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Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer

Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al.

N Eng J Med 2017;376(7):629-40.

<http://www.nejm.org/doi/full/10.1056/NEJMoa1612674>

Osimertinib, is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) for advanced NSCLC harboring exon 20 T790M resistance mutation after progression with first-line EGFR-TKI treatment. This study is a randomized, international, open-label, phase 3 trial. A total of 419 advanced NSCLC patients with T790M mutation after progression with first-line EGFR TKI treatment patients received 2:1 ratio to oral osimertinib (80mg once daily) or pemetrexed (500mg/m²) plus either carboplatin (5AUC) or cisplatin (75mg/m²) every 3 weeks for 6 cycles. Maintenance treatment with pemetrexed was permitted. Primary endpoint was investigator-assessed progression-free survival (PFS). Osimertinib prolonged PFS more than double as compared to chemotherapy (10.1 months vs 4.4 months) with hazard ratio of 0.30 (95%CI: 0.23, 0.41; $p<0.001$), and increased objective response rate – ORR 65% (95% CI: 59%, 70%) and 29% (95% CI: 21%, 37%) in osimertinib and chemotherapy arms, respectively ($p<0,0001$). In patients with brain metastases, osimertinib prolonged PFS as compared to pemetrexed doublet chemotherapy (8.5 months vs 4.2 months). The proportion of adverse events grade 3 or 4 was lower with osimertinib than with chemotherapy (23% vs 47%). In conclusion, osimertinib provides higher efficacy than pemetrexed doublet chemotherapy in EGFR T790M-positive NSCLCs after first line EGFR-TKI treatment, even in the presence of brain metastases.

Based on this study, the U.S. Food and Drug Administration granted regular approval to osimertinib for the treatment of patient with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), after disease progression on EGFR-TKI treatment.

Acquired EGFR C797S Mutation Mediates Resistance to AZD9291 in Non-Small Cell Lung Cancer Harboring EGFR T790M

Thress KS, Paweletz CP, Felip E, Cho BC, Stetson D, Dougherty B, et al.

Nat Med 2015;21(6):560-2.

<http://www.nature.com/nm/journal/v21/n6/full/nm.3854.html?foxtrotcallback=true>

In this article, the cell-free plasma DNA (cfDNA) from NSCLC subjects whose tumors had developed resistance to the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) AZD9291 during AURA clinical trial was studied. This study detected an acquired resistance to AZD9291 in EGFR C797S mutation, using next-generation sequencing, and provides mechanism of acquire resistance to AZD9291.

Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors.

Jia Y, Yun CH, Park E, Ercan D, Manuia M, Juarez J, et al.

Nature 2016;534(7605):129-32.

<http://www.nature.com/nature/journal/v534/n7605/full/nature17960.html?foxtrotcallback=true>

This article is highlighting the need for alternative mechanism to overcome acquired resistance to T790M and C797S, and the discovery of EAI045, an allosteric inhibitor that targets selected drug-resistant EGFR mutants and wild-type receptor. The compound inhibits L858R/T790M-mutant EGFR with low-nanomolar potency, synergized with cetuximab, an antibody therapeutic that blocks EGFR dimerization. EAI045 in combination with cetuximab is effective in mouse models of lung cancer driven by EGFR(L858R/T790M) and by EGFR (L858R/T790M/C797S). This finding utilized targeting allosteric sites to obtain mutant-selective inhibitors.

A Phase Ib/II Study of Afatinib in Combination with Nimotuzumab in Non-Small Cell Lung Cancer Patients with Acquired Resistance to Gefitinib or Erlotinib

Lee JY, Sun JM, Lim SH, Yoo KH, Jung KS, Song HN, et al.

Clin Cancer Res 2016;22(9):2139-45.

