Ochsner Journal 17:388–392, 2017

Molecular Targets in Non–Small Cell Lung Cancer

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Background: Lung cancer is the second most common cancer in the United States among men and women, and it is the most common cause of cancer-related death. Non–small cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases. Historically, patients with metastatic NSCLC received similar cytotoxic chemotherapy regimens. Genotyping studies have revealed genetic/molecular abnormalities in lung cancer. These *driver mutations* render a cancer dependent on that specific mutation's biochemical pathway for its growth and survival. With the development of tyrosine kinase inhibitors and antibodies against specific driver mutations, the landscape of lung cancer treatment has changed from treatment based on histologic subtype to treatment based on molecularly defined subtypes.

Methods: In this article, we review the current molecular-targeted therapies in lung cancer.

Results: We review landmark trials that have led to approval of molecular-targeted therapies against epidermal growth factor receptor, anaplastic lymphoma kinase, and ROS1. We also explore less common mutations/molecular abnormalities and review data on the use of targeted therapies against them. Finally, we offer a treatment algorithm for patients with metastatic NSCLC that harbors actionable mutations.

Conclusion: Patients with advanced NSCLC should undergo mutational testing to evaluate for actionable mutations. If such a mutation is discovered, targeted therapy should be considered for first-line treatment.

Keywords: *Anaplastic lymphoma kinase, carcinoma–non-small cell lung, molecular targeted therapy, receptor–epidermal growth factor, ROS1*

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INTRODUCTION

Lung cancer is the second most common cancer in the United States among men and women, and it is the most common cause of cancer-related death. In 2017, an estimated 222,500 new cases of lung cancer will be diagnosed and an estimated 155,870 deaths related to lung cancer will occur.[1]

The 2 classes of lung cancer are small cell lung cancer and non–small cell lung cancer (NSCLC). NSCLC represents approximately 85% of all lung cancer cases.[2] Histologically, NSCLC has several subtypes, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and mixed histology. Genotyping studies have revealed genetic/molecular abnormalities in the various subtypes of lung cancer. In adenocarcinoma, several *driver mutations* have been identified, including mutations/alterations of the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS1.[3] These driver mutations cause the signaling protein to be constitutively activated, leading to increased cell proliferation, angiogenesis, metastasis, and decreased apoptosis. Similarly, genotyping in squamous cell lung cancer has resulted in the discovery of several genetic abnormalities.[4]

For metastatic NSCLC, historically, all patients received similar first-line and second-line chemotherapy regimens. With the development of tyrosine kinase inhibitors (TKIs) and antibodies against specific driver mutations, the landscape of lung cancer treatment has changed from treatment based on histologic subtype to treatment based on molecularly defined subtypes. In this article, we review the current molecular-targeted therapies in lung cancer.

EPIDERMAL GROWTH FACTOR RECEPTOR

The EGFR is a cell-surface protein that when activated by the binding of the ligand to its extracellular component leads to a series of events that result in increased cell proliferation, angiogenesis, metastasis, and decreased apoptosis. EGFR is overexpressed in a majority of NSCLC cases. Activating mutations in EGFR most commonly occur as either in-frame amino acid deletions in exon 19 or L858R substitutions in exon 21.[5] An EGFR mutation makes the cancer cell reliant on EGFR for survival, a process termed *oncogene addiction*.[6] The phenomenon of oncogene addiction allows for response of these tumors to EGFR-specific TKIs.[7] Several EGFR TKIs are available in the United States, including erlotinib, gefitinib, afatinib, and osimertinib.

