Lung Cancer: Conference Highlights from the 2015 ASCO Annual Meeting

Estimated time to complete activity: 1.0 hour
Release date: Thursday, July 30, 2015 | Expiration date: Saturday, July 30, 2016

Disclosure of Commercial Support
This activity is supported by independent educational grants from the following: AstraZeneca, Genentech

Provider
This activity is provided by Educational Concepts Group, LLC.

Overview
The ASCO Annual Meeting is considered the premiere venue for the dissemination of vital research findings to the oncology community. These highlights will summarize key experimental and clincal data presented at the meeting providing optimal care for patients with lung cancer.

Target Audience
The target audience for this activity is medical oncologists, hematologist/oncologists, surgeons, radiation oncologists, pathologists, oncology pharmacists, and other allied healthcare professionals caring for patients with NSCLC.

Educational Objectives
At the conclusion of this activity, participants should be able to:

- Describe the most current advances for the diagnosis and staging of patients with lung cancer
- Describe the rationale for the development and integration of new therapeutic approaches in lung cancer
- Discuss the clinical implications of the results from pivotal clinical trials that have impacted the use of new approaches and strategies for the treatment of NSCLC

Faculty
Editors

Gregory Otterson, MD
Professor, Internal Medicine
Co-Director, Thoracic Oncology Program
Program Director, Hematology & Medical Oncology Fellowship Program
The Ohio State University Medical Center
Columbus, Ohio

Heather Wakelee, MD
Associate Professor
Department of Medicine, Division of Oncology
Co-Director, Thoracic Oncology Clinical Research Group
Stanford University
Stanford, California

Policy on Disclosure
It is the policy of ECG that the faculty, authors, planners, and other persons who may influence

content of this CME activity disclose all relevant financial relationships with commercial interests in order to allow ECG to identify and resolve any potential conflicts of interest.

The Following Faculty Members Have Declared Relevant Financial Relationships

Gregory Otterson, MD
Grants/Research Support: Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Clovis Oncology, Genentech, Pfizer Inc
Consultant Fees: Boehringer Ingelheim Pharmaceuticals, Inc., Genentech

Heather Wakelee, MD
Grants/Research Support: AstraZeneca, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Genentech, MedImmune, LLC., Novartis, Pfizer Inc, Roche, Xcovery
Consultant Fees: Peregrine Pharmaceuticals, Inc.

Staff Disclosure
Planners and managers at ECG have no relevant financial relationships to disclose.

Acknowledgement

The editors wish to thank Lisa van Devender, PharmD and Marie N. Becker, PhD for assistance in writing this document.

Continuing Education

Accreditation Statement

Educational Concepts Group, LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation Statement
Educational Concepts Group, LLC designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Method of Participation

There are no fees for participating and receiving CME credit for this activity. During the period Thursday, July 30, 2015 through Saturday, July 30, 2016, participants must 1) read the educational objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test and evaluation.

CME/CE Credit

Physicians who complete the post-test with a score of 80% or better may view and print their credit letter via the website, www.ecgcme.com.

Disclosure of Off-Label Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. ECG does not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity do not necessarily represent the views of ECG. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by

clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities. Please refer to the official prescribing information for each product or consult the *Physicians' Desk Reference* for discussion of approved indications, contraindications, and warnings.

CME/CE Inquiries:

For further information, please contact:
Educational Concepts Group, LLC
1300 Parkwood Circle SE, Suite 325
Atlanta, Georgia 30339
Phone: 1.866.933.1681
Fax: 1.866.933.1692
www.ecgcme.com

Hardware/Software Requirements

Below are the requirements to access online activities:

- The website is supported by the latest versions of Firefox, Chrome, Safari, and Internet Explorer
- Mediasite Player may be required for video or audio playback. To test your system requirements for Mediasite, please visit: http://www.sonicfoundry.com/site-requirements
- Enable JavaScript (1.2 or higher) in your browser
- Make sure cookies are enabled

Lung Cancer: Conference Highlights from the 2015 ASCO Annual Meeting

Introduction

The 2015 ASCO Annual Meeting, held May 29-June 2 in Chicago, Illinois, included numerous updates on the treatment of non-small-cell lung cancer (NSCLC). A number of studies were presented that offered encouraging data, including therapies targeting the programmed cell death protein 1 (PD-1) or its ligand programmed death-ligand 1 (PD-L1) in patients with advanced NSCLC; and therapies for patients harboring *EGFR* or *BRAF* mutations. This conference highlights provides an overview of the major clinical trial updates in NSCLC presented at this meeting that will likely influence clinical practice.

Early-Stage NSCLC

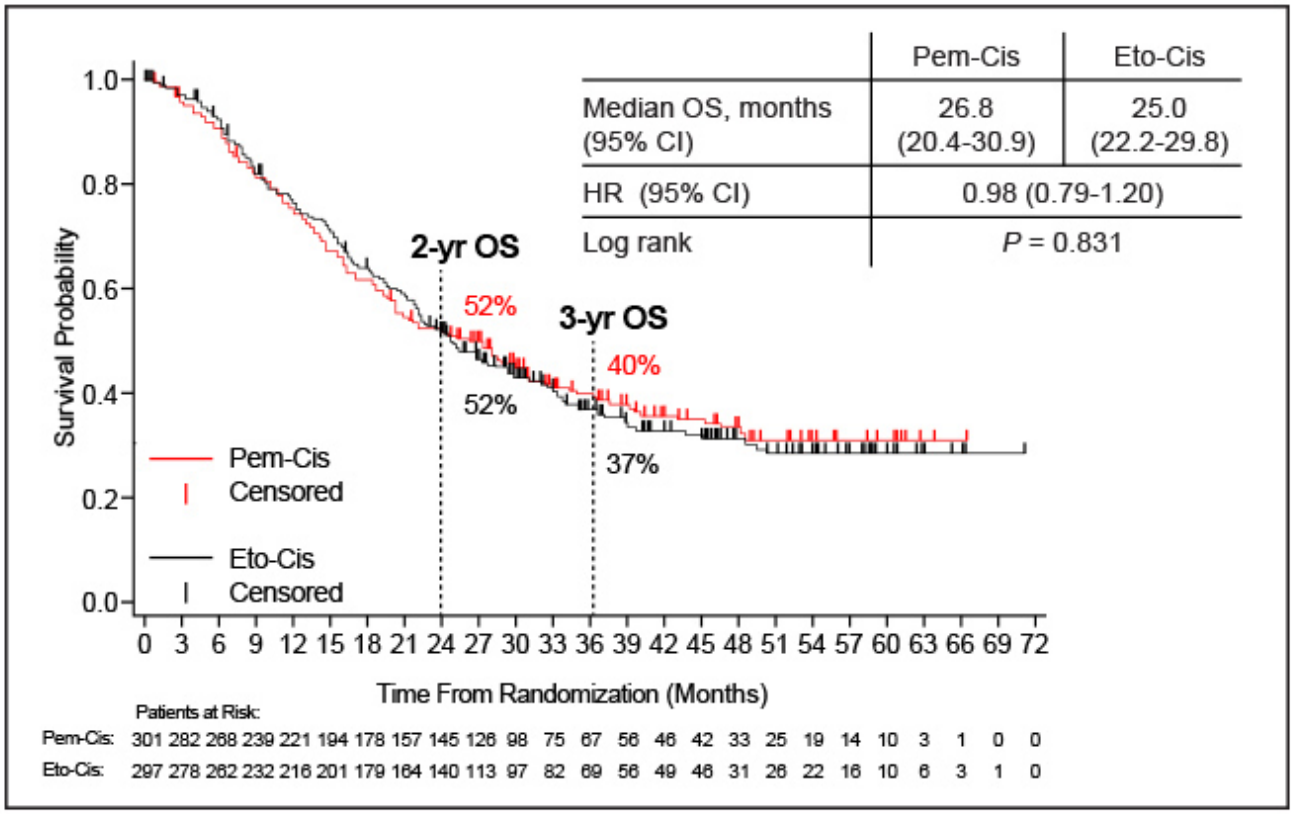
PROCLAIM Trial – Concurrent Chemotherapy With Concurrent Thoracic Radiotherapy (TRT) Followed by Consolidation Chemotherapy

The standard of care for inoperable stage III NSCLC is concurrent chemoradiotherapy[1,2]; however, the role of consolidation chemotherapy remains controversial. Pemetrexed is a multitargeted antifolate with selective activity in non-squamous NSCLC.[3] Pemetrexed-platinum combinations can be administered at full systemic doses with concurrent TRT.[4] The PROCLAIM trial, presented by Senan et al, was initiated to determine if concurrent pemetrexed/cisplatin and TRT followed by consolidation pemetrexed would result in a survival advantage versus a commonly used chemoradiation regimen followed by a consolidation regimen of choice.[5]

Patients with previously untreated stage IIIA-IIIB non-squamous NSCLC were eligible for this phase III study. A total of 598 patients were randomized 1:1 to pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 IV plus concurrent TRT (66.0 Gy) every 21 days x 3 cycles followed by pemetrexed consolidation every 21 days x 4 cycles vs etoposide 50 mg/m^2 + cisplatin 50 mg/m^2 IV plus concurrent TRT (66.0 Gy) every 28 days x 2 cycles followed by 2 cycles of a consolidation chemotherapy of choice: cisplatin + etoposide, cisplatin + vinorelbine, or paclitaxel + carboplatin. The primary objective was overall survival (OS); secondary objectives included progression-free survival (PFS), objective response rate (ORR), and safety.

Baseline characteristics and radiotherapy delivered were well balanced between the 2 treatment arms. Median OS was 26.8 months for pemetrexed + cisplatin vs 25.0 months for etoposide + cisplatin (P = 0.831; **Figure 1**), and median PFS was 11.4 months for pemetrexed + cisplatin vs 9.8 months for etoposide + cisplatin (P = 0.130). The ORR was also similar between treatment groups (35.9% for pemetrexed + cisplatin vs 33% for etoposide + cisplatin; P = 0.458). The disease control rate (DCR) was slightly higher in the pemetrexed + cisplatin arm (80.7% vs 70.7%, P = 0.004).

Figure 1. Median Overall Survival for Pemetrexed + Cisplatin vs Etoposide + Cisplatin.



The safety analysis showed that 67% of pemetrexed + cisplatin subjects vs 79.4% of etoposide + cisplatin subjects experienced ≥ 1 drug-related grade 3-5 adverse event (AE; $P = 0.001$). The pemetrexed + cisplatin arm also had a lower incidence of grade 3-4 neutropenia/granulocytopenia vs the etoposide + cisplatin arm (24.4% vs 44.5%; $P < 0.001$). Rates of pneumonitis and esophagitis were similar between pemetrexed + cisplatin and etoposide + cisplatin treatment arms (1.8% vs 2.6% and 15.5% vs 20.6%, respectively). Although this trial did not demonstrate superiority in OS, which was the primary endpoint of the study, PFS trended in favor of pemetrexed + cisplatin, and the pemetrexed + cisplatin arm had a significantly lower incidence of drug-related grade 3-4 AEs. Pemetrexed + cisplatin and concurrent TRT followed by pemetrexed consolidation showed an acceptable safety profile and is an acceptable regimen to consider for the treatment of stage III non-squamous NSCLC.