<http://clincancerres.aacrjournals.org/content/22/9/2139.long>

An approach for treatment beyond progression after EGFR TKI treatment that developed secondary acquired resistance exon 20 T790M was explored on dual targeting EGFR. In cancer cell line, combined treatment of EGFR TKIs and anti-EGFR monoclonal antibodies (mAbs), resulted in increased antitumor activity than single agent. Afatinib is an oral, irreversible pan ErbB family blocker. Nimotuzumab, a humanized IgG1 mAb against EGFR, with moderate activity. In this study, eligible patients, with advanced NSCLC with EGFR mutation (exon 19 deletion or exon 21 L858R) after progression with first-generation EGFR TKI were included. Afatinib 40mg was given with nimotuzumab 100mg or 200mg. Overall response rate was 23%, and median duration of response was 4.3 months. The median progression-free survival was 4.0 months (95% CI, 2.3-5.7months) and overall survival was 11.7 months (95% CI, 9.4-14.0). adverse effects includes diarrhea, skin rash, acne, fatigue. This study demonstrates a combination of afatinib and nimotuzumag showed acceptable safety profile and encouraging antitumor activities in advanced, secondary acquired resistance EGFR mutation NSCLC.

Dacomitinib versus Gefitinib for the First-Line Treatment of Advanced EGFR Mutation Positive Non-Small Cell Lung Cancer (ARCHER 1050): a Randomized Open-Label Phase III Trial

J Clin Oncol 2017;35(18):LBA9007.

Mok T, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al

http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18_suppl.LBA9007

This is a first phase III trial comparing Dacomitinib, a second-generation EGFR TKI, with gefitinib, as first-line therapy in patient with EGFR-activating mutation positive advanced NSCLC. In this study, newly diagnosed NSCLC patient with EGFR-activating mutation were randomized 1:1 to Dacomitinib (45mg once daily) or Gefitinib (250mg once daily). The primary end-point was progression free survival (PFS), secondary endpoint were Overall Survival (OS), objective response rate (ORR), duration of response (DR), PFS per Investigator (INV), time to treatment failure (TTF), restricted mean survival time (RMST) for PFS, safety and patient-reported outcomes (PROs). The ITT was 452 patients, with well balanced between arms. Median PFS was significantly longer in Dacomitinib group (14.7 months vs 9.2 months for gefitinib; $p < 0.0001$), and DR per IRC in responders was 14.8 months for Dacomitinib and 8.3 months for Gefitinib ($p < 0.0001$). Overall survival is still premature in this study. In this study, dacomitinib provides new data to be offered as a new first line treatment option in EGFR activating mutation positive NSCLC.

Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial.

Kim DW, Tiseo M, Ahn MJ, Reckamp KL, Hansen KH, Kim SW, et al.

J Clin Oncol 2017;May 5:JCO2016715904

<http://ascopubs.org/doi/full/10.1200/JCO.2016.71.5904>

Brigatinib is a next-generation ALK-inhibitor for crizotinib-refractory ALK-positive NSCLC. This Phase II study assessed two drug dose (90mg vs 180mg) in stratified NSCLC patients by brain metastases and best response to crizotinib. Subjects were randomly assigned (1:1) to receive Brigatinib 90mg once daily (arm A), or 180mg once daily with a 7-day lead-in at 90mg (arm B). Primary end point was investigator-assessed confirmed objective response rate (ORR). A total 222 patients (Arm A n=112, 109 treated; arm B n=110, 110 treated), 154 (54%) with brain metastases and 164 (74%) received prior chemotherapy. ORR was 45% (97.5% Ct, 34% to 56%) in arm A and 54% (97.5%CT, 43% to 65%) in Arm B. Progression-free survival was 9.2 months (95% CI, 7.4-15.6) and 12.9 months (96% CI, 11.1 to not reached) in arm A and B respectively. ORR in brain metastases subject was 42% (11 of 26 patients) and 67% (12 of 18 patients) in arm B. Among patients with intracranial response, 78% of patients in Arm A and 68% in arm B maintained an intracranial response for at least 4 months. The most common adverse reactions were nausea, diarrhea, fatigue, cough, and headache. The most common serious adverse reactions were pneumonia and ILD/pneumonitis (3.7%).

Based on this study, the U.S. Food and Drug Administration granted accelerated approval to brigatinib for the patient with metastatic anaplastic lymphoma kinase (ALK)-positive NSCLC who have progressed on or are intolerant to crizotinib.

Topics in Focus issue in Respiriology:

Lung cancer practice, implementing evidence around the world.

Series Editors: Nico van Zandwijk and Kwun M. Fong

Maintenance Erlotinib versus Erlotinib at Disease Progression in Patients with Advanced Non-Small Cell Lung Cancer Who Have Not Progressed Following Platinum-Based Chemotherapy (IUNO Study)

Cicenas S, Geater SL, Petrov P, Hotko Y, Hooper G, Xia F, et al.

