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**CONTACT:**  
**Susie Tappouni**  
**571-483-1355**  
[Susie.Tappouni@asco.org](mailto:Susie.Tappouni@asco.org)

## **ASCO RELEASES STUDIES FROM UPCOMING ANNUAL MEETING**

### **– Important Advances in Targeted Therapies, Screening, and Personalized Medicine –**

*Alexandria, Va.* – The American Society of Clinical Oncology (ASCO) today highlighted several studies in a press briefing from among more than 4,000 abstracts publicly posted online at [www.asco.org](http://www.asco.org) in advance of ASCO's 47<sup>th</sup> Annual Meeting. An additional 17 plenary, late-breaking and other major studies will be released in on-site press conferences at the Annual Meeting.

The meeting, which is expected to draw approximately 30,000 cancer specialists, will be held June 3-7, 2011, at McCormick Place in Chicago, Ill. The theme of this year's meeting is "Patients. Pathways. Progress."

"This year marks the 40th anniversary of the signing of the National Cancer Act, a law that led to major new investments in cancer research. Every day in our offices, and every year at the ASCO meeting, we see the results of those investments. People with cancer are living longer, with a better quality of life, than ever before," said George W. Sledge Jr, MD, President of ASCO, Ballve-Lantero Professor of Oncology and professor of pathology and laboratory medicine at the Indiana University School of Medicine.

"With our growing understanding of the nature of cancer development and behavior, cancer is becoming a chronic disease that a growing number of patients can live with for many years," said Dr. Sledge. "The studies released today are the latest examples of progress against the disease, from new personalized treatments, to new approaches to screening and prevention."

Studies highlighted in today's press briefing include:

- *First Large Study of HPV and Pap Co-Testing in Routine Clinical Practice Confirms Many Women Can Safely Extend Testing to Every Three Years; HPV Testing Alone Also Appears to be Superior to Pap Testing Alone:* The first large-scale study of both human papillomavirus (HPV) testing and Pap smear for cervical cancer screening in routine clinical practice confirms that women can safely extend their screening intervals from one to three years. The study also found that HPV testing may be more accurate than conventional Pap smear in determining cervical cancer risk.
- *Combined Screening with CA-125 and Transvaginal Ultrasound Does Not Reduce Ovarian Cancer Death Rate, Results in High Number of False Positives:* Findings from a large, long-term study – the Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial – showed that using a CA-125 blood test and transvaginal ultrasound for early detection of ovarian cancer did not reduce the risk of dying from the disease, and resulted in a large number of false positives and related follow-up procedures.

- *Novel Screening Approach Suggests PSA Levels Among Men Age 44-50 May Predict Long-Term Risk of Metastatic Prostate Cancer or Prostate Cancer-Related Death:* A large, population-based study of Swedish men showed that prostate-specific antigen (PSA) levels at the time of initial screening among men aged 44 to 50 can accurately predict the risk that a man will die of prostate cancer or develop metastatic prostate cancer up to 30 years later, suggesting half of men could undergo just three PSA tests in a lifetime.
- *Genetic Biomarkers Predict Taxane-Induced Neuropathy:* This study identified a genetic biomarker for nerve damage caused by paclitaxal, a complication of chemotherapy that can keep patients from functioning normally and interrupt their treatment.
- *Randomized Study Shows that Maintenance Therapy and PARP Inhibitors Could Play Important Roles in Treatment of Relapsed Ovarian Cancer:* A Phase II trial showed that the oral drug olaparib, given after chemo, improved progression-free survival in women with the most common type of relapsed ovarian cancer.
- *Novel Multi-targeted Agent Cabozantinib (XL184) Has Significant Effect on Several Advanced Solid Tumors, and Can Shrink or Eliminate Bone Metastases:* Cabozantinib demonstrated high rates of disease control in patients with prostate, ovarian and liver cancers. Importantly, it controlled bone metastases in patients with breast and prostate cancers and melanoma.
- *Long-Term Smoking, But Not Moderate Alcohol Use, Linked to Increased Risk of Common Cancers Among Women Already at High Risk of Breast Cancer:* A prospective study of more than 13,000 healthy women at high risk of breast cancer reported that the risks of invasive breast, lung and colon cancers were significantly higher in women with long smoking histories, compared to women who did not smoke or had shorter smoking histories. The study did not confirm previous reports of increased risk of cancer among those with moderate alcohol use, though it found that moderate alcohol use was associated with a lower risk of colon cancer. Low physical activity was associated with a significantly higher risk of endometrial cancer.

**Oral Abstract Session: *Cancer Prevention/***  
***Epidemiology***  
**Monday, June 6, 2011, 5:30-5:45 PM CDT**  
**Room: S100bc**

**Study Author: Hormuzd Katki, PhD**  
**National Cancer Institute**  
**Bethesda, MD**

**First Large Study of HPV and Pap Co-Testing in Routine Clinical Practice Confirms Most Women Can Safely Extend Screening to Every Three Years; HPV Testing Alone Also Appears to be Superior to Pap Testing Alone**

The first large-scale study of both human papillomavirus (HPV) testing and Pap test for cervical cancer screening in routine clinical practice confirms that women can safely extend their screening intervals from one to three years. The study also found that HPV testing may be more accurate than conventional Pap test in determining cervical cancer risk.

“Our results are a formal confirmation that the three-year follow-up is appropriate and safe for women who have a negative HPV test and normal Pap result,” said lead author Hormuzd Katki, PhD, principal investigator in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute. “These results also suggest that an HPV-negative test result alone could be enough to give a high level of security for extending the testing interval to every three years, but we’ll need additional evidence from routine clinical practice, and formal recommendations from guideline panels before that can be routinely recommended.”

