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Overcoming Resistance to EGFR-Tkis: The Potential Role of Third-Generation Inhibitors

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Introduction

The last decade has witnessed a silent revolution in the treatment of lung cancer: several randomized phase III studies have shown that EGFR-tyrosine kinase inhibitors (TKIs) significantly improve both response rate (RR), progression free survival (PFS) and quality of life (QoL) compared to platinum-based chemotherapy as first-line treatment of EGFR-mutated NSCLC patients [1-8]. Recently a pooled analysis of both LuxLung3 and LuxLung6 trials showed also an overall survival (OS) benefit in favour of the EGFR-TKI Afatinib, limited to the subgroup of patients with EGFR exon 19 deletion [9]. Overall, the results of all such studies convincingly and consistently demonstrated that for the 12% of patients whose tumors harbor an EGFR activating mutation, the optimal treatment strategy is starting with an EGFR-TKI, including gefitinib, erlotinib, or afatinib [10]. However, despite the great efficacy of these targeted agents, the majority of patients will develop disease progression (PD), usually within 1 year of treatment, because of the occurrence of acquired resistance [11]. Until last year, all the international guidelines recommended to continue the ongoing EGFR-TKI beyond PD, with or without loco-regional therapies, except for symptomatic, systemic progressions, which required platinum-chemotherapy treatment. It was supported by the results of the ASPIRATION study, which, even if limited by several weakness, have shown that continuing erlotinib beyond RECIST PD, would benefit a subgroup of patients with limited PD [12]. The identification of the molecular alterations underlying the development of resistance has led to the advent of a new class of TKIs, which have shown very promising activity in clinical setting, causing a paradigm shift in the management of patients who progressed to a first-generation TKI. Among the different mechanisms of acquired resistance, the secondary T790M point mutation in exon 20 of EGFR gene is described in about 50% of cases, followed by cMET amplification (5-15%), Her2 mutaions (3-12%), small cell lung cancer transformation (3-10%), and others [13,14]. Particularly, T790M gatekeeper mutation represents the most common alteration responsible for the development of resistance to first-generation TKIs, inducing both steric hindrance and increased binding affinity for adenosine triphosphate (ATP), which ultimately results in the reduction of both binding and potency of reversible TKIs [14]. The understanding of such molecular networks favoured the advent of third-generation, irreversible TKIs, which thanks to their peculiar pyrimidine-based structure, are able to target and inhibit not only EGFR activating mutations, but also the resistant T790M [15]. A very promising activity and a tolerable safety profile of such compounds emerged from the phase I studies, including patients with EGFR-mutated NSCLC who progressed to first-line EGFR-TKI (Table 1). Osimertinib (AZD9291) represents the compound in most advanced stage of clinical development. The AURA1 study has first shown an impressive ORR: 60%, DCR: 95%, PFS: 9.6 months in the subgroup of patients with 790M mutation, leading to the fast-track approval by regulatory authorities for the treatment of T790M-positive patients who develop resistance to first-generation TKIs [16]. Now we are eagerly waiting for the results of the phase III randomized confirmatory AURA III trial, comparing osimertinib *vs.* platinum-based chemotherapy in second-line setting. However the international guidelines have already incorporated osimertinib as recommended option for patients who progressed to first-generation TKI and are 790M-positive. As this new targeted agent is now available, re-biopsy at progression became mandatory, in order to determining tumor molecular profile and identifies T790M mutation or other mechanisms of acquired resistance. Growing evidences support the use of liquid biopsy to overcome several limitations of tissue biopsy [14]. Recent studies demonstrated that T790M mutation could be effectively detected by using plasma circulating tumor DNA (ctDNA) in NSCLC patients who progressed after EGFR-TKI [17]. Particularly, Oxnard et al. showed that outcomes of T790M-positive patients included in AURA1 study were similar if T790M was detected in plasma or tumor tissue. Conversely both RR and PFS of T790M-negative patients on plasma were significantly higher than T790M-negative on tissue, and further tumor genotyping of plasma T790M-negative patients allowed identifying a subgroup of T790M-positive patients on tumor tissues who had better outcomes. According to these data the authors supported plasma genotyping for the detection of T790M status at the time of PD. However, because of 30% false negative rate, patients with T790M-negative on plasma should repeat tumor biopsy [18]. In addition to plasma, urine genotyping has also shown a high sensitivity (75%) in T790M genotyping in preliminary studies [19], and is currently under investigation in trials including larger cohorts of patients. To date we are witnessing a second revolution in the management of EGFR-mutated NSCLC. Third generation EGFR-inhibitors seem to be very promising drugs, which thanks to their great activity and tolerable safety profile, will offer a new potential of cure for patients who failed first-generation EGFR-TKI and are T790M-positive. Osimertinib may be considered the first in class of such new family of compounds, as it has been already approved for clinical use, representing a new available weapon to overcome tumor resistance and ultimately improve patients' survival.

