Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: Clinical development of lenvatinib provides new treatment options for advanced renal cell carcinoma and unresectable hepatocellular carcinoma patients worldwide		
Period when the underpinning research was undertaken: 2005–present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): **(1)** Prof Jeff Evans; **(2)** Dr Hilary Glen.	**Role(s) (e.g. job title):** **(1)** Professor of Translational Cancer Research; **(2)** Clinical Research Fellow; Honorary Clinical Senior Lecturer and NHS Research Scotland Fellow.	**Period(s) employed by submitting HEI:** **(1)** 2005–present; **(2)** 2006–2013; 2013–present.
Period when the claimed impact occurred: 2016–present.		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Advanced renal cell carcinoma (RCC) and unresectable hepatocellular carcinoma (uHCC) have unmet therapeutic needs. UofG research enabled Japanese pharmaceutical company Eisai to develop lenvatinib for these cancers, from first-in-human studies through to pivotal clinical trials. Since 2016, lenvatinib has received worldwide approval as part of a second-line drug combination for RCC (>55 countries). Lenvatinib is also approved as first-line monotherapy for uHCC (>65 countries), the first new drug for this indication in a decade (and only the second licensed for first-line treatment). These therapies were subsequently incorporated into international guideline recommendations. Global sales of lenvatinib rose from JPY11.5 billion (2015/2016) to JPY111.9 billion (2019/2020), while a USD5.76 billion Global Strategic Oncology Collaboration with Merck has augmented Eisai's lenvatinib programme.

2. Underpinning research

Tyrosine kinase inhibitors (TKIs) comprise a family of drugs that molecularly target key drivers of malignant growth such as the formation of blood vessels (angiogenesis). In the early 2000s, Japanese pharmaceutical company Eisai developed a new molecule (E7080; generic name, lenvatinib) as an orally administered TKI targeting multiple angiogenic factors, including vascular endothelial growth factor (VEGF) receptors and fibroblast growth factor receptors. UofG researchers **Prof Jeff Evans** and **Dr Hilary Glen** have collaborated with Eisai on the key stages for laboratory and clinical evaluation of lenvatinib across multiple cancers with unmet clinical needs for new therapeutic options (2005–present).

The first-in-human trial of lenvatinib

Eisai recognised the expertise of UofG cancer researchers in Src tyrosine kinase biology and running first-in-human trials for various molecules, including TKIs. Consequently, Eisai invited **Evans** and **Glen** to develop lenvatinib in both clinical studies and associated laboratory studies (e.g. exploratory biomarkers). The first-in-human trial of this drug was led by **Evans** and **Glen**, in collaboration with Prof Jan Schellens (Netherlands Cancer Institute, Amsterdam). This phase 1 study (NCT00121719; 2005–2009) showed that lenvatinib was well tolerated among patients with a range of solid tumours; furthermore, encouraging signals of anti-tumour efficacy were observed for patients with melanoma or RCC [3.1].

Study 205 identifies lenvatinib as an effective treatment for RCC

RCC is among the top 10 most common cancers, affecting 400,000 people worldwide. Until the recent approval of immune checkpoint inhibitors, patients who experienced relapse after treatment with a first-line drug targeting VEGF had poor outcomes. Second-line options for such patients include monotherapy with everolimus (an inhibitor of mTOR) or a TKI (e.g. sorafenib); however, simultaneous targeted blockade of several different signalling pathways via combination therapy was expected to improve disease-free survival after relapse.

To further investigate the role of lenvatinib in RCC, **Glen** helped to design and deliver Eisai's 'Study 205' (NCT01136733; 2010–2014). This randomised phase 2 trial of lenvatinib alone or in combination with everolimus was conducted among patients with advanced (i.e. non-

operable or metastatic) RCC who had previously been treated with a first-line drug [3.2]. Led by Prof James Larkin (Royal Marsden Hospital, UK), Study 205 involved 153 patients at 37 centres in five countries. Glen contributed to the trial design; development of the methodology; data collection and analysis; and writing of the report. Study 205 established the efficacy of lenvatinib plus everolimus in RCC, offering an appreciable progression-free survival benefit of 9.1 months versus everolimus alone (revised to 10.1 months following post hoc analysis).