Lung Cancer 2016;102:30-37.

[http://www.lungcancerjournal.info/article/S0169-5002\(16\)30504-9/fulltext](http://www.lungcancerjournal.info/article/S0169-5002(16)30504-9/fulltext)

This study assessed the benefit of maintenance erlotinib versus erlotinib at progression in advanced/metastatic NSCLC after four cycles of platinum-based chemotherapy. In this phase III study, 643 advanced NSCLC with no known EGFR-activating mutation were randomized to receive erlotinib (n=322) or placebo (n=321), until disease progression, and both arm received erlotinib ("late erlotinib") on disease progression. Both arm also received second-line chemotherapy or best supportive care. The primary endpoint was overall survival (OS).

Median OS was 9.7 and 9.5 months with maintenance therapy and "late erlotinib" respectively (HR, 1.02, 95% CI: 0.85-1.22; log-rank $p=0.82$). This study concludes maintenance erlotinib was not superior to second-line treatment in patients whose tumor did not harbor and EGFR-activating mutation.

First-Line Ceritinib versus Platinum-Based Chemotherapy in Advanced ALK-Rearranged Non-Small Cell Lung Cancer (ASCEND-4): a Randomised, Open-Label, Phase III Study.

Soria JC, Tan DS, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al.

Lancet 2017;389:917-29.

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)30123-X/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30123-X/fulltext)

This study was to seek benefit of first-line ceritinib in ALK-rearranged advanced NSCLC over chemotherapy. This study was done in 134 centers 28 countries with 376 patients randomly assigned to received ceritinib 750mg/day (n=189) or platinum-based chemotherapy (cisplatin 75mg/m² or carboplatin AUC 5-6 plus pemetrexed 500mg/m²) every 3 weeks for four cycles followed by maintenance pemetrexed. Primary endpoint was progression-free survival, by blinded independent review committee. Between August 19, 2013 and May 11, 2015 the median PFS was 16.6 months (95% CI 12.6-27.2) in the ceritinib group and 8.1 months (5.8-11.1) in chemotherapy group (HR 0.55, 95% CI 0.42-0.73; $p<0.00001$). The most common adverse events were diarrhea, nausea, vomiting and increase in ALT. This results showed first-line ceritinib significantly increased progression-free survival versus chemotherapy, in patient with advanced ALK-rearranged NSCLC. Based on this study, ceritinib received approval for patients with ALK-positive metastatic NSCLC with anaplastic lymphoma kinase (ALK)-positive as detected by and FDA-approved test.

New
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Online ISSN: 2051-3380

Alectinib versus Crizotinib in Patients with ALK-Positive Non-Small Cell Lung Cancer (J-ALEX): An Open-Label, Randomised Phase 3 Trial.

Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, et al.

Lancet 2017;390:29-39.

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)30565-2/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30565-2/abstract)

This trial is open-label, randomised phase 3 trial comparing alectinib versus crizotinib in ALK-positive naive Japanese patients, who were chemotherapy naive or had received one previous chemotherapy regimens from 41 study sites in Japan. Patients were assigned 1:1 alectinib or crizotinib unless diseases progression, unacceptable toxicity, death, or withdrawal. Primary endpoint was progression-free survival assessed by an independent review. 207 patients were recruited and assigned to alectinib (n=103) or crizotinib (n=104). Median progression-free survival had not yet been reached with alectinib (95% CI 20.3-not estimated) and was 10.2 months (8.2-12.0) with crizotinib. Grade 3 or 4 adverse events occurred more frequent in crizotinib (54 or 52% of 104) than alectinib (27 or 26% of 103). This study provide efficacy and tolerability of alectinib compared to crizotinib in ALK-positive advanced NSCLC.

Alectinib versus Crizotinib in Treatment-Naive Advanced ALK-Positive Non-Small Cell Lung Cancer (NSCLC): Primary Result of the Global Phase 3 ALEX study

Shaw AT, Peters S, Mok T, Gadgeel SM, Ahn JS, Ou S-H I, et al.

