Effectiveness and safety of Osimertinib on non-small cell lung cancer therapy

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Abstract. Lung cancer is a disease causing millions of deaths around the globe without adequate means of medical treatment. As one subtype of lung cancer, non-small cell lung cancer (NSCLC) involves mutations in epidermal growth factor receptor (EGFR) and is commonly treated with EGFR tyrosine kinase inhibitors (TKI). Yet, cancer cells adapt and resist rapidly to TKIs and constant updates are required. Osimertinib (AZD9291) is the latest generation of EGFR-TKI designed to inhibit EGFR mutation and T790M, a second-site genetic mutation responsible for EGFR-TKI resistance. Nearly two-thirds of NSCLC patients who are EGFR mutation-positive and experience resistance after being treated with an EGFR-TKI develop the T790M mutation, for which there have been limited treatment options. Osimertinib arises as a potent drug against metastatic EGFR T790M mutation-positive NSCLC. Osimertinib has undergone an elevated FDA approval process to the market. This review summarizes clinical trials of different phases to illustrate the effectiveness of Osimertinib against NSCLC, as well as variable mutations in Osimertinib resistant patients. Further studies are required to address Osimertinib’s toxicity as well as treatments against resistance to Osimertinib.

Keywords: Non-small cell lung cancer, Osimertinib, tyrosine kinase inhibitor, EGFR, T790M

1. Introduction

Non-small cell lung cancer (NSCLC) is a collective name for a kind of lung cancer with a certain group of cancer cells under a microscope, including squamous cell carcinoma, large cell carcinoma, adenocarcinoma, and other rare lung cancers [1]. It is agreed that a major cause to NSCLC is smoking, i.e., those who have smoked or have been around smoke harbour a higher chance of getting lung cancer than others. Symptoms include coughing up blood, shortness of breath, wheezing, etc. [1] Moreover, NSCLC is metastatic, meaning that cancer cells can invade other parts of the body and cause more severe consequences. Studies have shown that the rate of its metastasis is as high as 47%, with common sites including bone, lungs, brain, adrenal glands and liver. [8] EGFR is found to be a frequently over-expressed protein in NSCLC patients [2]. The specificity of target offers great potential for targeted therapies for NSCLC.

From another perspective, NSCLC is less sensitive to traditional treatments such as chemotherapy compared to small cell lung cancer, making novel means of intervention necessary [1]. Lung cancer is also one of the major causes of death around the globe. Take USA for instance: there will be 236,740 estimated new cases and 130,180 deaths in 2022; the five year survival rate of patients with lung cancer from 2011 to 2017 is only 22% [1]. Altogether, the research into drug effectiveness, specifically EGFR-TKIs, is essential.

EGFR is a family of four members, EGFR itself, ErbB2 (HER2/Neu), ErbB3 (HER3) and ErbB4 (HER4). EGFR as a receptor tyrosine kinase consists of an extracellular ligand-binding domain, a transmembrane lipophilic domain, and an intracellular tyrosine kinase domain [3]. The members of EGFR family each has slight differences in the structures and properties in their domains, making it too complicated to be articulated. The general idea is that receptor tyrosine kinase is activated first through either dimerization of ligand-induced receptor or alteration of a pre-existing dimer. Intracellular kinase domain is then stimulated, together with auto phosphorylated tyrosine. Phosphorylation of the tyrosine triggers essential signalling pathways that regulate various cellular processes critical to proliferation, and cell survival.
EGFR mutation is either E19del, an in-frame deletion within exon 19, or L858R, a leucine-to-arginine point mutation at codon 858, both in its catalytic tyrosine kinase domain [3]. Through similar mechanisms, both mutation results in constitutive activation of signalling pathways such as Ras/Raf/MAPK, PI3K/Akt/mTOR, causing rapid growth of NSCLC cells [3].

The discovery of Osimertinib was initiated on year 2009, aiming to cope with T790M mutation by binding reversibly to inhibit EGFR. A compound was found having a remarkably high affinity to L858R/T790M EGFR compared to wide type, building the structural foundation. Further modifications were made to enhance the binding, as well as to reduce to the lipophilicity of the compound, all to raise its biochemical activity and effectiveness, finally gave birth to Osimertinib [9].

This review summarizes clinical trials of Osimertinib. Those trials offer essential data for the safety and effectiveness of Osimertinib as an inhibitor for EGFR-T790m mutation. Meanwhile, the potential reasons for resistance of cancer cells to Osimertinib is discussed, warning the field to develop again new generations of EGFR-TKI.

