treatment.