REFLECT establishes lenvatinib as a first-line option for uHCC

HCC accounts for 80%–95% of all primary liver cancer cases, and is the fourth leading cause of cancer-related death worldwide after lung, colorectal and stomach cancers. On a global scale, approximately 780,000 new cases are diagnosed annually, with most cases (80%) occurring in East Asia. Sorafenib was the first systemic therapy made available for patients with HCC (2007); however, no advances in first-line systemic treatment for non-operable disease (i.e. uHCC) had occurred since then.

Evans was involved in early oncology trials that investigated a range of agents for uHCC (2005–2017), including high-profile studies of sorafenib plus erlotinib (another TKI) [3.3]. Recognising his international track record in uHCC trials and experience with lenvatinib, Eisai invited Evans to join its international collaboration on uHCC, including the first multicentre international trial of lenvatinib monotherapy for this cancer. REFLECT (NCT01761266; 2013–2016) was a phase 3 non-inferiority trial conducted at 154 sites in 20 countries worldwide [3.4]. This study demonstrated that treatment with lenvatinib was non-inferior to the existing first-line drug sorafenib for the primary endpoint of overall survival (13.6 months versus 12.3 months; 1.3-month benefit). Moreover, REFLECT demonstrated improvements in the secondary endpoints of progression-free survival (3.7 months), time to progression (3.7 months) and objective response rate. Lenvatinib also offered an improved adverse effect profile and clinically meaningful enhancements in quality of life (QoL) when compared with sorafenib [3.4]. REFLECT was the first study in over 10 years to show meaningful success in uHCC.

Maximising the potential of lenvatinib for uHCC: the PIONEER programme

Evans is part of the Eisai PIONEER programme tasked with conducting post hoc studies to maximise information and outcomes from REFLECT following global marketing authorisations (2018–present). PIONEER evaluations (detailed in section 4) have provided insight on adverse effects of lenvatinib (e.g. proteinuria) [3.5]; overall survival following progression to a second-line therapy [3.6]; and reappraisal of overall survival with lenvatinib monotherapy [3.7].

3. References to the research (documents 2–4 available on request from HEI)

1. Boss DS, **Glen H**, […], **Evans TRJ** (2012) A phase I study of E7080, a multitargeted tyrosine kinase inhibitor, in patients with advanced solid tumours. *Br J Cancer*;106(10):1598–1604 (doi:10.1038/bjc.2012.154).
2. Motzer RJ, Hutson TE, **Glen H** *et al*. (2015) Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol*;16(15):1473–1482 (doi:10.1016/S1470-2045(15)00290-9).
3. Zhu AX, Rosmorduc O, **Evans TRJ** *et al*. (2015) SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol*;33:559–566 (doi:10.1200/JCO.2013.53.7746).
4. Kudo M, […], **Evans TRJ** *et al*. (2018) Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*;391(10126):1163–1173 (doi:10.1016/S0140-6736(18)30207-1).
5. **Evans TRJ** *et al*. (2019) Urine protein:creatinine ratio vs 24-hour urine protein for proteinuria management: analysis from the phase 3 REFLECT study of lenvatinib vs sorafenib in hepatocellular carcinoma. *Br J Cancer*;121:218–221 (doi:10.1038/s41416-019-0506-6).
6. Alsina A, […], **Evans TRJ** *et al*. (2020). Effects of subsequent systemic anticancer medication following first-line lenvatinib: a post hoc responder analysis from the phase 3 REFLECT study in unresectable hepatocellular carcinoma. *Liver Cancer*;9(1):93–104 (doi:10.1159/000504624).

7. Briggs A, […] **Evans TRJ** *et al*. (2020) Covariate adjusted analysis of the phase 3 REFLECT study of lenvatinib versus sorafenib in the treatment of unresectable hepatocellular carcinoma. *Br J Cancer*;122:1754–1759 (doi:10.1038/s41416-020-0817-7).