2. EGFR-Tkis

EGFR-TKIs are a class of drugs with inhibit the activity of EGFR, blocking downstream signalling pathways so that the cancer cells cannot proceed its division. There are three generations of EGFR-TKIs, in which Osimertinib is the third generation.

2.1. First generation

First generation of drugs targeting EGFR mutation are tyrosine kinase inhibitors (TKI), which acts by inhibiting autophosphorylation of the EGF receptor, thus inhibiting the binding of ATP to the tyrosine kinase domain [3]. This block hampers cell proliferation, ultimately leading to cell death. Erlotinib and gefitinib are two examples. Numerous research studies have proved the therapeutic efficacy of two drugs. For instance, lung cancer cell line PC9 with a deletion (del 746-750) in exon 19, as well as another lung cancer cell line H3255 with the L858R mutation in EGFR exon 21 are both proved to be sensitive to inhibition effect by gefitinib [4]. Further studies identified Akt and STAT 5 as major signalling pathways activated by mutant EGFR and patients with phosphorylated AKT–positive tumours had reasonably higher response rates, longevity and therapeutic effects when treated with gefitinib or erlotinib [4].

2.2. Second generation

Although first generation EGFR-TKI is significant in its treatment against NSCLC, second-site mutations typically occur in one year of treatment, rendering cancer cells resistant to TKIs. One important mutation is the acquired threonine-to-methionine mutation at codon 790 (T790M) within exon 20, accounting for half of all cases with resistance to first-generation TKI [3]. The mutation sits within the ATP-binding site of EGFR’s catalytic tyrosine kinase domain, affecting binding of TKI to EGFR by enhancing the affinity of the ATP receptor and reducing the potency of competitive EGFR TKIs, sterically hindering the binding of first-generation EGFR-TKIs to the ATP-binding site of EGFR [3, 5].

T790M increases the ATP affinity of the oncogenic L858R mutant significantly, leading to resistance to gefitinib/erlotinib. The T790M mutation also harbours escalated phosphorylating activity, especially cooccurring with the L858R mutation.

There is also another resistance mechanism in which kinase domains of EGFR and HER2/ErbB2 experience in-frame insertions in exon 20.

To cope with T790M mutation which develops first generation TKI resistance, inhibitors can be engineered to have a higher affinity for the T790M kinase than that of ATP for the mutant kinase [4]. This fuels the birth of second-generation EGFR-TKI, such as afatinib, dacomitinib, and neratinib. Afatinib as a pan-ErbB family inhibitor acts by a wide spectrum blocking in EGFR, HER2, and HER4
(ErbB4) through its binding to cysteine 797 of the EGFR and cysteines 805 and 803 of HER2 and HER4, respectively [3]. In this way, downstream signalling is inhibited.

Yet, second-generation EGFR-TKI is not promising enough to be an adequate treatment due to its severe side effects resulting from toxic nonselective inhibition of wild-type EGFR [6]. There comes the third-generation EGFR-TKI, namely Osimertinib.

2.3. Third generation-Osimertinib

Osimertinib is a mono-anilino-pyrimidine small molecule. Compared with second-generation TKI, which inhibits EGFR indiscriminately, Osimertinib inherits the merit that it can selectively bind to mutant EGFR, with ninefold lower affinity to wild-type EGFR [6]. This has decreased drug toxicity significantly. Osimertinib binds irreversibly to L858R and T790M mutant forms of EGFR via the C797 amino acid covalent bond, thus blocking several signalling pathways downstream [6].

3. Clinical trials

3.1. Phase I

Phase I clinical trials of Osimertinib aim to assess the safety and pharmacokinetics, involving a non-randomized, open-label single dose study [7]. 8 healthy volunteers with an average age of 42 years are given a solution of 20mg Osimertinib containing a nominal dose 1 μCi (0.037 MBq) at day 1 and closely monitored by a month. The primary pharmacokinetics data suggest that 81.9% of radioactively labelled drug dose was recovered from urine and feces up to day 85 [7]. Secondary data indicates that after ingestion, Osimertinib is decomposed to produce two major pharmacologically circulating metabolites, AZ5104 and AZ7550 with approximately the same concentration [7]. No severe adverse effects were observed among the 8 volunteers. Nevertheless, there were other adverse, non-serious events, including asthenopia, constipation, nausea, laceration, otitis media, back pain, headache, etc., with the highest number of volunteers suffering from headache (5 of 8) [7].