The Iressa Pan-ASia Study (IPASS) randomized previously untreated patients with advanced lung adenocarcinoma (stages IIIB and IV) to receive gefitinib or carboplatin-paclitaxel, a standard first-line chemotherapy regimen.[8] Patients were nonsmokers or light smokers and Asian, characteristics that had previously been associated with a higher frequency of EGFR mutations. The primary endpoint was progression-free survival (PFS). A total of 1,217 patients underwent randomization. The PFS for the subgroup of patients who were positive for an EGFR mutation was 9.6 months vs 6.3 months favoring gefitinib (hazard ratio [HR] 0.48; 95% confidence interval [CI] 0.36-0.64; $P<0.001$). However, among patients who were negative for the EGFR gene mutation, PFS was significantly longer for the patients randomized to carboplatin-paclitaxel. Median overall survival was 18.6 months for gefitinib vs 17.3 months for carboplatin-paclitaxel. This study confirmed that patients with an EGFR mutation responded better to gefitinib than to cytotoxic chemotherapy.

The EURopean TArceva vs Chemotherapy (EURTAC) trial randomized patients with advanced NSCLC (stages IIIB and IV) with EGFR mutations (exon 19 deletion or L858R mutation in exon 21) to receive erlotinib or standard platinum-based chemotherapy doublet.[9] The primary endpoint was PFS, and 173 patients underwent randomization. Median PFS was 9.7 months vs 5.2 months favoring erlotinib (HR 0.37; 95% CI 0.25-0.54; $P<0.0001$).

The LUX-Lung 3 trial randomized patients with EGFR mutation–positive lung adenocarcinoma to receive afatinib or cisplatin-pemetrexed.[10] The primary endpoint was PFS, and 345 patients underwent randomization. Median PFS was 11.1 months vs 6.9 months favoring afatinib (HR 0.58; 95% CI 0.43-0.78; $P=0.0004$).

The Table presents information on these and other trials evaluating EGFR TKIs in the treatment of advanced NSCLC.

In general, resistance to EGFR TKIs develops at 9-12 months.[8-14] In approximately 50% of cases, the mechanism of resistance is a second-site mutation, T790M within exon 20. In approximately 3% of cases, the mechanism of resistance is histologic transformation to small cell lung cancer.[15] Other less common mechanisms of resistance include amplifications of MET, HER2, and MAPK and mutations in BRAF and PIK3CA.[15] It is important to perform a repeat biopsy at the time of progression for patients on an EGFR TKI to evaluate for the specific mechanism of resistance.

Osimertinib is an oral, irreversible EGFR TKI that has efficacy against EGFR-mutated NSCLC with the T790M resistance mutation. The AURA3 trial randomized 419 patients with T790M-positive advanced NSCLC who had disease progression on first-line EGFR TKI therapy to osimertinib or platinum-based chemotherapy (cisplatin or carboplatin with pemetrexed).[16] PFS, the primary endpoint, was 10.1 months in the osimertinib cohort vs 4.4 months in the platinum-doublet chemotherapy cohort (HR 0.30; 95% CI 0.23-0.41; $P<0.001$). Osimertinib is approved for patients who harbor the T790M mutation and who have progressed on a first-line EGFR TKI.

Overall, patients tolerate EGFR TKIs much better than standard cytotoxic chemotherapy. The most common side effects include gastrointestinal upset (nausea, diarrhea) and dermatologic manifestations (a maculopapular, acneiform rash). There is an association between development of a rash while on an EGFR TKI and response and/or survival.[17] The positive correlation between rash and response/survival is stronger with erlotinib than with gefitinib.

ANAPLASTIC LYMPHOMA KINASE

A fusion gene of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the ALK gene occurs in approximately 3.8% of all NSCLC cases.[18,19] This fusion gene encodes a cytoplasmic protein with constitutive tyrosine kinase activity. The 3 US Food and Drug Administration–approved ALK inhibitors are crizotinib, ceritinib, and alectinib; several more are in development.

In a phase 1 dose-escalation trial, crizotinib had an overall response rate of 57% with an estimated probability of 6-month PFS of 72%.[20] The PROFILE 1014 study was a phase 3 trial that randomized treatment-naïve patients with locally advanced/recurrent/metastatic NSCLC with a positive ALK gene rearrangement to receive crizotinib or standard pemetrexed plus platinum chemotherapy.[21] The primary endpoint was PFS. Median PFS was 10.9 months in the crizotinib cohort vs 7.0 months in the pemetrexed plus platinum chemotherapy cohort (HR 0.45; 95% CI 0.35-0.60; $P<0.001$).