Cervical cancer is caused by infection with HPV, which is sexually transmitted and can be detected by testing a sample of cervical cells for viral DNA. HPV infection is almost always cleared by the body, but if not, cancer may develop, typically decades after initial infection. While Pap testing has dramatically reduced cervical cancer rates, incorporating HPV testing into screening programs could reduce cancer rates even further. Screening guidelines from American medical organizations such as the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) have endorsed the use of concurrent HPV testing with Pap tests as a safe alternative to Pap testing alone for women 30 and older, recommending co-testing every three years for women who are HPV-negative and have a normal Pap test. However, co-testing has not been widely adopted by physicians and women, many of whom are unsure about the safety of extending testing intervals for more than one year. This study provides substantial data from routine practice confirming that the practice is safe.

In the study, researchers followed 331,818 women ages 30 and older who enrolled in Kaiser Permanente Northern California’s co-testing program between 2003 and 2005 for five years. The researchers found that the five-year cancer risk for women who had both a normal Pap test and tested negative for HPV was very low: 3.2 per 100,000 women per year.

Looking at each test individually, HPV-negative women had half the cancer risk of women with a normal Pap test (3.8 per 100,000 women per year compared to 7.5 per 100,000), suggesting that HPV testing alone is more accurate than Pap testing alone, and that the cancer risk for HPV testing alone was similarly low, compared with HPV and Pap testing together (3.8 versus 3.2 per 100,000).

HPV testing also identified more women at high risk for cervical cancer than Pap tests. Women who tested HPV-positive at enrollment (regardless of Pap test results) had higher five-year risks of cervical cancer or pre-cancer than women with an abnormal Pap test at enrollment regardless of HPV test results (1.5 percent per year versus 0.9 percent per year). By finding, at enrollment, more women at risk for cancer, HPV testing facilitated earlier intervention to prevent cancer.

However, according to Dr. Katki, Pap tests remain important for determining which women who tested HPV-positive should have further screening. HPV-positive women who had an abnormal Pap test were more likely to have – or soon develop – cancer or precancer than HPV-positive women with a normal Pap test.

**Abstract 1508**

**Cervical cancer risk for 330,000 women undergoing concurrent HPV testing and cervical cytology in routine clinical practice.**

**Authors:** H. A. Katki, W. K. Kinney, B. Fetterman, T. Lorey, N. E. Poitras, L. Cheung, F. Demuth, M. Schiffman, S. Wacholder, P. E. Castle

**Background:** Concurrent HPV testing and cervical cytology (co-testing) is an approved and promising alternative to cytology alone in women aged 30 and older. However, broad acceptance of co-testing is being hindered by a lack of evidence about its performance in routine clinical practice, especially the safety of three-year screening intervals for women testing HPV-negative with normal cytology (HPV-/Pap-).

**Methods:** We estimated five-year cumulative incidence of cervical cancer and cervical intraepithelial neoplasia grade 3 (CIN3+) at Kaiser Permanente Northern California for 331,818 women enrolled in co-testing.

**Results:** HPV- women had a low five-year cancer risk similar to women who were HPV-/Pap- (3.8 vs. 3.2 per 100,000 women per year,  $p=0.8$ ) that was half the cancer risk of women who were Pap- (3.8 vs. 7.5 per 100,000 women per year,  $p=0.3$ ). HPV testing alone more clearly separated women with high/low 5-year CIN3+ risk (HPV+: 7.6% vs. HPV-: 0.17%) than cytology alone (Pap+: 4.7% vs. Pap-: 0.36%). Abnormal cytology greatly increased CIN3+ risk over five years for HPV+ women (12% vs. 5.9%,  $p<0.001$ ) but not for HPV- women (0.86% vs. 0.16%). However, 73% of HPV+ women had no cytologic abnormality, and they experienced 34% of the CIN3+, 29% of the cancers, and 63% of the adenocarcinomas.

**Conclusions:** In routine clinical practice, a single HPV test was clearly superior to a single Pap smear for predicting who would develop CIN3+ or cancer within 5 years. Cytology strongly modified risks only for HPV+ women. HPV-based screening promoted earlier identification of the women at high risk of cervical cancer (especially adenocarcinoma), gave strong reassurance against cervical cancer over five years for HPV- women, and allowed safely extended 3-year screening intervals for HPV-/Pap- women that reduced the burden of screening on women and clinicians. These results demonstrate that HPV-based screening can be feasibly implemented in routine clinical practice.

**Disclosures:** Mark Schiffman, M.D., M.P.H., Research Funding, BD Biosciences, Roche, Qiagen

**Oral Abstract Session: Ovarian Cancer**  
**Saturday, June 4, 2011, 1:45-2 PM CDT**  
**Room: S354a**

**Study Author: Saundra Buys, MD**  
**University of Utah**  
**Salt Lake City, Utah**

**Screening with CA-125 and Transvaginal Ultrasound Does Not Reduce Ovarian Cancer Death Rate, Results in High Number of False Positives**

*[Note: This summary contains updated data and a correction from the original abstract.]*

A randomized, multicenter screening study of nearly 80,000 women in the general population showed that using a CA-125 blood test and transvaginal ultrasound for early detection of ovarian cancer did not reduce the risk of dying from the disease, and resulted in a large number of false positives and related biopsies and follow-up procedures. The results indicate that while these tests are widely and appropriately used to evaluate symptoms, and to gauge disease status and effectiveness of treatment in women already diagnosed with ovarian cancer, they are not useful in screening the general population.

“There hasn’t been a good method for the early detection of ovarian cancer, and our hypothesis was that CA-125 and transvaginal ultrasound, which are useful in measuring disease, would also identify ovarian cancer early, at a stage in which it is more likely to be cured,” said lead author Saundra Buys, MD, professor of medicine at the University of Utah and Huntsman Cancer Institute in Salt Lake City. “The results were disappointing, but not necessarily surprising. The study shows that the available tests are not effective and may actually cause harm because of the high number of false positives. These results point to the continued need for more precise and effective screening tools for this disease.”

In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, 78,216 women ages 55 to 74 were assigned to either annual screening (39,105 women) or usual care (39,111 women) between 1993 and 2001. Women in the screening arm were offered annual CA-125 testing for six years and transvaginal ultrasound for four, and followed for up to 13 years. Those in the usual care arm were not offered the screening tests.