Metastatic NSCLC – Non-Targeted Therapy

Cabozantinib, Erlotinib, or Cabozantinib + Erlotinib in *EGFR* Wild-Type NSCLC

Cabozantinib is a small molecule multi-targeted tyrosine kinase inhibitor (TKI), which is approved for progressive, metastatic, medullary thyroid cancer and has demonstrated single-agent activity in NSCLC in a phase II clinical trial.[6] This agent targets MET and VEGFR2, as well as other kinases including RET, ROS1, AXL, KIT, and TIE-2. Erlotinib, an EGFR TKI, is FDA-approved for second- and third-line treatment of advanced NSCLC, and demonstrated improved PFS and OS in unselected patients compared with placebo.[7] Cabozantinib in combination with erlotinib has demonstrated good tolerability.[8] Results of a phase II study, based on the rationale that erlotinib has modest activity in *EGFR* wild-type NSCLC and that cabozantinib alone or in combination with erlotinib may improve efficacy in *EGFR* wild-type NSCLC patients compared with erlotinib alone, were presented by Neal et

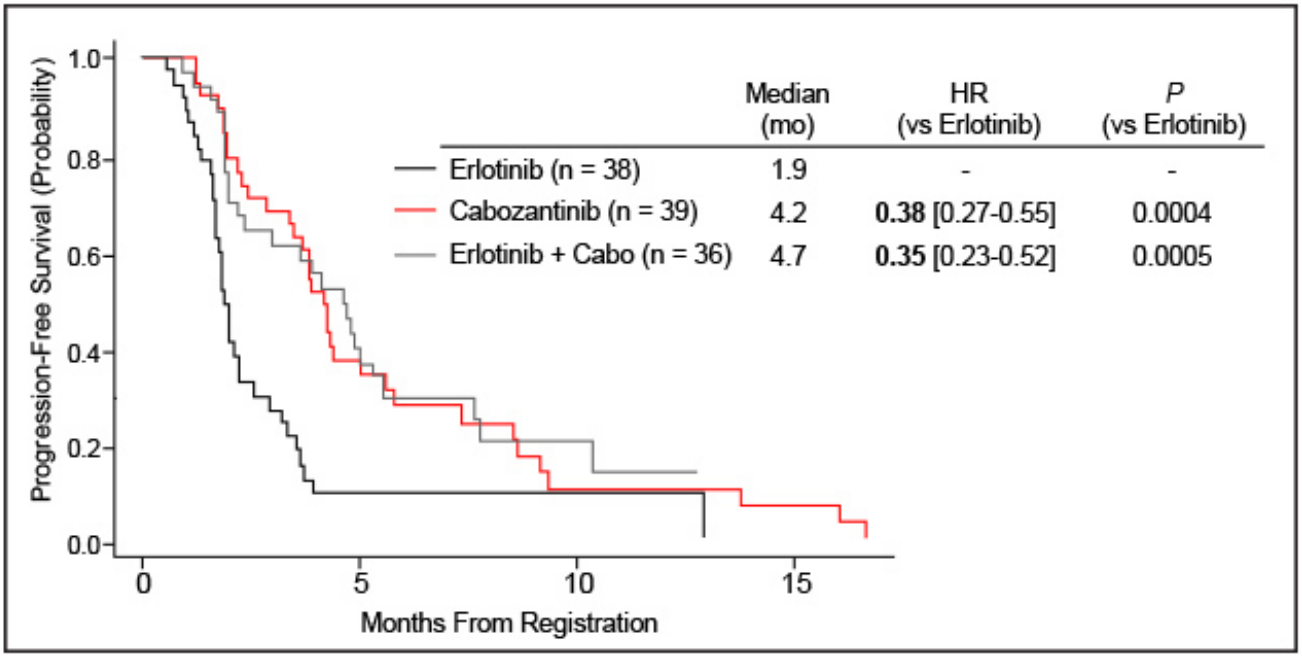
al.[9]

The ECOG-ACRIN E1512 trial included patients with metastatic non-squamous NSCLC who had received 1-2 prior lines of chemotherapy, had no *EGFR* mutation, no prior erlotinib therapy, and had tissue available for immunohistochemistry (IHC) analysis; previously treated brain metastases were allowed. Patients were randomized 1:1:1 to erlotinib 150 mg po daily, cabozantinib 60 mg po daily, or a combination of erlotinib 150 mg po daily + cabozantinib 40 mg po daily. Disease assessments were performed every 8 weeks. At the time of disease progression, patients on either single-arm treatment could cross over to combination therapy, and all patients were followed for survival. The primary endpoint of this study was PFS; secondary endpoints were OS, ORR, safety, and a MET outcomes interaction.

Of the 125 patients enrolled, 113 were eligible and treated (erlotinib n = 38; cabozantinib n = 39; erlotinib + cabozantinib n = 36), and 118 patients were included in the safety analysis. Patient characteristics were predominantly well balanced between arms, except for a higher rate of mediastinal metastases and a higher rate of previously treated brain metastases in both cabozantinib arms.

As shown in **Figure 2**, median PFS was significantly improved for patients on cabozantinib (4.2 months; $P = 0.0004$) and on erlotinib + cabozantinib (4.7 months; $P = 0.0005$), compared with erlotinib alone (1.9 months). Similarly, median OS was also significantly improved for cabozantinib and erlotinib + cabozatinib compared with erlotinib alone, although this data is not mature. Currently, follow-up is shorter on the combination arm, and the median OS for this arm may change with further analysis. Radiographic responses were infrequent among the 3 treatment arms, with partial response (PR) rates ranging from 3% to 14%. Stable disease (SD) was more common on either cabozantinib arm (42-45% vs 17%), whereas progressive disease (PD) was more common on the erlotinib arm (60% vs 23-24%).

Figure 2. Progression-Free Survival for Erlotinib vs Cabozantinib vs Erlotinib + Cabozantinib.



Of 115 tissue samples received for MET IHC testing, 100 passed quality control and were tested in 2 batches. Of these, 73% were membrane positive and 87% were cytoplasmic positive. Eighty-seven cases had both MET membrane and cytoplasmic staining. Patients treated with cabozantinib (arms combined) had a longer PFS than those treated with erlotinib regardless of MET status and MET status did not appear to be a predictor of outcome for any treatment group.

Generally, the AEs were consistent with the known safety profile of all 3 agents. The most commonly occurring treatment-related grade 3 AEs were diarrhea in the erlotinib + cabozantinib arm (27%), mucositis in the cabozantinib arm (10%), and hypertension in the cabozantinib arm (26%). Overall grade 3-5 AEs were more common in the cabozantinib and the erlotinib + cabozantinib arms.

In summary, cabozantinib, either alone or in combination with erlotinib, improved PFS and OS compared with single-agent erlotinib in *EGFR* wild-type NSCLC in the second- and third-line setting. There was some increase in toxicity with cabozantinib but overall the drug was well tolerated. A follow-up study is being planned.

Whole Brain Radiation Therapy Plus Radiosurgery in Brain Metastases

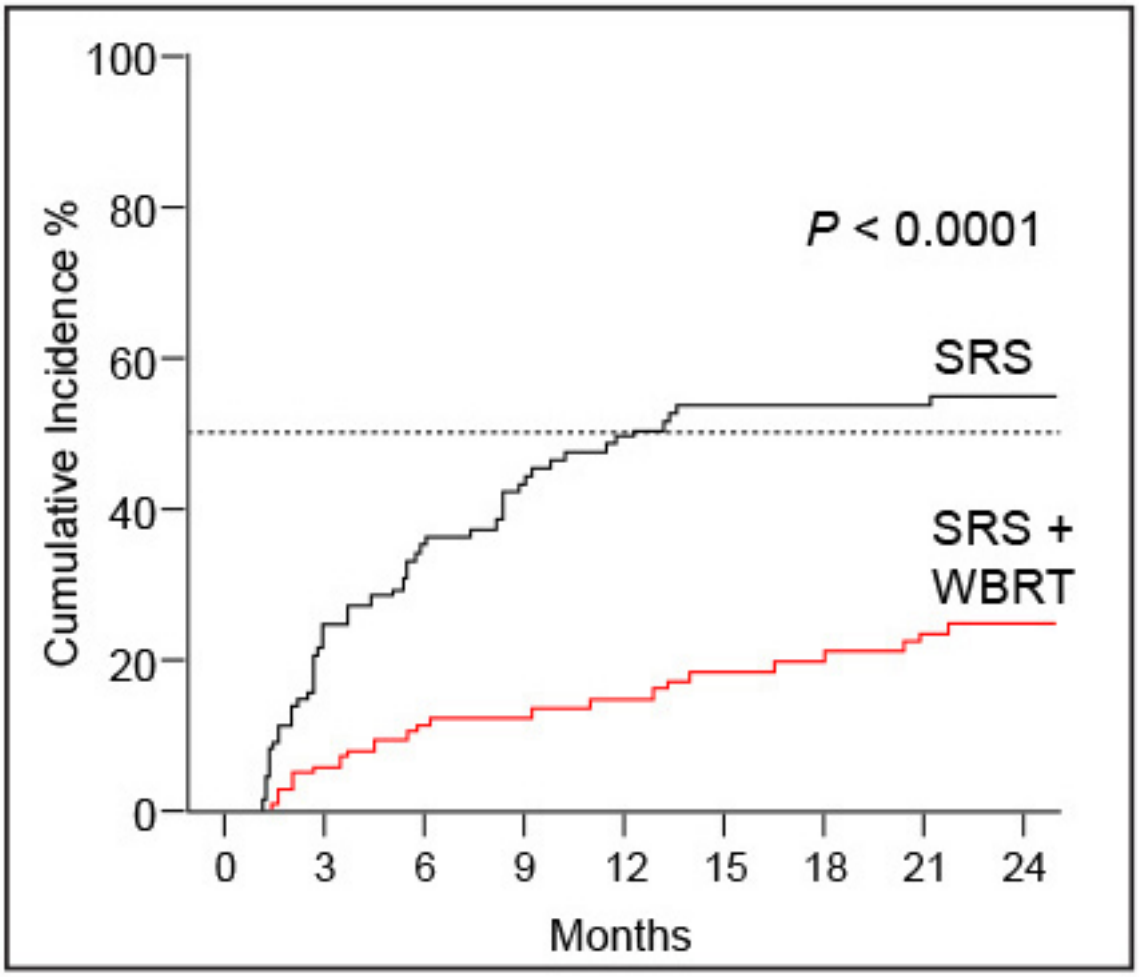
In the US alone, approximately 400,000 patients each year are diagnosed with brain metastases.[10] Although stereotactic radiosurgery (SRS) is an effective treatment for brain metastases, there is a high rate of development of new metastases with SRS alone and a significant proportion of patients have progression of the treated lesions. Adjuvant whole brain radiation therapy (WBRT) added to SRS improves local control from 70% to 90%, and adjuvant WBRT decreases new brain metastases from 50% to 30%.[11-13] Despite significant improvement in intracranial control, there is no improvement in survival with WBRT. Therefore, a clear understanding of the risks of WBRT, specifically cognitive function, becomes paramount in making treatment decisions and raises the question of whether tumor recurrence or WBRT has worse cognitive impact. A review of the literature of phase III trials revealed mixed results.[13-15] In a single-institution trial of SRS vs SRS + WBRT, SRS alone was associated with better cognitive function.[13] In contrast, a larger multicenter trial of SRS vs SRS + WBRT showed that tumor control was the most important factor,[14] which was confirmed by another study of palliative WBRT.[15] These discordant outcomes in the literature led to the design of the NCCTG N0574 trial, with results presented by Brown et al in the plenary session at ASCO 2015.[16]

The trial was designed for patients with 1-3 brain metastases (< 3 cm) to determine if cognitive progression 3 months post-SRS is less with SRS alone than with SRS + WBRT. The trial stratified patients by age, extra-cranial disease status, number of brain metastases, and institution, then randomized to SRS or SRS + WBRT. The dose of SRS was determined by lesion size, and patients randomized to the combination arm received a slightly lower dose of SRS. Assessments at baseline and over time included MRI scan, Functional Assessment of Cancer Therapy-Brain (FACT-Br), and a cognitive battery of tests that assesses multiple cognitive domains.