Research funding
Eisai funded the clinical studies of lenvatinib. **Glen** was supported by a Clinical Research Fellowship through the Cancer Research UK (CRUK) Beatson Institute and an NHS Research Scotland Fellowship. Delivery of the clinical studies was supported by the infrastructure of the Glasgow Experimental Cancer Medicine Centre, funded by CRUK and the Chief Scientist's Office, Scotland.

4. Details of the impact

Clinical research conducted by **Evans** and **Glen** on lenvatinib has shaped Eisai's development strategy for cancers with unmet therapeutic needs (**impact 1**); provided key evidence to support global licensing approvals (**impact 2**); boosted economic value for Eisai (**impact 3**); informed UK and international guideline recommendations (**impact 4**); and improved QoL and outcomes for patients (**impact 5**).

Impact 1. Influencing Eisai's development strategy for lenvatinib

Results from the first-in-human clinical trial of lenvatinib (**Glen**, **Evans**) [3.1] led Eisai to pursue the development of this drug, including as a potential treatment for RCC. Beyond his role in the REFLECT study [3.4], **Evans** has worked with Eisai on its strategic programme for lenvatinib in uHCC by undertaking post hoc analyses [3.5–3.7], and influencing post-approval marketing activities [5.A]. He was also one of two oncologists within Eisai's Panel of Experts (a group of five international opinion leaders) who, ahead of reporting the REFLECT findings and launch of lenvatinib for uHCC (2018), provided key input to Eisai's internal education programme for this indication. He delivered seminars and facilitated production of a film on the patient treatment journey for the Eisai marketing and medical science liaison teams [5.A]. He has supported high-profile dissemination of trial results and their implications through interviews and participation in key opinion leader panels at numerous international cancer conferences. For example, media activities at the 2018 American Society of Clinical Oncology (ASCO) meeting collectively reached 110,000 people [5.B]. Since 2019, Evans has engaged with clinicians on behalf of Eisai to support the transition from sorafenib to lenvatinib ahead of in-country launches by presenting REFLECT data and/or case studies [5.A].

In March 2020, the Eisai lenvatinib programme was honoured with the Pharmaceutical Society of Japan Award for Drug Research and Development. This award recognises "*outstanding research work that has contributed to medicine through the innovative development of a pharmaceutical drug … based on the ingenuity of the research itself as well as the effectiveness and safety of the related pharmaceutical product.*"

Impact 2: Worldwide regulatory approvals for lenvatinib

In May 2016, the US Food and Drug Administration (FDA) approved the use of lenvatinib (trade name, 'Lenvima') in combination with everolimus as a second-line treatment for RCC after one previous antiangiogenic therapy [5.C]. The European Medicines Agency subsequently approved lenvatinib (European trade name, 'Kisplyx') plus everolimus for use following one previous VEGF-targeted therapy (September 2016) [5.C]. This drug combination was approved in more than 55 countries by December 2020 [5.C]. Regulatory approvals for RCC were underpinned by Study 205 (co-designed by **Glen**) as the pivotal work [3.2], and realised the potential for this indication first highlighted by **Evans** and **Glen** in 2012 [3.1].

During 2018, REFLECT data [3.4] supported approval of lenvatinib as a monotherapy for first-line treatment of uHCC in Japan (March); USA (August); Europe (August, as a label change); South Korea (August); and China (September) [5.D]. More than 65 countries have now approved this indication [5.C]. Lenvatinib monotherapy was the only new first-line treatment for uHCC in a decade, thereby increasing the options available for oncologists and their patients. In 2018, Eisai reported that 2,800 uHCC patients had received lenvatinib during the first 4 months after approval, achieving 223% of the prescription target [5.D].

Impact 3: Economic value of regulatory approvals to Eisai

Global sales for all indications of lenvatinib (RCC, uHCC, thyroid cancer) rose from JPY11.5 billion in fiscal year (FY) 2015 to JPY111.9 billion in FY2019, with JPY103.8 billion recorded during the first three quarters of FY2020 (April–December) [5.E].