J Clin Oncol 2017;35(18):SLBA9008 (ASCO)

http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18_suppl.LBA9008

Alectinib, a tyrosine kinase inhibitor is FDA approved for the treatment of ALK-rearranged advanced NSCLC after progression with crizotinib on end of 2015. In previous study of Japanese population (J-ALEX study) showed superiority of alectinib 300ng vs crizotinib in ALK-rearranged NSCLC-crizotinib naive Japanese patients. In this open-label randomized multicenter phase III study, ALK+ NSCLC patients (n=303) determined by IHC testing was randomized 1:1 to receive alectinib 600mg or crizotinib 230mg BiD. Primary endpoint: investigator-assessed PFS (RECIST v1.1), with systematic CNS imaging in all patients. Secondary endpoint were independent review committee (IRC)-assessed PFS, IRC-assessed time to CNS progression (TTP), objective response rate (ORR), overall survival (OS) and safety. By February 2017, alectinib reduced risk or progression/death by 53% (HR 0.47, 95% CI 0.34-0.65, p<0.0001). Median PFS was not reached in alectinib group (95% CI 17.7-NE) and 11.1 months in crizotinib (95% CI 9.1-13.1). Secondary endpoints alectinib vs crizotinib respectively: median PFS 25.7 months (95% CI 19.9-NE0 vs 10.4 months (95% CI 7.7-14.6); CNS TTP, cause-specific HR of CNS progression 0.16 (95% CI 0.10-0.28; p<0.001), ORR (Inv (83% (95% CU 76-89) vs 76% (95% CI 68-82) p=0.09; OS based on 25% events HR 0.76 (95% CI 0,48-1.2; p=0.24). Grade 3 and 4 Aes were less frequent with alectinib 41%vs50% with crizotinib, fatal Aes occurred in 3% vs 5%.

This study showed that alectinib showed superior efficacy and favorable tolerability as compared with crizotinib.

Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small Cell Lung Cancer

Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al.

New Eng J Med 2017, June 6 2017 (online publication)

<http://www.nejm.org/doi/full/10.1056/NEJMoa1704795>

This is an open-label, phase 3 trial, randomized to assign 303 ALK-positive NSCLC to receive either alectinib (600mg twice daily) or crizotinib (250 mg twice daily). The primary endpoint was investigator-assessed progression-free-survival. Secondary endpoints were independent review committee-assessed progression-free survival, time to CNS progression, objective response rate, and overall survival. The PFS of this study was higher in alectinib than crizotinib (12-month event-free survival rate, 68.4% (95% CI 61.0 to 75.9) with alectinib vs 48.7% (95% CI 40.4 to 56.9) with crizotinib; hazard ratio for disease progression or death 0.47 (95% CI, 0.34 to 0.65); $p < 0.001$). The median progression-free survival with alectinib was not reached. A total of 18 patients (12%) in alectinib group had an event of CNS progression, as compared to 68 patients (45%) in crizotinib group (cause-specific hazard ratio, 0.16; 95% CI, 0.1 to 0.28; $p < 0.001$). Response rate was 82.9% (95% CI 76.0 to 88.5) and 75.5% (95% CI 67.8 to 82.1; $p = 0.09$). Grade 3 to 5 adverse events were less frequent with alectinib (41% vs 50% with crizotinib).

As conclusion, alectinib showed superior efficacy and lower toxicity for first-line treatment of ALK-positive NSCLC as compared to crizotinib.

Efficacy and Safety of Lorlatinib in Patients (pts) with ALK+ Non-Small Cell Lung Cancer (NSCLC) with One or More Prior ALK Tyrosine Kinase Inhibitor (TKI): a Phase I/II Study.

Shaw AT, Ou S-H I, Felip E, Bauer TM, Besse B, Gadgeel SM, et al.

J Clin Oncol 2015;35(15):supp 9006.

http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9006

Lorlatinib is a next generation ALK/ROS1 TKI against most known resistant mutation, selective, and potent. In phase I study, lorlatinib showed robust activity in ALK+ or ROS+ advanced NSCLC patients in most of CNS metastases, and heavily treated. This Phase I/II seeks efficacy and safety based on prior ALK TKI therapy. Primary objective was ORR and intracranial ORR (IC-ORR), by independent central review. In this study, lorlatinib showed compelling clinical activity, in ALK+ patients who received ≥ 1 prior ALK TKI.



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