THE NEW BIOLOGY OF NON-SMALL CELL LUNG CANCER

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists and other healthcare providers involved in the treatment of lung cancer.

OVERVIEW OF ACTIVITY

Lung cancer is a devastating disease with a broad-reaching impact on public health, accounting for 14% of all new cancer cases in the US and the most cancer-related deaths among both men and women. In the year 2015, it is estimated that 221,200 individuals will be diagnosed and 158,040 individuals will die from the disease. Importantly, despite the many advances over the past few decades related to surgery, radiation therapy and chemotherapy, death rates attributable to lung cancer have remained relatively unchanged. Today, many are optimistic that these trends have already started to change as recent research advances have led to an explosion in lung cancer genetic and biologic knowledge among scientists and clinicians working in this area of cancer medicine.

To bridge the gap between research and patient care, this video presentation by Dr Heather Wakelee uses a review of recent relevant publications and presentations, ongoing clinical trials and clinical investigator treatment preferences to assist medical oncologists and other healthcare providers involved in the treatment of lung cancer with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Discriminate among molecular determinates that may be used to refine non-small cell lung cancer (NSCLC) prognosis and/or predict therapeutic response to an individual treatment.
- Employ an understanding of personalized medicine to individualize the use of available EGFR inhibitors in the treatment of NSCLC.
- Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors (TKIs), and identify investigational therapeutic opportunities to circumvent these processes.
- Communicate the efficacy and safety of crizotinib, ceritinib (LDK378) and other investigational ALK inhibitors to appropriate patients with NSCLC, considering the predictive utility of ALK mutation testing.
- Describe emerging data on the efficacy and safety of tumor immunotherapy directed at the PD-1/PD-L1 pathway in lung cancer, and consider this information when counseling patients regarding clinical trial participation.
- Recognize the results of recently completed Phase III trials examining the efficacy and safety of the novel monoclonal antibodies necitumumab and ramucirumab for patients with advanced NSCLC.
- Assess new oncogenic pathways mediating the growth of unique NSCLC tumor subsets, and recall emerging data with experimental agents exploiting these targets.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Presenting Faculty Member

Heather Wakelee, MD
Associate Professor of Medicine
Division of Oncology
Stanford University School of Medicine
Stanford Cancer Institute
Stanford, California

Consulting Agreement: Peregrine Pharmaceuticals Inc; **Contracted Research:** AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Genentech BioOncology, Lilly, MedImmune Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc, Xcovery; **Grants:** AstraZeneca Pharmaceuticals LP, Clovis Oncology, MedImmune Inc, Xcovery.

Project Steering Committee Members

D Ross Camidge, MD, PhD
Director, Thoracic Oncology Clinical Program
Associate Director for Clinical Research
University of Colorado Cancer Center
Aurora, Colorado

Advisory Committee: ARIAD Pharmaceuticals Inc, Astex Pharmaceuticals, Clarient Inc, Exelixis Inc, Genentech BioOncology, ImmunoGen Inc, IndiPharm, Lilly, Servier; **Contracted Research and Honoraria:** ARIAD Pharmaceuticals Inc.

Leora Horn, MD, MSc
Associate Professor of Medicine
Assistant Director, Educator Development Program
Vanderbilt University Medical Center
Nashville, Tennessee

Advisory Committee: Bristol-Myers Squibb Company, Clovis Oncology, Helix BioPharma Corp, Puma Biotechnology Inc; **Consulting Agreements:** Bayer HealthCare Pharmaceuticals, Merck; **Contracted Research:** Astellas Scientific and Medical Affairs Inc; **Honoraria:** Boehringer Ingelheim Pharmaceuticals Inc.

Nathan A Pennell, MD, PhD
Assistant Professor, Hematology and Medical Oncology
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Director, Cleveland Clinic Lung Cancer Medical Oncology Program
Cleveland, Ohio

No real or apparent conflicts of interest to disclose.

Suresh S Ramalingam, MD
Professor of Hematology and Medical Oncology
Director, Division of Medical Oncology
Emory University
Winship Cancer Institute
Atlanta, Georgia

Advisory Committee: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, EMD Serono Inc; **Consulting Agreements:** AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Lilly, Merck, Novartis Pharmaceuticals Corporation.

Gregory J Riely, MD, PhD
Associate Attending
Memorial Sloan Kettering Cancer Center
New York, New York

Consulting Agreement: Novartis Pharmaceuticals Corporation; **Contracted Research:** GlaxoSmithKline, Infinity Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc, Takeda Oncology.

Lecia V Sequist, MD, MPH
Associate Professor of Medicine
Harvard Medical School
Center for Thoracic Cancers
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Consulting Agreements: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, Genentech BioOncology, Merrimack Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Taiho Oncology Inc.

David R Spigel, MD
Program Director, Lung Cancer Research
Sarah Cannon Research Institute
Nashville, Tennessee

No real or apparent conflicts of interest to disclose.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

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Select Publications

A phase III double-blind trial for surgically resected early stage non-small cell lung cancer: Crizotinib versus placebo for patients with tumors harboring the anaplastic lymphoma kinase (ALK) fusion protein. NCT02201992

A randomized phase II study of individualized combined modality therapy for stage III non-small cell lung cancer (NSCLC). NCT01822496

A randomized phase II trial of erlotinib alone or in combination with bevacizumab in patients with non-small cell lung cancer and activating epidermal growth factor receptor mutations. NCT01532089

Adjuvant lung cancer enrichment marker identification and sequencing trial. NCT02194738

Brahmer JR et al. **Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with non-small cell lung cancer (NSCLC): Overall survival and long-term safety in a phase 1 trial.** *Proc WCLC* 2013;**Abstract MO18.03**.