3.2. Phase II

Phase II studies of Osimertinib establish the drug’s effectiveness on NSCLC, involving two phase II studies, or AURA trials.

The first study involves 603 patients who had already received anti-cancer treatments with EGFR-TKIs but had their tumors regrow. This was also the first time Osimertinib was experimented on human patients with NSCLC. Patients were grouped into 6 cohorts including AZD9291 80mg Extension, dose escalation, dose expansion, first Line, 80mg Tablet and Japan cytology [10]. Patients are monitored through RECIST tumor assessments every six weeks during 21 months. RECIST, fully named Response Evaluation Criteria in Solid Tumors, is a standard way to measure the extent how
cancer patients respond to a particular treatment. Responses include complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD) [11].

Primary outcomes include objective response rate (ORR) of the two cohorts and best objective response (BOR) for dose escalation population. ORR is defined as having either complete response, which is disappearance of all target lesions and non-target lesions and no new lesions, or partial response, which is decrease in the sum of diameters of Target Lesions (compared to baseline) and no new lesions) [10]. Among more than 175 patients in dose expansion cohort, the ORR value is 61.7%; among 189 patients in 80mg AZD9291 extension cohort, ORR is 61.3% [10]. Similarly, BOR also includes CR (complete response) and PR (partial response), but also three additional parameters: progressive disease (PD), 20% increase in the sum of diameters of TLs, stable disease (SD), no sufficient growth or shrink of TLs, and not evaluable (NE). Among the 31 patients in dose escalation cohort, PR is 58.1%, SD is 19.4%, PR is 16.1%, and NE is 6.5% [10].

The first secondary outcome is duration of response (DoR) for dose expansion population, referred to the duration of CR and PR. The median value is 11.1 months. Another is progression-free survival (PFS) for dose expansion population, referred to as the time from the first dose to PD or death. The median value is 9.7 months. Third is best objective response (BOR) for 80mg AZD9291 Extension Population, with 0.5% CR, 70.1% PR, 22.9% SD, 6% PD and 0.5% NE [10].

Overall, the first AURA trial demonstrates Osimertinib’s effectiveness against advanced NSCLC and is the first clinical trial operating on patients. Yet, the study focuses only marginally on T790M positive NSCLC (only Japanese cohort), which is often the primary cause of tolerance to earlier generations of EGFR-TKIs. The second AURA trial, on the other hand, places its primary aim on T790M positive NSCLC.

Similarly, AURA 2 also employs RECIST to illustrate 210 patients’ response to Osimertinib. Patients are first given a biopsy to ensure that they are T790 positive. They ingest 80mg of Osimertinib daily for 11 months, and monitored every 6 weeks [12].

Primary outcome indicates that among 199 patients, ORR value is 70.9%. Secondary outcomes indicate that among 141 patients, the duration of response is 7.8 months [12]. Disease control rate, which is defined as the percentage of patients showing either CR, PR or SD after treatment, is 91.5%. Last but not least, among 210 patients, PFS is 8.6 months [12].

Both clinical trials reveal side effects of Osimertinib. In AURA I trial, the percentage of patients developing adverse events are approximately 25% of total population, and almost all patients develop non-serious adverse events [10]. Similarly, in AURA II trial, the percentage of patients developing adverse events is 20% of total population, and 91% of patients develop non-serious adverse events. This put the safety of Osimertinib at question, despite its impressing effectiveness against T790M NSCLC.

3.3. Phase III

Phase III trials are designed to be the definitive assessment of how effective the drug is and typically have a longer interval than phase II trials. This article cites a phase III study initiated in September 2015 and ended in April 2019 [13]. Patients are those with advanced NSCLC with T790M mutation and are provided with Osimertinib treatment as long as it is still exerting clinical benefit. This multinational and multi-center study has 3017 patients. They are given 80mg of Osimertinib once a day [13].
Table 1. Clinical trials of Osimertinib

| Phase | Design | Subjects | Treatment | Results | References |
|-------|--------|----------|-----------|---------|------------|
| I     | SC, NR, OL study | 8 healthy adults | 20 mg oral dose at day 1 | No severe adverse events | [7] |
| II    | SG, OL study | 603 Pre-treated T790M+ patients | 80 mg oral dose daily | High percentage of response, prolonged survival | [10] |
| II    | OL, SG study | 210 Pre-treated T790M+ patients | 80 mg oral dose daily | High percentage of response, prolonged survival | [12] |
| III   | OL, SG study | 3017 T790M+ patients | 80 mg oral dose daily | Prolonged survival, reduced tumor progression | [13] |
| III   | DB, R, PC | 682 patients with stage IB-III A NSCLC with T790M+ mutation | 80-40 mg oral dose daily | Prolonged survival, reduced tumor progression than placebo | [14] |

