



13th World Conference  
on Lung Cancer

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

August 3, 2009

# WCLC 2009 NEWS

JULY 31 - AUGUST 4, 2009

MOSCONE WEST

SAN FRANCISCO, USA

## New staging system reclassifies tumors, metastases

The new staging system for lung cancer, released at the beginning of this year's World Conference on Lung Cancer (WCLC), is based on survival outcomes of an extensive, international database of patients with comprehensive stage representation. Statistical analyses were performed on approximately 100,000 records in the Seattle-based Cancer Research and Biostatistics (CRAB) database,

This reclassification improves our understanding of the various prognostic categories and enables clinicians to make more informed recommendations.

The previous staging system divided tumors into two size groupings, with 3 cm as the cut-off. The new system creates five groupings, with cut-offs at 2, 3, 5, and 7 cm. The multiple cut-offs based classification will guide adjuvant therapy recommendations consistent with data from recent clinical trials.

The new staging system also shifts the grouping of T (umor) descriptors. T4 (satellite nodule in the same lobe) has been grouped with T3, since the two groups showed similar survival rates. Tumors with mediastinal invasion remain at T4, while T4 with pleural effusion is upstaged to M1.

Meanwhile, tumors in the same lung but a different lobe as the primary, formerly classified as M1, are now grouped into T4 based on their outcome.

While there is no recommended change in N staging, the new system consolidates the Mountain-Dressler lymph node mapping system (American Thoracic Society) and the Naruke system from Japan, correcting discrepancies in lymph node nomenclature between the two. Previously, for example, a lymph node designated as N2 in the U.S. might have received an N1 classification in Japan. For future classification, the IASLC has proposed a zonal chart to score N lesions.

*"This is an enormous event for IASLC, and for clinicians who will be using it as of this week."*

- Dr. Peter Goldstraw

The subgroups of metastatic disease have been realigned to more accurately reflect survival rates. Pleural dissemination and nodules of the contralateral lung are classified M1A, while distant metastases are designated M1B. Although the new system can guide appropriate treatment decisions, treatment must still be individualized given the complexity of some stages.

Visit Booth 1405 to purchase the IASLC staging manual and handbook, as well as a set of laminated reference cards.

## Plenary session focuses on state of the art therapies



Dr. Frances A. Shepherd co-chaired and presented at the State of the Art plenary Sunday morning.

Speakers in Sunday morning's plenary session reviewed the latest developments in targeted therapy, radiotherapy, surgery, and chemotherapy.

In the session, Dr. Frances A. Shepherd (Princess Margaret Hospital, Canada) discussed targeted therapy, noting that the most productive avenues of investigation in the past decade have been into inhibitors of either EGFR or angiogenesis. She said that some combinations of chemotherapy agents with monoclonal antibodies in these classes have been effective in treating non-small cell lung cancer (NSCLC). For example, trial results suggest that the addition of the EGFR inhibitor cetuximab and the angiogenesis inhibitor bevacizumab to chemotherapy improve outcomes.

Dr. Shepherd said that the most promising targeted therapies are among new investigational drugs, particularly IGF1R and Met inhibitors. IGF1R inhibitors have shown excellent preliminary results for squamous cancer and seem to complement the action of EGFR inhibitors in other

cancers. Agent 1066, a Met and ANK inhibitor currently under development by Pfizer, is showing dramatic initial responses in NSCLCs with the ALK fusion mutation. PARP inhibitors also seem very promising because of the importance of PARP in DNA repair; however, no clinical trial data on PARP inhibitors in lung cancer is available.

Later in the session, Dr. Hak Choy (University of Texas Southwestern Medical Center, USA) gave an update on technological improvements in radiation oncology, including 3-D imaging, improved tumor definition in CT scans, and conformal radiation techniques. He also cited Intensity Modulated Radiation Therapy (IMRT), which modulates beam intensity thereby reducing radiation exposure, as another beneficial technology. Dr. Choy said that radiotherapy treatment has improved greatly over the past ten years, and suggested that it may lead to the day when lung cancer becomes only a chronic disease.

## STAGING BY THE NUMBERS

Number of revisions to the TNM staging system since 1997: 1

Days since revision was released: 3

Approximate number of patient records in new database: 100,000

Factor by which size of the current database exceeds the previous: 20

Participating data centers: 45

Participating countries: 20+

Millions of US dollars invested to compile database: 1.4

Patients that will receive better treatment as a result: 1 in 6

## Researchers consider vandetanib as possible second-line therapy for NSCLC

Results of Phase II studies on vandetanib, a tyrosine inhibitor, as a second-line therapy for non-small cell lung cancer (NSCLC) have encouraged further research into its action both as a single agent and in combination with other drugs which have showed similar promise. Findings from a series of Phase III clinical trials indicate that vandetanib, alone or in combination, may provide expanded treatment options to

patients whose first-line treatment failed to halt disease progression.

