Institution: The Institute of Cancer Research

Unit of Assessment: Biological Sciences

Title of case study: Identifying *BRAF* as a key target for the development of novel cancer therapeutics

Period when the underpinning research was undertaken: 2002 to 2015

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:
Professor David Barford	ICR Team Leader	01/05/1999–01/11/2013
Professor Martin Gore	ICR Honorary Faculty and Professor	01/06/1999–10/01/2019
Professor Richard Marais	ICR Team Leader	01/09/1992–31/01/2012
Professor Chris Marshall	ICR Team Leader	30/05/1980–08/08/2015
Professor Caroline Springer	ICR Team Leader	01/10/1992–30/09/2017
Professor Michael Stratton	ICR Team Leader	17/06/1991–30/06/2010

Period when the claimed impact occurred: 2002 onwards

Is this case study continued from a case study submitted in 2014? Yes. Since the submission to REF 2014, there has been significant continued clinical impact in melanoma and new impact following the approvals of BRAF inhibitors in non-small cell lung cancer and colorectal cancer, and significant new clinical impact following the approvals for treatments with a combination of BRAF and MEK inhibitors.

1. Summary of the impact

Scientists at The Institute of Cancer Research (the ICR), in collaboration with the Wellcome Trust Sanger Institute, made the significant discovery that mutant *BRAF* is an oncogene and demonstrated the therapeutic potential of combining BRAF and MEK inhibition. This produced the following impact:

- **Clinical development of BRAF and MEK inhibitors.** An international search for these inhibitors resulted in novel drugs with global regulatory approval. There are now three BRAF inhibitor and MEK inhibitor combinations approved (dabrafenib plus trametinib; vemurafenib plus cobimetinib; and encorafenib plus binimetinib).
- **Patient benefit.** These drugs were a significant innovation and are improving outcomes for melanoma, non-small cell lung cancer, and colorectal cancer patients.
- **Commercial.** In 2018, the combination of dabrafenib with trametinib reached over USD1,000,000,000 in global sales for Novartis.

2. Underpinning research

Background. The *BRAF* gene encodes the BRAF protein—a member of the Raf kinase family of protein kinases. BRAF modulates the Raf-MEK-ERK signal transduction pathway, which regulates cell growth, proliferation, and differentiation.

Identifying BRAF as an oncogene. In 2001, ICR researchers (Professor Chris Marshall, Dr Richard Marais (became Professor in 2007), Professor Michael Stratton, and Dr Richard Wooster) in collaboration with the Wellcome Trust Sanger Institute started investigating mutations in the *BRAF* gene. It was discovered that *BRAF* was mutated in approximately 50% of melanomas, 10% of colorectal cancers, and a smaller percentage of other cancers—including lung cancers (**Ref. 1**). The majority of mutations were in the kinase domain of BRAF, with the V599E mutation reported as the most common (the reference sequence has changed since the original report and this mutation is now usually reported as V600E). The ICR Marais and Marshall teams carried out biological studies, and made the crucial observation that confirmed mutated BRAF acted as an oncogene (**Ref. 1**).

Structure and function of BRAF. Professor David Barford's team, with the Marais team, were the first to elucidate the crystal structure of mutant BRAF protein. Their work identified a structural region where a significantly high frequency of mutants are clustered. These mutations destabilise the inactive conformation of mutant BRAF, and so promote BRAF activity (**Ref. 2**). Research into the function of the *BRAF* gene continued at the ICR under the direction of Professor Marais and Professor Caroline Springer. They demonstrated that inhibition of BRAF in RAS mutant cancer cells leads to MEK hyperactivation through CRAF (**Ref. 3**). This conclusion was reached first on the basis of animal models, and then by analysis of patients who developed squamous cell carcinomas whilst being treated with selective BRAF inhibitors (**Ref. 4**). It was also shown in animal models that BRAF inhibitor-induced metastasis was blocked by MEK inhibition. This research also provided evidence that a combination of BRAF and MEK inhibitors could be an effective therapeutic approach.

3. References to the research

Key: **ICR employed staff** at the time of publication, **ICR Team Leader (including Honorary Faculty)** at the time of publication.