This multicenter trial enrolled 213 patients (2 ineligible and 3 canceled prior to receiving treatment) between 2002 and 2013, with a median follow-up of 7.2 months. Baseline characteristics were well distributed between both study arms without significant differences. The median age was 60 and approximately 70% of patients had a lung primary. Cognitive progression at 3 months was more frequent after SRS + WBRT vs SRS alone (91.7% vs 63.5%, respectively; $P = 0.0007$). This outcome persisted at 6 months for treatment with SRS + WBRT vs SRS alone (97.9% vs 77.8%, respectively; $P = 0.032$).

More specifically, there was more cognitive deterioration in the SRS + WBRT arm, which reached statistical significance at 3 months for immediate recall ($P = 0.004$), memory ($P = 0.002$), and verbal fluency ($P = 0.02$). WBRT did significantly improve intracranial control at 3 months, at 6 months, and beyond (**Figure 3**). However, despite the improvement in intracranial control, there was no difference between treatment arms in median OS (SRS 10.4 months vs SRS + WBRT 7.4 months; HR = 1.02). OS was not significantly different in any of the following subsets: age, systemic disease, and number of brain metastases. In all of these subsets, WBRT had no impact on survival. This may be explained by the fact that patients randomized to SRS alone underwent salvage therapy.

Figure 3. Time to Intracranial Progression for SRS vs SRS + WBRT.



More side effects were associated with WBRT, with specifically more alopecia ($P = 0.01$) and dermatitis ($P = 0.06$) at 6 weeks; however, there was no difference between study arms with respect to central nervous system (CNS) necrosis (SRS 6.8% vs SRS + WBRT 4.3%). Patient reported quality of life (QoL) for all measures were higher in the SRS arm, including overall QoL.

The overall results of this study indicate that, for patients with newly diagnosed brain metastases who are amenable to SRS, initial treatment with SRS alone and close monitoring to better preserve cognitive function and QoL are recommended compared to the use of WBRT.

LUX-Lung 8: Afatinib vs Erlotinib as Second-Line Therapy in Advanced Squamous Cell Carcinoma of the Lung

Squamous NSCLC (SQ) of the lung remains a disease with a high unmet clinical need, and treatment options for patients with disease progression after platinum-based chemotherapy are limited. Overexpression of *EGFR*, *ErbB* receptors, and dysregulation of their downstream pathways are implicated in SQ NSCLC pathobiology.[17-19] Erlotinib, a reversible *EGFR* TKI approved for second-line therapy in patients with SQ NSCLC, showed improved tolerability over docetaxel,[20] yet similar survival in second-line unselected and *EGFR* wild-type NSCLC.[21] Afatinib is an irreversible inhibitor of *EGFR*, HER2, and HER4, thus it was hypothesized that afatinib could confer additional benefit over erlotinib in patients with SQ NSCLC. Soria and colleagues presented results of an OS analysis from

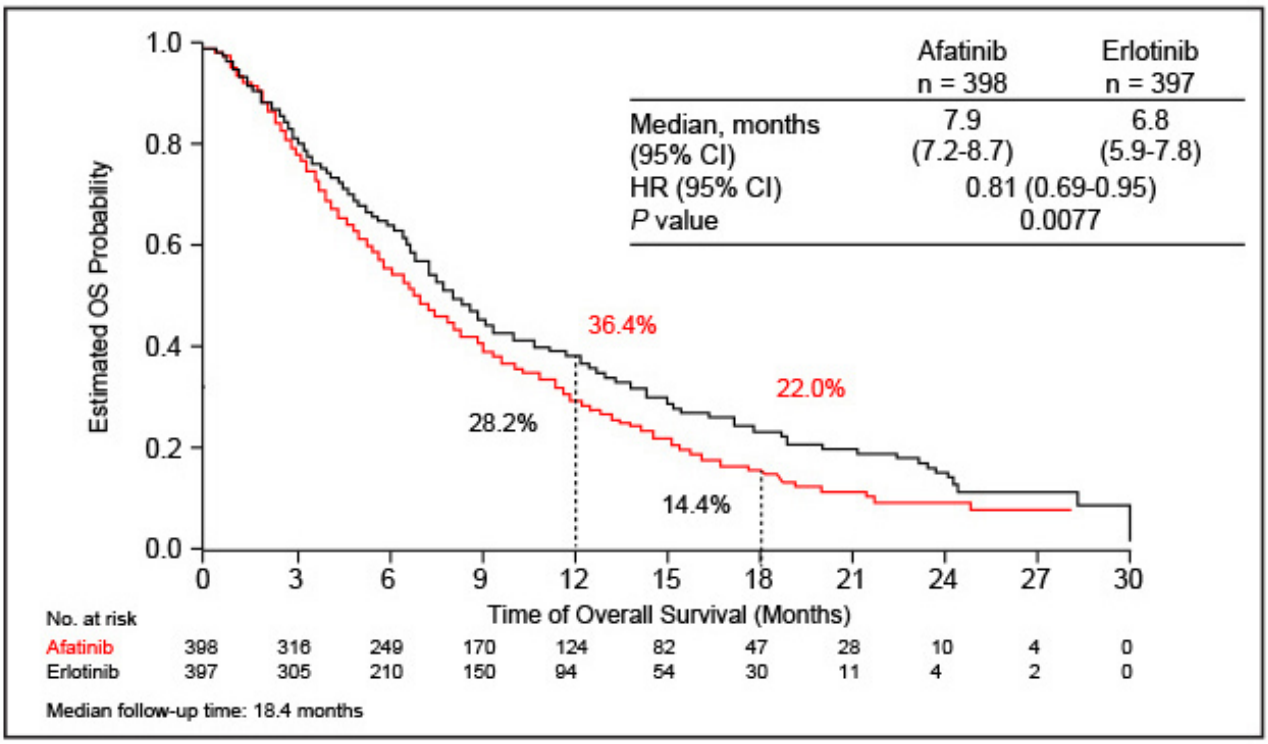
the global phase III LUX-Lung 8 trial.[22]

Patients with stage IIIB/IV SQ NSCLC who had progressed after ≥ 4 cycles of a first-line platinum doublet were randomized 1:1 to receive afatinib 40 mg/day or erlotinib 150 mg/day. The primary endpoint was PFS by independent review; secondary endpoints were OS, ORR, DCR, tumor shrinkage, patient reported outcomes (PRO), and safety. Recruitment for the trial occurred from March 2012 to January 2014. Results of the primary endpoint analysis in October 2013 were positive,[23] leading to a follow-up analysis in March 2015 (primary OS and updated PFS, ORR, DCR, PRO, and safety).

A total of 977 patients were assessed for eligibility and 795 were randomized to treatment, 398 to afatinib and 397 to erlotinib treatment. The majority of patients were male, current or former smokers, and all had squamous cell histology.

The primary analysis of OS showed that afatinib was significantly better than erlotinib, with a 19% reduced risk of death (median OS 7.9 vs 6.8 months; HR = 0.81; *P* = 0.0077), and a landmark analysis at 12 and 18 months showed that 8% more patients treated with afatinib were alive compared with erlotinib (**Figure 4**). Post-progression therapies were well balanced between treatment arms.

Figure 4. Overall Survival With Either Afatinib or Erlotinib.



Results of the updated PFS analysis were consistent with those of the earlier analysis, with a 19% reduced risk of progression or death for afatinib vs erlotinib (median 2.6 vs 1.9 months, respectively). Afatinib was also more favorable than erlotinib for ORR (5.5% vs 2.8%, respectively; *P* = 0.055), DCR (50.5% vs 39.5%, respectively; *P* = 0.002), and duration of response (DOR) (7.29 vs 3.71 months, respectively). Patient-reported outcomes, which focused on coughing, dyspnea, and pain, revealed that symptom improvement was better with afatinib than erlotinib with a longer time to deterioration.

Overall, AEs and serious adverse events (SAEs) were balanced between treatment arms. Afatinib was associated with more AEs leading to dose reduction, and 6 patients on afatinib vs 5 patients on erlotinib had drug-related fatal AEs. Afatinib had a higher incidence of drug-related grade 3/4

diarrhea (11% vs 3%) and grade 3 stomatitis (4% vs 0%) than erlotinib, whereas erlotinib had a higher incidence of grade 3 rash/acne (10% vs 6%) than afatinib.

Tumor genomic analysis is ongoing (FoundationOne™), with 238 patient samples analyzed. To date, *EGFR* aberrations are infrequent and balanced between treatment arms. There appears to be no correlation between *EGFR* aberrations and PFS or OS. Additional results are anticipated later in 2015.

In LUX-Lung 8, afatinib showed a significant reduction in death and disease progression compared with erlotinib. The authors argue that afatinib should be the TKI of choice in second-line treatment of patients with SQ NSCLC. The utility of *EGFR* TKIs in squamous cell lung cancer patients without *EGFR* mutations, however, remains an area of debate, especially in the era of the checkpoint inhibitors.

Immunotherapy

CheckMate 017: Nivolumab vs Docetaxel in Advanced Squamous NSCLC

Patients with SQ NSCLC have a worse prognosis and limited therapeutic options vs non-squamous NSCLC after frontline chemotherapy. Second-line therapy with docetaxel has modest clinical activity and is associated with significant toxicity. Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, has shown promising results in NSCLC and other cancer settings.[24] The results of CheckMate 017, a randomized, global, phase III study of nivolumab vs docetaxel in patients with advanced or metastatic SQ NSCLC after failure of platinum-based chemotherapy, were presented by Spigel et al[25] and simultaneously published in the *New England Journal of Medicine*.[26]

Patients with stage IIIb/IV SQ NSCLC and 1 prior platinum doublet-based chemotherapy (N = 272) were randomized 1:1 to receive nivolumab 3 mg/kg q2wk (n = 135) or docetaxel 75 mg/m^2 q3wk (n = 137) until disease progression or unacceptable toxicity. At enrollment, pre-treatment tumor samples were required for PD-L1 analysis. The primary endpoint was OS, and secondary endpoints included investigator-assessed ORR, PFS, efficacy by PD-L1 expression, QoL, and safety. There was 1 pre-planned interim analysis for OS. The boundary for declaring superiority for OS at this interim analysis was $P < 0.03$. At the time of the database lock (December 14, 2014), 199 deaths were reported (86% of deaths required for final analysis).