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Camidge DR et al. **Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC).** *Proc ASCO 2*014;**Abstract 8001**.

Camidge DR. **ALK rearrangements as a therapeutic target in advanced non-small cell lung cancer.** *Int J Target Ther Cancer* June 2012:30-3.

CheckMate 017: An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC). NCT01642004

CheckMate 026: An open-label, randomized, phase 3 trial of nivolumab versus investigator's choice chemotherapy as first-line therapy for stage IV or recurrent PD-L1+ non-small cell lung cancer. NCT02041533

CheckMate 057: An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated metastatic non-squamous non-small cell lung cancer (NSCLC). NCT01673867

Dolan DE, Gupta S. **PD-1 pathway inhibitors: Changing the landscape of cancer immunotherapy.** *Cancer Control* 2014;21(3):231-7.

Drilon A et al. **Next-generation sequencing (NGS) to identify actionable genomic alterations (GA) in "pan-negative" lung adenocarcinomas (ADC) from patients with no smoking or a light smoking (NS/LS) history.** *Proc ASCO* 2014;**Abstract 8029**.

Gadgeel SM et al. **Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): Results from the dose-finding portion of a phase 1/2 study.** *Lancet Oncol* 2014;15(10):1119-28.

Garon EB et al. **Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung.** *Proc ESMO* 2014;**Abstract LBA43**.

Garon EB et al. **Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial.** *Lancet* 2014;384(9944):665-73.

Horn L et al. **An analysis of the relationship of clinical activity to baseline EGFR status, PD-L1 expression and prior treatment history in patients with non-small cell lung cancer (NSCLC) following PD-L1 blockade with MPDL3280A (anti-PDL1).** *Proc WCLC* 2013;**Abstract MO18.01**.

Janjigian YY et al. **Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations.** *Cancer Discov* 2014;4(9):1036-45.

Janne PA et al. **Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor-resistant non-small cell lung cancer (NSCLC).** *Proc ASCO* 2014;**Abstract 8009**.

Keir ME et al. **PD-1 and its ligands in tolerance and immunity.** *Annu Rev Immunol* 2008;26:677-704.

Kelly K et al. **A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results.** *Proc ASCO* 2014;**Abstract 7501**.

KEYNOTE-010: A phase II/III randomized trial of two doses of MK-3475 (SCH900475) versus docetaxel in previously treated subjects with non-small cell lung cancer. NCT01905657

Select Publications

KEYNOTE-024: A randomized open-label phase III trial of MK-3475 versus platinum based chemotherapy in 1L subjects with PD-L1 strong metastatic non-small cell lung cancer. NCT02142738

KEYNOTE-042: A randomized, open label, phase III study of overall survival comparing pembrolizumab (MK-3475) versus platinum based chemotherapy in treatment naïve subjects with PD-L1 positive advanced or metastatic non-small cell lung cancer. NCT02220894

Kris MG et al. **Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs.** *JAMA* 2014;311(19):1998-2006.

Leighl NB et al. **Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guideline.** *J Clin Oncol* 2014;32(32):3673-9.

Lindeman NI et al. **Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology.** *Arch Pathol Lab Med* 2013;137(6):828-60.

Lung-MAP: S1400 phase II/III biomarker-driven master protocol for second line therapy of squamous cell lung cancer. NCT02154490

LUX-Lung 3: A randomised, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation. NCT00949650

LUX-Lung 6: A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation. NCT01121393

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National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology. Non-small cell lung cancer — Version 2.2014.** Available at: **http://www.nccn.org/professionals/physician_gls/f_guidelines.asp**.

Pardoll DM. **The blockade of immune checkpoints in cancer immunotherapy.** *Nat Rev Cancer* 2012;12(4):252-64.

Planchard D et al. **Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): A multicenter, open-label, phase II trial (BRF113928).** *Proc ESMO* 2014;**Abstract LBA38_PR**.

RADIANT: A multi-center, randomized, double-blind, placebo-controlled, phase 3 study of single-agent Tarceva® (erlotinib) following complete tumor resection with or without adjuvant chemotherapy in patients with stage IB-IIIA non-small cell lung carcinoma who have EGFR-positive tumors. NCT00373425

Randomized double blind placebo controlled study of erlotinib or placebo in patients with completely resected epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC). NCT02193282

REVEL: A randomized, double-blind, phase 3 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy. NCT01168973

Rizvi NA et al. **Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): A phase 2, single-arm trial.** *Lancet Oncol* 2015;16(3):257-65.

Rizvi NA et al. **Clinical trials of MPDL3280A (anti-PDL1) in patients (pts) with non-small cell lung cancer (NSCLC).** *Proc ASCO* 2014;**Abstract TPS8123**.

Sequist LV et al. **First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M).** *Proc ASCO* 2014;**Abstract 8010**.

Seto T et al. **Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): An open-label, randomised, multicentre, phase 2 study.** *Lancet Oncol* 2014;15(11):1236-44.

Shaw AT et al. **Ceritinib in ALK-rearranged non-small-cell lung cancer.** *N Engl J Med* 2014;370(13):1189-97.

Shaw AT et al. **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.** *N Engl J Med* 2013;368(25):2385-94.

Select Publications

Spigel DR et al. **Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2013;**Abstract 8008**.

US Food and Drug Administration. **FDA approves nivolumab for previously treated metastatic squamous NSCLC** [press release]. March 4, 2015. Available at: **http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm436566.htm**.

US Food and Drug Administration. **FDA expands approved use of Cyramza to treat aggressive non-small cell lung cancer** [press release]. December 12, 2014. Available at: **http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426720.htm**.

Yang JC et al. **Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of overall survival data from two randomised, phase 3 trials.** *Lancet Oncol* 2015;16(2):141-51.