In March 2018, Eisai signed a USD5.76 billion Global Strategic Oncology Alliance with Merck to co-develop and co-commercialise lenvatinib as both monotherapy and combination therapy with Merck's immunotherapeutic drug pembrolizumab, thereby maximising the value of lenvatinib for both current indications and across a range of additional cancers [5.E]. Given his expertise in clinical trials, immunotherapy and lenvatinib, Evans was selected as one of three UK investigators to participate in the phase 1b/2 study of lenvatinib plus pembrolizumab for first-line treatment of uHCC. In July 2019, this drug combination was awarded FDA Breakthrough Therapy designation [5.E], which accelerates development and review of medicines for serious or life-threatening conditions. Efficacy and safety data for lenvatinib plus pembrolizumab in uHCC and RCC were reported at the May 2020 ASCO meeting [5.E].

Impact 4. Uptake of lenvatinib by UK and international clinical guidelines

Study 205 [3.2] provided key evidence for recommending lenvatinib plus everolimus for RCC:

- The 2018 UK National Institute for Health and Care Excellence (**NICE**) Technology Assessment TA498 recommends this therapy as an option for second-line treatment of advanced RCC in adults [5.F]. This decision was based solely on Study 205 data indicating that "*on average, people live around 10.1 months longer if they have lenvatinib plus everolimus rather than everolimus alone."* A cost-effectiveness analysis demonstrated combination therapy to be equivalent to, or more effective and less costly, than existing second-line monotherapies for RCC. The Scottish Medicines Consortium (**SMC**) approved this therapy for use within NHS Scotland in November 2019 [5.F].
- The National Comprehensive Cancer Network (**NCCN**)—a consortium of 23 US centres of clinical excellence in cancer care—lists this therapy as a 'category 1' recommendation (high level evidence, uniform NCCN consensus) for relapsed stage IV RCC in its online kidney cancer guidelines (updated July 2020 as version 1.2021) [5.F]. Most US health insurers reimburse category 1 and 2A NCCN recommendations.

REFLECT [3.4] provided key evidence for recommending lenvatinib monotherapy for uHCC:

- **NICE** TA551 (2018) [5.G] recommends this therapy as an option for adults with untreated advanced uHCC solely on the basis of REFLECT [3.4]. This indication was subsequently approved for use by NHS Scotland (**SMC**; April 2019) [5.G].
- The **NCCN** online guideline for hepatobiliary cancer (updated August 2020 as version 5.2020) recommends this therapy for uHCC (Child–Pugh Class A only; category 1 recommendation) [5.H]. The 2018 American Association for the Study of Liver Diseases (**AASLD**) also recommends lenvatinib as a first-line treatment [5.H].
- The 2018 European Association for the Study of the Liver (**EASL**) guidelines recommend lenvatinib as first-line therapy among patients with well-preserved liver function (Child–Pugh class A), good performance status and advanced tumours (evidence high; recommendation strong) [5.I]. The 2018 European Society for Medical Oncology (**ESMO**) guidelines also recommend lenvatinib as a first-line systemic treatment, with the highest evidence level (category I, A) [5.I].
- The 2019 Japan Society of Hepatology (**JSH**) guidelines recommend lenvatinib or sorafenib as first-line molecular therapies for advanced uHCC, referencing an ASCO conference abstract of the REFLECT trial (Cheng et al. 2017; **Evans** listed as a co-author) [5.J].

Impact 5: Improved QoL and outcomes for patients with uHCC

The availability of lenvatinib for treating uHCC has improved QoL and outcomes among patients with this cancer of previously unmet need. Patients have benefited by either taking part in a clinical trial or from being prescribed lenvatinib following regulatory approval.

Lenvatinib offers improvements in key QoL domains that affect patients' daily lives. Fewer instances of hand-and-foot syndrome, diarrhoea and alopecia were recorded with lenvatinib

versus sorafenib in REFLECT [3.4]. Lenvatinib also delays worsening of physical function, pain, diarrhoea, body image and nutrition [5.K]. Although lenvatinib is associated with increased rates of proteinuria and hypertension [3.4], these adverse effects are both manageable and more acceptable to patients than the debilitating hand-and-foot syndrome and diarrhoea seen with sorafenib. For example, proteinuria requires regular monitoring; however, **Evans'** work on the Eisai PIONEER programme demonstrated that using spot urine samples to calculate the urine protein-to-creatinine ratio could offer less burdensome monitoring than collection of 24-hour urine samples [3.5]. This report also provided guidelines to control proteinuria [5.K], which support clinical management of uHCC patients treated with lenvatinib.

