Institution: The University of Manchester		
Unit of Assessment: 1 (Clinical Medicine)		
Title of case study: New targeted therapies in non-small cell lung cancer improve patient outcomes		
Period when the underpinning research was undertaken: January 2005 – October 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Fiona Blackhall	Professor of Thoracic Oncology Clinical Senior Lecturer Honorary Senior Lecturer	2016 – present 2012 – 2016 2007 – 2012
Malcom Ranson	Professor of Medical Oncology	1995 – 2014
Period when the claimed impact occurred: 1 August 2013 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Lung cancer is the commonest cause of cancer-related mortality worldwide. University of Manchester (UoM) researchers have driven pivotal trials leading to international licensing and routine clinical use globally of two new therapies, benefitting thousands of non-small cell lung cancer (NSCLC) patients worldwide and improving average survival from one year to four years. Osimertinib is licensed by the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the Japanese Ministry of Health, Labour and Welfare (MHLW), recommended in European and US clinical guidance and available in >80 countries for treatment of epidermal growth factor receptor positive (EGFR+) NSCLC. Crizotinib is licensed by EMA and FDA, recommended in European and US clinical guidance and approved in >90 countries for treatment of anaplastic lymphoma kinase positive (ALK+) NSCLC.

2. Underpinning research

Context

There are around 2,000,000 new cases of lung cancer globally per annum. NSCLC is the commonest type accounting for around 85% of cases. EGFR mutant (EGFR+) and ALK gene rearranged (ALK+) are genetic subtypes of NSCLC that are more prevalent in never-smokers and worldwide account for an estimated 250,000 and 70,000 new cases per year, respectively. EGFR+ NSCLC is more prevalent in Asia (where it accounts for up to 50% of all lung cancer), in women and at a younger age than smoking related lung cancer. ALK+ NSCLC has a median age of onset of 54; most cases are never-smokers and are diagnosed at an advanced, incurable stage.

EGFR+ and ALK+ are two of the first subtypes of NSCLC in which specific targeted therapies have proved to be effective. Prior to these treatments, outcomes were poor even on chemotherapy, for instance in a 2014 Blackhall-led publication [5] progression-free survival in patients treated with chemotherapy was just 7 months.

Key research findings relevant to Osimertinib for treatment of EGFR+ NSCLC

Osimertinib (AZD9291) is a third generation targeted therapy, belonging to a class of drug termed Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs). Ranson, in collaboration with other international cancer researchers and pharma collaborators, pioneered the introduction of practice-changing first generation EGFR-TKIs (e.g. Gefitinib) and Blackhall conducted studies of second generation EGFR-TKIs (e.g. Dacomitinib). Osimertinib was developed by Astrazeneca to overcome acquired genetic resistance to first and second generation inhibitors. Ranson was the sole UK academic researcher in the global steering committee with intellectual responsibility for the design,

conduct, analysis and interpretation of the 'AURA' trials programme. He led the AURA 1 trial that confirmed high clinical efficacy and safety of Osimertinib in patients with EGFR-TKI resistant disease [1]. The AURA phase II extension study tested a fixed dose of 80mg, selected from the AURA 1 trial results. Patients were selected on the basis of a positive test for the resistance mutation EGFR T790M in their cancer cells. The study demonstrated a high rate of efficacy with a disease control rate of 90% despite prior EGFR-TKI resistance [2].

Key research findings relevant to Crizotinib for treatment of ALK+ NSCLC

Crizotinib was the first-in-class targeted therapy to be developed and licensed specifically for the treatment of ALK+ NSCLC with goals to improve symptoms, quality of life and extend survival. The clinical development of Crizotinib required international collaboration in the 'PROFILE' trials programme due to the rarity of ALK+ NSCLC. Blackhall was the sole UK lung cancer researcher in the global steering committee with intellectual responsibility for the design, conduct, analysis and interpretation of the 'PROFILE' trials. PROFILE 1005 [3], for which she led the final analysis, was the largest single study to be conducted for a targeted therapy in ALK+ patients, with 1,069 patients monitored for clinical efficacy and safety. In PROFILE 1007 [4] Blackhall led on the patient-reported quality of life analysis that showed better symptom control and quality of life on Crizotinib treatment. PROFILE 1014 [5], co-chaired by Blackhall and a collaborator in Australia, provided definitive, practice changing evidence for the use of Crizotinib as first line treatment of newly diagnosed patients with ALK+ NSCLC. In this phase III trial that enrolled 343 patients, the final analysis [6] showed an unprecedented 56.6% probability of survival at 4 years (95% Confidence Interval, 48.3% to 64.1%) compared to a historical 2 year survival probability of 11%.