The results showed no statistically significant difference in ovarian cancer cases or mortality between the two arms. Ovarian cancer was diagnosed in 212 women in the screening group arm compared to 176 in the usual care arm; 118 women in the screening arm died from ovarian cancer, while 100 died from ovarian cancer in the usual care group.

Among women in the screening arm, there were a high number of false positives – 3,285 false positives, compared to just 212 true positives. Of women who had a false positive test, 1,080 underwent surgery for biopsy – the procedure generally required to evaluate positive test results; 163 of them had serious complications.

The authors emphasized that the study results don’t apply to screening women with symptoms or abnormal findings on physical examination. Physical examination based on symptoms and appropriate follow-up testing remains the best available approach for ovarian cancer detection.

**Abstract 5001****Effect of screening on ovarian cancer mortality in the prostate, lung, colorectal and ovarian (PLCO) cancer randomized screening trial.**

**Authors:** S. S. Buys, E. Partridge, A. Black, C. Johnson, L. Lamerato, C. Isaacs, D. Reding, R. Greenlee, B. Kessel, M. Fouad, D. Chia, L. Ragard, J. Rathmell, P. Hartge, P. Pinsky, G. Izmirlian, J. L. Xu, P. Prorok, C. D. Berg.

**Background:** Ovarian cancer is among the five leading causes of cancer death in women in the United States. Women diagnosed with early stage disease have significantly improved survival compared to women diagnosed with advanced ovarian cancer. However, the effect on mortality of screening for the early detection of ovarian cancer with CA-125 and transvaginal ultrasound (TVU) is unknown. We evaluated the effect on mortality of screening for ovarian cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

**Methods:** PLCO is a randomized controlled trial involving 10 screening centers across the U.S. that recruited 78,216 women aged 55-74 years. Women were randomized to receive either annual screening (intervention arm; 39,105 participants) or usual care (39,111 participants) between November 1993 and July 2001. Women in the intervention arm were offered annual CA-125 testing for 6 years and TVU for 4 years. Participants and their health care providers received the screening test results and managed evaluation of abnormal results. All participants were followed for up to 13 years for cancer diagnoses and death. The primary outcome was ovarian cancer mortality. Secondary outcomes included ovarian cancer incidence and complications associated with screening exams and diagnostic procedures.

**Results:** Ovarian cancer was diagnosed in 212 women in the intervention arm and 176 in the usual care arm, for a rate ratio of 1.21 (95% Confidence Interval (CI) 0.99 – 1.48). There were 118 deaths from ovarian cancer in the intervention arm and 100 in the usual care arm, for a mortality rate ratio of 1.18 (95% CI 0.91-1.54). Of 3,285 women undergoing surgery following a false positive exam, 166 encountered at least one serious complication\*. Deaths from all other causes (excluding ovarian, colorectal and lung cancer) were 2,924 and 2,914 in the intervention and usual care arms, respectively.

**Conclusions:** Screening simultaneously with CA-125 and TVU did not reduce ovarian cancer mortality in women from the general population, and there was evidence of harm from diagnostic evaluation following a false positive screening test.

**Disclosures:** Christine D. Berg, MD Research Funding NCI

*\*Correction: Of the 3,285 women who received a false positive exam, 1,080 underwent surgery. Of those surgical patients, 163 encountered at least one serious complication.*

**Oral Abstract Session: *Genitourinary Cancer***  
**(*Prostate*)**  
**Monday, June 6, 2011, 2-2:15 PM CDT**  
**Room: Hall D1**

**Study Author: Hans Lilja, MD, PhD**  
**Memorial Sloan-Kettering Cancer Center**  
**New York, NY**

**Novel Screening Approach Suggests PSA Levels Among Men Age 44-50 May Predict Long-Term Risk of Metastatic Prostate Cancer or Prostate Cancer-Related Death**

A large retrospective, case control study of previously unscreened Swedish men showed that prostate-specific antigen (PSA) levels at the time of initial screening among men aged 44 to 50 can accurately predict the risk that a man will die of prostate cancer or develop metastatic prostate cancer up to 30 years later. The authors suggest that the initial PSA test result for men in this age group could enable approximately 50 percent of men to undergo just three PSA tests in their lifetime.

The study found that 44 percent of prostate cancer deaths occurred in men who had the top 10 percent of PSA levels (greater than 1.6 ng/ml) when they were tested between the ages of 44 and 50. As a result, the authors say, nearly half of all prostate cancer deaths could potentially be prevented by intense surveillance of this small group of men. In addition, they found that men with low PSA values for their age group are at comparatively lower risk (28 percent to 0.5 percent) of developing metastatic prostate cancer or dying of prostate cancer decades later and may only need to be tested three times in their lifetime. The findings could have important implications in deciding who should be screened with frequency.

“Doctors have urgently needed an effective PSA testing strategy that accurately distinguishes men at high risk for prostate cancer who need aggressive monitoring from those at low-risk of the disease, who can be safely spared from frequent testing. If confirmed in prospective trials, this approach could have a significant impact on future prostate cancer screening programs,” said lead author Hans Lilja, MD, PhD, attending research clinical chemist at Memorial Sloan-Kettering Cancer Center in New York. “Our results appear to identify a subgroup of relatively young men at very high risk of aggressive prostate cancer who would likely benefit from close monitoring as they age.”

In the study, researchers analyzed PSA in archived blood samples from 12,090 men provided between 1974 and 1986, and 4,999 repeat samples six years later as part of the Swedish Malmo Preventive Project.

