Osimertinib (AZD9291)—a science-driven, collaborative approach to rapid drug design and development

introduction

Advances in understanding the molecular drivers of lung cancer have shown that 25% overall (10%–60% depending on ethnicity and clinical characteristics) of non-small-cell lung cancers (NSCLCs) are driven by specific activating mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase domain, leading to addiction of the tumour to signalling through this pathway. The presence of these mutations sensitises tumours to treatment with EGFR-tyrosine kinase inhibitors (TKIs), of which gefitinib, erlotinib and afatinib are currently recommended as first-line therapy for patients with advanced NSCLC harbouring these mutations [1, 2].

Typically, most patients treated with a currently approved first-line EGFR-TKI develop resistance and in ~60% of cases this is caused by a resistance mutation in the ATP-binding domain of the EGFR gene, the T790M resistance mutation [3].

Osimertinib (TAGRISSO™, AZD9291; AstraZeneca PLC, London, UK) was designed to inhibit EGFR in a covalent irreversible manner, while harbouring preferential activity against sensitising and T790M resistance mutations, relative to the wild-type form of the receptor (in most cases, the T790M mutation exists together with a sensitising mutation in the EGFR molecule and therefore will be referred to as a double mutation). Osimertinib is a potent, oral, irreversible inhibitor selective for sensitising (EGFRm) and T790M resistance mutations that has demonstrated clinical efficacy in patients with advanced T790M-positive NSCLC [4].

The development of osimertinib followed a science-driven, adaptive approach that involved close collaboration with industry partners and global regulatory bodies including the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Discussion here includes the key elements of the osimertinib development pathway, outlining how this approach led to the rapid development of this novel therapeutic agent. On 13 November 2015, osimertinib received FDA approval for patients whose tumours have a specific EGFR mutation (T790M) and whose disease has become worse after treatment with other EGFR-blocking therapy, following a clinical development period of just over 2.5 years (Figure 1). This was followed by a positive opinion from the Committee for Medicinal Products for Human Use on 18 December 2015, recommending the marketing authorisation of osimertinib for the treatment of adults with locally advanced or metastatic NSCLC with a specific mutation (T790M) of the EGFR. The European Commission approval was received on 2 February 2016, making osimertinib the first new medicine to be approved under the EMA expedited process.

science-driven drug design and engineering

The discovery of osimertinib began with finding a compound that would preferentially inhibit the EGFR-TKI-resistant, double-mutant form of EGFR relative to the wild-type form [5]. The ultimate goal was to develop a compound that would demonstrate clinical activity against single- and double-mutant EGFR, while reducing the toxicity caused by inhibiting wild-type EGFR.

Several aspects of drug discovery were involved, including a novel and systematic approach to compound generation, structure-based design of an irreversible inhibitor, physical property-based evolution and structure activity relationship development to drive increased kinase selectivity, ultimately arriving at a promising clinical candidate (Figure 2). The project progressed with exceptional speed, starting in 2009 and delivering a candidate drug molecule in <36 months (Figure 1A) [5, 6].

The initial hypothesis was to target the mutant methionine in the T790M form of the EGFR receptor, commonly referred to as the ‘gatekeeper’ residue [5]. Early compounds had promising biochemical potency and selectivity versus wild-type, but activity was reduced against the double-mutant EGFR in cellular assays. It was thought that this was due to the ATP affinity of the double-mutant form of EGFR, so work proceeded in an attempt to convert the promising candidates from reversible inhibitors to covalent, irreversible inhibitors while hopefully maintaining a good selectivity over wild type.

Further evolution achieved improved potency, while maintaining intrinsic reactivity, and reducing off-target activity against other kinases, such as insulin-like growth factor 1 receptor (IGF1R) and insulin receptor (IR), which can be a cause of toxicity that could limit clinical dose levels [5, 6]. Ultimately, the compound now known as osimertinib was chosen for further development.

preclinical evaluation

Pre-clinically, osimertinib potently inhibits signalling pathways and cellular growth of EGFRm and T790M resistant cell lines in vitro [7]. Osimertinib has high in vitro potency towards inhibition of EGFR phosphorylation across cell lines harbouring EGFR mutations as well as significantly less activity against phospho-EGFR in wild-type cell lines. The compound demonstrates a good margin of selectivity against wild-type EGFR activity and a high degree of selectivity against other kinases. In vivo, this translates into sustained tumour regression in EGFR-mutant tumour
xenograft and transgenic single- and double-mutant models. These data confirmed osimertinib had the potential to be clinically active in tumours that harbour the T790M mutation following progression on currently approved EGFR-TKIs and as a treatment in the first-line setting for patients with EGFRm NSCLC. The margin of selectivity against the wild-type EGFR receptor was expected to result in a favourable tolerability profile in the clinic.