3. References to the research

1. Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, Ahn MJ, Kim SW, Su WC, Horn L, Haggstrom D, Felip E, Kim JH, Frewer P, Cantarini M, Brown KH, Dickinson PA, Ghiorghiu S, **Ranson M**. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *New England Journal of Medicine*. 2015 Apr 30;372(18):1689-99. DOI:10.1056/NEJMoa1411817
2. Yang JC, Ahn MJ, Kim DW, Ramalingam SS, Sequist LV, Su WC, Kim SW, Kim JH, Planchard D, Felip E, **Blackhall F**, Haggstrom D, Yoh K, Novello S, Gold K, Hirashima T, Lin CC, Mann H, Cantarini M, Ghiorghiu S, Jänne PA. Osimertinib in Pretreated T790M-Positive Advanced Non-Small-Cell Lung Cancer: AURA Study Phase II Extension Component. *Journal of Clinical Oncology*. 2017 Apr 20;35(12):1288-1296. DOI:10.1200/JCO.2016.70.3223
3. **Blackhall F**, Ross Camidge D, Shaw AT, Soria JC, Solomon BJ, Mok T, Hirsh V, Jänne PA, Shi Y, Yang PC, Pas T, Hida T, Carpeño JC, Lanzalone S, Polli A, Iyer S, Reisman A, Wilner KD, Kim DW. Final results of the large-scale multinational trial PROFILE 1005: efficacy and safety of crizotinib in previously treated patients with advanced/metastatic ALK-positive non-small-cell lung cancer. *European Society for Medical Oncology Open*. 2017 Aug 17;2(3):e000219. DOI:10.1136/esmoopen-2017-000219
4. **Blackhall F**, Kim DW, Besse B, Nokihara H, Han JY, Wilner KD, Reisman A, Iyer S, Hirsh V, Shaw AT. Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer. *Journal of Thoracic Oncology*. 2014 Nov;9(11):1625-33. Erratum in: *Journal of Thoracic Oncology*. 2015 Nov;10(11):1657. DOI:10.1097/JTO.0000000000000318
5. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, **Blackhall F;** PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *New England Journal of Medicine*. 2014 Dec 4;371(23):2167-77. Erratum in: *New*

England Journal of Medicine. 2015 Oct 15;373(16):1582. DOI:10.1056/NEJMoa1408440 *1775 citations Scopus 6.11.20*

6. Solomon BJ, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Tang Y, Wilner KD, **Blackhall F**, Mok TS. Final Overall Survival Analysis From a Study Comparing First-Line Crizotinib Versus Chemotherapy in ALK-Mutation-Positive Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*. 2018 Aug 1;36(22):2251-2258. DOI:10.1200/JCO.2017.77.4794

4. Details of the impact

Context

Osmertinib and Crizotinib are tyrosine kinase inhibitors (TKIs) which specifically target the genetic characteristics of cancers, are taken orally, and are well tolerated even by frail and elderly patients compared to intravenous chemotherapy that is more toxic and resource intense to deliver. The EGFR+ and ALK+ types of NSCLC are identified with genetic tests on cancer biopsies.

Pathways to impact

Ranson and Blackhall's expertise in cancer biomarkers and phase I-III clinical trials ensured that study designs were fit for purpose and patients readily identified through establishing genetic tests ahead of National Health Service (NHS) availability. Patients were referred nationwide to Manchester for these trials.

