2016 NCCN CONGRESS SERIES™
National Comprehensive Cancer Network

LIVE WEBINARS

Sequencing Targeted Therapy for Patients with Metastatic Non-Small Cell Lung Cancer

Presented by:

David S. Ettinger, MD, FACP, FCCP
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

July 20, 2016

Moderated by Shannon K. Ryan
NCCN, Conferences and Meetings Department

Supporters

- This activity is supported by educational grants from Ariad, AstraZeneca, Ethicon, Foundation Medicine, Genentech, Lilly, Novartis Pharmaceuticals Corporation, and Pfizer.
- This activity is supported by independent educational grants from Abbvie and Merck.

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- If you are participating with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity.
- Lists can be sent to **education@nccn.org** and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.
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Accreditation Information

Intended Audience

This educational program is designed to meet the educational needs of oncologists, nurses, pharmacists, and other health care professionals who manage patients with non-small cell lung cancer (NSCLC).

Learning Objectives

- Following this program, participants should be able to:
- Review recent updates for targeted therapies in management of patients with metastatic NSCLC.
- Appropriately sequence targeted therapies in treatment of patients with metastatic NSCLC.

Accreditation Information

Physicians

National Comprehensive Cancer Network (NCCN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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Kristina M. Gregory, RN, MSN, OCN, is our lead nurse planner for this educational activity.

Accreditation Information

Pharmacists

Pharmacy Educational Objective: *After completing this activity, the participant should be able to:*

- Provide accurate and appropriate counsel as part of the treatment team.

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Type of Activity: Knowledge

UAN: 0836-0000-16-074-L01-P

Credit Designation: National Comprehensive Cancer Network designates this continuing education activity for 1.0 contact hour (0.10 CEUs) of continuing education credit in states that recognize ACPE accredited providers.

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Accreditation Information

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All credit claiming must be done online through NCCN's continuing education portal at **http://education.nccn.org/node/79137.**

Should you not receive an e-mail within 5 days, please contact us at **education@nccn.org.**

Accreditation Information

- It is required by the ACCME that all educational activities are designed to change participant ***competence, performance, or patient outcomes.***
- To meet this requirement, NCCN asks that all participants complete the outcomes measures described below:
  - The post-test and evaluation as indicated in e-mail you will receive within 3-5 business days of the conclusion of this activity. This is required to receive credits or your certificate of completion. You must be registered in advance to receive credits or certificate. Certificates will be generated automatically upon successful completion of this step.
    - There will be a separate WebEx evaluation at the conclusion of this program, which is optional and does not go to NCCN.
  - The follow-up post test (to be sent 30 days after the activity has ended to demonstrate an increase in participant competence)
- NCCN greatly appreciates your compliance with completing the aforementioned post-test and surveys. All of these measures will be available by logging into your account at **http://education.nccn.org**. Reminder e-mails will be sent to the participants via e-mail. If you have any questions or concerns, please e-mail **education@nccn.org**.

Disclosures

The ACCME/ANCC/ACPE defines “conflict of interest” as when an individual has an opportunity to affect CE content about products or services of a commercial interest with which he/she has a financial relationship.

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All faculty for this continuing education activity are competent in the subject matter and qualified by experience, training, and/or preparation to the tasks and methods of delivery.

Faculty Disclosures

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Faculty Disclosures

The faculty listed below have disclosed the following relevant financial relationships:

David S. Ettinger, MD
ARIAD Pharmaceuticals, Inc.: Scientific Advisor
Boehringer Ingelheim GmbH: Scientific Advisor
Bristol-Myers Squibb Company: Consulting Fees, Honoraria
Eli Lilly and Company: Scientific Advisor
EMD Serono: Scientific Advisor
Genentech, Inc.: Scientific Advisor
Golden Biotechnology Corporation: Grant/Research Support
Helsinn Pharmaceutical: Scientific Advisor

NCCN Staff Disclosures

NCCN Staff Disclosures
The activity planning staff listed below has no relevant financial relationships to disclose:

Ann Gianola, MA; Mark Geisler; Kristina M. Gregory, RN, MSN, OCN; Kristin Kline Hasson; Rose Joyce; Joan S. McClure, MS; Diane McPherson; Melanie Moletzsky; **Deborah Moonan, RN, BSN; Lisa Perfidio; Liz Rieder; Shannon K. Ryan; Kathy Smith; Jennifer McCann Weckesser**

The NCCN clinical information team listed below, who have reviewed content, has no relevant financial relationships to disclose:

Ellen Erkess; Kristina M. Gregory, RN, MSN, OCN; Miranda Hughes, PhD

Faculty Biography

David S. Ettinger, MD, is the Alex Grass Professor of Oncology and Professor of Medicine, Otolaryngology-Head and Neck Surgery, Obstetrics and Gynecology, and Radiation Oncology and Molecular Radiation Sciences at The Johns Hopkins University School of Medicine.

Dr. Ettinger received his medical degree from the University of Louisville School of Medicine. His postgraduate training included an internship at Albany Medical Center Hospital. He also completed fellowships at the Mayo Graduate School of Medicine in Rochester, Minnesota and The Johns Hopkins University School of Medicine. Dr. Ettinger is board-certified in internal medicine with a subspecialty in medical oncology.

Dr. Ettinger has served as a consultant for dozens of organizations. He is widely published and has authored or co-authored more than 200 articles for journals such as *The New England Journal of Medicine*, *Journal of Clinical Oncology*, and *Cancer*. He is a Fellow of the American College of Physicians and American College of Chest Physicians and a member of the American Society of Clinical Oncology, American Society for Therapeutic Radiology and Oncology, American Association for Cancer Research, Multinational Association of Supportive Care in Cancer, and the International Association for the Study of Lung Cancer.

Dr. Ettinger is a member of the NCCN Lung Cancer Screening Panel and Chair of the NCCN Non-Small Cell Lung Cancer/ Malignant Pleural Mesothelioma/Thymomas and Thymic Carcinomas Panel, Occult Primary Cancers Panel, and Antiemesis Panel. He is a member of the editorial board for the *Journal of the National Comprehensive Cancer Network* (*JNCCN*) and serves as a member of several committees and advisory boards for the NCCN Oncology Research Program. Dr. Ettinger also serves on the NCCN Guidelines Steering Committee, the NCCN International Program Steering Committee, the NCCN Educational Programs Advisory Committee, and the NCCN Board of Directors.