Using these samples, the investigators assessed the median PSA levels for ages 44 to 50, 51 to 55 and 60. These median levels at baseline served as the base to distinguish men at high or low risk of dying of prostate cancer or developing metastatic prostate cancer. As men aged, if their PSA level remained below the median for the population in their age group, the risk of death from metastatic prostate cancer progressively declined. They found that 28 percent of metastases or deaths from prostate cancer over the next 27 years occurred in men ages 44 to 50 who had a PSA below the median in the population (0.7 ng/ml). For men ages 51 to 55 with a PSA less than the median, 0.8, the risk of metastatic prostate cancer or death was lower – only 18 percent. At age 60, only 0.5 percent of deaths or metastases occurred in men with a PSA less than median for that age, 1.1 ng/ml.

While these figures – 28 percent and 18 percent – may seem high, Dr. Lilja said, the short-term risk (15 years) of metastatic prostate cancer or dying from prostate cancer is very low. Based on progressively declining risks, the researchers conclude that men with PSAs below population median in each age group remain at increasingly lower risk for dying of prostate cancer as they age. As a result, testing three times

between ages 44 and 60 could be recommended for 50 percent of men. The other half of men with PSAs above the median would be followed more closely.

“Such a scenario could avoid more intense, costly PSA testing that could result in over-diagnosis and unnecessary treatment that potentially has little benefit, since they would be at extremely low risk,” Dr. Lilja said.

**Abstract 4512**

**Towards a rational strategy for prostate cancer screening based on long-term risk of prostate cancer metastases and death: Data from a large, unscreened, population-based cohort followed for up to 30 years.**

**Authors:** H. Lilja, C. Savage, A. Gerdtsson, T. Bjork, J. Manjer, P. Nilsson, A. Dahlin, A. Bjartell, P. T. Scardino, D. Ulmert, A. J. Vickers.

**Background:** Prostate-specific antigen (PSA) testing remains controversial due to high number of men need to be screened to prevent one death. Current screening recommendations are based on few data. We analyzed PSA in archived blood plasma collected in 1974–92 as part of the Malmö Preventive Project. This is a large, representative cohort of Swedish men not subject to screening, chiefly accruing at age 44-50 (i.e. shortly before PSA is recommended to begin in US) and followed for up to 30 years. The study is a unique “natural experiment” to understand the association between early PSA and long-term risk of prostate cancer morbidity and mortality.

**Methods:** We conducted a case control study nested within a cohort of 12090 men providing blood in 1974-86 and 4999 providing a repeat sample 6 years later and an independent cohort of 1167 men with blood provided at age 60. 252 men with carefully ascertained evidence of prostate cancer metastasis or death were matched 3:1 with controls. Anti-coagulated plasma was analyzed using methods shown to give highly accurate PSA values.

**Results:** PSA was strongly associated with risk of prostate cancer death or metastasis up to 30 years later (AUC 0.70, 0.76 and 0.90 at age 44-50, 51-55 and 60 respectively,  $p < 0.005$ ). At age 44-50, 44% of cancer deaths occurred in men with PSA  $> 1.6$  ng/ml (top 10%) at a median follow up of 27 years. PSA at median at age 44-50 did not rule out risk of metastases or death but did so in older men: 28%, 18% and 0.5% of metastases occurred in men with PSA at median ( $< 0.7$ ,  $< 0.8$  and  $< 1.1$  ng/ml at age 44-50, 51-55 and, 60 respectively). The risk of prostate cancer metastasis by 15 years for men with PSA at median was never greater than 0.3% at any age.

**Conclusions:** PSA is highly predictive of long-term risk of prostate cancer morbidity and mortality. Close to half of all deaths could be prevented by intense surveillance of a small proportion of men with the highest PSA levels at age 44-50. For men with lower PSA, testing at age 51-55 and age 60 is sufficient to capture risk of prostate cancer metastases or death 10+ years in advance. This strategy would allow 50% of men to have only three lifetime PSA tests.

**Disclosures:** Hans Lilja, MD, PhD Stock Ownership, Arctic Partners

**Oral Abstract Session: *Host Genomics and Treatment Outcomes in Breast Cancer***  
**Saturday, June 4, 2011, 3:15-3:30 PM CDT**  
**Room: Hall B1**

**Study Author: Bryan Schneider, MD**  
**Indiana University**  
**Indianapolis, IN**

### **Genetic Biomarker Predicts Taxane-Induced Neuropathy**

A new study has identified the first genetic biomarkers for taxane-induced peripheral neuropathy, a potentially severe complication of taxane chemotherapy that affects nerves in about one-third of patients with cancer receiving such treatment. The finding may eventually lead to a simple blood test to determine whether a patient is at high risk for neuropathy.

“If these findings can be replicated, this may allow physicians to know prior to recommending therapy whether the patient is at an inordinate risk for developing taxane-induced neuropathy,” said Bryan P. Schneider, MD, lead author and a physician/researcher at the Indiana University Melvin and Bren Simon Cancer Center and Associate Director for the Indiana Institute for Personalized Medicine. “This may allow for better counseling, use of alternative drugs or schedules, or omission of taxanes in the appropriate settings. These genetic findings might also provide insight into the mechanism of this side effect and help develop drugs to prevent this toxicity altogether.”

Such damage to the nerves can cause pain and numbness and limit the dose of chemotherapy a patient can receive. While only a few factors seem to predict which patients are likely to get peripheral neuropathy, including a history of diabetes and advanced age, genetic variations may explain why some patients are more sensitive to taxanes.

The authors conducted a genome wide association study on 2,204 patients enrolled in an Eastern Cooperative Oncology Group clinical trial (E5103) in which all patients received taxane-based chemotherapy. The study looked for variations in DNA called single nucleotide polymorphisms, or SNPs, evaluating more than 1.2 million SNPs in each patient. With a median follow-up of 15 months, the study identified genetic subgroups that were markedly more likely to develop peripheral neuropathy. Those who carried two normal nucleotides in a specific regulatory gene had a 27 percent chance of experiencing neuropathy. But those who carried one normal nucleotide and one SNP had a 40 percent chance and those who carried two SNPs had a 60 percent chance. The study also found that older patients and African Americans were much more likely to have peripheral neuropathy, and further analysis of SNPs in these groups is underway.