Ceritinib is approved for patients with ALK-positive, metastatic NSCLC who have progressed on crizotinib. In a single-arm phase 1/2 trial, 80 patients with metastatic ALK-positive NSCLC who had progressed on crizotinib received ceritinib.[22] The objective response rate was 56% (95% CI 45%-67%); the median PFS was 7.0 months.

Table. Studies of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (TKIs) in the Treatment of Advanced Non–Small Cell Lung Cancer

Study	Design	Response Rate, TKI vs Standard Chemotherapy	Progression-Free Survival, Months (Hazard Ratio)
IPASS, 2009[8]	Gefitinib vs carboplatin-paclitaxel	71.2% vs 47.3%	9.6 vs 6.3 (0.48)
EURTAC, 2012[9]	Erlotinib vs platinum doublet	56% vs 15%	9.7 vs 5.2 (0.37)
LUX-Lung 3, 2013[10]	Afatinib vs cisplatin-pemetrexed	56% vs 23%	11.1 vs 6.9 (0.58)
OPTIMAL, 2011[11]	Erlotinib vs carboplatin-gemcitabine	83% vs 36%	13.1 vs 4.6 (0.16)
WJTOG 3405, 2010[12]	Gefitinib vs cisplatin-docetaxel	62% vs 32%	9.2 vs 6.3 (0.49)
NEJ 002, 2010[13]	Gefitinib vs carboplatin-paclitaxel	73.7% vs 30.7%	10.8 vs 5.4 (0.30)
LUX-Lung 6, 2014[14]	Afatinib vs cisplatin-gemcitabine	66.9% vs 23.0%	11.0 vs 5.6 (0.28)
AURA3, 2017[16]	Osimertinib vs platinum-pemetrexed	71% vs 31%	10.1 vs 4.4 (0.30)

Ceritinib has also been shown to have efficacy in the first-line setting. The ASCEND-4 study was a phase 3 trial in which 376 previously untreated patients with stage IIIB/IV ALK-rearranged nonsquamous NSCLC were randomized to receive ceritinib or standard pemetrexed plus platinum chemotherapy.[23] The primary endpoint was PFS. Median PFS was 16.6 months in the ceritinib cohort vs 8.1 months in the pemetrexed plus platinum chemotherapy cohort (HR 0.55; 95% CI 0.42-0.73; $P<0.00001$). Importantly, ceritinib showed efficacy for patients with brain metastases; the overall intracranial response rate was 73.7% vs 27.3% with pemetrexed plus platinum chemotherapy.

Alectinib is another ALK inhibitor approved for patients with ALK-positive, metastatic NSCLC who have progressed on crizotinib. The approval was based on 2 single-arm trials.[24,25] The first trial was a phase 2 study that enrolled patients with ALK-positive NSCLC who had progressed on crizotinib to receive alectinib. The primary endpoint, overall response rate, was 48% (95% CI 36%-60%).[24] The second trial was also a phase 2 study that enrolled patients with crizotinib-refractory ALK-positive NSCLC to receive alectinib. The primary endpoint, overall response rate, was 50% (95% CI 41%-59%).[25]

Mechanisms of resistance to ALK TKIs include biologic factors (increased EGFR signaling, ALK mutations, etc) and pharmacologic factors (failure of the drug to adequately reach the central nervous system).[26] In approximately 30%-35% of cases, the mechanism of resistance is increased EGFR signaling; in approximately 28%-49% of cases, the mechanism of resistance is an ALK target alteration (ALK mutation or ALK amplification).[27,28] For patients with progressive disease, the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC suggest that if a patient is asymptomatic, continuing the initial ALK inhibitor is reasonable.[29] If the patient is symptomatic, local therapy and continuation of the ALK inhibitor or switching to another ALK inhibitor should be considered.