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Sequencing Targeted Therapy for Patients with Metastatic Non-Small Cell Lung Cancer

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Learning Objectives

- Review recent updates for targeted therapies in management of patients with metastatic NSCLC.
- Appropriately sequence targeted therapies in treatment of patients with metastatic NSCLC.

Learning Objectives

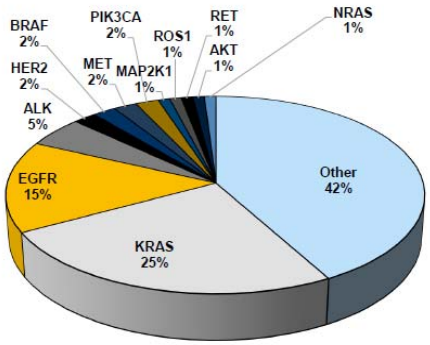
- Review of 1st Generation (erlotinib, gefitinib), 2nd Generation (afatinib) and 3rd Generation (osimertinib, etc.) EGFR TKIs
- Understand when to sequence the EGFR TKIs (acquired resistance to treatment with 1st Generation EGFR TKIs
- Review inhibitors of ALK – crizotinib, ceritinib, alectinib
- ASP8273, a new 3rd Generation EGFR TKI
- Other studies with EGFR TKIs

CME Disclosure

This talk includes information on several non-FDA approved drugs for completeness sake:

- Brigatinib
- PF - 06463922

Non-Small Cell Lung Cancer Is Increasingly Treated According to Driver Mutation



- Activating mutations in EGFR found in approximately 15% of NSCLC (adenocarcinoma predominant)
  - Twice as common in East Asians
- Standard of care in front-line *EGFR*-mutant NSCLC is a first- or second-generation EGFR TKI

Blakely CM, Bivona TG. *Cancer Discov* 2012;2:872-5

Targeting EGFR

Common Adverse Events Following Use of EGFR TKIs

Adverse event, %	Afatinib (n=229)[1]		Erlotinib (n=84)[2]		Gefitinib (n=1126)[3]	
	Any grade	Grade 3+	Any grade	Grade 3+	Any grade	Grade 3+
Diarrhea	96	15	62	5	29	3
Rash	90	16	85	14	--	--
Paronychia	58	11	14	0	--	--
Stomatitis/mucositis*	71	9	18	1	7	0.3
Pruritus	21	0	16	0	--	--
Dry skin	31	0	21	1	--	--
Skin reactions†	--	--	--	--	47	2
Nail disorders††	--	--	--	--	5	0.1

† Includes acne, acne pustular, dermatitis, dermatitis acneiform, dermatitis exfoliative, drug eruption, dry skin, erythema, exfoliative rash, folliculitis, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin toxicity, xeroderma
†† Includes ingrowing nail, nail bed infection, nail disorder, nail infection, onychoclasis, onycholysis, paronychia

*Only includes mucositis for erlotinib

1. Afatinib package insert; 2. Erlotinib package insert; 3. Gefitinib package insert.

Incidence of Interstitial Lung Disease (ILD) with EGFR TKIs

Therapy	ILD incidence, %
Erlotinib[1]	1.1
Gefitinib[2]	1.3
Afatinib[3]	1.5

1. Erlotinib package insert; 2. Gefitinib package insert; 3. Afatinib package insert.

Randomized Studies of First Line EGFR TKI in Patients with EGFR Mutations

Author	Study	Agent	N (EGFRm+)	RR	Median PFS (months)	Median OS (months)
Mok et al.	IPASS	Gef	261	71.2% vs 47.3%	9.8 vs 6.4	21.6 vs 21.9
Lee et al.	First-SIGNAL	Gef	42	84.6% vs 37.5%	8.4 vs 6.7	27.2 vs 25.6
Mitsudomi et al.	WJTOG 3405	Gef	177	62.1% vs 32.2%	9.2 vs 6.3	35.5 vs 38.8
Maemondo et al.	NEJGSG002	Gef	230	73.7% vs 30.7%	10.8 vs 5.4	30.0 vs 23.6
Zhou et al.	OPTIMAL	Erl	154	83% vs 36%	13.1 vs 4.6	22.6 vs 28.8
Rosell et al.	EURTAC	Erl	154	54.5% vs 10.5%	9.2 vs 5.4	19.3 vs 19.5
Yang et al.	LUX-Lung 3	Afat	345	56% vs 23%	13.6 vs 6.9	31.6 vs 28.2
Wu et al.	LUX-Lung 6	Afat	364	67% vs 23%	11.0 vs 5.6	23.6 vs 23.5

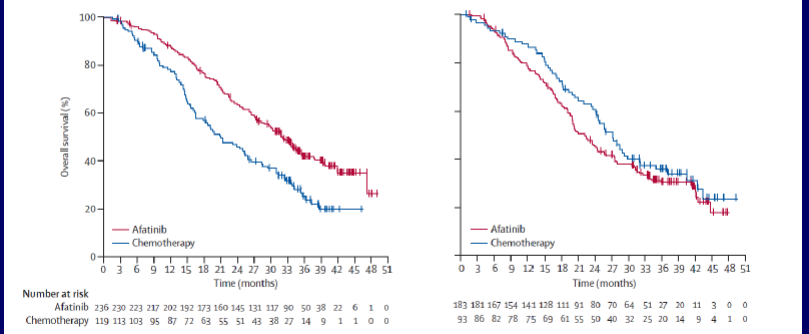
Mok et al. *N Engl J Med.* 2009;361:947-57
Lee et al. WCLC 2009
Mitsudomi et al. *Lancet Oncol.* 2010;11;121-8
Maemondo et al. *N Engl J Med.* 2010;262:2380-88
Zhou et al. ESMO 2010
Rosell et al. ASCO 2011
Yang et al. ASCO 2012, Sequist IASLC 2012
Wu et al. ASCO 2013

Cross-over to an EGFR TKI in the control groups felt to reduce detectability of any possible OS benefit (all mutations)

OS Advantage in Del19 Mutation but not Leu 858Arg Mutation with Afatinib in LUX-Lung 3 and 6

	Afatinib (n=236)	Chemotherapy (n=119)
Median, mo (95% CI)	31.7 (28.1–35.1)	20.7 (20.7–25.6)
HR (95% CI)	0.59 (0.45–0.77)	
P value	0.0001	

	Afatinib (n=183)	Chemotherapy (n=93)
Median, mo (95% CI)	22.1 (19.6–25.4)	26.9 (23.2–31.7)
HR (95% CI)	1.25 (0.92–1.71)	
P value	0.16	

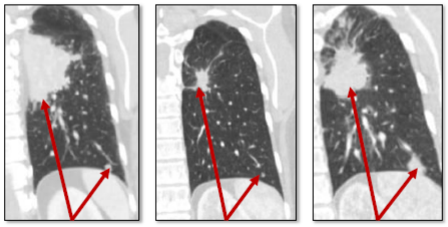


Yang JC-H et al. *Lancet Oncol.* 2015;16:141-151.