The authors plan to continue their work in additional trials to validate these findings and to determine whether a different type or schedule of taxane therapy would result in less neuropathy in the more susceptible genetic groups. The authors also are collaborating with neurobiologists to understand why these genetic variations might make the nerves more sensitive to these drugs.

#### **Abstract 1000**

##### **Genetic associations with taxane-induced neuropathy by genome wide association study (GWAS) in E5103.**

**Authors:** B. P. Schneider, L. Li, K. Miller, D. Flockhart, M. Radovich, B. A. Hancock, N. Kasseem, T. Foroud, D. L. Koller, S. S. Badve, Z. Li, A. H. Partridge, A. M. O'Neill, J. A. Sparano, C. T. Dang, D. W. Northfelt, M. L. Smith, E. Railey, G. W. Sledge  
**Background:** Neuropathy, one of the most common toxicities associated with taxane therapy, may be severe, function-limiting, and sometimes irreversible. Established predictors for increased risk include advanced age, diabetes, and type/dose/schedule of taxane. No established biomarkers have been identified to predict patients at greatest risk.

**Methods:** E5103 is a randomized phase III trial comparing standard adjuvant chemotherapy for patients with early stage breast cancer with the same chemotherapy plus concurrent bevacizumab or concurrent and sequential bevacizumab. All 3 arms include weekly paclitaxel for 12 weeks. A GWAS was performed using the Infinium Human Omni1 array on 2204 patients. The primary

hypothesis was to identify SNPs associated with time to report of first grade 2-4 neuropathy. SNP data underwent rigorous review to assess both SNP and sample quality. Analyses were performed using Cox regression model including established clinical trial covariates. Bonferroni corrections for multiple comparisons were made.

**Results:** Interim toxicity data from E5103 demonstrated that 613 patients had grade 2-4 neuropathy and 1591 did not. Significant clinical predictors of neuropathy included age (12.9% increase with each 10yrs;  $p=0.004$ ) and African American race ( $HR=2.1$ ;  $p=4.5 \times 10^{-11}$ ). Six SNPs with  $MAF>5\%$  were associated with time to neuropathy ( $p<5 \times 10^{-7}$ ). These SNPs resided in two genes: *RWDD3* and *TECTA*. A missense SNP in *RWDD3* was associated with likelihood of neuropathy at 15 months: 27% for patients with homozygous wild-type, 40% for heterozygous, 60% homozygous variant (allele dose-effect:  $HR=1.5$ ;  $p=8.5 \times 10^{-8}$ ). A *TECTA* SNP was associated with likelihood of neuropathy at 15 months: 29% for homozygous wild-type, 32% for heterozygous, and 57% for homozygous variant (recessive-effect:  $HR=2.1$ ;  $p=3.2 \times 10^{-7}$ ). Multiple other SNPs with  $MAF<5\%$  were also associated with neuropathy ( $p<5 \times 10^{-7}$ ). Analysis in the African American subgroup is underway.

**Conclusions:** Using a genome wide approach, we have found several SNPs associated with time to neuropathy in patients undergoing paclitaxel therapy. This is the first time a genetic predictive biomarker has been reported for taxane-induced neuropathy.

**Disclosures:** Bryan P. Schneider, MD, Consultant or Advisory Role, Genentech, Honoraria, Genentech; Kathy Miller, MD, Consultant or Advisory Role, Genentech, Research Funding, Genentech; Joseph A. Sparano, MD, Consultant or Advisory Role, Genentech, Chau T. Dang, MD, Consultant or Advisory Role, Genentech, Research Funding, Genentech; Mary Lou Smith Employment/Leadership Position, Research Advocacy Network, Elda Railey, Employment/Leadership Position, Research Advocacy Network;

**Oral Abstract Session: *Gynecologic Cancer***  
**Saturday, June 4, 2011, 3:00 – 3:15 PM CDT**  
**Room: E354a**

**Study Author: Jonathan Ledermann, MD**  
**University College**  
**London, England, UK**

**Randomized Study Shows that Maintenance Therapy and PARP Inhibitors Could Play Important Roles in Treatment of Relapsed Ovarian Cancer**

A Phase II randomized trial showed that maintenance treatment with the oral PARP inhibitor drug olaparib improved progression-free survival by about four months in women with the most common type of relapsed ovarian cancer. This is the first randomized trial to demonstrate a benefit for maintenance therapy for recurrent ovarian cancer, and the first randomized trial in ovarian cancer of a PARP inhibitor – a novel class of molecularly targeted drugs.

The results of this study, if confirmed in larger trials, could lead to a new treatment approach for recurrent ovarian cancer in which drugs like olaparib are given over a long period of time to prevent recurrences or prolong remissions. This somewhat novel approach, called maintenance therapy, has already proven useful in lung cancer. Standard treatment for ovarian cancer includes platinum-based chemotherapy. After this regimen, patients are observed until recurrence, and then treated with another course of chemotherapy. While some tumors respond well to chemotherapy, the regimens are too toxic for patients to take continuously, and clinical trials haven't shown any benefit for extended courses of chemotherapy.

“A well-tolerated antitumor agent that could be used for months or perhaps years as maintenance therapy after standard chemotherapy could be a big step forward and ultimately extend survival,” said lead author Jonathan A. Ledermann, MD, principal investigator of the study and Professor of Medical Oncology at UCL Cancer Institute, University College London. “This study demonstrates proof of principle for the concept of maintenance therapy in ovarian cancer using a PARP inhibitor. Our progression-free survival difference was very impressive and better than we anticipated.”

The multicenter, international study randomized 265 women with high-grade serous ovarian cancer to either olaparib or placebo. Patients were enrolled in the trial within 8 weeks of having achieved either a complete or partial response to platinum-based treatment. PARP inhibitors have been shown to work better in patients whose tumors have responded to platinum.