Side effects of crizotinib include visual disturbance (blurry vision, diplopia, photophobia), gastrointestinal upset, and elevated liver function tests. Side effects of ceritinib and alectinib include gastrointestinal upset, elevated liver function tests, and myelosuppression.

ROS1

ROS1 is a receptor tyrosine kinase of the insulin receptor family; it is located on chromosome 6. A ROS1 gene rearrangement results in constitutive activation of the tyrosine kinase. ROS1 gene rearrangements occur in approximately 2% of all NSCLC cases.[30] Crizotinib has shown activity in patients with advanced NSCLC with a ROS1 gene rearrangement.

In a phase 1 study that included an expansion cohort of patients with advanced ROS1-rearranged NSCLC, patients were treated with crizotinib and assessed for safety, pharmacokinetics, and response to therapy.[31] The objective response rate was 72%, and the median PFS was 19.2 months.

OTHER MUTATIONS

Several less common mutations in lung cancer have been identified. For example, in lung adenocarcinoma, mutations in HER2, BRAF, MET, and RET occur, each at incidences of 1%-3%.[5] The NCCN guidelines for NSCLC contain a section on ''Emerging Targeted Agents for Patients with Genetic Alterations,'' including HER2 mutations, BRAF V600E mutations, high-level MET amplification or MET exon 14 skipping mutations, and RET rearrangements.[29]

In a retrospective review of 65 patients with advanced NSCLC that harbored a HER2 in-frame insertion in exon 20, in which 16 patients received anti-HER2 treatments after conventional therapy, the overall response rate was 50%, and the median PFS was 5.1 months.[32]

In a phase 2 basket study of vemurafenib (a selective oral inhibitor of the BRAF V600 kinase) in BRAF V600 mutation–positive non-melanoma cancers, a cohort of 20 patients with NSCLC had an overall response rate of 42%.[33] In a phase 2 trial of pretreated patients with metastatic BRAF V600E–mutant NSCLC, the combination of dabrafenib (an oral BRAF inhibitor) and oral trametinib (an oral inhibitor of mitogen-activated extracellular kinase 1 and 2) resulted in an overall response rate of 63.2%.[34]

The use of crizotinib in patients with MET exon-14-altered NSCLC has been studied. In an expansion cohort of the phase 1 PROFILE 1001 study, 21 patients with MET exon 14–altered NSCLC received crizotinib. The objective response rate was 44% (95% CI 22%-69%).[35] Data are also available on antitumor activity with the use of cabozantinib[36] and vandetanib[37] in patients with NSCLC who harbor a RET gene fusion. In an open-label phase 2 trial, 25 patients with metastatic RET-arranged NSCLC received cabozantinib, a multi-TKI with activity against RET.[36] The overall response rate was 28% (95% CI 12%-49%). In an open-label phase 2 trial, 18 patients with advanced RET-rearranged NSCLC who had failed platinum-based chemotherapy received vandetanib.[37] Three patients had a partial response, and 8 patients had stable disease.

TREATMENT ALGORITHM FOR PATIENTS WITH ADVANCED/METASTATIC NON–SMALL CELL LUNG CANCER

All patients with metastatic NSCLC should undergo molecular profiling to evaluate for actionable mutations. The NCCN guidelines for NSCLC recommend broad molecular profiling, including testing for less frequent driver mutations for which drugs are readily available.[27] While most of these mutations are less common in the squamous-cell subtype of NSCLC, we recommend a standardized approach for both squamous cell and nonsquamous cell subtypes of NSCLC. If a driver mutation is discovered, a targeted treatment should be started. We provide a diagnostic and treatment algorithm in the Figure.

CONCLUSION

Patients with advanced NSCLC should undergo mutational testing to evaluate for actionable mutations. If such a mutation is discovered, targeted therapy should be considered for first-line treatment.

