Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Establishing the evidence for treatment to improve outcomes in patients with lung cancer

1. Summary of the impact

Lung cancer is the commonest cause of cancer-related mortality worldwide. The University of Manchester (UoM) Lung Cancer Group has generated insights that underpin new standards of care in the treatment of advanced, metastatic small cell (SCLC) and non-small cell lung cancer (NSCLC), contributed to the results required for licensing of new drugs and secured approval for new treatment regimens now in routine clinical use internationally. Key contributions include an increase in survival of 23% in advanced NSCLC with the use of chemotherapy and doubling one-year survival from 13% to 27% in patients with incurable, extensive stage SCLC by the use of prophylactic cranial irradiation. The Group's research has impacted on outcomes for thousands of patients worldwide.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

The impact is based on research that took place at UoM from 1993 to 2013. Key researchers:

- **Fiona Blackhall** (NHS Consultant, 2005; Honorary Senior Clinical Lecturer, 2007-2012; Senior Clinical Lecturer in Oncology, 2012-date)
- **Corinne Faivre-Finn** (NHS Consultant, 2003; Honorary Senior Clinical Lecturer, 2007-2013; Reader, 2013-date)
- **Paul Lorigan** (Senior Lecturer, 2002-2004; Reader, 2004-date)
- **Malcolm Ranson** (Senior Lecturer, 1995-2004; Professor of Medical Oncology, 2004-date)
- **Nicholas Thatcher** (Professor of Oncology, 1996-2010)

The research established an evidence base for treatments that have improved outcomes for patients with lung cancer.

1. Effective treatments for non-small cell lung cancer (NSCLC)

The Group designed and conducted ~30 early phase I/II trials of new agents and regimens to establish dosing schedules, side effect profiles and efficacy in NSCLC. This research has led to the design and conduct of randomised phase III trials that have defined new standards of care. UoM researchers performed the first studies of paclitaxel, gemcitabine and gefitinib, all now routinely used for the first line treatment of metastatic lung cancer (1-3).

2. Optimising treatment for small cell lung cancer (SCLC)

The Group's phase I-III clinical trials have provided evidence for platinum and etoposide chemotherapy, thoracic and prophylactic cranial irradiation in small cell lung cancer, and important evidence against dose intense chemotherapy regimens and newer chemotherapy drugs such as pemetrexed (4-6).

The Group has designed, conducted, analysed and published results from 77 clinical trials of new treatments or regimens in patients with lung cancer since 1993, 28 of which were published from 2008 to present.

3. References to the research

Key publications:

1. **Ranson M**, Hammond LA, Ferry D, Kris M, Tullo A, Murray PI, Miller V, Averbuch S, Ochs J, Morris C, Feyereislova A, Swaisland H, Rowinsky EK. ZD1839, a selective oral epidermal growth

factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. *Journal of Clinical Oncology*. 2002;20(9):2240-50. DOI: 10.1200/JCO.2002.10.112

2. Danson S, Middleton MR, O'Byrne KJ, Clemons M, **Ranson M**, Hassan J, Anderson H**,** Burt PA, **Faivre-Finn C,** Stout R, Dowd I, Ashcroft L, Beresford C, **Thatcher N.** Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. *Cancer*. 2003;98(3):542-53. DOI: 10.1002/cncr.11535

3. **Thatcher N,** Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V, Carroll K. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *The Lancet*. 2005;366(9496):1527-37. DOI: 10.1016/S0140-6736(05)67625-8

4. Slotman B, **Faivre-Finn C,** Kramer G, Rankin E, Snee M, Hatton M, Postmus P, Collette L, Musat E, Senan S, Group ERO, Lung Cancer G. Prophylactic cranial irradiation in extensive small-cell lung cancer. *The New England Journal of Medicine*. 2007;357(7):664-72. DOI: 10.1056/NEJMoa071780

5. Baka S, Califano R, Ferraldeschi R, Aschroft L, **Thatcher N,** Taylor P, **Faivre-Finn C, Blackhall F**, **Lorigan P**. Phase III randomised trial of doxorubicin-based chemotherapy compared with platinum-based chemotherapy in small-cell lung cancer. *British Journal of Cancer*. 2008;99(3):442-7. DOI: 10.1038/sj.bjc.6604480

6. Socinski MA, Smit EF, **Lorigan P**, Konduri K, Reck M, Szczesna A, Blakely J, Serwatowski P, Karaseva NA, Ciuleanu T, Jassem J, Dediu M, Hong S, Visseren-Grul C, Hanauske AR, Obasaju CK, Guba SC, **Thatcher N.** Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naive patients with extensive-stage small-cell lung cancer. *Journal of Clinical Oncology*. 2009;27(28):4787-92. DOI: 10.1200/JCO.2009.23.1548

4. Details of the impact

See section 5 for corroborating sources S1-S7.