On Monday, Dr. Ronald B. Natale will present results of the ZEST trial, a randomized, double-blind study that compared vandetanib monotherapy to erlotinib in treatment of patients with advanced, previously treated NSCLC. The two presentations that follow will provide the results of trials that evaluated the efficacy of two vandetanib combinations.

Dr. Roy S. Herbst will present results of the ZODIAC trial, which tested a combination of vandetanib plus docataxel, a mitosis inhibitor. Dr. Richard H. de Boer will present results of the ZEAL trial, which tested a combination of vandetanib plus pemetrexed, a folate antimetabolite. Progression-free survival (PFS) was a primary endpoint in all three trials. In ZEST, patients

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[2009worldlungcancer.org](http://2009worldlungcancer.org)



Dr. Desmond Carney



Dr. Andrew Turrisi



Dr. Nico van Zandwijk



Dr. David Johnson



Dr. Jack Roth



Dr. Nobuyuki Yamamoto



Dr. David Jablons

## New board takes office

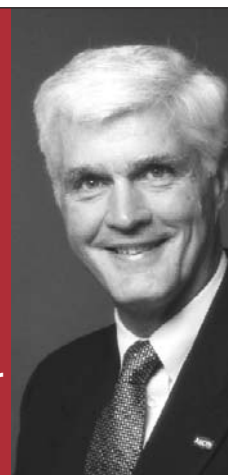
During the IASLC business meeting later today, participants will acknowledge the long-standing dedication of (l to r) departing Board members Dr. Desmond Carney, Dr. Andrew Turrisi, Dr. Nico van Zandwijk, Dr. David Johnson, Dr. Jack Roth, Dr. Nobuyuki Yamamoto,

and Dr. David Jablons. The 2009-2011 Board of Directors consists of Dr. David Gandara (President), Dr. Peter Goldstraw (President-Elect), Dr. Nagahiro Saijo (Past President), Dr. Fred Hirsch (Treasurer), Dr. Paul Bunn, Jr. (Executive Director), Dr. Wilfried Eberhardt, Dr. Joan Schiller,

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## Paul A. Bunn, Jr., MD

Executive Director, International Association for the Study of Lung Cancer



While much has changed in our understanding of lung cancer since the founding of the International Association for the Study of Lung Cancer (IASLC) over 25 years ago, the Association's basic principles remain the same: to promote the study of lung cancer and facilitate the sharing of research information.

The World Conference on Lung Cancer (WCLC) is our largest educational activity, supporting these principles by bringing together thousands of individuals from around the world to share and discuss information and issues related to lung cancer. This year's conference in San Francisco is our largest, featuring over 180 exhibitors and over 1,500 abstracts—more than at any previous WCLC meeting.

Since our last conference two years ago in Seoul, our understanding of the molecular mechanisms involved in lung cancer has advanced considerably. We now recognize the large role of gene mutations in directing the development of lung cancers. We have discovered that agents targeting those mutations are more efficacious than traditional chemotherapy drugs. We now know that response to specific therapies may vary according to which mutations are present in a tumor. As we move forward, we recognize that mutation testing, interpretation of results, and the development of treatment plans around these results will become increasingly important.

Despite these advances, we still face basic challenges. With the numbers of smokers increasing around the world, primarily in developing countries, prevention is a key concern. Another challenge is early detection, considering that far too often lung cancer is diagnosed late in the course of the disease, when outcomes are less favorable. The WCLC offers an excellent opportunity for participants to discuss challenges like these and, ultimately, to work toward the elimination of lung cancer.

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IASLC President Dr. Nagahiro Saijo is assistant director of the Tokyo National Cancer Center Hospital

East, chair of the Japanese Society of Medical Oncology, and vice-president of the Japanese Lung Cancer Society. His specialties and research interests include cancer chemotherapy, drug resistance, the pharmacology of anticancer drugs, and tumor immunology. He is one of the founders of pharmacogenomics and of medical oncology in Japan.

Dr. Saijo has published more than 800 articles in Japanese and more than 500 in English, and has received numerous awards for his research. He has served on the Boards of ASCO and the IASLC. During his tenure as President-Elect and President of IASLC, the Society has witnessed tremendous growth in all areas.

## IN THE HALLS

### How will the new staging affect your work?

"The new system will be more accurate and enable us to better predict how patients will be doing in the future. It will definitely change how pathology is practiced."