In the study, the progression-free survival (PFS) – the amount of time during and after treatment in which the cancer does not return – was significantly longer in the group receiving olaparib than the placebo group, with a median of 8.4 months versus 4.8 months. At the time of data analysis, half the patients randomized to olaparib (68 patients) had not relapsed and were still receiving the drug, while only 16 percent (21 patients) remained on placebo – so overall survival data were not yet available for analysis.

Adverse events were more commonly reported in the group receiving olaparib than placebo, including nausea, fatigue, vomiting, and anemia, but the majority of these were not severe. Dose reductions to manage side effects were allowed in the study and were more prevalent in the olaparib group (23 percent) compared to the placebo group (7 percent).

Olaparib inhibits the enzyme Poly ADP ribose polymerase (PARP), which is involved in DNA repair. Up to half of women with high-grade serous ovarian cancer – the most common type of ovarian cancer – may have a DNA repair deficiency that makes them more susceptible to treatment with PARP inhibitors.

A number of PARP inhibitors are in Phase II and Phase III clinical trials as single agents and in combination with standard chemotherapies and radiation in some types of breast and ovarian cancers believed to have DNA repair defects.

#### **Abstract 5003**

#### **Phase II randomized placebo-controlled study of olaparib (AZD2281) in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC).**

**Authors:** J. A. Ledermann, P. Harter, C. Gourley, M. Friedlander, I. B. Vergote, G. J. S. Rustin, C. Scott, W. Meier, R. Shapira-Frommer, T. Safra, D. Matei, E. Macpherson, C. Watkins, J. Carmichael, U. Matulonis.

**Background:** Olaparib (AZD2281) is an oral PARP inhibitor that has shown antitumor activity in patients (pts) with high-grade serous ovarian cancer (SOC) with and without *BRCA1* or *BRCA2* mutations. This randomized, double-blind, multicenter, placebo-controlled Phase II study evaluated maintenance treatment with olaparib in pts with high-grade PSR SOC (clinicaltrials.gov; NCT00753545).

**Methods:** Pts with PSR SOC who had received  $\geq 2$  previous platinum regimens and were in a maintained partial or complete response following their last platinum-containing regimen were randomized to oral olaparib 400 mg bid or placebo. The primary endpoint was progression-free survival (PFS) by RECIST. Secondary endpoints included time to progression (TTP) by CA-125 (GCIG criteria) or RECIST, overall survival (OS) and safety.

**Results:** 265 pts were randomized (136 to olaparib and 129 to placebo). Demographics and baseline characteristics were generally well balanced. At data cut-off there were 153 (58%) progression events. PFS by RECIST was significantly longer in the olaparib than the placebo group (HR, 0.35; 95% CI 0.25–0.49;  $P < 0.00001$ ; median 8.4 vs 4.8 months). TTP by CA-125 or RECIST was also significantly longer in the olaparib than the placebo group (HR, 0.35; 95% CI 0.25–0.47;  $P < 0.00001$ ; median 8.3 vs 3.7 months). At data cut-off OS data were too immature for analysis. 68 (50%) and 21 (16%) remain on olaparib or placebo, respectively. AEs more commonly reported on olaparib than placebo (by  $> 10\%$ ) were nausea (68% vs 35%), fatigue (49% vs 38%), vomiting (32% vs 14%) and anemia (17% vs 5%); the majority of AEs were CTCAE grade 1 or 2. The most frequently reported CTCAE grade  $\geq 3$  events were fatigue (9 pts) and anemia (7 pts) for olaparib, and abdominal pain and fatigue (4 pts each) for placebo. 3 (2.2%) pts on olaparib and 1 (0.8%) on placebo had AEs that led to treatment discontinuation. 31 pts (23%) in the olaparib group and 9 (7%) in the placebo group had both dose reductions and interruptions.

**Conclusions:** In pts with PSR SOC, maintenance treatment with olaparib 400 mg bid provided a significant improvement in PFS. Olaparib was well tolerated, and toxicities were consistent with previous studies.

**Disclosures:** Philipp Harter, MD, PhD, Consultant or Advisory Role, AstraZeneca, Honoraria, AstraZeneca, Research Funding, AstraZeneca; Charlie Gourley, PhD, FRCPE, Consultant or Advisory Role, Roche, GlaxoSmith Kline, Schering-Plough, Honoraria, GlaxoSmith Kline, Merck Sharp & Dohme, Honoraria, GlaxoSmithKline, Merck Sharp & Dohme, Other Remuneration, GlaxoSmithKline, Merck Sharp & Dohme; Michael Friedlander, FRACP, PhD, Consultant or Advisory Role, AstraZeneca, Honoraria, AstraZeneca; Gordon J. S. Rustin, MD, MBBS, Honoraria, AstraZeneca, Research Funding, AstraZeneca; Euan Macpherson, Employment/Leadership Position AstraZeneca, Stock Ownership, AstraZeneca; Claire Watkins, Employment/Leadership Position, AstraZeneca, Stock Ownership, AstraZeneca; James Carmichael, MD, Employment/Leadership Position AstraZeneca, Stock Ownership, AstraZeneca; Ursula Matulonis, MD, Research Funding, AstraZeneca

**Oral Abstract Session: *Developmental Therapeutics/***  
***Experimental Therapeutics***  
**Sunday, June 5, 2011, 12:00-12:15 PM CDT**  
**Room: Arie Crown Theater**

**Author: Michael Gordon, MD**  
**Pinnacle Oncology Hematology**  
**Scottsdale, AZ**

**Novel Multi-targeted Agent Cabozantinib (XL184) Has Significant Effect on Several Advanced Solid Tumors, and Can Shrink or Eliminate Bone Metastases**

Cabozantinib (XL184) – an oral inhibitor of MET and VEGFR2, kinases involved in the development and progression of many cancers – showed strong responses in patients with various advanced cancers in a Phase II trial. The drug demonstrated particularly high rates of disease control for advanced prostate, ovarian and liver cancers, which are historically resistant to available therapies. The drug also fully or partially eliminated bone metastases in patients with breast and prostate cancers and melanoma.