ACKNOWLEDGMENTS

Robert A. Ramirez, DO, FACP serves as a consultant for Ipsen Biopharmaceuticals Inc. and BioTheranostics Inc., as well as a speaker for Merck & Co. Inc., Genentech, Astra Zeneca, and Ipsen Biopharmaceuticals. Ryan Griffin, MD has no conflicts of interest to disclose.

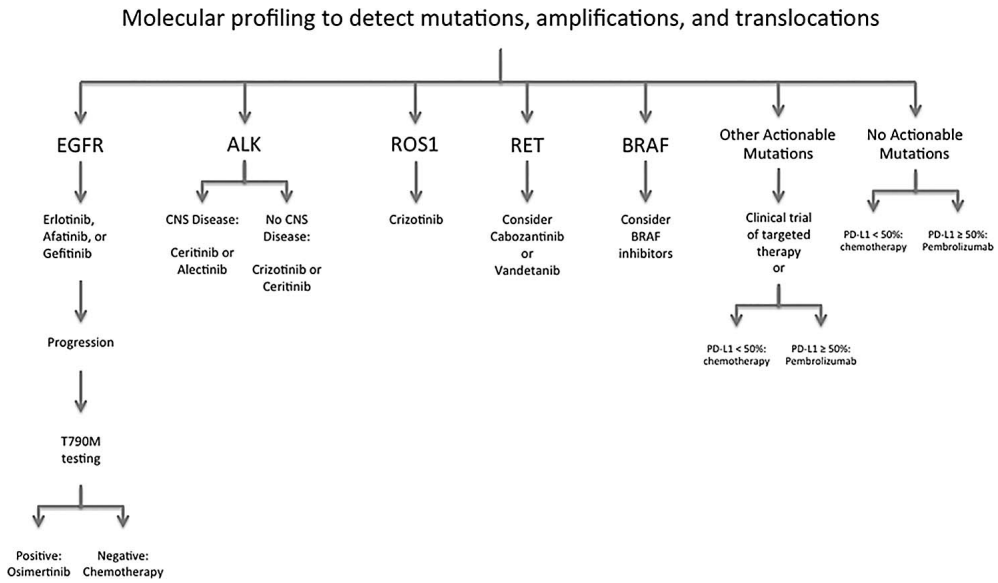

Figure. Treatment algorithm for patients with advanced/metastatic non–small cell lung cancer. ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; CNS, central nervous system; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; ROS1, ROS1 proto-oncogene; RET, RET proto-oncogene.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017 Jan;67(1):7-30. doi: 10.3322/caac.21387.
2. Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. *J Clin Oncol*. 2013 Mar 10;31(8):1039-1049. doi: 10.1200/JCO.2012.45.3753.
3. Pao W, Hutchinson KE. Chipping away at the lung cancer genome. *Nat Med*. 2012 Mar 6;18(3):349-351. doi: 10.1038/nm.2697.
4. Sos ML, Thomas RK. Genetic insight and therapeutic targets in squamous-cell lung cancer. *Oncogene*. 2012 Nov 15;31(46):4811-4814. doi: 10.1038/onc.2011.640.
5. Li AR, Chitale D, Riely GJ, et al. EGFR mutations in lung adenocarcinomas: clinical testing experience and relationship to EGFR gene copy number and immunohistochemical expression. *J Mol Diagn*. 2008 May;10(3):242-248. doi: 10.2353/jmoldx.2008.070178.
6. Weinstein IB. Cancer. Addiction to oncogenes–the Achilles heal of cancer. *Science*. 2002 Jul 5;297(5578):63-64.
7. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004 May 20;350(21):2129-2139.
8. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009 Sep 3;361(10):947-957. doi: 10.1056/NEJMoa0810699.
9. Rosell R, Carcereny E, Gervais R, et al; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012 Mar;13(3):239-246. doi: 10.1016/S1470-2045(11)70393-X.
10. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013 Sep 20;31(27):3327-3334. doi: 10.1200/JCO.2012.44.2806.
11. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011 Aug;12(8):735-742. doi: 10.1016/S1470-2045(11)70184-X.
12. Mitsudomi T, Morita S, Yatabe Y, et al; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010 Feb;11(2):121-128. doi: 10.1016/S1470-2045(09)70364-X.
13. Maemondo M, Inoue A, Kobayashi K, et al; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010 Jun 24;362(25):2380-2388. doi: 10.1056/NEJMoa0909530.
14. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014 Feb;15(2):213-222. doi: 10.1016/S1470-2045(13)70604-1.
15. Stewart EL, Tan SZ, Liu G, Tsao MS. Known and putative mechanisms of resistance to EGFR targeted therapies in NSCLC patients with EGFR mutations-a review. *Transl Lung Cancer Res*. 2015 Feb;4(1):67-81. doi: 10.3978/j.issn.2218-6751.2014.11.06.
16. Mok TS, Wu Y-L, Ahn M-J, et al; AURA3 Investigators. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017 Feb 16;376(7):629-640. doi: 10.1056/NEJMoa1612674.
17. Peréz-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol*. 2005 Aug 1;23(22):5235-5246.
18. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007 Aug 2;448(7153):561-566.
19. Solomon B, Varella-Garcia M, Camidge DR. ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. *J Thorac Oncol*. 2009 Dec;4(12):1450-1454. doi: 10.1097/JTO.0b013e3181c4dedb.

20. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010 Oct 28;363(18):1693-1703. doi: 10.1056/NEJMoa1006448.
21. Solomon BJ, Mok T, Kim DW, et al; PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014 Dec 4;371(23):2167-2177. doi: 10.1056/NEJMoa1408440.
22. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014 Mar 27;370(13):1189-1197. doi: 10.1056/NEJMoa1311107.
23. Soria JC, Tan DS, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. 2017 Mar 4;389(10072):917-929. doi: 10.1016/S0140-6736(17)30123-X.
24. Shaw AT, Gandhi L, Gadgeel S, et al; study investigators. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol*. 2016 Feb;17(2):234-242. doi: 10.1016/S1470-2045(15)00488-X.
25. Ou SH, Ahn JS, De Petris L, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. *J Clin Oncol*. 2016 Mar 1;34(7):661-668. doi: 10.1200/JCO.2015.63.9443.
26. Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumours: learning from lung cancer. *Nat Rev Clin Oncol*. 2014 Aug;11(8):473-481. doi: 10.1038/nrclinonc.2014.104.
27. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Sci Transl Med*. 2012 Feb 8;4(120):120ra17. doi: 10.1126/scitranslmed.3003316.
28. Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res*. 2012 Mar 1;18(5):1472-1482. doi: 10.1158/1078-0432.CCR-11-2906.
29. Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2017 Apr;15(4):504-535.
30. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012 Mar 10;30(8):863-870. doi: 10.1200/JCO.2011.35.6345.
31. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014 Nov 20;371(21):1963-1971. doi: 10.1056/NEJMoa1406766.
32. Mazières J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol*. 2013 Jun 1;31(16):1997-2003. doi: 10.1200/JCO.2012.45.6095.
33. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. 2015 Aug 20;373(8):726-736. doi: 10.1056/NEJMoa1502309.
34. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016 Jul;17(7):984-993. doi: 10.1016/S1470-2045(16)30146-2.
35. Drilon A, Ou SH, Clark J, et al. MA16.09 antitumor activity and safety of crizotinib in patients with MET exon 14-altered advanced non-small cell lung cancer. *J Thorac Oncol*. 2017 Jan;12(1):S438-S439. doi: 10.1016/j.jtho.2016.11.512.
36. Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol*. 2016 Dec;17(12):1653-1660. doi: 10.1016/S1470-2045(16)30562-9.
37. Lee SH, Lee JK, Ahn MJ, et al. A phase II study of vandetanib in patients with non-small cell lung cancer harboring RET rearrangement. *J Clin Oncol*. 2016 May;34(suppl 15):9013.

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