- USA

## Research addresses controversies in supportive care

High quality research to guide supportive care for cancer patients has been scarce, says Dr. Shun Lu (Shanghai Lung Cancer Center, China), but it is critical for improving the quality of life of cancer patients. Presentations at this year's conference address some of the current controversies concerning supportive care of lung cancer patients receiving toxic chemotherapies.

One controversy concerns the optimal dose of palonosetron, the serotonin antagonist (5-HT<sub>3</sub>) of choice to relieve chemotherapy-induced nausea and vomiting (CINV). Researchers reviewed the efficacy of high and low doses of palonosetron compared with other 5-HT<sub>3</sub>s in two meta-analyses of large single agent randomized clinical trials (RCT). Controversy ensued after a RCT tested the 0.75 mg palonosetron dose (0.25 mg are the norm) in combination with dexamethasone. In a meta-analysis, Dr. Martin Lesser (North Shore - LIJ Health System, USA) and his colleagues found virtually the same emetic outcomes for both doses of palonosetron for all endpoints tested, including complete response.

Another controversy involves the impact of safety-related restrictions for erythropoiesis stimulating

agents (ESA). Results of 2006 and 2008 studies revealed the toxicity of ESA, but, before that, ESAs were used liberally in cancer patients. Increased thrombosis and negative survival rates associated with ESA led to restricted FDA labeling. Despite the unfavorable risk/benefit of ESA, fears persisted surrounding the possible increase in transfusion in the absence of ESA. Using data compiled annually from 2006 to 2008, Dr. Harry Raftopoulos (North Shore-LIJ Health System, USA) and his colleagues showed that as ESA injections dropped as a percentage of total visits from 24% (2006) to 5.2% (2008), thrombosis-related discharges also dropped 21% from 2.0% to 1.58% of total visits, while transfusions increased minimally from 6.2% to 6.4% of total visits. This data suggest that a marked decrease in ESA does not increase demand for transfusion significantly.

Dr. Lu says that these studies illustrate the complexities which are involved in conducting supportive care research. Nevertheless, he says, "there is a critical need [in oncology] to develop and rigorously test clinically feasible and sustainable interventions targeting distress and quality of life."

## New technologies support early detection, prevention

Lung cancer is detected too late for the overwhelming majority of patients, and many patients find themselves with no chance for cure based on existing treatments. In contrast, cure rates for other cancers, such as prostate and breast cancer, are very high because large percentages of cases are detected at Stage I. In several Proffered Paper Sessions during the conference, presenters will discuss a variety of papers that describe useful research and promising technologies in the early detection and prevention of lung cancer.

A research team in Colorado (USA) performed a phase II trial to evaluate the potential benefits of iloprost (synthetic prostacyclin) as a lung cancer preventative for current and former smokers (see abstract 7753: Oral iloprost improves endobronchial dysplasia in former smokers). Preclinical research indicates that prostaglandin metabolism is disrupted in the majority of NSCLC cases, suggesting that restoration of normal prostaglandin metabolism could potentially prevent lung cancer. Subjects with 20 or more pack years of tobacco use were randomized into oral iloprost and placebo groups, treated for 6 months, and

monitored with bronchoscopy. Researchers observed highly significant changes in the iloprost group as compared with the placebo group for worst biopsy score (-0.59 vs. 0.50,  $p=0.004$ ), dysplasia index (-8.84 vs. 0.10,  $p=0.019$ ), and average of all biopsy scores (-0.33 vs. -0.02,  $p=0.046$ ). While results showed no benefit for current smokers, they did demonstrate that iloprost may be an effective preventative for former smokers.

VisionGate, Inc. (Gig Harbor, Washington) has developed a computer tomography-based imaging device called Cell-CT that generates 2D and 3D images of cells at submicron resolution. In conjunction with researchers at the University of Washington, VisionGate is developing an automated test called LuCED that scores sputum samples processed by the Cell-CT for evidence of cell dysplasia or cancer (see abstract 7618: The lung cell evaluation device (LuCED)—early detection of lung cancer in sputum based on 3D morphology). Early results for detecting squamous cell cancer in sputum using the Cell-CT and LuCED show very high discrimination. With additional development, this promising technology may provide research

benefit and expanded clinical testing options for assessment of lung cancer risks of various types.

A Japanese research team has performed repeated CT screening on a group of over 2,100 participants to establish the relationship between lung cancer pathological stage and tumor size at baseline screening (see abstract 6698: Stage-size relationship in long-term repeated CT screening for lung cancer). The study data demonstrate that baseline lesion size is highly correlated with pathological stage. One hundred percent of subjects with lesions under 10 mm had no metastases (NOM0), compared to 89% of

subjects with 11–15 mm lesions, 62% with 16–20 mm lesions, 83% with 21–30 mm lesions, 50% with 31–40 mm lesions, and 33% with 41 mm and above lesions. This evidence suggests that early detection of lesions under 15 mm may produce better outcomes in asymptomatic patients.