“Cabozantinib appears to have significant effects on several treatment-resistant tumors, as well as impressive effects on bone metastases. In addition, these effects are associated with rapid improvement in pain, a reduction in opiate narcotic requirements and improvement in anemia,” said lead author Michael S. Gordon, MD, a medical oncologist at Pinnacle Oncology Hematology in Scottsdale, AZ. “The implications of these results are very exciting—it is unusual to find a targeted therapy, absent of a molecular mutation in tumors, that works in bony disease and has this activity.”

To be eligible for the study, patients had to have advanced, progressive solid tumors, with or without bone metastases. Of 398 evaluable patients (of 483 enrolled in the trial), 39 percent had bone metastases at baseline. Patients received cabozantinib over 12 weeks. The trial was designed as a “discontinuation” trial, in which those who had partial responses stayed on the drug; those with stable disease were randomized to cabozantinib or placebo; and patients with progressive disease were removed from the trial. This novel type of clinical trial design more quickly evaluates the disease-stabilizing activity of growth-inhibitory agents like cabozantinib, compared to the traditional model of randomizing all patients to either the experimental arm or placebo.

Among 398 patients evaluable with all types of cancer included in the trial, the response rate was 9 percent (34 of 398). The highest disease control rates (partial response and stable disease) at week 12 were 76 percent for liver cancer (22 of 29 patients), 71 percent for prostate cancer (71 of 100 patients), and 58 percent for ovarian cancer (32 of 51 patients).

Fifty-nine of 68 patients with bone metastases (including patients with breast and prostate cancers and melanoma) experienced either partial or complete disappearance of the cancer on bone scans, often with significant pain relief and other improved cancer-related symptoms.

The reduction of bone metastases and pain relief was an unexpected finding in this study, Dr. Gordon said. Independent review by radiologists confirmed that bone metastases disappeared in the majority of patients who had bone metastases when they entered the study. The majority of these patients had castration-resistant prostate cancer (CRPC), but patients with breast cancer and melanoma also had disappearance of bone metastases. Bone metastases greatly contribute to morbidity and mortality in patients with these types of cancer, which typically spread to the bone.

Due to these results, the study has been expanded to include more CRPC patients. Similarly, the high rate of lasting responses in ovarian cancer patients led researchers to also expand the study to evaluate the drug’s effect on patients with a particularly resistant form of the disease known as platinum-resistant/refractory ovarian cancer.

This study expansion results will help determine the design of future Phase III trials, which will assess whether the drug extends patients lives or has other longer-term benefits among patients with specific cancer types. At present, cabozantinib is being investigated for use as a single agent. Additional studies will evaluate the efficacy and tolerability of appropriate combinations with other agents for future indications.

The most common grade three or above adverse events were fatigue (9 percent) and hand-foot syndrome (8 percent). Dose reductions were required in 41 percent of patients due to side effects; 12 percent were removed from the trial for adverse events.

#### **Abstract 3010**

#### **Cabozantinib (XL184) has activity in both soft tissue and bone: Results of a phase II randomized discontinuation trial (RDT) in patients (pts) w/ advanced solid tumors.**

**Authors:** M. S. Gordon, N. J. Vogelzang, P. Schoffski, A. Daud, A. I. Spira, B. A. O'Keeffe, T. Rafferty, Y. Lee, R. Berger, G. Shapiro

**Background:** Cabozantinib (Cabo) is an oral, potent inhibitor of MET and VEGFR2. A RDT evaluated clinical efficacy and safety in 9 tumor types: breast (B), gastric/GEJ (G), non-small cell lung (NS), ovarian (O), pancreatic (PA), castration resistant prostate (P), small cell lung (S), hepatocellular (H) and melanoma (M). Indications were selected based on the role of MET and VEGFR2 in tumor biology.

**Methods:** All eligible pts had progressive measurable disease +/- bone metastasis (mets). Pts received Cabo at 100 mg qd over a 12 wk Lead-in stage. Tumor response (mRECIST) assessed q6 wks. Treatment  $\geq$  wk 12 was based on response: pts with PR continued open-label Cabo, pts with SD were randomized to Cabo vs placebo, and pts with PD discontinued. Primary endpoint was ORR in the lead-in stage. Accrual in any cohort could be halted for either high rates of ORR or PD.

**Results:** 398/483 enrolled pts were evaluable for the Lead-in stage. 154/398 (39%) had bone mets at baseline (68 with bone scan f/u). Median # prior regimens was 2. Most common related AEs Grade  $\geq$ 3: fatigue (9%), hand-foot syndrome (8%) and HTN (5%). Dose reductions and permanent discontinuations for AEs occurred in 41% and 12% of pts, respectively. Soft Tissue Effects: ORR at wk 12: overall = 34/398 (9%); O 12/51 (24%), H 4/29 (14%), P 5/100 (5%), NS 6/60 (10%), B 2/20 (10%), S 1/21 (5%), M 4/76 (5%). 12 additional PRs await confirmation. 226/328 (69%) with  $\geq$ 1 post-baseline scan had tumor regression. Highest DCR (PR + SD) at wk 12: H (76%), P (71%), and O (58%). Bone Effects: 59/68 pts (P, B and M) with bone mets and  $\geq$ 1 post-baseline bone scan had partial or complete bone scan resolution, often with symptom improvement seen by wk 6. Osteoclast effects were observed across tumor types: 66/121 (55%) pts +/- bone mets had declines of  $\geq$ 50% in plasma C-Telopeptide. Decreased serum tALP seen in P. Median max rise in hemoglobin in anemic pts (Hb < 11 g/dL) = 2.3 g/dL. All max Hb changes w/in first 12 wks. Randomization in cohorts P and O was halted and pts unblinded due to observed efficacy.

**Conclusions:** Cabo is broadly active with cPRs in 8/9 indications, with high DCRs in H, P and O. Complete or partial resolution of bone scan lesions was observed in 3 tumor types.