Despite Initial Clinical Benefit, Acquired Resistance to Front-Line Therapy Remains a Challenge

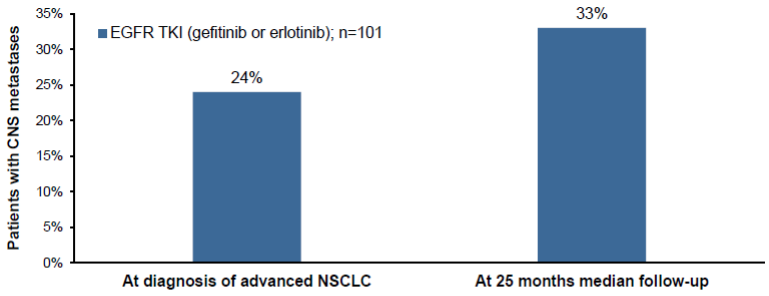
Study	Median PFS (months)
IPASS (EGFR mutant, gefitinib)[1]	9.6
EURTAC (EGFR mutant, erlotinib)[2]	9.7
LUX-Lung 3 (EGFR mutant, afatinib)[3]	11.1
OPTIMAL (EGFR mutant, erlotinib)[4]	13.1

Patient treated with front-line erlotinib



1. Mok TS, et al. *N Engl J Med* 2009;361:947-57; 2. Rosell R, et al. *Lancet Oncol* 2012;13:239-46;
3. Sequist LV, et al. *J Clin Oncol* 2013;31:3327-34; 4. Zhou C, et al. *Lancet Oncol* 2011;12:735-42

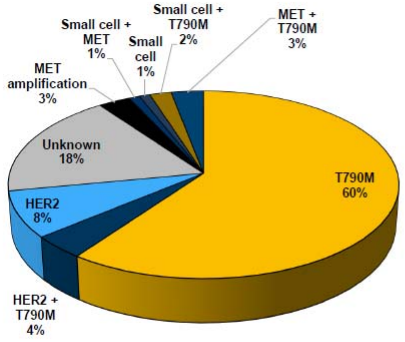
CNS Metastases Are Common at Diagnosis and Increase Throughout the Course of Treatment



- At diagnosis, many patients have CNS metastases[1,2]
- In one study, the incidence of CNS metastases in *EGFR* mutant-positive NSCLC on first generation EGFR TKI was 33%[2]
- Frequency of CNS progression on TKI higher if CNS disease is present at baseline (40% at 2 years)[2]

1. Fan Y, et al. *Onco Targets Ther* 2014;7:2075-2084; 2. Heon S, et al. *Clin Cancer Res* 2012;18:4406-4414

T790M Is the Dominant Cause of Acquired Resistance to EGFR TKIs



- Patients with activating EGFR mutations initially respond to EGFR TKIs
- Approximately 60% develop resistance and progressive disease predominantly due to the emergence of the *T790M* secondary *EGFR* mutation[1]
  - The incidence of T790M was found to be approximately 70% in combination with other mutations[1]

1. Yu HA, et al. *Clin Cancer Res* 2013;19:2240-47

Progressive Disease After Initial TKI Treatment of EGFR-Mutated Lung Cancer: What To Do?

Study	Type/Study (pts.)	Question	1° Endpoint	Results
ASPIRATION	Phase 2 (207)	Continue Erlotinib or switch to chemotherapy	PFS	PFS 1° - 10 mo. PFS 2° - 14.1 mo.
IMPRESS	Phase 3 (265)	Cis/Pem + Gefitinib vs. Cis/Pem + Placebo	PFS	NS

a – time to RECIST PD; b – PD by physician assessment
PFS – progression free survival, PD – progressive disease, TKI Tyrosine kinase inhibitor

Park K, et al. JAMA Oncol. 2016;2(3):305-312
Soria JC, et al. Lancet 2015; 16:990-998

Second-Generation TKIs Less Effective in *T790M*-Positive NSCLC

Activity of second-generation pan-HER inhibitors in *T790M*-positive NSCLC

Second Generation TKI	Patients with T790M Positive NSCLC, n	Objective Response Rate (CR+PR), %	Median PFS
Neratinib (HKI-272)[1]	12	0	Not reported
Afatinib (BIBW-2992)[2]	14	14	2.9 months
Afatinib + cetuximab[3]	71	32	4.8 months
Dacomitinib (PF-299804)[4]	6	0	7 weeks

Second-generation TKIs show limited activity in EGFR-TKI resistant NSCLC

1. Sequist LV, et al. *J Clin Oncol* 2010;28:3076-3083; 2. Yang JC, et al. *J Thorac Oncol* 2013;8(Suppl 2):O03.05; 3. Janjigian YY, et al. *Cancer Discov* 2014;4:1036-1045; 4. Reckamp KL, et al. *Cancer* 2014;120:1145-1154

Current Treatment Paradigms Following First-Line Treatment of NSCLC with EGFR TKIs

- Local ablative therapy and continuation of TKI for oligoprogression (CNS or extra-CNS)[6]
- Chemotherapy ± ongoing TKI (line of cytotoxic therapy determination of ± TKI?)[1]
- Monotherapy with second-generation EGFR TKIs[2-3,5]
- Consideration of afatinib + cetuximab[4]
- Retreatment with a first-generation EGFR TKI after non-EGFR directed therapy