Some of the most important preclinical characterisation was the pharmacokinetic (PK) and pharmacodynamic (PD) modelling of osimertinib [8]. A mathematical mouse model of PD and tumour growth inhibition was then combined with modelling of predicted human PK to simulate tumour growth inhibition and predict efficacious doses in man. These models suggested that osimertinib could have clinical activity at doses of 5–10 mg once daily, a key assessment in selecting the starting dose of osimertinib to be used for clinical evaluation.

**phase I design and implementation**

The AURA dose-escalation and expansion study (phase I component; NCT01802632) was conducted with the primary objective of determining the safety, tolerability and efficacy of osimertinib in patients with advanced EGFR-mutated NSCLC whose disease had progressed on prior therapy with an EGFR-TKI [4]. The novel study design used the standard phase I ‘rolling six’ design but also incorporated expansion cohorts (Figure 3) designed to provide information to guide the further clinical development of osimertinib.

The flexible/adaptive design with rolling enrolment was extremely important for the success of and rapid recruitment into the study because it allowed for parallel recruitment to dose-escalation and biomarker-defined expansion cohorts (Figure 3). The first patient was enrolled on 6 March 2013 (Figure 1). Patients were eligible for inclusion in the study if they had a known EGFR-TKI-sensitising mutation or had had prior clinical benefit from treatment with an EGFR-TKI. EGFR T790M testing was optional for inclusion in the escalation cohorts. T790M status was determined before inclusion in the expansion cohorts and was predominantly based on local testing of tumour tissue samples taken following progression on the latest line of therapy. Local test results were retrospectively confirmed by a central laboratory test. Blood samples for circulating tumour (ct)DNA testing were tested retrospectively by a central laboratory to determine the clinical utility of this test method. The 20 mg starting dose was selected on the basis of preclinical data and modelling, which predicted this dose would be sufficient to inhibit the T790M mutant form of the EGFR receptor [6].

There was a clear scientific rationale for each expansion cohort. Both T790M-positive and T790M-negative cohorts were included (40, 80 and 160 mg cohorts) to demonstrate any
differences in outcome based on the presence or absence of this specific biomarker. This was also adapted as the study progressed, with the highest dose (240 mg) only tested in T790M-positive cohorts. First-line EGFRm cohorts could provide early clinical evidence and rationale for expanding the development of osimertinib into earlier treatment settings where it may have potential benefits compared with currently approved EGFR-TKIs. Paired biopsy cohorts enabled translational analysis of tumour samples to characterise PD changes on treatment. The tablet cohort allowed characterisation of the PK of the to-be-commercialised tablet formulation, confirming the equivalence to the early-development capsule formulation. The Japan-only cytology cohort evaluated the use of a liquid cytology sample for detection of the T790M mutation, as not all patients are able to undergo biopsy of a solid tumour.

Building on knowledge and learnings from clinical studies of gefitinib (IRESSA®, AstraZeneca PLC, London, UK), the AURA study incorporated a biomarker-defined patient selection from the outset, which improved the chances of demonstrating clinical activity. The first-time-in-man dose escalation recruited patients with advanced NSCLC who had an EGFR-TKI-sensitising mutation or who had prior clinical benefit from treatment with an EGFR-TKI. This meant that the study included patients with both T790M-positive and -negative disease. In recognition of the high unmet need, disease prevalence and varying practice patterns by region, the study deliberately included global sites recruiting Asian and Caucasian patients.

Results were highly encouraging. Among 31 patients enrolled in the dose-escalation cohorts, no dose-limiting toxic effects occurred at doses of 20–240 mg once daily. An additional 222 patients were treated in five expansion cohorts. The overall confirmed objective tumour response rate was 51% [95% confidence interval (CI) 45–58]. Among 127 patients with EGFR T790M mutation-positive NSCLC confirmed by a central laboratory who could be evaluated for response, the response rate was 61% (95% CI 52–70) [4].