The first primary outcome is the overall survival of patients, as referred to the time when the subject receives the first dose to his/her death. Among 3014 patients, overall survival is 22.8 months [13]. The second primary outcome is the number of patients with adverse events or non-serious adverse events. Among 3014 patients, a third of them exhibit adverse events, and 152 of them are severe enough to cause death [13].

The first secondary outcome is progression free survival of 11.1 months among 3014 patients [13]. Time to treatment discontinuation follows as a summary to PFS, which is the time from the first dose of Osimertinib to discontinuation of treatment, regardless of its reason. Among 3014 patients, TTD is 13.4 months. Last but not least, response rate, the number of patients with a best response, is 57.3% among 2900 patients [13].

Overall, the mortality rate of this phase III study is considerably elevated compared to phase II study to 45%, near a half. 21.8% patients show adverse events and 12.6% patients show non-serious adverse events [13]. Such result not only demonstrates Osimertinib’s effectiveness in lengthening patients’ longevity, but also points out the potential safety hazards in receiving treatment of Osimertinib.

On the other hand, another phase III study was double-blind, randomized, and placebo-controlled, involving 682 patients with stage IB-IIIA NSCLC with T790M mutation. Both Osimertinib and placebo were offered 80mg once daily, which later decreased to 40mg daily [14].

The primary outcome is disease free survival (DFS), which is from the date of oral dosing to the date of disease recurrence or death. For 339 patients dosing with Osimertinib, their DFS is not available, meaning that no significant disease recurrence toward the end of study, elongated than that for 343 patients with placebo, whose DFS is 27.5 months [14]. Furthermore, the DFS rate of Osimertinib patients is 89.1% at 2 years and 78.9% at 3 years; that for placebo patients is only 52.4% at 2 years and 40% at 3 years. The overall survival rate for Osimertinib patients at 2 years is 99.6%, and 93.9% at 3 years; that for placebo patients at 2 years is 94.7% and 91.8% at 3 years [14].

Among 337 Osimertinib patients, 16% of them developed serious adverse events while 92% of them developed non-serious adverse events, which is quite consistent with safety data from the first study [14].

Different from the first study, this study involved a comparison between Osimertinib and placebo, and experimented patients were not at advanced stages of NSCLC so had a longer survival. The relatively early stages of patients also allowed researchers in second study to focus more on long-term patient survival than short-term responses. Nevertheless, both studies indicate the effectiveness of Osimertinib and suggest similar rate of side effects.
4. Resistance to Osimertinib

Despite the potent therapeutic effect of Osimertinib against T790M positive NSCLC, it is discovered that tertiary mutation occurs to impair Osimertinib, leaving no backup treatments. Osimertinib resistance can be classified to two types: EGFR dependent or independent resistance [15].

4.1. EGFR-dependent resistance

Table 2. Mutations inducing Osimertinib resistance

| Mutation                  | Type       | Mechanism                                                                 | References |
|---------------------------|------------|---------------------------------------------------------------------------|------------|
| C797, G796                | EGFR-dependent | Weaken the binding of Osimertinib to EGFR by interrupting the covalent bond | [15]       |
| L792, L718, G719          | EGFR-dependent | Weaken the binding of Osimertinib to EGFR by sterically hindering the binding of Osimertinib to kinase domain | [15]       |
| G724                      | EGFR-dependent | Weaken the binding of Osimertinib to EGFR by conformationally change the structure of receptor | [15]       |
| MET, HER2 amplification   | EGFR-independent | Activate signaling pathways downstream of EGFR | [15]       |
| RAS-MAPK pathway, PI3K pathway activation | EGFR-independent | Activate signaling pathways downstream of EGFR | [15]       |
| Oncogenic fusions         | EGFR-independent | Combine oncogenic genes to produce novel oncogenic genes | [15]       |
| Histologic and phenotypic transformation | EGFR-independent | Not clearly understood | [15]       |

In a phase III AURA 3 clinical trial, researchers randomized between chemotherapy and Osimertinib in a 1:2 ratio on 279 patients to compare the effectiveness of two treatments through plasma samples [15]. Among data obtained from 88 patients, 73 of them displayed T790M mutation, or L858R, exon 19 deletion [15]. Among 73 patients, 36 of them were detected losing T790M mutation, a resistance mechanism against Osimertinib referred to as EGFR-dependent resistance. In this way, Osimertinib loses its target of inhibition thus lose its potency [15].