1. Mok TS, et al. Presented at: ESMO Annual Meeting 2014; Madrid, Spain. 26-30 Sep 2014
2. Sequist LV, et al. *J Clin Oncol* 2010;28:3076-83
3. Yang JC, et al. *J Thorac Oncol* 2013;8(Suppl 2):O03.05
4. Janjigian YY, et al. *Cancer Discov* 2014;4:1036-45
5. Reckamp KL, et al. *Cancer* 2014;120:1145-54
6. Weickhardt et al, *J Thorac Oncol* 2012; 2012 7(12):1807-14

Osimertinib
Mechanism of Action

- Osimertinib is kinase inhibitor of the EGFR, which binds irreversibly to certain mutant forms of EGFR (T790M, L858R, and exon 19 deletion) at approximately 9-fold lower concentrations than wild-type
- In cultured cells and animal tumor implantation models, osimertinib exhibited anti-tumor activity against NSCLC lines harboring EGFR-mutations (T790M/L858R, L858R, T790M/exon 19 deletion, and exon 19 deletion) and, to a lesser extent, wild-type EGFR amplifications

Clinical Studies

- The efficacy of osimertinib was demonstrated in two multicenter, single-arm, open-label clinical trials, Study 1 and Study 2, in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI
- All patients were required to have EGFR T790M mutation-positive NSCLC as detected by the Cobas® EGFR mutation test and received osimertinib 80 mg once daily
- The major efficacy outcome measure of both trials was ORR according to RECIST v1.1 as evaluated by a BICR. DOR was an additional outcome measure

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016.
Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Clinical Studies (cont'd)

- Study 1 population characteristics were:
  - Median age 62 years (range 37 to 89)
  - Female (66%)
  - White (38%), Asian (58%)
  - Never smoker (67%)
  - WHO PS 0 (34%) or 1 (66%)
  - Adenocarcinoma histology (97%)
  - 1 prior line of therapy [EGFR-TKI treatment only, second line, chemotherapy-naïve] (30%), 2 or more prior lines of therapy (70%)
  - Sites of extra-thoracic metastases included liver (32%), bone (51%), and brain (37%)
  - Somatic EGFR mutations in addition to T790M were exon 19 deletion (71%), L858R (25%), G719X (2%), and S7681 (2%)

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016.
Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Clinical Studies (cont'd)

- Study 2 population characteristics were:
  - Median age 64 years (range 35 to 88)
  - Female (70%)
  - White (34%), Asian (63%)
  - Never smoker (76%)
  - WHO PS 0 (40%) or 1 (60%)
  - Adenocarcinoma histology (95%)
  - 1 prior line of therapy [EGFR-TKI treatment only, second line, chemotherapy-naïve] (32%), 2 or more prior lines of therapy (68%)
  - Sites of extra-thoracic metastases included liver (26%), bone (43%), and brain (41%)
  - Somatic EGFR mutations in addition to T790M were exon 19 deletion (65%), L858R (32%), G719X (2%), and S7681 (1%)

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016.
Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Clinical Trials Experience

- Serious adverse reactions reported in 2% or more patients were pneumonia and pulmonary embolus
- There were 4 patients (1%) treated with osimertinib who developed fatal adverse reactions of ILD/pneumonitis. Other fatal adverse reactions occurring in more than 1 patient included pneumonia (4 patients) and CVA/cerebral hemorrhage (2 patients)
- Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients treated with osimertinib. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis and CVAs/infarctions.
- Additional clinically significant reactions occurring in 2% or more of patients treated with osimertinib included CVA (2.7)

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016.
Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Clinical Trials Experience (cont'd)

Adverse Reactions (>10% for all NCI CTCAE Grades or >2% for Grades 3-4) in Study 1 and Study 2

Adverse Reactions	Osimertinib (N=411)	
	All Grades (%)	Grades 3-4 (%)[a]
Gastrointestinal disorders		
Diarrhea	42	1.0
Nausea	17	0.5
Decreased appetite	16	0.7
Constipation	15	0.2
Stomatitis	12	0

[a] No grade 4 events have been reported
CTCAE = Common Terminology Criteria for Adverse Events

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016.
Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Clinical Trials Experience (cont'd)

Adverse Reactions (>10% for all NCI CTCAE Grades or >2% for Grades 3-4) in Study 1 and Study 2 (CTCAE = Common Terminology Criteria for Adverse Events)

Adverse Reactions	Osimertinib (N=411)	
	All Grades (%)	Grades 3-4 (%)[a]
Skin disorders		
Rash	41	0.5
Dry Skin	31	0
Nail Toxicity	25	0
Pruritus	14	0
Eye Disorders[b]	18	0.2
Respiratory		
Cough	14	0.2

[a] No grade 4 events have been reported

[b] Includes dry eye, vision blurred, keratitis, cataract, eye irritation, blepharitis, eye pain, lacrimation increased, vitreous floaters. Other ocular toxicities occurred in <1% of patients.

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016; Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Clinical Trials Experience (cont'd)

Adverse Reactions (>10% for all NCI CTCAE Grades or >2% for Grades 3-4) in Study 1 and Study 2 (CTCAE = Common Terminology Criteria for Adverse Events)

Adverse Reactions	Osimertinib (N=411)	
	All Grades (%)	Grades 3-4 (%)[a]
General		
Fatigue	14	0.5
Musculoskeletal		
Back pain	13	0.7
Central Nervous System		
Headache	10	0.2
Infections		
Pneumonia	4	2.2
Vascular events		
Venous thromboembolism[b]	7	2.4

[a] No grade 4 events have been reported

[b] Includes deep vein thrombosis, jugular venous thrombosis, and pulmonary embolism

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016; Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Clinical Trials Experience (cont'd)

Common Laboratory Abnormalities (≥20% for all NCI CTCAE grades) in Study 1 and Study 2

Laboratory Abnormality	Osimertinib (N=411)	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)[a]
Clinical Chemistry		
Hyponatremia	26	3.4
Hypermagnesemia	20	0.7
Hematologic		
Thrombocytopenia	54	1.2
Anemia	44	0.2
Neutropenia	33	3.4

[a] The only grade 4 laboratory abnormality was 1 patient with grade 4 thrombocytopenia
CTCAE = Common Terminology Criteria for Adverse Events

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016.
Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Interstitial Lung Disease (ILD)/Pneumonitis

- Across clinical trials, ILD/pneumonitis occurred in 3.3% (n=27) of osimertinib treated patients (n=813; 0.5% (n=4 were fatal
- Withhold osimertinib and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g. dyspnea, cough and fever)
- Permanently discontinue osimertinib if ILD is confirmed

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016.
Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Osimertinib Results

- Based on 2 AURA phase II studies (n=411) with EGFR T790M mutation
- Overall objective response rate (ORR) was 59% (95% CI: 54% to 64%)
- In a separate part of the AURA study in 63 patients, ORR was 51%, median duration of response was 12.4 months

Osimertinib tablet, for oral use: U.S. prescribing information. Accessed May 4, 2016.
Janne PA, et al, N Engl J Med 2015; 372:1689-1699.