The final selection of the dose to be used for commercialisation, as well as phase III development, was made in February 2014, i.e. 11 months after the first dose in man (Figure 1B). It was based on an array of preclinical modelling together with clinical efficacy and safety data.

PK/PD models of cell lines indicated that maximum tumour growth inhibition would be at 80 mg once daily, a dose that could also potentially have an effect on brain metastases [9]; xenograft modelling indicated there would be no benefit of dosing above 80 mg. PK analyses showed that the 80 mg dose ensured exposure levels greater than that observed for the 20 mg or 40 mg dose, which also demonstrated clinical activity in the AURA phase I study. The 80 mg dose provided substantial clinical efficacy and was associated with fewer dose reductions and a lower incidence of skin disorders, nail effects and diarrhoea than the 160 and 240 mg doses, which appeared unlikely to provide additional efficacy. The 80 mg dose demonstrated the optimal benefit:risk profile, ensured that patients received a clinically

<table>
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<tr>
<th>EGFRm sensitising mutation cell IC50 (pEGF μM)</th>
<th>Compound 1</th>
<th>Compound 2</th>
<th>Compound 3</th>
<th>Compound 4</th>
<th>Compound 5 (osimertinib)</th>
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<td>23</td>
<td>48</td>
<td>194</td>
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</table>

Figure 2. Steps in the development of osimertinib. Screening of insulin-like growth factor 1 receptor (IGF1R) inhibitors led to the identification of compounds such as 1, which showed good affinity for the double-mutant form of the epidermal growth factor receptor (EGFR) and selectivity over the wild type. In spite of this promising selectivity profile, these compounds failed to show a significant level of cellular potency in cell lines. Further modifications were necessary to develop this as an irreversible inhibitor and to improve the physical properties for balance of potency and lipophilicity. Compound 5 was identified, which showed double-mutant xenograft activity at 5 mg/kg and the best overall balance of properties, including a dramatically improved IGF1R selectivity profile. Compound 5 was ultimately selected for further development and became known as osimertinib. IR, insulin receptor; p, phosphor; SM, sensitising mutation.
active dose regardless of inter-patient variability in exposure, and allowed for dose reduction if necessary.

**early engagement with health authorities**

Close communications with health authorities have allowed for on-going discussions to define the overall programme design and plan and identify the type, scope, maturity and level of data that are required to meet regulatory requirements for initial approval.

Discussions with health authorities centred around four critical aspects identified as rate-limiting for a rapid drug development: patient population; reproduction of evidence; chemistry, manufacturing and controls; and validation studies. Based on the initial clinical data from the phase I component of the AURA trial, the FDA granted osimertinib Breakthrough Therapy Designation on 16 April 2014 for the treatment of patients with metastatic, EGFR T790M mutation-positive NSCLC, whose NSCLC has progressed during treatment with an FDA-approved EGFR-TKI.

Further to this, the development team at AstraZeneca was able to agree with regulators that a 13-week efficacy follow-up of patients in the phase II studies would be sufficient for initial marketing application submissions, supported by the entire safety population. Additional follow-up data were provided to regulators during the application reviews as agreed during consultations. Regulatory submissions were supported by a large dataset from a clearly defined patient population. The evidence generated by the AURA phase II extension component was successfully reproduced through the set-up and conduct almost in parallel of a nearly identical open-label, single-arm study (AURA2, NCT02094261).

To proceed quickly into confirmatory phase studies, a rapid transfer from clinical-phase to commercial-phase chemistry, manufacturing and controls, with associated scale up in scope, was needed; seven million dose units have been produced as of the end of 2015 in support of the clinical and early access programme. The phase I escalation and expansion components of the AURA study were mostly conducted using a capsule formulation, with one cohort receiving a tablet formulation. The commercial formulation, a film-coated tablet, was developed in parallel and used in all subsequent clinical studies including the AURA extension and AURA2 phase II studies. The tablet has been shown to provide similar exposure to the capsule formulation; therefore, the results from the AURA phase I study are relevant to the commercialised tablet formulation and could be used as supportive evidence in marketing application submissions.