EGFR-TKI	Dose	ORR	Toxicity	Status
AZD9291	80 mg QD	61%	Diarrhea, rash, nausea, ILD	Phase III (Approved)
CO-1686	500 mg BID	45%	Hyperglicemia, nausea, diarrhea	Stopped
HM61713	800 mg QD	43%	Diarrhea, rash, nausea, dry skin	Phase II

EGF816	320 mg/day	44%	Rash, Diarrhea, stomatitis, pruritus	Phase II
ASP 8273	300 mg QD	38%	Diarrhea, nausea, vomiting, rash, ILD	Phase II
AC 0010	250 mg BID	62%	Diarrhea, ALT/AST rash, pruritus, nausea	Phase I

Table 1: Third-generation EGFR-TKIs in clinical development in NSCLC.

References

1. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, et al. (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361: 947-957.
2. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, et al. (2010) 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 11: 121-128.
3. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, et al. (2010) Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362: 2380-2388.
4. Han JY, Park K, Kim SW, Lee DH, Kim HY, et al. (2012) First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 30: 1122-1128.
5. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, et al. (2012) 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 13: 239-246.
6. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, et al. (2011) 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. 12: 735-742.
7. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, et al. (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31: 3327-3334.
8. Wu YL, Zhou C, Hu CP, Feng J, Lu S, et al. (2014) 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 15: 213-222.
9. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, et al. (2015) Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 16: 141-151.
10. Bronte G, Rolfo C, Giovannetti E, Cicero G, Pauwels P, et al. (2014) Are erlotinib and gefitinib interchangeable, opposite or complementary for non-small cell lung cancer treatment? Biological, pharmacological and clinical aspects. Crit Rev Oncol Hematol 89: 300-313.
11. Rolfo C, Giovannetti E, Hong DS, Bivona T, Raez LE, et al. (2014) Novel therapeutic strategies for patients with NSCLC that do not respond to treatment with EGFR inhibitors. Cancer Treat Rev 40: 990-1004.
12. Park K, Yu CJ, Kim SW, Lin MC, Sriuranpong V, et al. (2016) First-Line Erlotinib Therapy Until and Beyond Response Evaluation Criteria in Solid Tumors Progression in Asian Patients With Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer: The ASPIRATION Study. JAMA Oncol 2: 305-312.
13. Socinski MA, Villaruz LC, Ross J (2016) Understanding Mechanisms of Resistance in the Epithelial Growth Factor Receptor in Non-Small Cell Lung Cancer and the Role of Biopsy at Progression. Oncologist .
14. Passiglia F, Bronte G, Castiglia M, Listì A, Calò V, et al. (2015) Prognostic and predictive biomarkers for targeted therapy in NSCLC: for whom the bell tolls? Expert Opin Biol Ther 15: 1553-1566.
15. Gao X, Le X, Costa DB (2016) The safety and efficacy of osimertinib for the treatment of EGFR T790M mutation positive non-small-cell lung cancer. Expert Rev Anticancer Ther 16: 383-390.
16. Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, et al. (2015) AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 372: 1689-1699.
17. Sueoka-Aragane N, Katakami N, Satouchi M, Yokota S, Aoe K, et al. (2016) Monitoring EGFR T790M with plasma DNA from lung cancer patients in a prospective observational study. Cancer Sci 107: 162-167.
18. Oxnard GR, Thress KS, Alden RS, Lawrance R, Paweletz CP, et al. (2016) Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 34: 3375-3382.
19. Reckamp KL, Melnikova VO, Karlovich C, Sequist LV, Camidge DR, et al. (2016) A Highly Sensitive and Quantitative Test Platform for Detection of NSCLC EGFR Mutations in Urine and Plasma. J Thorac Oncol 11: 1690-1700.