Osimertinib (AZD 9291), As First-Line Treatment for EGFR Mutation Positive Advanced NSCLC: Results from a Phase I Expansion Cohort

- AURA Study: Treatment-naïve pts. with EGFR mutation in Advanced NSCLC received osimertinib at doses of 80mg/d or 160 mg/d
- Objective: Safety, tolerability, activity
- Results: 60 pts. Enrolled; 30 pts. on each arm
- Conclusion: osimertinib – has manageable tolerability profile and promising activity. A phase 3 study comparing osimertinib tolerability versus gefitinib has been initiated.

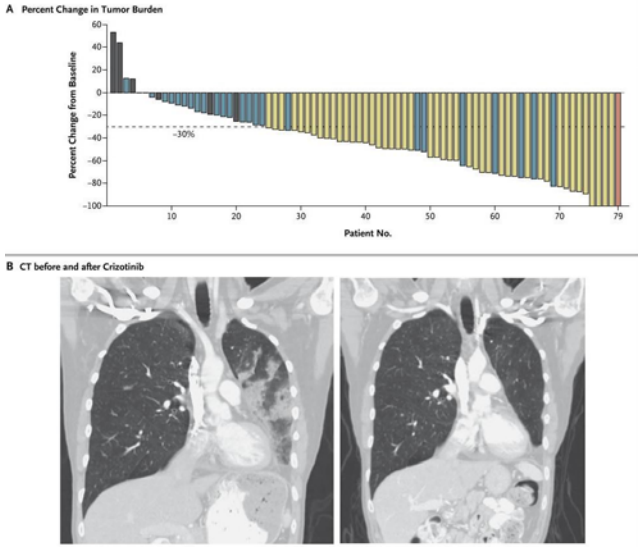
Ramalingam SS, et al., ASCO 2015 Meeting abstr 8000.

Ongoing Studies with Third Generation EGFR TKIs

- With osimertinib
  - Randomized, phase II study of osimertinib versus gefitinib or erlotinib in treatment-naïve pts. with advanced NSCLC and an EGFR-sensitizing mutation
  - A multi-arm phase Ib trial of osimertinib combined with MED14736, AZD6094 or selumetinib in EGFR-mutant lung cancer

Targeting ALK

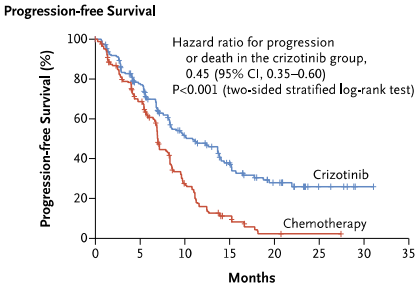
Crizotinib in ALK-Positive NSCLC



Kwak EL et al, NEJM 2010; Camidge DR et al. Lancet Oncol 2012; Shaw AT, J Clin Oncol 2009

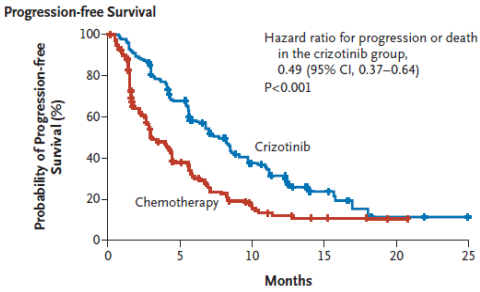
Crizotinib in ALK-Rearranged NSCLC

PROFILE 1014



Endpoint	
ORR %	74%
Median PFS	10.9 months
Median Duration of Response	11.3 months

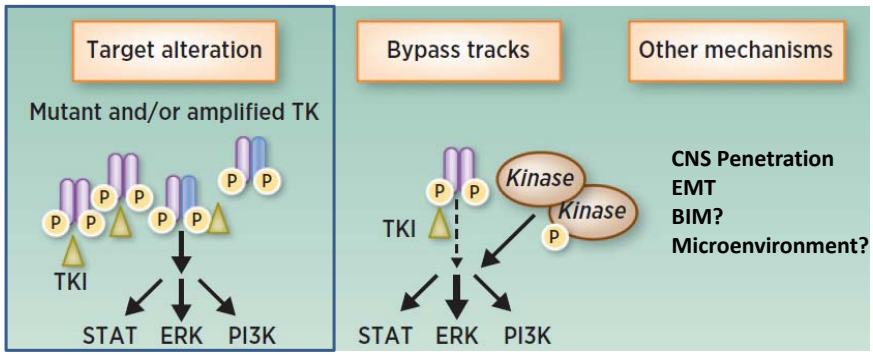
PROFILE 1007



Endpoint	
ORR %	65%
Median PFS	7.7 months
Median Duration of Response	8 months

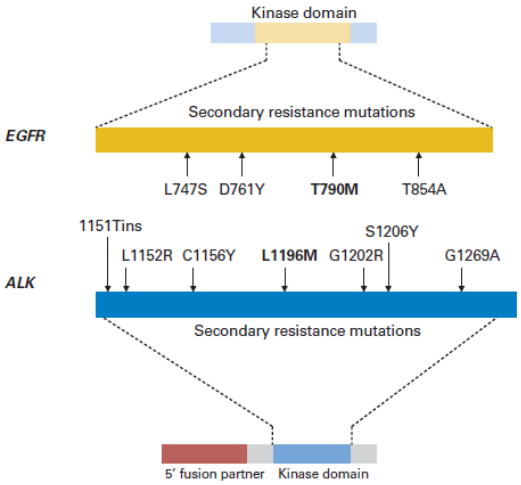
Solomon BJ, et al. NEJM 2014; Shaw AT, et al. NEJM 2013