An American team working with nanotechnology specialists in Israel is developing a non-invasive bedside tool to analyze exhaled breath using nanotechnology-based sensors (see abstract 7122: The unique “smell print” of NSCLC cell lines). The sensors can detect specific proteins in the parts-per-billion range. The team studied the

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## Presenters provide three perspectives on overcoming barriers in lung cancer

In many countries, there has not been substantial improvement in understanding and treating lung cancer, nor is cancer a high priority on national health agendas. During the Global Lung Cancer Coalition Symposium, session speakers representing different perspectives in the lung cancer field discussed barriers in lung cancer investigation and proposed strategies for overcoming them.

Dr. Thierry le Chevalier (Institut Gustave Roussy, France) represented the research clinician's perspective and described the issue of late lung cancer diagnosis. Dr. le Chevalier said that patients who are diagnosed late do not have time to participate in clinical trials and, being at an inoperable late stage of disease, they cannot provide sufficient tumor banking samples,


perpetuating a poor understanding of the disease.

From the nurse's perspective, Liz Darlison (University Hospitals of Leicester, UK) pointed out the shortage of cancer nurse specialists compared to the high number of patients. Unfortunately, financially justifying the development of this role is difficult because of poor patient survival. Still, poor patient

survival is often the impetus for patient advocacy and support groups which give lung cancer patients a quiet public voice.

Andy Miller (Lance Armstrong Foundation [LAF], USA) discussed the LAF's efforts to increase public awareness, reduce associated lung cancer stigma, and make cancer a global health priority. The Global Cancer Summit and World Cancer Declaration are two means of recruiting world leaders and individuals to the global campaign against the disease.

A survey of audience attitudes showed that the majority believes that public education about disease symptoms, treatment options, and outcomes as well as reducing the stigma associated with the disease can better prevent late diagnoses and poor prognoses of lung cancer. The majority agreed that advocacy is needed to improve funding for lung cancer treatment and research.



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## Lipocalin-2 interactions shed light on erlotinib resistance

EGFR tyrosine kinase inhibitors (EGFR TKIs) are 70-75% effective in regulating EGFR signaling, thus prolonging patient survival in instances of non-small cell lung cancer (NSCLC) containing EGFR mutations. However, approximately 30% of patients are intrinsically resistant to EGFR TKIs, and otherwise effectively treated patients develop resistance to EGFR TKIs within months of initial treatment.

To determine the underlying mechanism of EGFR TKI resistance, researchers developed cell lines resistant to erlotinib, one available EGFR TKI. In session C3, Dr. Xiaoyan Cui (UCLA, USA) reported that researchers identified neutrophil gelatinase associated lipocalin (NGAL, also known as lipocalin-2)

as a candidate target gene; its upregulation in erlotinib resistant cells is 200 times that of parental cells. This is consistent with observations that late stage NSCLC patients receiving erlotinib who have progressive disease have higher serum NGAL levels than patients receiving erlotinib who have partial response.

In two stable NGAL overexpressing NSCLC cell lines, researchers observed a decrease in the expression of the proapoptotic protein Bim, suggesting that NGAL upregulation contributes to increased Bim degradation and decreases NSCLC sensitivity to erlotinib-induced cell death. Confirming this observation, researchers found that mice with tumors derived from NGAL overexpressing

NSCLC cells were much more resistant to erlotinib treatment.

These studies reveal a correlation between NGAL molecular interactions and erlotinib resistance in NSCLC. Dr. Cui said that next steps for research include validating this correlation in a larger clinical sample set and defining the role of NGAL in signaling pathways in cancer development. He added that further research is necessary to determine whether NGAL may be utilized as an additional biomarker to plan therapeutic strategies in NSCLC.



## Vandetanib

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received 300 mg vandetanib per day, compared with 100 mg per day in ZODIAC and ZEAL.

Results from the trials were somewhat disappointing in some areas. For example, among the studies, only ZODIAC met its primary endpoint of PFS, with the vandetanib/docetaxel combination showing significant improvement in PFS compared with placebo plus docetaxel (HR 0.79, 97.5% CI 0.70-0.90; 2-sided p<0.001). In all three studies, the fraction of participants who experienced progression was high; results for ZEAL were 83%, for ZODIAC 87%, and for ZEST 88%. At 67%, the rate of deaths occurring within the study period was highest for ZEST, while it was 50% for ZEAL and 59% for ZODIAC. In all three studies, adverse events fell within the range expected for Phase III trials.