4.1.1 Mutation in C797, G796

Another resistance mechanism is mutation in C797. As mentioned before, Osimertinib acts by binding irreversibly to L858R and T790M EGFR mutants via the C797 amino acid covalent bond [15]. Cysteine at codon 797 within the ATP-binding site is substituted for by serine in C797S mutation, resulting in the loss of the covalent bond between Osimertinib and the mutant EGFR, silencing the effect of drug [15]. Similarly, mutations in G796 also weakens the binding of Osimertinib with EGFR, with G796R having a major impact [15].

4.1.2 Mutation in L792, L718

L792 mutation acts through another mechanism, affecting Osimertinib-EGFR interaction by sterically hindering the binding of Osimertinib to kinase domain [15]. Similarly, L718 mutation in ATP-binding site of kinase domain of EGFR hinders TKI-EGFR interaction sterically [15].

Overall, EGFR dependent resistance mechanism can be described as hindering the interaction between Osimertinib and EGFR.
4.2. EGFR-independent resistance

Again, Osimertinib acts by binding to EGFR and inhibiting downstream signalling pathways. EGFR independent resistance activates those signaling pathways, such that although Osimertinib-EGFR interaction is not weaken, its therapeutic effect is still hampered [15].

4.2.1. MET and HER2 amplification

MET amplification is the most common resistance to EGFR-TKIs. In the same AURA 3 trial on 279 patients, 14 of 73 patients develop MET amplification [15]. MET gene amplification leads to activation of signaling pathways downstream of EGFR such as STAT, PI3K-Akt, etc., even if inhibited by Osimertinib. Fortunately, co-superscription with Met inhibitor such as crizotinib with Osimertinib has the potential of overcome such resistance [15].

HER2, a member in EGFR family, could also be amplified such that PI3K–Akt and MAPK/extracellular signal-regulated kinase (ERK) kinase (MEK)–ERK/MAPK pathways are activated in the presence of Osimertinib [15]. Others, including RAS–MAPK pathway activation and PI3K pathway activation, acts in a similar mechanism in resisting Osimertinib.

4.2.2 Oncogenic fusion

Oncogenic fusion is another resistance mechanism other than activating downstream pathways. This process can be defined as combining oncogenic genes to produce novel fusion genes.

4.3. Against Osimertinib resistance

Despite versatile mechanisms, there are specified treatments against resistance depending on the type of resistance. For instance, when T790M mutation is lost, first generation EGFR-TKI can be reused since it does not target T790M; when MET amplification occurs, crizotinib can be dosed in combination with Osimertinib [15]. Such co-dosing technique is a hotpot to fight against further resistance against Osimertinib.

5. Conclusion

As the only third-generation EGFR-TKI, Osimertinib bears great potential in the treatment of NSCLC with second mutation. Phase I clinical trials on healthy volunteers show the general safety of oral dosing without severe side effects. Phase II studies, or two AURA trials, proves the effectiveness of Osimertinib with a majority of patients having positive responses. Yet, about 25% patients develop severe adverse events. Although these data are not perfect in the demonstration of safety, the side effects of chemotherapy are inevitable, at least under current medical development. Phase III studies on patients with advanced NSCLC suggests elongation of survival by Osimertinib, yet a higher percentage of adverse effects compared to phase II studies still renders Osimertinib’s safety an issue worth discussing. Moreover, despite Osimertinib’s effectiveness, some patients develop either EGFR-dependent or independent resistance against the TKI. Former one hampers the binding of Osimertinib with EGFR while the latter one activates signaling pathways downstream of EGFR, triggering the proliferation of cancer cells even after the binding of Osimertinib. Although specific treatment plans are available to cope with such resistance, further developments are still required to have a more comprehensive EGFR-TKI.