Baseline characteristics were evenly balanced between treatment arms, with the majority of patients being male, having an ECOG performance status of 1, and being current/former smokers. Eighty-three percent of patients had quantifiable PD-L1 expression, which was balanced between arms.

Results for the primary endpoint showed that nivolumab was superior to docetaxel with a 1-year OS rate of 42% vs 24%, respectively (**Figure 5**). This advantage for nivolumab was also true for the endpoints of ORR and PFS (**Table 1**). Median DOR was 8.4 months for docetaxel and has not been reached for nivolumab; median time to response was 2.2 months for nivolumab and 2.1 months for docetaxel. In the nivolumab arm, 28 patients were treated beyond RECIST-defined progression, and a non-conventional benefit was seen in 9 of those patients.

Figure 5. Overall Survival in Squamous NSCLC After Nivolumab or Docetaxel Treatment.

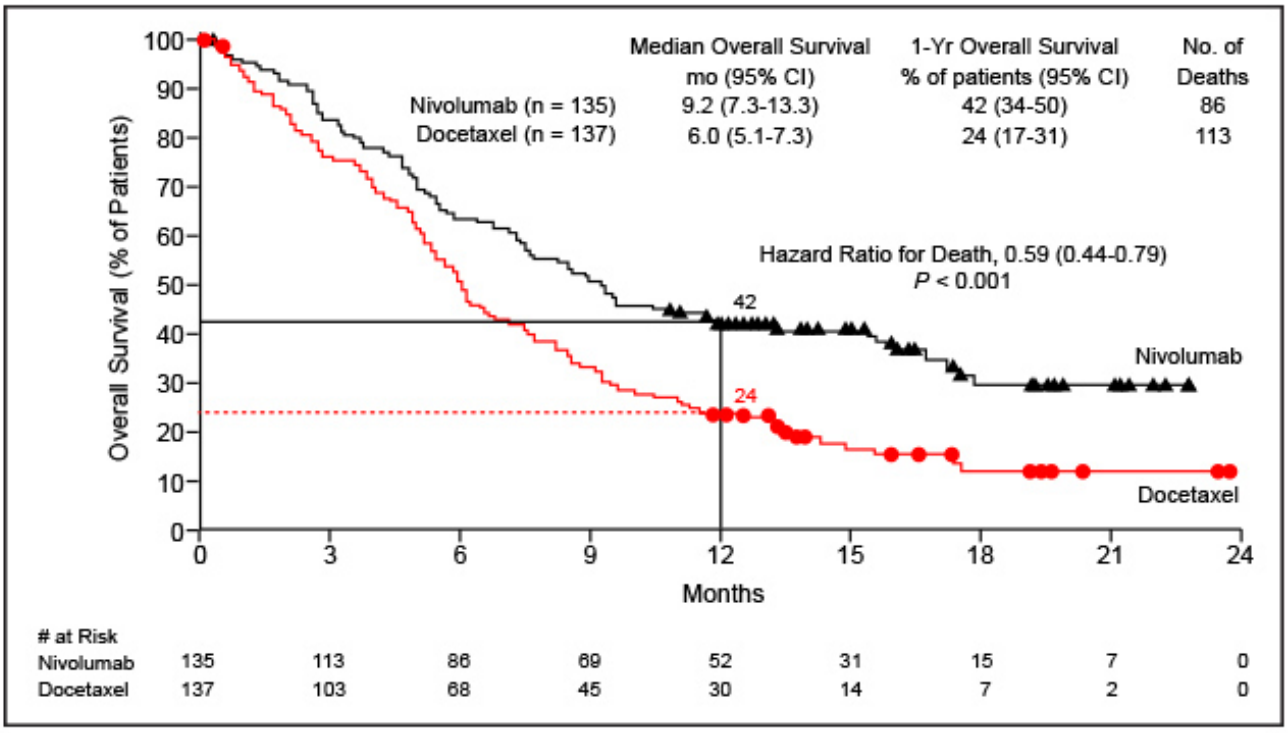


Table 1. Efficacy Results for Nivolumab vs Docetaxel in Squamous-NSCLC.

Efficacy Measure	Nivolumab n = 135	Docetaxel n = 137	HR, 95% CI	*P* Value
1-yr OS, % (95% CI)	42 (34-50)	24 (17-31)		
mOS, mo (95% CI)	9.2 (7.3-13.3)	6.0 (5.1-7.3)	0.59 (0.44-0.79)	0.00025
1-yr PFS, % (95% CI)	21 (14-28)	6.4 (3-12)		
mPFS, mo (95% CI)	3.5 (2.1-4.9)	2.8 (2.1-3.5)	0.63 (0.47-0.81)	0.0004
ORR, % (95% CI)	20 (14-28)	9 (5-15)	0.26* (1.3-3.5)	0.008
DOR, (range)	NR (2.9 to 21+)	8.4 (1.4+ to 15+)		

*Odds ratio.

mOS, median overall survival; CI, confidence interval; ORR, overall response rate; DOR, duration of response; mPFS, median progression-free survival.

Compared with 33% of docetaxel-treated patients who responded, 63% of nivolumab-treated patients who responded demonstrated an ongoing response. The survival benefit with nivolumab was independent of PD-L1 expression level, and nivolumab was superior to docetaxel for OS, regardless of the PD-L1 expression cutoff point in this patient population with squamous histology. The magnitude of this benefit was consistent across the various PD-L1 expression levels. The ORR was also independent of PD-L1 expression and consistently higher for nivolumab vs docetaxel.

Grade 3-5 treatment-related AEs occurred in 7% of nivolumab vs 57% of docetaxel patients with no

grade 5 events reported for nivolumab. Grade 3-5 treatment-related AEs leading to discontinuation were also lower in the nivolumab arm, 2% vs 7% in docetaxel patients. No nivolumab-related deaths occurred while 2 docetaxel-related deaths occurred. The most common AEs were fatigue, decreased appetite, and asthenia with nivolumab. Pneumonitis of any grade occurred in 5% of the nivolumab patients with 1% at a grade 3/4 level. There were no cases of pneumonitis in the docetaxel arm.

In summary, nivolumab demonstrated a significant survival benefit versus standard-of-care docetaxel in SQ NSCLC patients as second-line therapy. Nivolumab also demonstrated superiority over docetaxel across all secondary endpoints. The benefit of nivolumab was independent of PD-L1 expression. The safety profile of nivolumab was favorable and consistent with prior studies. The recent FDA approval of nivolumab for the treatment of SQ NSCLC adds to the armamentarium of clinicians treating patients with SQ NSCLC.

CheckMate 057: Nivolumab vs Docetaxel in Advanced Non-Squamous NSCLC

Treatment options for patients with advanced non-squamous NSCLC who progress after platinum-based doublet chemotherapy are limited. Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, has demonstrated durable anti-tumor activity and a manageable safety profile across NSCLC histologies as well as OS benefit in a phase III study of advanced SQ NSCLC.[26] CheckMate 057 is a randomized, global phase III study that sought to evaluate the efficacy and safety of nivolumab vs docetaxel in patients with advanced non-squamous NSCLC after failure of platinum-based doublet chemotherapy, the results of which were presented by Paz-Ares et al.[27]

A total of 582 patients with stage IIIb/IV non-squamous NSCLC were randomized to nivolumab 3 mg/kg IV q2wk (n = 292) or doxetaxel 75 mg/m^2 IV q3wk (n = 290) until disease progression or discontinuation due to toxicity/other reasons. The primary endpoint was OS; secondary endpoints were investigator-assessed ORR, PFS, efficacy by PD-L1 expression, QoL, and safety.

Baseline characteristics were well balanced between treatment arms, with the majority of patients being current/former smokers and having received 1 prior systemic regimen. Tumor PD-L1 expression was quantifiable in 455/582 (78%) patients, and baseline PD-L1 expression was well balanced between treatment arms.

The 1-year OS rate was 51% for nivolumab vs 39% for docetaxel, which corresponded to a median OS of 12.2 vs 9.5 months, respectively (HR = 0.73, *P* = 0.0015; **Figure 6**). Similarly, rates for ORR, DOR, and PFS were favorable for nivolumab compared with docetaxel (**Table 2**).

Figure 6. Overall Survival in Non-Squamous NSCLC After Nivolumab or Docetaxel Treatment.

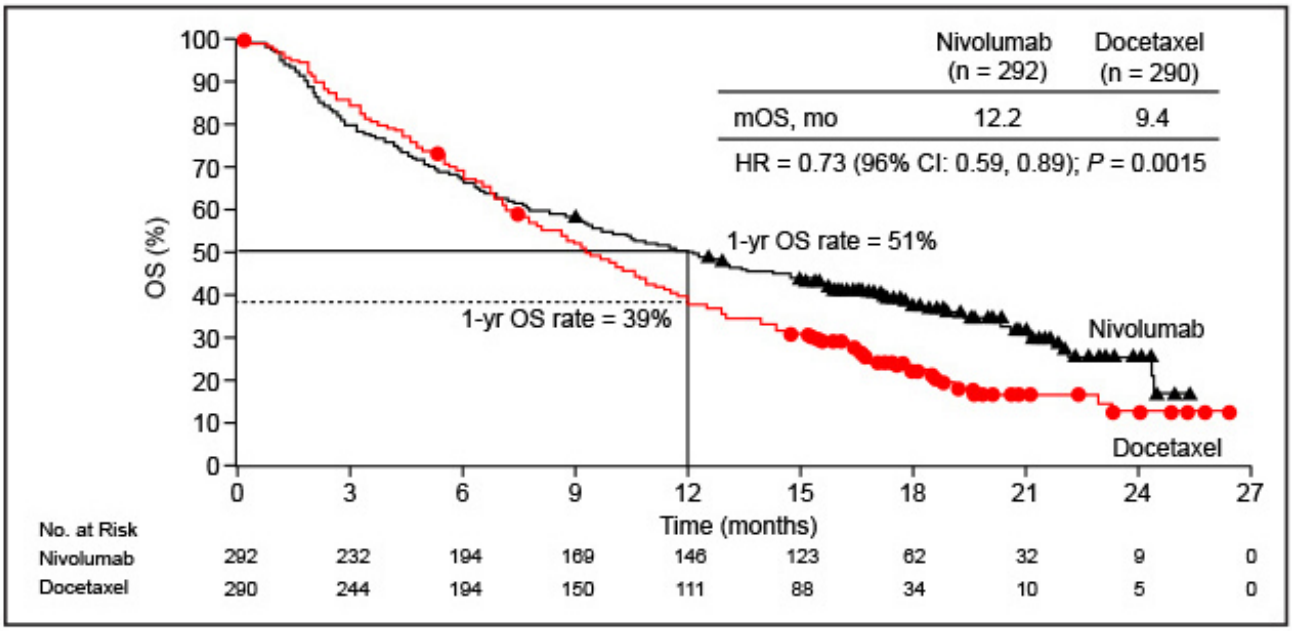


Table 2. Outcomes for Nivolumab or Docetaxel Therapy in Non-Squamous NSCLC.