Context

Lung cancer is the commonest cause of cancer-related morbidity and mortality worldwide. 30,000 cases are diagnosed annually in the UK. The majority of patients have metastatic disease for which there is no curative treatment. Historically lung cancer is classified into small cell (SCLC) or non-small cell (NSCLC) subtypes according to microscopic appearances. In the 1990s it was believed that chemotherapy for NSCLC was ineffective. The UoM Lung Cancer Group led in research to identify effective chemotherapy treatments for patients with NSCLC and to address the 'therapeutic nihilism' surrounding NSCLC.

Reach and significance of the impact

Effective treatments for non-small cell lung cancer (NSCLC)

a) UoM research contributed significantly to establishing the evidence base and the role for chemotherapy compared with best supportive care and for gemcitabine and platinum (GP) based chemotherapy in the first line treatment for advanced NSCLC (2, S1). Key outcomes demonstrated were a relative increase in survival of 23% for chemotherapy and better quality of life, less toxicity and fewer hospital admissions for GP compared with older chemotherapy regimens (2). As a result of our research, chemotherapy, including the GP regimen, is now a universal standard of care for patients with metastatic NSCLC, as evidenced in the UK guidelines (S2), European guidelines (S3) and the US guidelines (S4).

b) Gefitinib is the first targeted treatment for lung cancer to be licensed (in 2009) for patients with NSCLC bearing epidermal growth factor receptor (EGFR) gene mutations. This treatment

represents a landmark for personalised medicine in lung cancer. The first patient worldwide to receive gefitinib was in Manchester (1) and the group have continued to play a major role in the clinical development of this drug (1, 3), notably identifying patient populations with increased chance of benefit. This latter observation led to other researchers identifying the mutation to predict for benefit. The treatment is available worldwide and at least 1 million (likely more) patients have received it (S5, S6).

Optimising treatment for small cell lung cancer (SCLC)

a) UoM research has contributed to the evidence base for platinum etoposide as the standard first line chemotherapy for SCLC (5, 6). Platinum etoposide was standard in the US but not in Europe. UoM researchers demonstrated grade 3 and 4 neutropenia rates of 90% versus 57% and grade 3 and 4 infection rates of 73 vs 29% with anthracycline versus platinum based regimens respectively. UoM researchers have also demonstrated lack of benefit of 'newer' chemotherapy agents with a 20% lower response rate and worse survival for pemetrexed based treatment. These studies have contributed to a shift from using more toxic anthracycline based regimens in Europe and platinum – etoposide as the mainstay of standard treatment worldwide (S2, S7).

b) UoM research has significantly contributed to the evidence base that prophylactic cranial irradiation reduces the incidence of symptomatic brain metastases by 25% and doubles one year survival from 13% to 27% in patients with incurable, extensive stage SCLC without adverse impact on quality of life (4) (S2, S4).

Significance of changes to guidelines

The guidelines ensure that optimal treatment regimens are administered worldwide such that patients can expect the same clinical outcomes regardless of where they live and are treated. In the early 1990s, fewer than 10% of patients with lung cancer survived for one year from diagnosis. While there is still much progress to be made, today, with treatment such as gemcitabine-based chemotherapy, survival of around one year is achieved for most patients with advanced lung cancer, and around 25% of patients can now expect to survive for two years or more. With respect to targeted therapy with gefitinib, average survival is ~20 months compared with less than 4 months with no treatment and 9 months with chemotherapy alone.

The UK NICE guidelines for lung cancer treatment also inform the treatments that are reimbursed by National Health Service Funding. UoM research contributed to the evidence for licensing and funding for gemcitabine, gefitinib and erlotinib. The compliance with NICE guidance is audited nationally to ensure patients are benefiting from evidence based practice.

5. Sources to corroborate the impact

S1. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *Journal of Clinical Oncology*. 2008;26(28):4617-25. DOI: 10.1200/JCO.2008.17.7162

S2. National Institute for Health and Care Excellence. The diagnosis and treatment of lung cancer. CG121. London: National Institute for Health and Care Excellence, 2011. Available from: http://guidance.nice.org.uk/cg121

S3. Felip E, Gridelli C, Baas P, Rosell R, Stahel R, Panel Members. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. *Annals of Oncology*. 2011;22(7):1507-19. DOI: 10.1093/annonc/mdr150.

S4. NCCN guidelines (US clinical guidelines for lung cancer treatment) for SCLC and NSCLC. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

S5. Campbell L, **Blackhall F, Thatcher N.** Gefitinib for the treatment of non-small-cell lung

cancer. *Expert Opinion on Pharmacotherapy*. 2010;11(8):1343-57. DOI: 10.1517/14656566.2010.481283.

S6. **Blackhall F, Ranson M, Thatcher N**. Where next for gefitinib in patients with lung cancer? *The Lancet Oncology*. 2006;7(6):499-507.DOI: 10.1016/S1470-2045(06)70725-2

S7. Stahel R, **Thatcher N**, Früh M, Le Péchoux C, Postmus PE, Sorensen JB, Felip E, Panel Members. 1st ESMO Consensus Conference in lung cancer; Lugano 2010: Small-cell lung cancer. *Annals of Oncology*. 2011;22(9):1973-80. DOI: 10.1093/annonc/mdr313