References

[1] “Non-Small Cell Lung Cancer Treatment (PDQ®)–Patient Version.” National Cancer Institute, https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq.

[2] N. Karachaliou, M. F. Bruno, J. W. P. Bracht, R. Rosell. EGFR first- and second-generation TKIs—there is still place for them in EGFR-mutant NSCLC patients. 2018. Vol 8, Supplement 1 (January 2019): Translational Cancer Research (Targeted Therapy and Non-Small Cell Lung Cancer: A New Era?)
[3] C. O’Leary, H. Gasper, K. B. Sahin, M. Tang, A. Kulasinghe, M. N. Adams, D. J. Richard, and K. J. O’Byrne, Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small-Cell Lung Cancer (NSCLC), in: Pharmaceuticals, vol. 13, no. 10, 2020, pp. 273, DOI: https://doi.org/10.3390/ph13100273

[4] K. Suda, R. Onozato, Y. Yatabe, T. Mitsudomi, EGFR T790M Mutation: A Double Role in Lung Cancer Cell Survival? in: Journal of Thoracic Oncology, vol. 4, no. 1, 2009, pp. 1–4, DOI: https://doi.org/10.1097/JTO.0b013e3181913c9f

[5] T. Jiang, C. Su, S. Ren, F. Cappuzzo, Gaetano Rocco, J. D. Palmer, N. V. Zandwijk, F. Blackhall, X. Le, N. A. Pennell, C. Zhou, A consensus on the role of osimertinib in non-small cell lung cancer from the AME Lung Cancer Collaborative Group, in: Journal of Thoracic Disease, vol. 10, no. 7, 2018, pp. 3909–3921. DOI: https://doi.org/10.21037/jtd.2018.07.61

[6] H. Zhang, Osimertinib making a breakthrough in lung cancer targeted therapy, in: Onco Targets and Therapy, Volume 9, 2016, pp. 5489–5493. DOI: https://doi.org/10.2147/OTT.S114722

[7] Study Evaluating the Pharmacokinetic and Mass Balance of Single Dose [14C] AZD9291 in Volunteers. https://clinicaltrials.gov/ct2/show/results/NCT02096679?term=osimertinib&recrs=e&phase=0&draw=2&rank=2.

[8] T. Tamura, K. Kurishima, K. Nakazawa, K. Kagohashi, H. Ishikawa, H. Satoh, N. Hizawa, Specific organ metastases and survival in metastatic non-small-cell lung cancer, in: Molecular and Clinical Oncology, vol. 3, no. 1, 2014, pp. 217–221. DOI: https://doi.org/10.3892/mco.2014.410

[9] F. Wittlinger, S. A. Lauffer, The Pre-Clinical Discovery and Development of Osimertinib Used to Treat Non-Small Cell Lung Cancer, in: Expert Opinion on Drug Discovery, vol. 16, no. 10, 2021, pp. 1091–1103. DOI: https://doi.org/10.1080/17460441.2021.1936496

[10] AZD9291 First Time In Patients Ascending Dose Study (AURA). https://clinicaltrials.gov/ct2/show/results/NCT01802632.

[11] “RECIST”. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/recist.

[12] Phase II AZD9291 Open Label Study in NSCLC After Previous EGFR TKI Therapy in EGFR and T790M Mutation Positive Tumours (AURA2).

[13] N.B. Leighl , S.K.-Reid, P.K Cheema, J. Laskin , A. Karsan, T. Zhang, T. Stockley, T.A Barnes, R. A Tudor, G. Liu, S. Owen, J. Rothenstein, R. L Burkes, M. Iqbal, A. Spatz, L.C. van Kempen, I. Izevbaye, D. Laurence, L.W. Le, M.-S. Tsao, Multicenter Validation Study to Implement Plasma Epidermal Growth Factor Receptor T790M Testing in Clinical Laboratories, in: JCO Precision Oncology, no. 4, 2020, pp. 520–533. DOI: https://ascopubs.org/doi/10.1200/PO.19.00335

[14] AZD9291 Versus Placebo in Patients With Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy. (ADAURa) https://www.clinicaltrials.gov/ct2/show/results/NCT02511106?term=Osimertinib&recrs=d&phase=2&draw=2&rank=3

[15] A. Leonetti, S. Sharma, R. Minari, P. Perego, E. Giovannetti, M. Tiseo. 2019. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. https://www.nature.com/articles/s41416-019-0573-8.