	Nivolumab n = 292	Docetaxel n = 290	Odds Ratio/HR (95% CI)	*P* Value
ORR	19%	12%	1.72 (1.1-2.6)*	0.0246
DOR, months	17.2	5.6	NR	NR
Median PFS	2.3	4.2	0.92 (0.77-1.11)†	0.3932

ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; NR, not reported.
*Odds ratio.
†Hazard ratio (HR).

A survival benefit with nivolumab treatment was observed in predefined subgroups based on age, gender, and baseline ECOG performance status, but not in those who were never smokers or who harbored EGFR mutations in their tumor.

Unlike SQ NSCLC, PD-L1+ status was a significant predictive factor for OS outcome in nivolumab-treated patients with non-squamous NSCLC. Patients treated with nivolumab had higher OS than those treated with docetaxel using predefined cutoffs for PD-L1 expression of ≥ 1%, 5%, and 10% (**Table 3**). However, PD-L1 negative status was not associated with differences in survival between the 2 treatment arms. The magnitude of benefit for PD-L1 expressors was evident for both OS and PFS. By contrast, this benefit was not seen in PD-L1 non-expressors. Interaction *P* values confirmed interaction between PD-L1 expression in tumor and treatment effect, with all values being highly significant. PD-L1 expression was also a predictor of ORR, with response rates significantly higher for nivolumab vs docetaxel in PD-L1 expressors (≥ 1%: 31% vs 12%; ≥ 5%: 36% vs 13%; ≥ 10%: 37% vs 13%).

Table 3. Overall Survival by PD-L1 Expression Level.

PD-L1 expression level	Nivolumab (mo)	Docetaxel (mo)	HR (95% CI)
≥ 1%	17.2	9.0	0.59 (0.43-0.82)
≥ 5%	18.2	8.1	0.43 (0.30-0.63)
≥ 10%	19.4	8.0	0.40 (0.26-0.59)
≤ 1%	10.4	10.1	0.90 (0.66-1.24)
≤ 5%	9.7	10.1	1.01 (0.77-1.34)
≤ 10%	9.9	10.3	1.00 (0.76-1.31)

mo, months; HR, hazard ratio; CI, confidence interval.

Overall, the incidence of severity of AEs was higher for docetaxel than for nivolumab. For grade 3-4 AEs, the incidence was higher for docetaxel compared with nivolumab for treatment-related AEs (54% vs 10%, respectively), for treatment-related SAEs (18% vs 5%, respectively), and for treatment-related AEs leading to discontinuation (7% vs 4%, respectively). The most common AEs in the nivolumab arm were fatigue, nausea, and decreased appetite.

In summary, nivolumab significantly improved OS and ORR and demonstrated a favorable safety profile vs docetaxel in previously treated patients with advanced non-squamous NSCLC. Moreover, PD-L1 expression was predictive of benefit with nivolumab in this trial, starting at the expression level of 1%, with ORR of nivolumab almost 3 times that of docetaxel in PD-L1 expressors using the 1% cut-off.

POPLAR: Atezolizumab (MPDL3280A) vs Docetaxel in Second- and Third-Line NSCLC

Atezolizumab (MPDL3280A) is a humanized anti-PD-L1 antibody that inhibits the binding of PD-L1 to PD-1 and B7.1. This checkpoint blockade can restore anti-tumor T-cell activity, enhance T-cell priming, and restore immune recognition of tumors. Targeting PD-L1 rather than PD-1 leaves the PD-L2/PD-1 interaction intact, thereby potentially preserving peripheral immune homeostasis. Atezolizumab has demonstrated promising response rates in NSCLC that correlated with PD-L1 expression on tumor cells (TC) and/or tumor-infiltrating immune cells (IC).[28,29] Results of an interim analysis of the POPLAR trial, which compared atezolizumab with docetaxel as second- and third-line (2L/3L) therapy in NSCLC, were presented by Spira et al.[30]

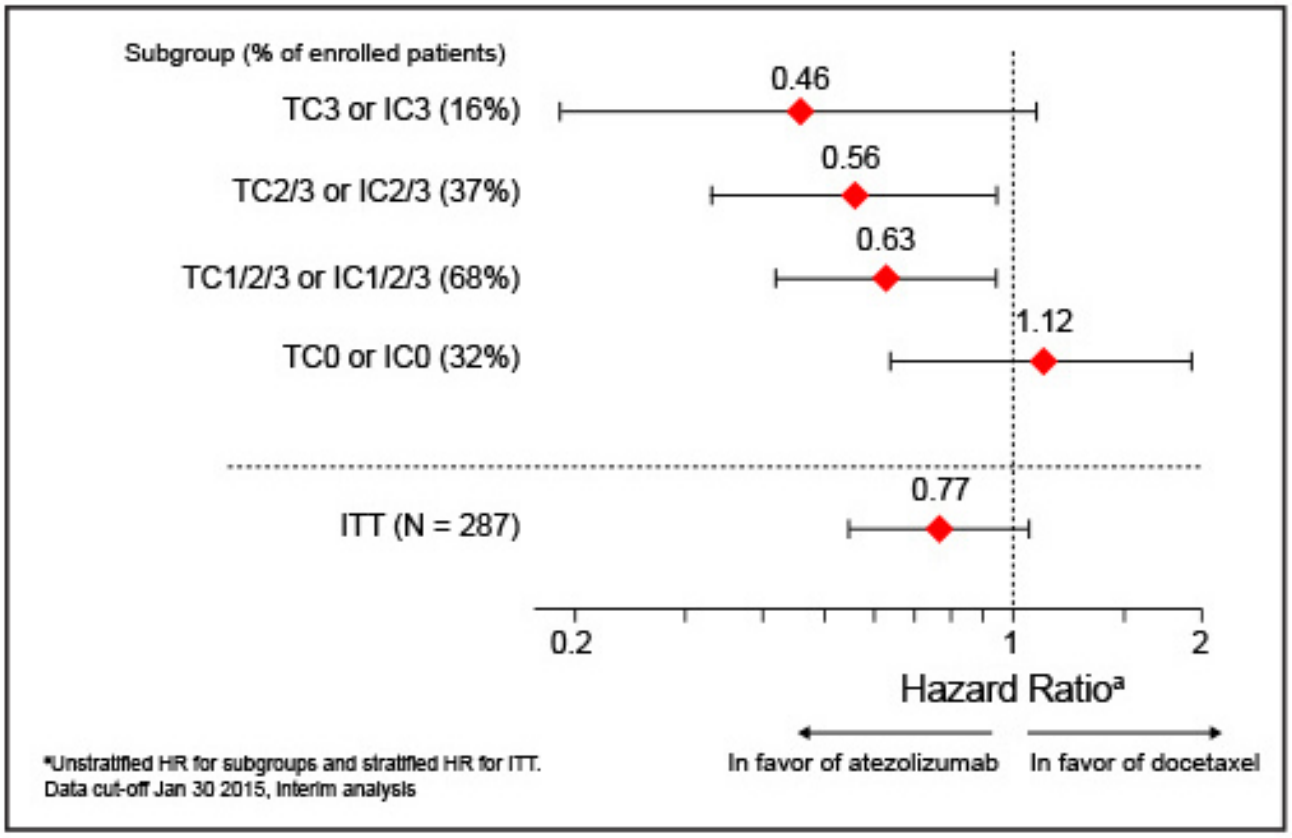
PD-L1 expression on TC and IC is a potential predictive biomarker for efficacy of atezolizumab in NSCLC. The SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC. Previous phase I data with atezolizumab demonstrated a correlation between efficacy of atezolizumab and PD-L1 expression utilizing the same assay. A scoring system was developed from tumor specimens required for the study and staining them for PD-L1. Patients were scored as TC0, 1, 2, or 3 and IC0, 1, 2, or 3. In patients with the highest level of PD-L1 expression, there was little overlap between the 2 independent groups; however, there was more overlap at the intermediate level (≤ 30%).

In the phase II POPLAR study, 287 patients with 2L/3L NSCLC who had disease progression on prior platinum chemotherapy were randomized 1:1 to receive atezolizumab 1200 mg IV q3wk until loss of clinical benefit or docetaxel 75 mg/m^2 IV q3wk until disease progression. The arms were stratified by PD-L1 IC expression, histology, and the number of prior chemotherapy regimens. The primary

endpoint was OS in PD-L1 selected and ITT populations; secondary endpoints were PFS, ORR, DOR, and safety for selected and ITT populations. The interim analysis presented was based on 153 events with a minimum follow-up of 10 months. Baseline characteristics were well balanced between treatment arms, with 12% more women in the docetaxel arm, which would have theoretically biased outcomes in favor of the docetaxel arm.

In this interim analysis, the OS HR in the ITT population was 0.77 in favor of atezolizumab. As shown in **Figure 7**, increasing PD-L1 expression was associated with improved OS for patients treated with atezolizumab (TC3 or IC3 HR 0.46; TC2/3 or IC2/3 HR 0.56; TC1/2/3 or IC1/2/3 HR 0.63), whereas there was essentially no difference between treatment arms for TC0/IC0 (HR 1.12).

Figure 7. Overall Survival by PD-L1 Expression Level After Atezolizumab Treatment.



In the ITT population, the median OS for the atezolizumab arm was 11.4 months vs 9.5 months in the docetaxel arm. Progression-free survival by PD-L1 expression subgroup showed a similar trend in favor of atezolizumab (TC3 or IC3 HR 0.57; TC2/3 or IC2/3 HR 0.70; TC1/2/3 or IC1/2/3), with little difference between treatment arms for TC0/IC0 (HR 1.17). There was no difference between treatment arms with respect to ITT ORR (atezolizumab 15% vs docetaxel 15%); however, for patients in the TC3 or IC3 subgroups, ORR was atezolizumab 38% vs docetaxel 13%. The median DOR was not reached for the atezolizumab arm and was 7.8 months for the docetaxel arm.

Despite a longer median treatment duration for atezolizumab vs docetaxel (3.6 vs 2.1 months), substantially fewer treatment-related grade 3-4 AEs occurred in atezolizumab- vs docetaxel-treated patients (12% vs 39%, respectively). Overall, the AE profiles of each drug were consistent with previous studies. Common AEs associated with atezolizumab were decreased appetite, dyspnea, and nausea. Immune-mediated AEs in response to atezolizumab included increased AST or ALT (4% each), 2% pneumonitis, 1% colitis, and 1% hepatitis.

The results of the POPLAR trial demonstrated a pattern of improved survival that correlated with increasing PD-L1 expression in favor of atezolizumab, as well as a favorable safety profile of atezolizumab.