In 2018, REFLECT reported that lenvatinib is non-inferior to sorafenib for the primary endpoint of overall survival [3.4]. A 2020 post-hoc covariate adjusted analysis found that the original report had underestimated the true effect of lenvatinib in this outcome owing to imbalances in baseline prognostic covariates and an increased use of post-intervention therapies in the sorafenib arm [3.7]. Another post-hoc analysis showed that among the subset of REFLECT participants who went on to second-line anticancer medication, median overall survival was increased for patients randomised to first-line lenvatinib (25.7 months) versus those who had received first-line sorafenib (22.3 months) [3.6]. Finally, objective response rates in clinical practice mirror those observed among participants in clinical trials of lenvatinib, confirming the utility of this drug in real-world treatment [5.K].

5. Sources to corroborate the impact

PDFs uploaded for all items, unless indicated otherwise.

A. Examples of Prof Evans' consultancy work with Eisai, including activities to disseminate clinical trials data and promote uptake of lenvatinib for patients with uHCC (2017–2020).
B. Media coverage of REFLECT [3.4] (ASCO meeting, 2018): (1) The Pharma Letter; (2) Pharmaphorum; (3) Touch Oncology [YouTube video]; (4) Statement from Eisai to substantiate the reach of this coverage.
C. Approvals of lenvatinib + everolimus for advanced RCC (2016) based on Study 205 [3.2]: (1) USA and Europe; (2) Global approvals of lenvatinib for all indications (2020). See p.2.
D. Approvals of lenvatinib monotherapy for uHCC (2018) based on REFLECT [3.4]: (1) Japan, USA, Europe, South Korea and China; (2) Eisai 2018 Q1 report. See p.11 for prescribing data.
E. Economic benefits for Eisai: (1) Q1 FY2016 financial report. See p.15 for FY2015 sales; (2) FY2019 financial report. See p.9; (3) Q3 FY2020 financial report. See p.13; (4) Press releases for the Global Strategic Oncology Alliance with Merck (March 2018, July 2019, May 2020).
F. UK and international guidelines for advanced RCC citing Study 205 [3.2]: (1) NICE TA498 (2018). Cited throughout as 'HOPE 205'; (2) SMC2199 (2019). Cited as ref. 3. See p.2–6; (3) NCCN kidney cancer version 1.2021 (July 2020). Cited as ref. 153. See p.KID-C 2 of 2 and p.MS-18.
G. UK guidelines for uHCC citing REFLECT [3.4]: (1) NICE TA551 (2018). Cited throughout this document; (2) SMC2138 (2019). Cited as ref. 3. See p.2–7.
H. US guidelines for uHCC citing REFLECT [3.4]: (1) NCCN hepatobiliary cancer version 5.2020 (August 2020). Cited as ref. 3 (see p.HCC-F) and ref. 427 (see p.MS-30). Conference abstract for Alsina et al. [3.6] cited as ref. 4 (see p.HCC-F); (2) AASLD Practice Guidance (2018). Cited as ref 168. See p.742, p.744, Table 3.
I. European guidelines for uHCC citing REFLECT [3.4]: (1) EASL guidelines (2018). Cited as ref. 323. See p. 213–215, Table 5, Figs. 3 and 9; (2) ESMO guidelines (2018). Cited as ref. 118. See p.246–247, p.250, Table 4, Fig. 1.
J. Asian guidelines for uHCC citing REFLECT data: JSH guidelines (2019). See p.4. This cites the ASCO conference abstract (Cheng et al. 2017) as ref. 14.
K. Patient benefits: (1) Eisai press release on QoL (2017); (2) Proteinuria guidelines (cited as Supplementary Table 2 in Evans et al. [3.5]); (3) Eisai presentation on Japanese clinical practice (2018). See slide 44.