(Ref. 1) Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, **Garnett MJ**, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, **Hooper S**, **Wilson R**, **Jayatilake H**, Gusterson BA, **Cooper C**, **Shipley J**, **Hargrave D**, **Pritchard-Jones K**, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JWC, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, **Paterson H**, **Marais R**, **Marshall CJ**, **Wooster R**, **Stratton MR**, Futreal PA. 2002, Mutations of the *BRAF* gene in human cancer, Nature. 417, 949-954. (http://dx.doi.org/10.1038/nature00766). *Times cited: 7,030 (WOS).*

(Ref. 2) **Wan PTC**, **Garnett MJ**, **Roe SM**, **Lee S**, **Niculescu-Duvaz D**, **Good VM**, Cancer Genome Project, **Jones CM**, **Marshall CJ**; **Springer CJ**; **Barford D**; **Marais R**. 2004, Mechanism of Activation of the RAF-ERK Signaling Pathway by Oncogenic Mutations of B-RAF, Cell. 116 (6), 855-867. (http://dx.doi.org/10.1016/S0092-8674(04)00215-6). *Times cited: 1,912 (WOS).*

(Ref. 3) **Heidorn SJ**, **Milagre C**, **Whittaker S**, **Nourry A**, **Niculescu-Duvas I**, **Dhomen N**, Hussain J, **Reis-Filho JS**, **Springer CJ**, Pritchard C, **Marais R**. 2010, Kinase-Dead BRAF and Oncogenic RAS Cooperate to Drive Tumor Progression through CRAF, Cell. 140 (2), 209-221. (http://dx.doi.org/10.1016/j.cell.2009.12.040). *Times cited: 1,020 (WOS).*

(Ref. 4) Su F, **Viros A, Milagre C**, Trunzer K, Bollag G, Spleiss O, **Reis-Filho JS**, Kong X, Koya RC, Flaherty KT, Chapman PB, Jung Kim M, **Hayward R, Martin M,** Yang H, Wang Q, Hilton H, Hang JS, Noe J, **Lambros M, Geyer F, Dhomen N, Niculescu-Duvaz I, Zambon A, Niculescu-Duvaz I, Preece N**, Robert L, Otte NJ, Mok S, Kee D, Ma Y, Zhang C, Habets G, Burton EA, Wong B, Nguyen H, Kockx M, Andries L, Lestini B, Nolop KB, Lee RJ, Joe AK, Troy JL, Gonzalez R, Hutson TE, Puzanov I, Chmielowski B, **Springer CJ,** McArthur PA, Sosman JA, Lo RS, Ribas A, **Marais R**. 2012. RAS Mutations in Cutaneous Squamous-Cell Carcinomas in Patients Treated with *BRAF* Inhibitors, N Engl J Med. 366, 207-215. (http://dx.doi.org/10.1056/NEJMoa1105358). *Times cited: 736 (WOS).*

4. Details of the impact

Drug development and regulatory approval of BRAF inhibitors in melanoma. In 2001, following the discovery that mutated *BRAF* was an oncogene (**Ref. 1**), the ICR—in partnership with the Wellcome Trust—patented mutant *BRAF* as a target for drug screens and patient testing **[A]**. The patent has five inventors, four of which were ICR Team Leaders at that time (Marshall, Marais, Stratton, and Wooster), demonstrating the pivotal role that the ICR played in the discovery. The patent has enabled the ICR to out-license widely, on a non-exclusive basis,

to facilitate worldwide drug discovery. Currently there are 12 licensees of this patent and, since 2013, GBP727,250 of licensing income has been received. ICR research showed that BRAF inhibitors could have clinical activity in *BRAF*-mutant melanomas, which alongside ICR structural studies of mutant BRAF resulted in significant activity in the pharmaceutical industry to develop selective inhibitors of V600-mutant BRAF. Vemurafenib was the first-in-class agent, developed by Plexxikon (now part of Daiichi-Sankyo) and Genentech. The results of the phase 3 trial of vemurafenib in 675 patients (BRIM3) demonstrated a clinical benefit not previously observed in metastatic melanoma. Vemurafenib was associated with a relative reduction of 63% in the risk of death and 74% in the risk of either death or disease progression. Dabrafenib, another selective BRAF inhibitor, was developed by Novartis soon after. This drug led to progression-free survival of 5.1 months compared to 2.7 months with standard treatment, in a clinical trial of 250 patients.

Based on these clinical efficacy data, vemurafenib and dabrafenib received approval from the US Food and Drug Administration (FDA) for the treatment of melanoma, in 2011 and 2013 respectively. Both vemurafenib and dabrafenib were approved by the European Medicines Agency (EMA) in 2012 and 2013, and were approved by NICE in 2012 and 2014 **[B]**. Following the NICE approval, there was an increase in prescriptions of vemurafenib, peaking between 2013 and 2014. Following the NICE recommendation in 2014, prescribing of dabrafenib increased rapidly (see *Figure 1).*