Acquired Resistance



Modified from Katayama R, et al. Clin Cancer Res 2015; 21(10):2227-35

Secondary Mutations: EGFR versus ALK



Gainor JF, Shaw AT, J Clin Oncol 2013

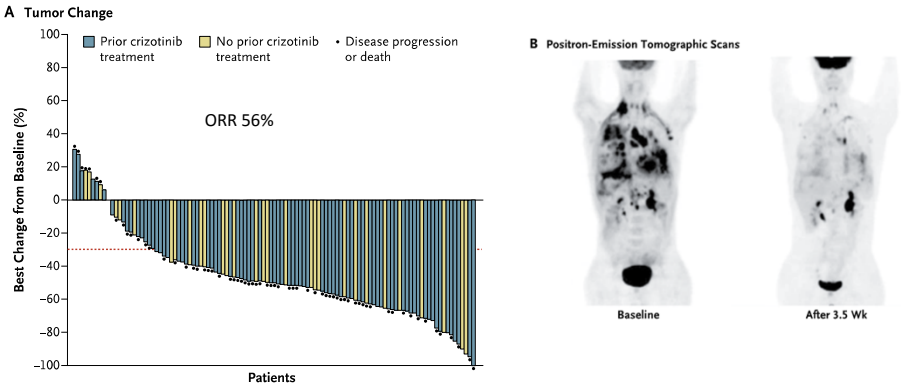
Alterations in the Target: Treatment Approaches

Select List of Next-Generation Inhibitors

ALK	ROS1
Ceritinib*	Ceritinib
Alectinib#	PF-06463922
Brigatinib#	Entrectinib
PF-06463922	DS-6051b
CEP-37440	
Entrectinib	
TSR-011	
X-396	

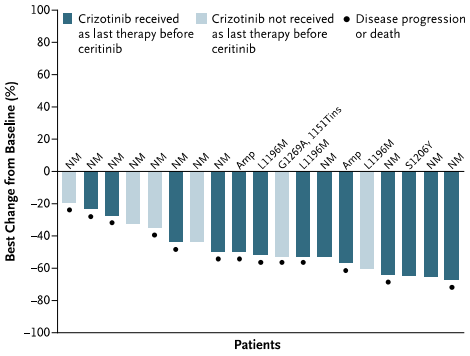
* FDA-approved for patients previously treated with crizotinib.
# FDA Breakthrough therapy designation

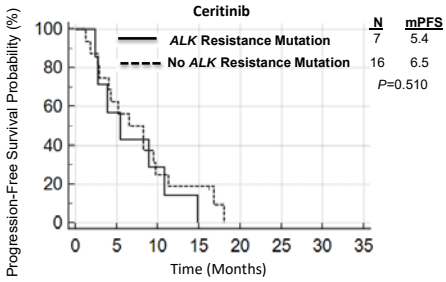
Ceritinib in Crizotinib-Resistant Disease



Shaw AT, NEJM 2014

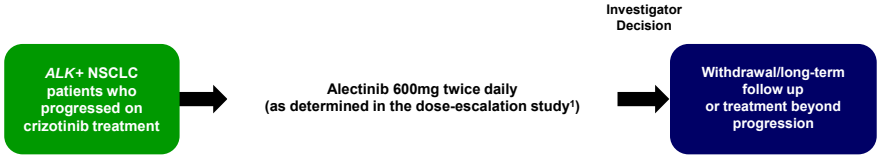
Ceritinib: Impact of ALK Resistance Mutations





Shaw AT, et al. NEJM 2014; Gainor JF, et al. Clin Cancer Res 2015

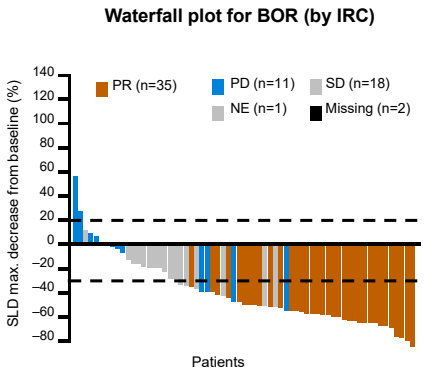
Trial designs: NP28761 and NP28673



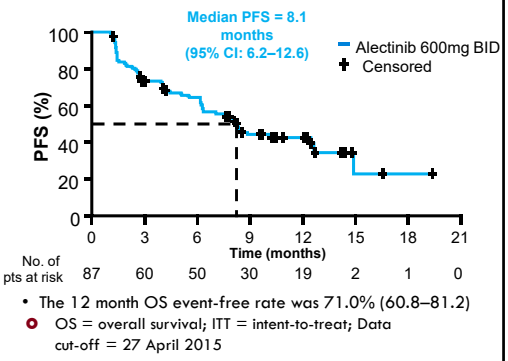
	NP28761; NCT01871805 (N. America)	NP28673; NCT01801111 (Global)
	Alectinib 600mg BID (n=87)	Alectinib 600mg BID (n=138)
Primary endpoint(s)	Objective response rate (ORR) by IRC in RE population	ORR by IRC in RE population and prior chemo subgroup (co-primary endpoints)
Key secondary endpoints	CNS ORR; CNS duration of response (DOR)	CNS ORR; CNS DOR

- Response was determined according to RECIST v1.1. All patients underwent imaging at baseline and had regular scheduled CNS scans to assess CNS metastases (every 6 weeks for NP28761 and every 8 weeks for NP28673)
- IRC = independent review committee; RE = response evaluable

Alectinib U.S. phase II study



ORR=52.2%
(Global study 51%)



- The 12 month OS event-free rate was 71.0% (60.8–81.2)
- OS = overall survival; ITT = intent-to-treat; Data cut-off = 27 April 2015

Median PFS=8.1 months (95%CI: 6.2-12.6)
Global study 8.9 months

Shaw, A et al., WCLC 2015

Safety overview: grade ≥3 AEs in ≥2% of patients (U.S. study)

