Targeted Treatment of Non-Small Cell Lung Cancer

Current Algorithms and New Agents

CME Information

TARGET AUDIENCE

This activity is intended for hematologists, medical oncologists and other healthcare providers involved in the treatment of non-small cell lung cancer (NSCLC).

OVERVIEW OF ACTIVITY

Lung cancer is a devastating disease with broad-reaching impact on public health, as it accounts for 15% 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. 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, however, there is renewed optimism that these trends have 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. A major focus of recent lung cancer research has been the development — and subsequent approval — of a number of molecular-targeted agents and the identification of related biomarkers to help guide treatment selection for those individuals who harbor specific oncogenic alterations.

These video proceedings from a CME symposium held in conjunction with the 16th World Conference on Lung Cancer feature discussions with leading researchers regarding actual cases of patients with NSCLC and tumor driver mutations from the practices of general medical oncologists and related clinical research findings to address existing uncertainties and help keep clinicians up to date and informed on the targeted treatment of NSCLC.

LEARNING OBJECTIVES

- Discriminate among molecular determinants that may be used to refine NSCLC prognosis and/or predict therapeutic response to an individual treatment, and apply available clinical guidelines to appropriately select patients for biomarker assessment.
- Employ an understanding of personalized medicine to individualize the use of available EGFR inhibitors in the long-term management of EGFR mutation-positive NSCLC.
- Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors (TKIs), and identify investigational therapeutic opportunities to circumvent this process.
- Communicate the efficacy and safety of crizotinib, ceritinib and other emerging ALK inhibitors to appropriate patients with NSCLC, considering the predictive utility of ALK and ROS1 mutation testing.
- Consider available clinical data and investigator perspectives when caring for patients with EGFR- or ALK-positive NSCLC and brain metastases.
- Assess new oncogenic pathways mediating the growth of unique NSCLC tumor subsets, and recall emerging data with experimental agents exploiting these targets.
- Recognize the abilities and limitations of multiplex and next-generation sequencing platforms, and determine their clinical and/or research application for patients with NSCLC.
- Appreciate the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in NSCLC, and counsel appropriately selected patients about study participation.

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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:

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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

Mark G Kris, MD

D'Angelo SP et al. **Distinct clinical course of EGFR-mutant resected lung cancers: Results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib.** *J Thorac Oncol* 2012;7(12):1815-22.

Davies C et al. **Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.** *Lancet* 2013;381(9869):805-16.

ENSURE: A multicenter, open-label, randomized phase III study to evaluate the efficacy and safety of erlotinib (Tarceva®) versus gemcitabine/cisplatin as the first-line treatment for stage IIIb/IV non-small cell lung cancer (NSCLC) patients with mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) in their tumors. NCT01342965

Fukuoka M et al. **Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS).** *J Clin Oncol* 2011;29(21):2866-74.

Ichihara E et al. **Phase II trial of gefitinib in combination with bevacizumab as first-line therapy for advanced non-small cell lung cancer with activating EGFR gene mutations: The Okayama Lung Cancer Study Group trial 1001.** *J Thorac Oncol* 2015;10(3):486-91.

Inoue A et al. **Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002).** *Ann Oncol* 2013;24(1):54-9.

Jackman DM et al. **Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib.** *Clin Cancer Res* 2006;12(13):3908-14.

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**.

Lee CK et al. **Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: A meta-analysis.** *J Clin Oncol* 2015;33(17):1958-65.

Li N et al. **Pemetrexed-carboplatin adjuvant chemotherapy with or without gefitinib in resected stage IIIA-N2 non-small cell lung cancer harbouring EGFR mutations: A randomized, phase II study.** *Ann Surg Oncol* 2014;21(6):2091-6.

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Neal JW et al. **The SELECT study: A multicenter phase II trial of adjuvant erlotinib in resected epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract 7010**.

Riely GJ et al. **Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib.** *Clin Cancer Res* 2006;12(3):839-44.

Riely GJ et al. **Update on epidermal growth factor receptor mutations in non-small cell lung cancer.** *Clin Cancer Res* 2006;12(24):7232-41.

Rosell R et al. **Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial.** *Lancet Oncol* 2012;13(3):239-46.

Rudin R. **Targeting epigenetic changes in lung cancer.** *Proc IASLC* 2013;**Abstract MS02.4**.

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50.

Sequist LV et al. **Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.** *J Clin Oncol* 2013;31(27):3327-34.

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.

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.

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Yoshioka H et al. **Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR).** *Proc ASCO* 2014;**Abstract 8117**.

Zhou C et al. **Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract 7520**.

Pasi A Jänne, MD, PhD

Ellis PM et al. **Dacomitinib compared with placebo in pretreated patients with advanced or metastatic non-small-cell lung cancer (NCIC CTG BR.26): A double-blind, randomised, phase 3 trial.** *Lancet Oncol* 2014;15(12):1379-88.

Goto Y et al. **ASP8273, a mutant-selective irreversible EGFR inhibitor in patients (pts) with NSCLC harboring EGFR activating mutations: Preliminary results of first-in-human phase I study in Japan.** *Proc ASCO* 2015;**Abstract 8014**.

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.

Jänne PA et al. **A phase I study of AZD9291 in patients with EGFR-TKI-resistant advanced NSCLC — Updated progression free survival and duration of response data.** *Proc European Lung Cancer Conference* 2015;**Abstract LBA3**.

Jänne PA et al. **AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer.** *N Engl J Med* 2015;372(18):1689-99.