KEYNOTE-021: Pembrolizumab Plus Ipilimumab as Second-Line Therapy for Advanced NSCLC

Pembrolizumab is a humanized monoclonal antibody targeted against PD-1 that prevents PD-1 from binding to its ligands, PD-L1 and PD-L2. Pembrolizumab has demonstrated activity against a wide variety of tumor types and as monotherapy for previously treated and treatment-naïve advanced NSCLC as demonstrated in the KEYNOTE-001 trial.[31] The rationale for combining anti-PD-1 and anti-CTLA-4 antibodies is their complementary mechanisms of action, with PD-1 functioning at the effector stage and CTLA-4 functioning at the activation stage of the anticancer immune response. Preclinical data have demonstrated synergistic anticancer activity in multiple models.[32,33] The combination of nivolumab plus ipilimumab has shown significant efficacy and manageable toxicity in the treatment of advanced melanoma[34,35] and NSCLC.[36] Dr Patnaik and colleagues presented interim results from the phase I KEYNOTE-021 study evaluating pembrolizumab plus ipilimumab (Pem/Ipi) in patients with recurrent NSCLC.[37]

Patients were enrolled using a 3+3 dose escalation design. The 4 planned dosing levels were as follows:

- Pembrolizumab 10 mg/kg q3w + ipilimumab 1 mg/kg q3w (Pem-10/Ipi-1)
- Pembrolizumab 10 mg/kg q3w + ipilimumab 3 mg/kg q3w (Pem-10/Ipi-3)
- Pembrolizumab 10 mg/kg q3w + ipilimumab 0.3 mg/kg q3w (Pem-10/Ipi-0.3)
- Pembrolizumab 2 mg/kg q3w + ipilimumab 1 mg/kg q3w (Pem-2/Ipi-1)

Patients aged 18-75 years with stage IIIB/IV NSCLC who had received ≥ 1 prior therapy, including ≥ 1 platinum doublet, received Pem/Ipi q3wk for 4 cycles, followed by maintenance pembrolizumab q3wk up to 2 years. Patients were eligible for the study with any PD-L1, *EGFR*, or ALK status; however, they were not permitted to receive prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 therapy. Based on emerging data from a study of NSCLC with nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3wk that showed a high incidence of grade 3 TEAEs,[36] the protocol was amended to treat subsequent patients with reduced doses of 2 mg/kg for pembrolizumab and 1 mg/kg for ipilimumab. The primary endpoint was safety and incidence of dose-limiting toxicities (DLTs) in the first 3 weeks of dosing; secondary endpoints were overall safety and tolerability and ORR. Response was assessed every 6 weeks per RECIST v1.1.

A total of 18 patients were enrolled. At the time of protocol amendment, there were no DLTs in the 3 patients treated with Pem-10/Ipi-1 or in 3 patients treated with Pem-10/Ipi-3. Following protocol amendment, no DLTs occurred in 12 patients treated with Pem-2/Ipi-1. Median time on therapy has been 20 weeks, mean number of doses is 5, and 8 patients have discontinued therapy, while treatment is ongoing in 10 patients and median followup duration is 31 weeks.

The most common grade AEs were fatigue (39%), decreased appetite (22%), myalgia, pruritus, and rash (17% each). Adrenal insufficiency, drug eruption, and maculopapular rash occurred as grade 3 AEs. There were no grade 4 events or treatment-related deaths and 2 treatment-related discontinuations.

Best ORR was 39% (CR in 1 patient, PR in 6 patients), the DCR was 83%, and SD ≥ 6 weeks occurred in 44% of patients (**Table 4**). Regarding change from baseline in tumor size, 71% of patients showed a decrease in the target lesion burden. Median PFS has not been reached and all responses are ongoing as of the data cutoff of March 31, 2015.

Table 4. Best Overall Response by Investigator Assessment.

Efficacy Measure	Pem 10 mg/kg + IPI 1 or 3 mg/kg (n = 6)	Pem 2 mg/kg + IPI 1 mg/kg (n = 12)	Total (N = 18)
ORR, n (%) [95% CI]	3 (50) [12-88]	4 (33) [10-65]	7 (39) [17-64]
DCR, n (%) [95% CI]	6 (100) [54-100]	9 (75) [43-94]	15 (83) [59-96]
Best overall response, n (%)			
CR	1 (17)	0 (0)	1 (6)
PR	2 (33)	4 (33)	6 (33)
SD ≥ 6 weeks	3 (50)	5 (42)	8 (44)
PD	0 (0)	3 (25)	3 (17)

Pem, pembrolizumab; IPI, ipilimumab; ORR, overall response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Though results are preliminary, the investigators concluded that pembrolizumab 2 mg/kg + ipilimumab 1 mg/kg has a manageable toxicity profile and shows preliminary evidence of robust durable anti-tumor activity in patients with advanced NSCLC. This combination will be further characterized in a currently enrolling dose expansion cohort of 32 patients

Targeting *EGFR* Mutations

AURA: AZD9291 as First-Line Treatment in *EGFR*+ Advanced NSCLC

For patients with advanced NSCLC whose tumors bear an *EGFR* mutation, *EGFR* TKIs are preferred over chemotherapy as first-line therapy. However, regardless of the extent of initial response to *EGFR* TKIs, patients almost universally develop resistance to therapy. In approximately 60% of cases, this resistance is mediated by the *EGFR* T790M mutation.[38] AZD9291 is an irreversible *EGFR* TKI with activity against the sensitizing *EGFR* mutations and the T790 resistance mutation.[39] In patients with acquired resistance to *EGFR* TKIs that bear a secondary T790M mutation, AZD9291 (80 mg/day) has demonstrated promising response rates and a median PFS of 13.5 months by independent review.[40] In preclinical models, AZD9291 considerably delayed the emergence of resistance in cells with the *EGFR* exon 19 deletion compared with other EGFR TKIs.[41] Ramalingam and colleagues presented results from the expansion cohorts of the AURA study of AZD9291 as first-line therapy for *EGFR* mutation-positive advanced NSCLC.[42]

In the phase I AURA study, sequential cohorts received AZD9291 at doses ranging from 20 mg to 240 mg, with predefined expansion cohorts at the 80 mg/day and 160 mg/day dose levels. The expansion cohorts enrolled patients with treatment-naïve advanced NSCLC containing an *EGFR* mutation. *EGFR* mutation status of these patients was tested locally at the treating site and/or confirmed by central testing. Salient eligibility criteria included the presence of measurable disease, WHO performance status of 0 or 1, and acceptable organ function.

In total, 60 patients received AZD9291 (80 mg, n = 30; 160 mg, n = 30), and all patients were included in the evaluable for response population. The median duration of RECIST follow-up was 9.6

months. Currently, 48 patients continue to receive treatment (80 mg, n = 23; 160 mg,n = 25) with 6 being treated beyond progression. Baseline demographics and disease characteristics were similar between the 2 cohorts, however; there were more patients with T790M mutation in the 80 mg cohort (4) vs 1 in the 160 mg cohort.

Overall, the incidence of any grade ≥ 3 AE was 38%, with a higher incidence in the 160 mg cohort compared with the 80 mg cohort (43% vs 33%, respectively). The incidence of AEs leading to dose reduction were also higher in the 160 mg cohort than in the 80 mg cohort (43% vs 10%, respectively), and AEs leading to discontinuation occurred in 4 patients total. Grade ≥ 3 TEAEs occurred in 15% of patients overall (20% in 160 mg vs 10% in 80 mg); 3 patients discontinued treatment due to drug-related toxicity. The most common all-causality AEs in both groups were rash, diarrhea, dry skin, and stomatitis.

Disease outcomes, including ORR of 73%, are shown in **Table 5**. The data are too immature to estimate median PFS; however, 81% of patients remain alive and progression-free at 9 months.

Table 5. Efficacy Outcomes of AURA Study.

Efficacy Measure	AZD9291 80 mg n = 30	AZD9291 160 mg n = 30	Total N = 60
ORR, % (95% CI)	63 (44-80)	83 (65-94)	73 (60-84)
DCR, % (95% CI)	93 (78-99)	100 (88-100)	97 (89-100)
Best objective response			
CR	0	1	1
PR	19	24	43
SD	9	5	14
PD	2	0	2
PFS, % (95% CI) 12 months	73 (51-87)	NC	72 (55-84)
DOR, % (95% CI) 12 months	79 (46-93)	NC	75 (48-89)
Maximum DOR	13.8 (ongoing)	9.7 (ongoing)	

ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease; DOR, duration of response, NC, not calculable.

In conclusion, AZD9291 demonstrates encouraging clinical activity and a manageable safety profile in treatment-naive patients with *EGFR* mutation positive advanced NSCLC. The ongoing phase III FLAURA study compares AZD9291 80 mg qd with erlotinib or gefitinib.

TIGER-X: Rociletinib in T790M+ NSCLC

Third-generation *EGFR* TKIs are important because they can overcome the T790M resistance mutation while sparing the wild-type toxicity. Rociletinib (CO-1686) is an oral third-generation *EGFR* TKI that inhibits activity against both activating mutations and T790M and spares wild-type *EGFR*.[43] Rociletinib was studied initially in single-arm studies in mutant *EGFR* NSCLC patients with acquired resistance to TKI therapies.[44] Sequist et al presented the updated results of TIGER-X, the initial phase I/II trial of rociletinib.[45]

For the overall phase I/II study, patients had activating *EGFR*-mutant NSCLC, prior treatment with *EGFR*-directed therapy, and acquired resistance to a prior *EGFR* TKI. All patients underwent a biopsy

at study entry. For the phase II portion, the biopsy was required to demonstrate T790M+ and patients must have progressed on a prior *EGFR* TKI. Plasma testing was conducted for *EGFR* mutations (L858R, del 19, and T790M) with digital PCR followed by flow cytometry (BEAMing test).

In the expansion (phase II) study, patients received rociletinib 500 mg bid, 625 mg bid, 750 mg bid, or 1000 mg bid. To date, 456 patients have been treated with rociletinib (safety analysis); 243 patients have centrally confirmed tissue-based T790M+ status (efficacy analysis ORR); 188 patients have both plasma and tissue T790M results available (comparative group); and 147 patients are plasma T790M+ (efficacy analysis ORR). Median age was 63 years, 66% female, 82% had immediate prior TKI therapy, and 41% had history of CNS disease.

Best response to rociletinib by tissue and plasma T790M+ patients is shown in **Table 6**. Because the study is ongoing, PFS estimates are immature. As of April 27, 2015, only 35% of patients had reached a PFS endpoint event, with a median PFS of 8 months for all patients and 10.3 months for patients with baseline CNS disease, but those numbers are expected to change with maturity of the data. Using tissue as a reference, there was 81% positive agreement between tissue and plasma for T790M mutation and 87% positive agreement for activating mutations. It should be noted that 20 patients who underwent a tumor biopsy had inadequate tissue for analysis, 12 of whom were T790M+; in the end, both plasma and tissue detected about the same number of T790M+ patients from the cohort. In terms of acquired resistance, there has been no evidence to date of C797S in 20 acquired resistance patients studied. Emergence of C797S has been reported as a potential resistance mechanism following treatment with AZD9291.

Table 6. Best Response to Rociletinib by T790 Status.