**Disclosures:** Michael S. Gordon, MD, Research Funding, Exelixis; Nicholas J. Vogelzang, MD, Research Funding, Exelixis; Adil Daud, MD, Research Funding, Exelixis; Bridget A O'Keeffe, PhD, Employment/Leadership Position, Exelixis, Stock Ownership, Exelixis; Teresa Rafferty, MBA, RN Employment/Leadership Position, Exelixis, Stock Ownership, Exelixis; Yihua Lee, PhD, Employment/Leadership Position, Exelixis, Stock Ownership, Exelixis; Raanan Berger, MD, Research Funding, Exelixis; Geoffrey Shapiro, MD, PhD, Research Funding, Exelixis

**Oral Abstract Session: Cancer Prevention/**

**Long-Term Smoking, But Not Moderate Alcohol Use, Linked to Increased Risk of Multiple Common Cancers among Women Already at High Risk of Breast Cancer**

*[Note: This summary contains updated data not in the abstract]*

A large prospective study of more than 13,000 healthy women at high risk of breast cancer identified several important lifestyle factors associated with cancer risk. The study reported that the risks of invasive breast, lung and colon cancers were significantly higher in women with long smoking histories, compared to women who did not smoke or had shorter smoking histories. Investigators also found a significant association between low levels of physical activity and endometrial cancer risk. Use of alcohol, however, was not associated with increased cancer risk.

“The NSABP study was the first large study to prospectively examine the impact of smoking in women at high risk of breast cancer,” said Stephanie Land, PhD, study author and Research Associate Professor in the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh. “Our results showed an even greater increase in risk than has been shown in previous studies, suggesting that for women who are at risk of breast cancer because of family history or other factors, smoking cigarettes is even more risky than for other women. It sends a very important message for women with family histories of breast cancer about the long-term risks of smoking, as well as the importance of staying physically active. We’re seeing again that smoking cessation is one of the most effective tools we have for reducing risk of many cancers.”

The study analyzed the risk of several common cancers in 13,388 women at increased risk for breast cancer (as defined by age, a diagnosis of lobular carcinoma in situ, family history, or other factors) who participated in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial, based on their baseline self-reported smoking, alcohol use, and physical activity.

The study found that the risk of invasive breast cancer was higher in smokers than in non-smokers, and increased with more years of cigarette smoking. Compared to women who never smoked, those who smoked at least 35 years had a 60 percent higher risk of invasive breast cancer, and those who smoked between 15 and 35 years had a 34 percent higher risk. Those who smoked less than 15 years had no increased risk of breast cancer. This is the third large, prospective study to report a strong association between smoking and breast cancer, and is the first to show further elevation of cancer risk in women already at high risk of breast cancer.

The incidence of colon cancer was also significantly higher for women with long histories of cigarette smoking. The risk of getting colon cancer was over four times higher for women who smoked more than 35 years versus those who had never smoked; risk was 7 percent higher for women who smoked for 15 to 35 years. This result confirmed findings of previous studies of women already at high risk of breast cancer.

Similarly, women who smoked had a significantly higher risk of lung cancer, a finding that confirms many previous studies. Those who smoked more than one pack of cigarettes per day for over 35 years had a risk that was 30 times higher than women who never smoked. Women who smoked less than one pack per day for over 35 years had a 13-fold increase in lung cancer risk.

Alcohol use was not associated with breast cancer risk in this study. Moderate alcohol consumption of up to one drink a day was associated with a 60 percent decreased risk of colon cancer compared to those who did not drink. Several factors might have been different in this study from past studies that have shown associations between alcohol use and cancer risk, Dr. Land said. In particular, there were fewer heavy drinkers enrolled in this study, compared to other studies. Also, the results of this study are based on a one-time self-report of alcohol drinking habits.

Low physical activity was not associated with breast, lung or colon cancer risk, though it was associated with a 70 percent increased risk of endometrial cancer. Investigators said this may be due to the association between fitness and obesity, also a risk factor for endometrial cancer.

**Abstract 1505**

**Cigarette smoking, fitness, and alcohol use as predictors of cancer outcomes among women in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT).**

**Authors:** S. R. Land, N. Christian, D. L. Wickerham, J. P. Costantino, P. A. Ganz

**Background:** The double-blind, prospective, BCPT demonstrated a 50% reduction in the risk of breast cancer for tamoxifen (T) v placebo (P). We present the risk of cancer at the most common sites, based on the participants' baseline self-reported cigarette smoking, alcohol use, and leisure-time physical activity.

**Methods:** 13,338 women at high risk of bc. Were randomly assigned 6/92-9/97 to 20 mg/day T v P; we analyzed the 11,064 enrolled more than 3 years (yrs) before the trial unblinding 3/98. Endpoints invasive cancer of the breast (ibc), endometrium (ec), lung (lc), and colon (cc) were analyzed with Cox proportional hazards regression. Covariates were baseline estimated breast cancer risk, treatment assignment, race, age, and co-morbidities. Hazards ratios (HR) are given with 95% bracketed confidence intervals.

**Results:** At baseline, 45.7% had moderate/heavy physical activity. 20.5%, 65.8%, 13.3% drank 0, 0-1, 1+ alcoholic drinks/day. 12.8% were current smokers. At median 8.7 years potential follow-up, baseline smoking predicted ibc (p=.021; HR=1.40 [1.05-1.86]; n=360 events) and lc (p<.001; HR=7.66 [4.62-12.70], n=64). Low physical activity predicted ec (p=.030, HR=1.8 [1.1-3.0], n=68). Moderate alcohol use (0-1 drink/day) was associated with decreased risk of cc (p=.017; HR=.38 [.18-.81] versus no alcohol, n=36). 1+ drinks/day was not associated with increased cancer risk.

**Conclusions:** This prospective study in women at high risk of breast cancer confirms previously reported cancer risk associated with smoking and fitness, but did not confirm previously reported associations with excessive alcohol use.

**Disclosures:** Donald Lawrence Wickerham, MD, Consultant or Advisory Role, Lilly, Honoraria, AstraZeneca

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