It should be noted that the studies did have some positive implications. ZEAL results showed some definite evidence of clinical benefit from the vandetanib/pemetrexed combination, with positive trends in PFS and significant advantages in overall response rate (ORR) for the combination. In the ZODIAC study, a delay in symptom deterioration was evident. Results of both the ZEAL and ZODIAC studies showed statistically significant ORR for their respective vandetanib combinations versus single agents (ZEAL: 19.1% vs. 7.9%, 2-sided p<0.001; ZODIAC: 17% vs. 10%, 2-sided p<0.001).

These three studies show that some combinations with vandetanib exhibit both direct and indirect effects that combat disease progression. Also, the results of the trials represent some progress in overcoming the known problem of declining epithelial growth factor (EGFR) effectiveness after six to 12 months of treatment.

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## New technologies for early detection and prevention

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profile of the volatile organic compounds (VOCs) that appear in association with adenocarcinoma and squamous carcinoma by sampling and analyzing the gas headspace above cancerous and non-cancerous cell lines. This has yielded a preliminary set of VOC markers specific to lung cancer. This interesting technology merits close attention as it moves through clinical validation.

Researchers in the Netherlands have used quantitative methylation-specific PCR on sputum samples to evaluate hypermethylation as a diagnostic

marker for lung cancer (see abstract 7725: Methylation analysis in spontaneous sputum is suitable for lung cancer diagnosis). Cancers often exhibit an aberrant methylation of gene promoter regions that is associated with loss of gene function. When methylated bases are found in the promoter region of genes, the binding of transcriptional factors is altered and other proteins such as methyl-DNA binding proteins are able to bind, resulting in gene silencing. Researchers in this study have identified methylated markers that correlate reasonably well with a diagnosis of lung cancer.

### IN THE HALLS

"The new staging system will be implemented in every aspect of my work. I'm a resident working in pulmonary diseases. I had already heard about the new system at the 10th European Congress: Perspectives in Lung Cancer, held in Brussels in March. I will be reading the material available here to learn all the details."

- Netherlands

"I think the new system really reflects what we're already doing. One of the most significant changes is the inclusion of stage 3, such as pleural effusion, in stage 4, and we're already considering the patients in that group non-curative and taking a palliative approach. The new staging system makes what we're already doing more explicit."

- Canada

## Investigating ASA404 (vadimezan)\* in Stage IIIb/IV Non-Small Cell Lung Cancer

New Enrolling

Two prospective, randomized, double-blind, placebo-controlled, international, multi-center studies



### First-line

Patients with newly diagnosed or recurrent stage IIIb or stage IV NSCLC that has never been treated

N = 1200

Randomization 1:1

ASA404 + PACLITAXEL + CARBOPLATIN  
Primary Endpoint: OS  
PLACEBO + PACLITAXEL + CARBOPLATIN

Schedule and Dosing: ASA404: 1800 mg/m<sup>2</sup> IV q3w, Paclitaxel: 200 mg/m<sup>2</sup> q3w, Carboplatin: AUC 6 q3w. Treatment on d1 q3w Max. 6 cycles Paclitaxel + Carboplatin.

Maintenance treatment: Patients who complete 6 cycles of combination therapy without progressive disease as confirmed per RECIST will continue to receive blinded study drug, either ASA404 1800 mg/m<sup>2</sup> or placebo, as maintenance treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

### Second-line

Patients with stage IIIb or stage IV NSCLC who have progressed while on or following first-line systemic chemotherapy

N = 900

Randomization 1:1

ASA404 + DOCETAXEL  
Primary Endpoint: OS  
PLACEBO + DOCETAXEL

Schedule and Dosing: ASA404: 1800 mg/m<sup>2</sup> IV q3w, Docetaxel: 75 mg/m<sup>2</sup> q3w. Treatment on d1 q3w Max. 6 cycles Docetaxel.

Maintenance treatment: Patients who complete 6 cycles of docetaxel therapy, or discontinue docetaxel prior to receiving 6 cycles (minimum of 2 cycles received) due to toxicity, without progressive disease as confirmed per RECIST will continue to receive blinded study drug, either ASA404 1800 mg/m<sup>2</sup> or placebo, as maintenance treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

For more information, visit [www.attractstudy.com](http://www.attractstudy.com) or call 1-800-340-6843

\*ASA404 (vadimezan, formerly AS1404 or DMXAA) is an investigational new drug licensed from Antisoma. Efficacy and safety have not been established. There is no guarantee that ASA404 will become commercially available.