AE, n (%)	Alectinib 600mg BID (n=87)
Blood creatine phosphokinase increased	7 (8.0)
Alanine aminotransferase increased	5 (5.7)
Aspartate aminotransferase increased	4 (4.6)
Dyspnea	3 (3.4)
Hypertriglyceridemia	2 (2.3)
Hypokalemia	2 (2.3)
Hypophosphatemia	2 (2.3)

- No GI toxicities leading to treatment withdrawal or dose reduction were reported
- Overall, dose reductions, interruptions and withdrawals were reported in 16%, 36% and 2% of patients, respectively; mean dose intensity was 92%

*AEs reported in more than 1 patient
AE = adverse event; Data cut-off = 27 April 2015

Shaw, A et al., WCLC 2015

Efficacy of alectinib in CNS

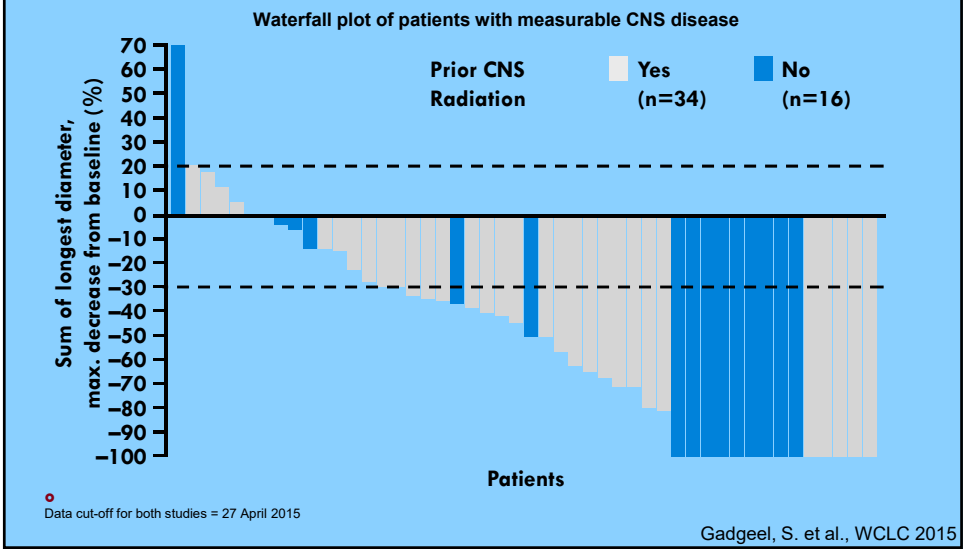
	Alectinib 600mg BID	
	Measurable CNS disease (n=50)*	Measurable and non-measurable CNS disease (n=136)*
CNS ORR, % (95% CI)	64.0 (49.2–77.1)	42.6 (34.2–51.4)
Complete response, n (%)	11 (22.0)	37 (27.2)
Partial response, n (%)	21 (42.0)	21 (15.4)
Stable disease, n (%)	13 (26.0)	58 (42.6)
Progressive disease, n (%)	3 (6.0)	12 (8.8)
CNS DCR, n (%)	45 (90.0)	116 (85.3)
[95% CI]	[78.2–96.7]	[78.2–90.8]
Median CNS DOR, months (95% CI)	10.8 (7.6–14.1)	11.1 (10.3–NE)

- Median duration of follow-up was 12.4 months (range: 0.9–19.7)
- 26 patients with only non-measurable CNS disease achieved a CNS CR (30.2% CNS CR rate)

*2/50 patients in the measurable group and 8/136 in the measurable and non-measurable group were not evaluable for response;
Data cut-off for both studies = 27 April 2015; DOR is based on 56% and 45% of events in measurable and measurable/non-measurable groups

Gadgeel, S. et al., WCLC 2015

Alectinib is active in CNS regardless of prior radiation



Data cut-off for both studies = 27 April 2015

Gadgeel, S. et al., WCLC 2015

Next-Generation ALK TKIs in Crizotinib-Resistant Disease

	Ceritinib	Alectinib	Brigatinib
Study	Phase I (ASCEND-1)	Global Phase II (NP28673)	Phase I/II
Sample Size	163	138	70
ORR	55%	50%	71%
Intracranial ORR	34.5%	57%	53%
Median PFS	6.93 months	8.9 months	13.4 months*

*Includes only patients with a follow-up scan

Shaw AT et al. NEJM 2014; Shaw AT, et al. ESMO 2014; Felip E, et al. ESMO 2014; Ou I, et al. JCO 2015; Camidge DR, et al., ASCO 2015

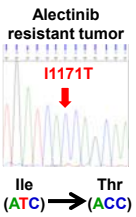
Different Resistance Mutations Emerge to Different ALK Inhibitors

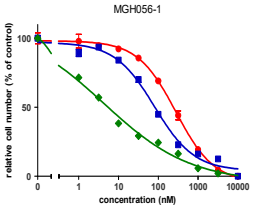
Crizotinib	Ceritinib	Brigatinib	Alectinib
1151Tins			
L1152R			
C1156Y			
F1174V/L	F1174V/C		
L1196M			
G1202R	G1202R	G1202R	G1202R
D1203N		D1203N + E1210K	
S1206Y			
G1269A			
			I1171T/N/S V1180L

Slide Courtesy of Dr. Alice Shaw

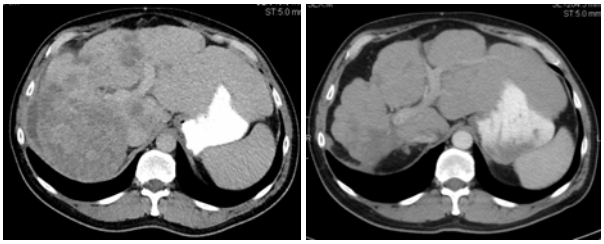
Katayama et al., Sci Transl Med 4(120): 120ra17, 2012; Doebele et al., CCR 18(5): 1472-82, 2012; Friboulet et al., Cancer Discov 4(6): 662-73, 2014; Ou et al., JTO 9(4): 549-53, 2014; Katayama et al., CCR 2014; Ou et al., JTO 2014

ALK Resistance Mutations May Differ Across Next Generation Inhibitors





Drug	IC50 (nM)
Crizotinib	236 nM
Alectinib	80 nM
Ceritinib	4.3 nM



Baseline
(post-criz, post-alectinib)