Reach and significance of the impact

Impacts on regulatory approvals

Osimertinib (marketed as Tagrisso) was approved in the US (FDA- November 2015) [Ai], Europe (EMA- February 2016) [Aii] and Japan (MHLW- March 2016) [Aiii]. Approvals were for EGFR T790M mutation-positive NSCLC for patients with metastatic disease who have progressed on or after EGFR TKI therapy (FDA), irrespective of prior EGFR-TKI treatment (EMA) and for EGFR T790M+ patients with inoperable or recurrent NSCLC resistant to EGFR TKI therapy (MHLW) [A]. All were based on the AURA extension [2] and AURA2 (conducted outside UK) clinical trials [Ai,Aii,Aiii]. The Chief Executive Officer of AstraZeneca said "*The FDA approval of TAGRISSO marks an important milestone for lung cancer patients who urgently need new treatment options. We….acted on the breakthrough clinical evidence to ensure this next-generation medicine reaches patients in record time*" [Ai].

A National Institute for Health and Care Excellence (NICE) technology appraisal (October 2016), referencing the AURA extension, recommended Osimertinib as an option for locally advanced or metastatic EGFR T790M mutation-positive NSCLC in adults with progression following TKI treatment [Bi, 2]

NICE produced Covid-19 rapid guidance (updated April 2020) endorsing interim treatment regimens for some cancer medicines [Ci] in which Osimertinib was confirmed as a first-line therapy option for NSCLC to delay the need for subsequent chemotherapy [Cii].

Crizotinib (marketed as Xalkori) was approved by EMA (November 2015) for first line treatment of adults with ALK+ NSCLC based on the results of PROFILE 1014 [D, 5].

NICE Technology appraisal Sept 2016 recommended Crizotinib as "*an option for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults*" [Bii]. The main trial that presented clinical effectiveness was PROFILE 1014 [5]. PROFILE 1007 [4] was also cited in the final appraisal.

Impact on clinical guidance

The European Society of Medical Oncology (ESMO) September 2016 and 2019 guidelines incorporate Osimertinib and Crizotinib into standard of care treatment for EGFR+ and ALK+ NSCLC respectively, according to their licensed indications. [E,1,4,5].

National Comprehensive Cancer Network® (NCCN®) is an alliance of 30 leading North American cancer centres. NCCN Guidelines® have been downloaded in more than 180 countries. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), updated in April 2016, stated, "*NCCN Panel recommends osimertinib as subsequent therapy for patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on erlotinib, gefitinib, or afatinib therapy"* with the Aura Phase Extension trial initially cited as evidence [F, 2]. Crizotinib is recommended as first line therapy for ALK+ patients based on the 1014 trial and FDA approval [F, 5]. In 2019, NCCN's Non-Small Cell Lung Cancer Guidelines were downloaded 605,446 times.

Patient impacts

Osimertinib

In June 2019, Public Health England reported on the 'real-world' treatment effectiveness of Osimertinib during the period October 2016 to September 2018. During this time 386 Cancer Drug Fund applications for treatment through NHS were made. After exclusions, 357 patients who received treatment were studied. Median survival was 13.9 months. Survival at 6 months was 78% and 12 months survival was 56% [Gi].

Crizotinib

Public Health England advised that as of January 2020, 231 patients have now received Crizotinib as treatment for NSCLC through NHS [Gii].

Impacts from further studies based on early work led by Manchester

Follow on trials, such as 'FLAURA' for Osimertinib, would not have been possible without the underpinning AURA studies. Based on FLAURA, FDA approval was secured in April 2018 for Osimertinib to be used as first line treatment for EGFR mutation positive NSCLC irrespective of T790M status [Hi]. EMA approval followed in June 2018 [Hii].

Commercial Impacts

Following the results of the Aura trials (involving UK academic leads Ranson [1] and Blackhall [2]), Osimertinib (Tagrisso) is now approved in 80 countries for first line EGFR+ NSCLC and >85 countries for second line use in patients with EGFR T790M NSCLC [Ii]. It realised sales of USD423,000,000 in its first full year (2016) of which USD82,000,000 were from Japan, following launch there in May 2016. (EGFR+ NSCLC is more prevalent, accounting for up to 50% of all lung cancer in Asia). By 2019, total sales had grown to USD3,189,000,000 [Iii].