Miller VA et al. **Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial.** *Lancet Oncol* 2012;13(5):528-38.

Park K et al. **Updated safety and efficacy results from phase I/II study of HM61713 in patients (pts) with EGFR mutation positive non-small cell lung cancer (NSCLC) who failed previous EGFR-tyrosine kinase inhibitor (TKI).** *Proc ASCO* 2015;**Abstract 8084**.

Sacher AG et al. **Management of acquired resistance to epidermal growth factor receptor kinase inhibitors in patients with advanced non-small cell lung cancer.** *Cancer* 2014;120(15):2289-98.

Sequist LV et al. **Rociletinib in EGFR-mutated non-small-cell lung cancer.** *N Engl J Med* 2015;373(6):578-9.

Soria JC et al. **Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): A phase 3 randomised trial.** *Lancet Oncol* 2015;16(8):990-8.

Tan DSW et al. **First-in-human phase I study of EGF816, a third generation, mutant-selective EGFR tyrosine kinase inhibitor, in advanced non-small cell lung cancer (NSCLC) harboring T790M.** *Proc ASCO* 2015;**Abstract 8013**.

Yu HA et al. **Phase I dose escalation study of ASP8273, a mutant-selective irreversible EGFR inhibitor, in subjects with EGFR mutation positive NSCLC.** *Proc ASCO* 2015;**Abstract 8083**.

Yu HA et al. **Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers.** *Clin Cancer Res* 2013;19(8):2240-7.

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A phase 1, two-part, multi-center, non randomized, open-label, multiple dose first-in-human study of DS-6051b, an oral ROS1 and NTRK inhibitor, in subjects with advanced solid tumors. NCT02279433

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Camidge DR et al. **Safety and efficacy of brigatinib (AP26113) in advanced malignancies, including ALK+ non-small cell lung cancer (NSCLC).** *Proc ASCO* 2015;**Abstract 8062**.

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Camidge DR et al. **Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: Updated results from a phase 1 study.** *Lancet Oncol* 2012;13(10):1011-9.

Felip E et al. **Efficacy and safety of ceritinib in patients (pts) with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): An update of ASCEND-1.** *Proc ESMO* 2014;**Abstract 1295P**.

Gainor JF et al. **Alectinib salvages CNS relapses in ALK-positive lung cancer patients previously treated with crizotinib and ceritinib.** *J Thorac Oncol* 2015;10(2):232-6.

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Katayama R et al. **Two novel ALK mutations mediate acquired resistance to the next-generation ALK inhibitor alectinib.** *Clin Cancer Res* 2014;20(22):5686-96.

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Phase 1/2 study of PF 06463922 (an ALK/ROS1 tyrosine kinase inhibitor) in patients with advanced non-small cell lung cancer harboring specific molecular alterations. NCT01970865

PROFILE 1001: Phase 1 safety, pharmacokinetic and pharmacodynamic study of PF-02341066, a c-MET/HGFR selective tyrosine kinase inhibitor, administered orally to patients with advanced cancer. NCT00585195

PROFILE 1014: Phase 3, randomized, open-label study of the efficacy and safety of crizotinib versus pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with non-squamous carcinoma of the lung harboring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus. NCT01154140

Shaw A et al. **Clinical activity and safety of PF-06463922 from a dose escalation study in patients with advanced ALK+ or ROS1+ NSCLC.** *Proc ASCO* 2015;**Abstract 8018**.

Shaw A et al. **Ceritinib (LDK378) for treatment of patients with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) and brain metastases (BM) in the ASCEND-1 trial.** *Proc SNO* 2014;**Abstract BM-32**.

Shaw AT et al. **Crizotinib in ROS1-rearranged non-small-cell lung cancer.** *N Engl J Med* 2014;371(21):1963-71.

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Birchmeier C et al. **Met, metastasis, motility and more.** *Nat Rev Mol Cell Biol* 2003;4(12):915-25.

Blume-Jensen P, Hunter T. **Oncogenic kinase signalling.** *Nature* 2001;411(6835):355-65.

Camidge DR et al. **Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC).** *Proc ASCO* 2015;**Abstract 8001**.

Chen B et al. **Sequence-dependent antiproliferative effects of gefitinib and docetaxel on non-small cell lung cancer (NSCLC) cells and the possible mechanism.** *PLoS One* 2014;9(12):e114074.

Drilon AE et al. **Phase II study of cabozantinib for patients with advanced RET-rearranged lung cancers.** *Proc ASCO* 2015;**Abstract 8007**.

Drilon A et al. **Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas.** *Cancer Discov* 2013;3(6):630-5.

Feng Y et al. **MET signaling: Novel targeted inhibition and its clinical development in lung cancer.** *J Thorac Oncol* 2012;7(2):459-67.

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Nakaoku T et al. **Druggable oncogene fusions in invasive mucinous lung adenocarcinoma.** *Clin Cancer Res* 2014;20(12):3087-93.

Organ SL, Tsao MS. **An overview of the c-MET signaling pathway.** *Ther Adv Med Oncol* 2011;3(1):7-19.

Paik PK et al. **Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping.** *Cancer Discov* 2015;5(8):842-9.

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Planchard D et al. **Interim results of a phase II study of the BRAF inhibitor (BRAFi) dabrafenib (D) in combination with the MEK inhibitor trametinib (T) in patients (pts) with BRAF V600E mutated (mut) metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2015;**Abstract 8006**.

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Vaishnavi A et al. **Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer.** *Nat Med* 2013;19(11):1469-72.