On ceritinib
(After 18 weeks)

Katayama et al., Clin Cancer Res 20:5686-96, 2014

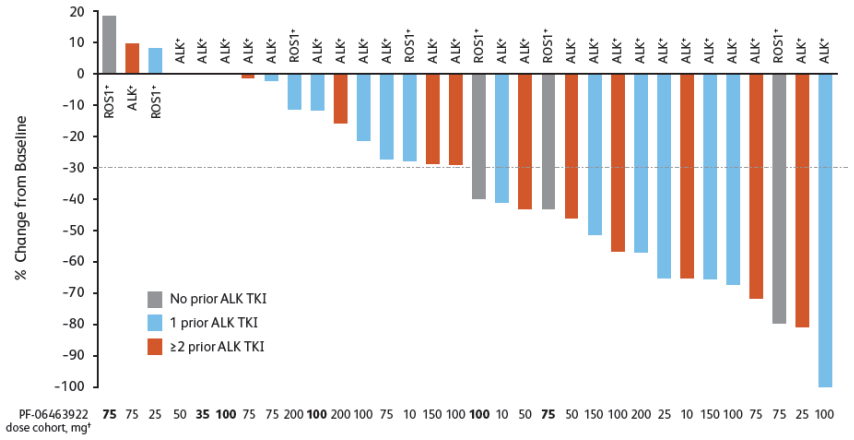
PF-06463922 Is Active Against All Known ALK Resistance Mutations

Mutation Status	Cell Line	Cellular ALK Phosphorylation Mean IC_{50} (nM)			
		PF-06463922	Crizotinib	Ceritinib (LDK-378)	Alectinib (CH-5424802)
EML4-ALK v1	NIH3T3	1.3	80	NA	62
	BaF3	3.6	90	41	24
EML4-ALK L1196M	NIH3T3	21	843	NA	250
	BaF3	43	1154	70	113
EML4-ALK G1269A	NIH3T3	15	605	NA	NA
	BaF3	80	689	134	112
EML4-ALK G1202R	NIH3T3	77	1003	>1000	>10,000
	BaF3	113	562	549	362
EML4-ALK I1171Tins	NIH3T3	38	1268	1066	1770
	BaF3	50	902	296	126
EML4-ALK S1206Y	NIH3T3	4.2	626	NA	NA
	BaF3	3.2	152	60	29
EML4-ALK C1156Y	NIH3T3	1.6	478	NA	NA
	BaF3	15	406	177	21
EML4-ALK F1174L	NIH3T3	0.2	165	NA	NA
	BaF3	4.0	150	161	26

IC_{50} < 100 nM
IC_{50} ≥ 100 < 200 nM
IC_{50} ≥ 200 nM

1. Zou HY, et al. AACR-NCI 2013, poster A277.

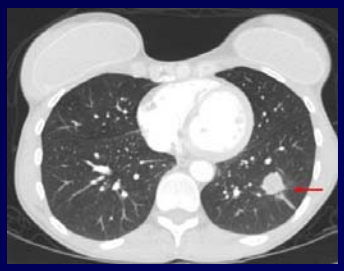
Clinical Activity of PF-06463922 in Advanced ALK+ and ROS1+ NSCLC



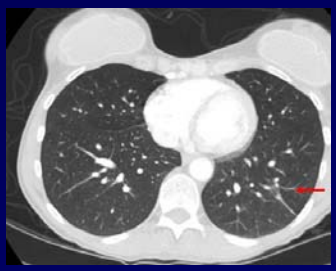
Shaw et al., ASCO 2015

PF-06463922 Is Active Against the Most Refractory ALK Resistance Mutation G1202R

ALK+ NSCLC Patient:
Previously treated with criz and AP26113
Local testing post AP26113 with G1202R
Started PF-06463922 at 200 mg QD
Dose reduced to 100 mg QD
Ongoing at >8 months



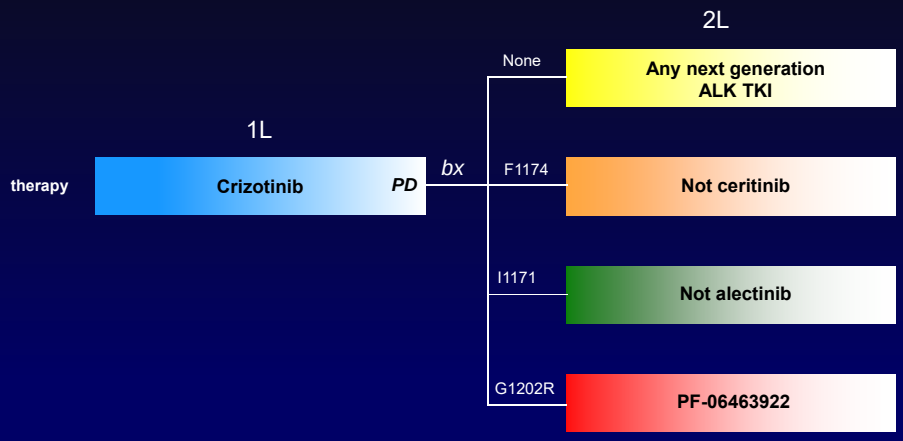
August 5, 2014



April 20, 2015

Shaw et al., ASCO 2015

Selection of Second-Line Next Generation ALK Inhibitors Based on ALK Mutation Status



Conclusions

In 2016 and beyond, targeted therapy for NSCLC patients with EGFR mutations and/or T790M mutations, ALK rearrangement and/or resistant disease, ROS1 and other targetable mutations will continue to develop and improve.

Q&A SESSION

Please use the Q&A feature on the right-hand portion of your screen to submit clinical questions to the speaker.

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- If you participated with a group of peers, a list of everyone who attended in your group must be submitted to **education@nccn.org** within the next two weeks.
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UPCOMING WEBINARS

- **Minimizing Risk from Lung Cancer Screening**
  Friday, July 22 at 2:00 PM [EDT]
  Douglas E. Wood, MD
  Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
- **Treatment of Older Adult Patients with Non-Small Cell Lung Cancer**
  Tuesday, July 26 at 1:30 PM [EDT]
  Neelesh Sharma, MD, PhD, *Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute*

Register at NCCN.org/events

Thank you for your participation in today's program!