Global sales of Crizotinib (Xalkori) were USD438,000,000 in 2014 (primary indications were ALK+ NSCLC and ROS1+ NSCLC) [Ji] and peaked at USD594,000,000 in 2017 [Jii]. By September 2017, Crizotinib (Xalkori) had received approval for ALK+ NSCLC in >90 countries worldwide [Jiii].

5. Sources to corroborate the impact

A. AstraZeneca press releases confirming approvals for Osimertinib as a treatment for EGFR T790M mutation-positive NSCLC patients – ***approvals based on Aura Extension UoM reference 2***.

i. AstraZeneca press release 13 November 2015 including quote from AstraZeneca's Chief Executive Officer– ***confirms US (FDA) approval***

ii. AstraZeneca press release 3 February 2016 ***– confirms European (EMA) approval***

iii. AstraZeneca press release 29 March 2016 – ***confirms Japanese (MHLW) approval***

B. UK NICE technology appraisals

i. October 2016. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation positive non-small-cell lung cancer 26/10/16 TA416 ***– cites UoM reference 2***

ii. September 2016 Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small cell lung cancer TA406 – ***cites UoM references 4 and 5***

C. UK NICE- treatment changes due to Covid-19

i. COVID-19 rapid guideline: delivery of systemic anticancer treatments, NG161 (20 March 2020) - ***NHS England endorsed interim treatment regimens for some cancer medicines (including Osimertinib)***

ii. Interim treatment regimens (9 April 2020) ***– confirms option to give Osimertinib as a first line therapy to delay the need for subsequent chemotherapy***

D. Pfizer press release confirming EMA regulatory approval for Crizotinib. November 2015 https://bit.ly/15CzPFZr – ***approval cites PROFILE 1014 UoM reference 5***

E. ESMO Clinical Practice Guidelines. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2016 and September 2019. – ***European guidelines include Osimertinib and Crizotinib as standard of care treatments, citing UoM references 1,4 and 5.***

F. NCCN Guidelines for Non-Small Cell Lung Cancer Version 4.2016. ***Guidelines citing UoM references 2 and 5***. Referenced with permission from the NCCN Guidelines® for Non-Smal Cell Lung Cancer V4.2016. © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed [Aug 20, 2016]. To view the most recent and complete version of the guideline, go online to www.NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

G. Patient evidence

i. NICE Committee papers (Cancer Drugs Fund review of TA416 October 2020) containing Public Health England Osimertinib for treating previously treated metastatic epidermal growth factor receptor and T790M mutation-positive non-small-cell lung cancer review – June 2019 ***– report showing 'real world' effectiveness of Osimertinib***

ii. Public Health England National Cancer Registration and Analysis Service Information Request- ***count of patients receiving Crizotinib for NSCLC***

H. Approval of Osimertinib for first line treatment- ***based on FLAURA trial which was underpinned by AURA research***

i. FDA press release 19 April 2018 – ***confirming FDA US approval***

ii. AstraZeneca press release 8 June 2018 – ***confirming EMA European approval***

I. Astra Zeneca annual reports - ***showing sales figures for Osimertinib (Tagrisso) and number of countries approved in***

i. AstraZeneca Annual Report 2016 – ***showing sales figures for Osimertinib***

ii. AstraZeneca Annual Report 2019 - ***showing increased sales figures for Osimertinib and confirming the number of countries the product is approved in.***

J. Pfizer annual reports 2016 and 2019 - ***showing sales figures for Crizotinib (Xalkori)*** and 2017 Pfizer press release

i. Pfizer Annual Report 2016 - ***showing sales figures for Crizotinib 2014-2016***

ii. Pfizer Annual Report 2019 - ***showing sales figures for Crizotinib 2017-2019***

iii. Pfizer press release 11 September 2017 on Xalkori overall survival – ***confirming number of countries in which Crizotinib is approved***