	ORR (%)	DCR (%)
Tissue T790M+ Patients		
500 mg (n = 48)	60	90
625 mg (n = 114)	54	84
750 mg (n = 77)	46	82
1000 mg (n = 4)	75	100
Total (n = 243)	53	85
Plasma T790M+ Patients		
500 mg (n = 30)	57	80
625 mg (n = 49)	55	84
750 mg (n = 65)	49	82
1000 mg (n = 3)	67	100
Total (n = 147)	53	82
T790M- Patients (13/35)	37	NR

ORR, objective response rate; DCR, disease control rate; NR, not reported.

Rociletinib is generally well tolerated, with the primary AE being hyperglycemia, followed by diarrhea, nausea, and fatigue. Compared with the higher dose levels, the 500 mg dosage level demonstrated an improved safety profile, with a decreased incidence of the common toxicities and a grade 3-4 hyperglycemia rate of 17% (vs 24%, 36%, and 33% for 625, 750, and 1000 mg levels,

respectively). Hyperglycemia resulting from rociletinib treatment is caused by iatrogenic insulin resistance, mediated by a rociletinib metabolite (M502) that inhibits IGF1-R/IR. A monitoring and treatment algorithm has been implemented in trial protocols, which has been successful in reducing grade ≥ 3 hyperglycemia from 22% to 5%.

In conclusion, rociletinib demonstrates good activity and is well tolerated at the recommended dose of 500 mg bid in *EGFR*-mutant NSCLC patients with PD after immediate prior TKI therapy. Hyperglycemia can be managed effectively with oral agents.

AZD3759 for NSCLC With Brain Metastasis: Preclinical and Clinical Evidence

EGFR TKIs are the standard of care of patients with *EGFR*-mutant NSCLC. However, brain metastasis are not uncommon in these patients, but current TKIs have limited penetration crossing the blood brain barrier (BBB), resulting in an unmet need for TKIs with better BBB penetration. AZD3759 is an oral *EGFR* TKI specifically designed to penetrate the BBB for the treatment of brain metastasis and leptomeningeal metastasis. Kim and colleagues presented preclinical findings and preliminary results of a phase I study of AZD3759 in *EGFR*-mutant NSCLC patients with brain metastasis.[46]

Preclinically, AZD3759 was assessed in both in vitro and in vivo assays, including CNS penetration in rats, mice, and monkeys. Blood and brain tissues were collected for pharmacokinetics, histopathology, and phosphorylated *EGFR* expression analyses. In vivo evaluation of BBB penetration showed that AZD3759 is not a substrate of P-glycoprotein or the breast cancer resistance protein (BCRP) efflux transporters, and shows significantly better penetration crossing the BBB than other approved *EGFR* TKIs. Estimated Kpuu, brain value (the ratio of unbound brain concentration/unbound plasma concentration) for humans, based on PET scan data in monkeys, is close to 1.0.

For anti-tumor efficacy, a brain metastasis mouse model was established by intra-carotid artery injection of luciferase-labeled PC-9 cells. Better tumor regression and prolongation of animal survival were observed with AZD3759 treatment in this brain metastasis mouse model compared to gefitinib or erlotinib.

A phase I dose escalation trial is ongoing in patients with *EGFR*-mutant NSCLC who received ≥ 1 line of *EGFR* TKI and 1 line of chemotherapy prior to enrollment. To date, 12 patients (10 females, 2 males; range 41-68 years) have been enrolled in the AZD3759 50 mg bid (n = 5) and 100 mg bid (n = 7) cohorts.

Of 4 patients showing tumor shrinkage, 3 of these were CNS tumors, thus preliminary evidence of intracranial tumor shrinkage was observed in this study. Grade 1-2 AEs of skin rash, diarrhea, constipation, and fatigue were consistent with wild-type *EGFR* inhibition. To date, there have been no dose-limiting toxicities and the maximum tolerated dose has not been reached.

Promising preclinical and clinical evidence are supportive of AZD3759 as an *EGFR* TKI with good BBB penetration and the potential to treat *EGFR*-mutant NSCLC patients with brain metastasis.

Targeting *BRAF* Mutations

Dabrafenib + Trametinib in *BRAF*-Mutated NSCLC

A small percentage (1.7-2%) of NSCLC patients harbor *BRAF* V600E mutations in their tumors, which tend to show aggressive histologic features.[47] Patients whose tumors carry this mutation tend to demonstrate less favorable outcomes with platinum-based chemotherapy.[47,48] Dabrafenib inhibits BRAF V600E kinase, whereas trametinib inhibits downstream MEK signaling.[49-52] The rationale for

combining dabrafenib and trametinib was based on preclinical models, which showed that the combination of these 2 agents was more effective than either agent alone.[50] In the monotherapy phase of this study (Cohort A), dabrafenib monotherapy demonstrated clinically meaningful anti-tumor activity with durable objective responses in *BRAF*-mutated V600E NSCLC.[53] Dr Bruce Johnson presented results of Cohort B (combination therapy dabrafenib + trametinib) of the phase II BRF113928 study on behalf of Planchard et al.[54]

Forty patients with stage IV *BRAF* V600E mutant advanced NSCLC who had received 1-3 treatment lines (including ≥ 1 platinum-based chemotherapy) were treated with dabrafenib 150 mg bid + trametinib 2 mg qd. The study occurred in 2 stages: stage 1 (n = 20), with a response necessary in ≥ 6 patients in order to progress to stage 2 (n = 20). The primary endpoint of Cohort B was investigator-assessed ORR; secondary endpoints were PFS, DOR, OS, safety, tolerability, and population pharmacokinetics. The efficacy population (≥ second-line) defined as having had either 2 post-baseline scans or had discontinued study treatment, consisted of 24 patients, and the safety population (all treated) consisted of 33 patients.

At the time of the interim analysis, 27 patients remained on treatment and 6 had discontinued study treatment, 4 from disease progression and 2 from an AE. Median age was 66 years, 21 were female, 12 were male, and the majority of patients (58%) had undergone one prior systemic regimen for metastatic disease.

Twenty-four patients were evaluable for efficacy, with an ORR of 63% (**Table 7**). Median DOR was not reached. The majority of patients remain on treatment, with a median time on study treatment of 108 days (range 1-244 days). An independent review of best confirmed response for ≥ second-line patients revealed a nearly identical ORR and DCR (68% and 86%, respectively).

Table 7. Best Response Rates for Dabrafenib + Trametinib in *BRAF*-Mutated NSCLC.

Best Response	≥ Second-Line (N = 24) n (%)
CR	0
PR	15 (63)
SD*	6 (25)
PD	2 (8)
NE	1 (4)
ORR (confirmed CR + PR) [95% CI]	63% [40.6, 81.2]
DCR (CR + PR + SD) [95% CI]	88% [67.6, 97.3]

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, non-evaluable; ORR, overall response rate; DCR, disease control rate; CI, confidence interval.
*Met SD ≥ 12 weeks.

The most common AEs in ≥ 20% of patients were pyrexia, diarrhea, nausea, vomiting, decreased appetite, asthenia, cough, peripheral edema, and rash (mostly grade 1 or 2). Grade 3 AEs occurred in 39% of patients and grade 4-5 AEs occurred in 3% of patients. Fourteen (42%) patients experienced a serious AE and there was 1 fatal serious AE.

In summary, the combination dabrafenib + trametinib demonstrated clinically meaningful anti-tumor

activity with a higher ORR when compared indirectly with dabrafenib monotherapy (Cohort A) (63% vs 32%, respectively) in *BRAF* V600E-mutant NSCLC. Cohort B has completed recruitment with 59 patients, and a third cohort investigating dabrafenib + trametinib in previously untreated patients with *BRAF* V600E-mutant NSCLC is currently recruiting.

Other Mutations

Stage IV Lung Adenocarcinoma With *MET* Exon 14 Skipping: Response to Crizotinib and Cabozantinib

Mutations at the splice acceptor or donor sites of exon 14 can lead to exon skipping and thus an aberrant *MET* protein which cannot bind the Cbl E3 ligase. In preclinical models *MET* gene exon 14 skipping mutations are oncogenic.[55] These mutations are relatively uncommon, comprising just 4% of the NSCLC cases.[56] Paik and colleagues presented responses to the MET inhibitors crizotinib and cabozantinib in patients with stage IV lung adenocarcinomas harboring mutations leading to *MET* exon 14 skipping.[57]

Patients with stage IV lung adenocarcinomas harboring *MET* exon 14 splice site mutations (N = 8) or a deletion of Y1003 in exon 14 (N = 1) were identified through next-generation sequencing of 341 oncogenes and tumor suppressor genes. An analysis of MET expression was performed by IHC on archival FFPE tissue. Exon 14 skipping was confirmed by nanoString analysis of mRNA. Radiographic response was assessed using RECIST v1.1 and PERCIST criteria.

To date, 3 patients have been treated with crizotinib and 1 patient has been treated with cabozantinib (NCT01639508). Three of 4 patients (75%) developed a PR to treatment (all with crizotinib), and the remaining patient had SD by RECIST v1.1 (with cabozantinib), with PET imaging demonstrating a complete PERCIST response (**Table 8**).

Table 8. Response to MET Inhibitors.

MET Exon 14 Splice Site Mutation	MET Amplification Ratio	Prior Treatment	MET Therapy (3rd-line)	Response (%)	DOR (mos)
MET c 3028G>C	6	Docetaxel, gemcitabine	Cabozantinib	SD 0% CR (PERCIST)	6.5 (PD)
MET c.3024_3028delAGAAGGTATATT	Not amplified	Carboplatin + pemetrexed + bevacizumab; abraxane	Crizotinib	PR ~ 30%	3.6*
MET p.V1001_F1007del (c.3001_3021delGTA GACTACCGAGCTAC TTTT)	3.8	Cisplatin + pemetrexed + bevacizumab; gemcitabine	Crizotinib	PR ~ 31%	4.6 (PD)
MET c 3028G>T	Not amplified	Docetaxel; pemetrexed	Crizotinib	PR ~ 47%	6.2+

*Pneumonia-unrelated death.
Amp, amplification; DOR, duration of response; SD, stable disease; CR, complete response; PR, partial response; mos, months; PD, progressive disease.

MET exon 14 skipping is a novel oncogenic event that predicts response to MET inhibitors. This appears to be a substantially better predictor of response than either protein expression or gene amplification. The authors propose that patients with these splice site mutations should be treated on a clinical trial of a MET inhibitor.

Summary

The 2015 ASCO Annual Meeting provided an excellent venue for the dissemination of important clinical trial information on the treatment of NSCLC that may impact clinical practice positively.

In locoregionally advanced NSCLC, the combination of pemetrexed+cisplatin and concurrent TRT showed favorable results in PFS and an acceptable safety profile, although it did not demonstrate superiority to etoposide + cisplatin in OS.

Highlights of non-targeted therapy in metastatic NSCLC included treatment of *EGFR* wild-type NSCLC with cabozantinib alone or in combination with erlotinib, with findings that combination therapy or cabozantinib alone improved PFS and OS as second- or third-line therapy compared with single-agent erlotinib. A study that assessed the combination of WBRT plus SRS in patients with newly diagnosed brain metastases concluded that initial treatment with SRS alone and close monitoring are recommended to minimize cognitive changes. Results of the LUX-Lung 8 study, which compared afatinib with erlotinib in patients with stage IIIb/IV SQ NSCLC, predominantly without *EGFR* mutations, affirmed afatinib as an option for second-line therapy in this patient population.