Finally, the scope of the definitive studies required to support the anticipated post-marketing requirements were pre-agreed.
with several major health authorities, including the need for a phase III study. AURA3 (NCT02151981), a phase III study comparing osimertinib 80 mg once daily versus platinum-based doublet chemotherapy in patients with EGFRm and T790M-positive advanced NSCLC whose disease has progressed following prior therapy with an EGFR-TKI, was rapidly initiated. The first patient was dosed in August 2014, before the phase II studies completed recruitment in October 2014 (Figure 1B).

**timely development of accompanying diagnostic**

Recently, there has been significant change in the diagnostic/testng environment for advanced NSCLC with current guidelines necessitating an EGFR mutation test to identify patients eligible for treatment with an EGFR-TKI [1, 2]. In Europe, IRESSA® was the first approved therapy for NSCLC that required a diagnostic test to confirm the presence of the EGFR mutation in tumour DNA before first-line treatment. Subsequently, IRESSA was the first EGFR-TKI (in Europe) with a label allowing the use of ctDNA, obtained from a blood sample, to be used for the assessment of EGFR mutation status in those patients where a tumour sample was not an option.

Osimertinib was specifically designed to target both EGFR-TKI-sensitising mutations and T790M resistance mutations, so there was a need for a companion diagnostic test to support the identification of patients most likely to respond to therapy. In July 2014, AstraZeneca partnered with Roche Molecular Systems, Inc., to develop a companion diagnostic test for osimertinib that could identify patients with tumours containing the T790M mutation. The cobas® EGFR Mutation Test v2 is a real-time polymerase chain reaction test for the qualitative detection and identification of somatic mutations in exons 18, 19, 20 and 21 of the tyrosine kinase domain of the EGFR gene in DNA derived from formalin-fixed paraffin-embedded human NSCLC tumour tissue.

The cobas® EGFR Mutation Test v2 is approved as a companion diagnostic for osimertinib in the United States. In September 2015, the test was launched as a Conformité Européene In Vitro Diagnostic (CE-IVD) in the EU for use with both tissue and ctDNA plasma samples, therefore allowing patients who cannot provide a tissue biopsy upon diagnosis of progression (the current gold standard) to be tested. An application for use with both tissue and plasma samples has been submitted for Pharmaceutical and Medical Devices Agency (PMDA, Japan) approval.

**discussion**

The development programme for osimertinib is the most rapid to date, taking just 24 months from filing the FDA Investigational New Drug Application to submitting the FDA New Drug Application and just 2 years, 8 months and 1 week from the first patient dosed to the first approval. This was made possible by multiple factors, the most relevant of which was the experience of developing gefitinib, an EGFR-TKI indicated for the first-line treatment of patients with metastatic NSCLC with EGFR mutations. AstraZeneca’s experience meant that the company had accumulated strong, top-level expertise in the biology of the EGFR and in the chemistry of EGFR-TKI inhibitors, with experience extending back to the 1990s through the development of the first-in-class EGFR-TKI IRESSA. The acceptance and widespread clinical use of current EGFR-TKIs and the understanding of resistance to these agents also played a role; understanding the patient population most likely to benefit from the treatment was key, but investigators’ familiarity with this class of drugs also ensured that adverse events were well managed. A second factor was the changes implemented to the US Food, Drug and Cosmetic Act that allowed for Breakthrough Designation, which aimed to expedite the development and availability of drugs to treat serious diseases; osimertinib was granted a Breakthrough Therapy Designation in 2014. In addition, osimertinib was the first new medicine to be approved under the EMA accelerated assessment process. A final success factor was the high priority status of the project within the AstraZeneca oncology portfolio. The rapid and successful establishment of the manufacturing processes at the commercial supply sites was critical to ensure both robust long-term supply of drug to patients and the ability to launch rapidly following regulatory approvals—brining osimertinib to patients who desperately needed this new treatment option. In the United States, the first commercial drug shipments to distributors were made within 6 h of the approval by the FDA.

Patients with NSCLC whose tumours are shown to be T790M positive after treatment with a currently approved EGFR-TKI represent a substantial unmet medical need. This, combined with the desire of AstraZeneca to build upon a strong legacy of developing targeted EGFR-TKIs, led to the discovery and subsequent development of osimertinib, a potent, oral, irreversible inhibitor selective for EGFR-TKI-sensitising and T790M resistance mutations. The design and development of osimertinib was centred on a science-driven, adaptive approach that involved close collaboration between AstraZeneca, industry partners and regulatory bodies.

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**disclosure**

The author is an employee and shareholder of AstraZeneca.

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