Some of the most promising and exciting data came in the area of immunotherapy with encouraging results for treatment with nivolumab, atezolizumab, and pembrolizumab. Trials of nivolumab showed an OS benefit versus docetaxel in both non-squamous and squamous NSCLC. In the CheckMate 017 trial, nivolumab demonstrated a 41% OS improvement versus docetaxel in patients with squamous NSCLC. In the CheckMate 057 trial, the OS benefit with nivolumab was 27% in patients with non-squamous NSCLC. The standard of care of squamous NSCLC has already changed as a result of the approval of nivolumab for use in this population and may be changing for non-squamous NSCLC as well. Reports from 2 other trials provided evidence that atezolizumab (MPDL3280A) provides a survival benefit as second-line therapy and this effect is correlated with PD-L1 expression. A phase I study of pembrolizumab + ipilimumab showed preliminary evidence of robust anti-tumor activity in patients with advanced NSCLC.

For patients with *EGFR*-mutant NSCLC, particularly those with resistance caused by the secondary T790M mutation, the third-generation *EGFR* TKIs AZD9291 and rociletinib (CO-1686) have continued to demonstrate encouraging results. Preliminary efficacy and safety data from first-line expansion of the AURA phase I study showed impressive results for AZD9291 in treatment-naïve advanced NSCLC patients with *EGFR* mutation. In patients with *EGFR*-mutant NSCLC with progressive disease after immediate prior TKI therapy, rociletinib demonstrated compelling activity and was well tolerated at a dose of 500 mg bid. Another *EGFR* inhibitor, AZD3759, showed promising preclinical and clinical outcomes, including good BBB penetration and the potential to treat the *EGFR*-mutant NSCLC patient with brain metastasis.

Regarding other specific mutations, a single-arm phase II study of the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib showed promising efficacy and a tolerable safety profile in patients with *BRAF* V600E-mutant NSCLC. *MET* exon 14 skipping is the next largest actionable oncogenic subgroup in lung adenocarcinomas after *EGFR* mutations and *ALK* fusions. A small trial showed favorable response to crizotinib and cabozantinib in late-stage lung adenocarcinoma with *MET* exon 14 skipping mutations.

The data presented at the 2015 ASCO Annual Meeting provided new therapeutic options as well as additional evidence for new clinical trials. The 2016 ASCO Annual Meeting will be held June 3-7, 2016 in Chicago, Illinois.

References

1. Bezjak A, Temin S, Franklin G, et al. Definitive and adjuvant radiotherapy in locally advanced non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. *J Clin Oncol*. May 5, 2015. Epub ahead of print.
2. Vansteenkiste J, DeRuysscher D, Eberhardt WE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(suppl 6):89-98.
3. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in non-squamous non-small cell lung cancer. *J Thoracic Oncol*. 2011;6(1):64-70.
4. Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. *Lung Cancer*. 2015;87(3):232-240.
5. Senan S, Brade AM, Wang L, et al. Final overall survival (OS) results of the phase III PROCLAIM trial: pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced non-squamous non-small cell lung cancer (nsNSCLC). *J Clin Oncol*. 2015;33(15 suppl). Abstract 7506.
6. Hellerstedt BA, Edelman G, Vogelzang NJ, et al. Activity of cabozantinib (XL184) in metastatic NSCLC: Results from a phase II randomized discontinuation trial (RDT). *J Clin Oncol*. 2012;30(15 suppl). Abstract 7514.
7. Shepherd FA, Rodrigues PJ, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353(2):123-132.
8. Wakelee HA, Gettinger SN, Engelman JA, et al. A phase Ib/II study of XL184 (BMS 907351) with and without erlotinib (E) in patients (pts) with non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2010;28(suppl 15). Abstract 3017.
9. Neal JW, Dahlberg SE, Wakelee HA, et al. Cabozantinib (C), erlotinib (E) or the combination (E+C) as second- or third-line therapy in patients with EGFR wild-type (wt) non-small cell lung cancer (NSCLC): a randomized phase 2 trial of the ECOG-ACRIN Cancer Research Group (E1512). *J Clin Oncol*. 2015;33(15 suppl). Abstract 8003.
10. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007-2011. *Neuro Oncol*. 2014;16(suppl 4):iv1-iv63.
11. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. 2011;29(2):134-141.
12. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483-2491.
13. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037-1044.
14. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiation Oncology Biol Phys*. 2007;68(5):1388-1395.
15. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol*. 2007;25(10):1260-1266.
16. Brown PD, Asher AL, Ballman KV, et al. NCCTG N0574 (Alliance): a phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. *J Clin Oncol*. 2015;33(15 suppl). Abstract LBA4.
17. Heinmoller P, Gross C, Beyser K, et al. HER2 status in non-small cell lung cancer: results from patient screening for enrollment to a phase II study of herceptin. *Clin Cancer Res*. 2003;9(14):5239-5243.
18. Ugocsai K, Mandoky L, Tiszlavicz L, Molnar J. Investigation of HER2 overexpression in non-

small cell lung cancer. *Anticancer Res*. 2005;25(4):3061-3066.
19. Cancer Genome Atlas Res Network. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012;489:519-525.
20. Lee CK, Brown C, Gralla RJ. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst*. 2013;105(9):595-605.
21. Li N, Yang L, Ou W, Zhang L, Zhang SL, Wang SY. Meta-analysis of EGFR tyrosine kinase inhibitors compared with chemotherapy as second-line treatment in pretreated advanced non-small cell lung cancer. *PLoS One*. 2014;9(7):e102777.
22. Soria JC, Felip E, Cobo M, et al. Afatinib (A) vs erlotinib (E) as second-line therapy of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following platinum-based chemotherapy: overall survival (OS) analysis from the global phase III trial LUX-Lung 8 (LL8). *J Clin Oncol*. 2015;33(15 suppl). Abstract 8002.
23. Goss G, Felip E, Cobo M, et al. A randomized, open-label, phase III trial of afatinib vs erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung following first-Line platinum-based chemotherapy: Lux-Lung 8. *ESMO 2014 Congress*. Abstract 12220.
24. Brahmer JR, Hammers H, Lipson EJ. Nivolumab: targeting PD-1 to bolster antitumor immunity. *Future Oncol*. 2015;11(9):1307-1326.
25. Spigel DR, Reckamp KL, Rizvi NA, et al. A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2015;33(15 suppl). Abstract 8009.
26. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. May 31, 2015. Epub ahead of print.
27. Paz-Ares, Horn L, Borghaei H, et al. Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2015;33(15 suppl). Abstract LBA109.
28. Horn L, Spigel DR, Gettinger SN, et al. Clinical activity, safety and predictive biomarkers of the engineered antibody MPDL3280A (anti-PDL1) in non-small cell lung cancer (NSCLC): update from a phase Ia study. *J Clin Oncol*. 2015;33(15 suppl). Abstract 8029.
29. Liu SV, Powderly JD, Camidge DR, et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with platinum-based doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2015;33(15 suppl). Abstract 8030.
30. Spira AI, Park K, Mazieres J, et al. Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in 2L/3L NSCLC (POPLAR). *J Clin Oncol*. 2015;33(15 suppl). Abstract 8010.
31. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028.
32. Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A*. 2010;107(9):4275-4280.
33. Selby MJ, Engelhardt JJ, Quigley M, et al. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. *Cancer Immunol Res*. 2013;1(1):32-42.
34. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122-133.
35. Postow MA, Chesney J, Pavlick AC,et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006-2017.
36. Antonia SJ, Gettinger SN, Chow LQ, et al. Nivolumab and ipilimumab in first-line NSCLC: Interim phase 1 results. *J Clin Oncol*. 2014;32(suppl 15). Abstract 8023.
37. Patnaik A, Socinski MA, Gubens MA, et al. Phase 1 study of pembrolizumab (pembro; MK-3475) plus ipilimumab (IPI) as second-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohort D. *J Clin Oncol*. 2015;33(15 suppl). Abstract 8011.
38. Yu HA, Arcila ME, Rekhtman N, 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):2240-2247.
39. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*.

2014;4(9):1046-1061.
40. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372(18):1689-1699.
41. Eberlein C, Ratcliffe L, O'Brien L, et al. Investigating resistance to AZD9291. AACR Annual Meeting 2014. Abstract 1722.
42. Ramalingam SS, Yang JCH, Lee CK, et al. AZD9291, a mutant-selective EGFR inhibitor, as first-line treatment for EGFR mutation-positive advanced non-small cell lung cancer (NSCLC): Results from a phase 1 expansion cohort. *J Clin Oncol*. 2015;33(15 suppl). Abstract 8000.
43. Walter AO, Sjin RT, Haringsma HJ, et al. Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC. *Cancer Discov*. 2013;3 (12):1404-1415.
44. Sequist LV, Soria JC, Goldman JW, et al. Rociletinib in EGFR-mutated non-small-cell lung cancer. *N Engl J Med*. 2015;372(18):1700-1709.
45. Sequist LV, Goldman JW, Wakelee HA, et al. Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts). *J Clin Oncol*. 2015;33(15 suppl). Abstract 8001.
46. Kim DW, Yang JCH, Chen K, et al. AZD3759, an EGFR inhibitor with blood brain barrier (BBB) penetration for the treatment of non-small cell lung cancer (NSCLC) with brain metastasis (BM): preclinical evidence and clinical cases. *J Clin Oncol*. 2015;33(15 suppl). Abstract 8016.
47. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998-2006.
48. Cardarela S, Ogino A, Nishino M, et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. *Clin Cancer Res*. 2013;19(16):4532-4540.
49. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417(6892):949-954.
50. Platz A, Egyhazi S, Ringborg U, Hansson J. Human cutaneous melanoma; a review of NRAS and BRAF mutation frequencies in relation to histogenetic subclass and body site. *Mol Oncol*. 2008;1(4):395-405.
51. Long GV, Strovakoyskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. 2014;371(20):1877-1888.
52. Gilmartin AG, Bleam MR, Groy A, et al. GSK1120212 (JTP-74057) is an inhibitor of MEK activity and activation with favorable pharmacokinetic properties for sustained in vivo pathway inhibition. *Clin Cancer Res*. 2011;17(5):989-1000.
53. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): a multicenter, open-label, phase II trial (BFR113928). *Ann Oncol*. 2014;25(suppl 4). Abstract LBA38_PR.
54. Planchard D, Groen HJM, Kim TM, 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 with BRAFV600E mutated metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2015;33(15 suppl).Abstract 8006.
55. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. *Cancer Res*. 2006;66(1):283-289.
56. The Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511(7511):543-550.
57. Paik PK, Drilon AE, Yu HA, et al. Response to crizotinib and cabozantinib in stage IV lung adenocarcinoma patients with mutations that cause MET exon 14 skipping. *J Clin Oncol*. 2015;33(15 suppl). Abstract 8021.

Lung Cancer: Conference Highlights from the 2015 ASCO Annual Meeting