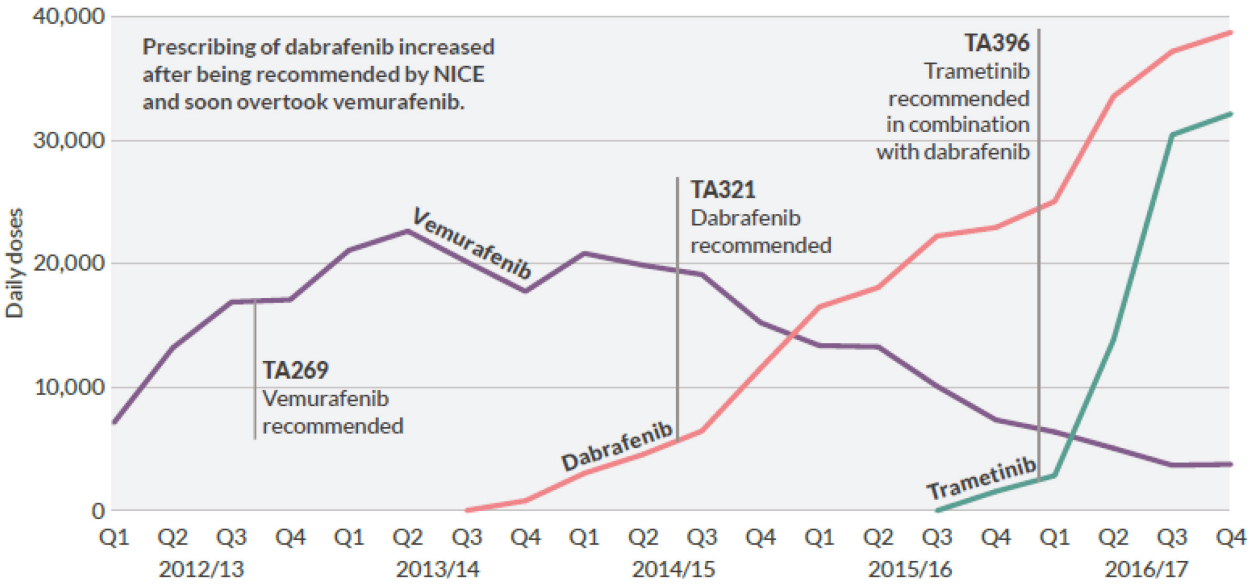

Figure 1: Prescribing for advanced BRAF V600 mutation-positive melanoma. Adapted from NICEimpact cancer **[B]**

Development and regulatory approval of BRAF/MEK inhibitor combinations in melanoma. ICR-based research (**Ref. 3** and **Ref. 4**) alongside the research of others, resulted in a series of clinical trials evaluating dabrafenib in combination with trametinib (a MEK inhibitor). Two international phase 3 clinical trials, COMBI-d and COMBI-v, showed the clinical benefit of the combination as compared to single therapy with either dabrafenib or vemurafenib. The combination of dabrafenib with trametinib is now approved in the US, EU, Japan, Australia, Canada, and elsewhere for patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation **[C]**. In June 2016, NICE recommended the combination therapy, leading to a rapid increase in prescribing of trametinib (*Figure 1*). This combination therapy is more effective than therapy with a single BRAF inhibitor, without any increase in adverse effects.

> *"The committee concluded that the availability of a new combination treatment that slows disease progression and improves quality of life is very important to patients and their families."* **[D]**

There are two further BRAF and MEK inhibitor combinations approved: vemurafenib and cobimetinib (Cotellic, Roche) and encorafenib (Braftovi, Pierre Fabre) with binimetinib (Mektovi, Array Biopharma).

Impact on melanoma patients. ICR research into *BRAF* has led to significant benefits for patients, especially for the ~50% of melanoma patients with tumours harbouring *BRAF* mutations. Melanoma is the fifth most common cancer in the UK, with around 16,000 new cases annually (2014–2016)—incidence rates for melanoma skin cancer are projected to rise by 7% in the UK between 2014 and 2035. Before 2011 (and the approval of any BRAF inhibitors), metastatic melanoma was considered a devastating disease with a median overall survival of around 9 months. The approval of BRAF inhibitors as a monotherapy provided an important new treatment option for these patients in an area of unmet need. In 2012, only 41% of people diagnosed with stage 4 melanoma were alive a year after diagnosis; by 2015 this had increased to 51% **[B]**.

According to clinical trial data, the combination of trametinib and dabrafenib increased median progression-free survival by a statistically significant 2.2 months as compared with dabrafenib alone, and by 5.3 months as compared with vemurafenib alone; the combination increased median *overall* survival by a statistically significant 6.4 months as compared with dabrafenib alone, and by 7.6 months as compared with vemurafenib alone. Despite the substantial increase in efficacy of the combination therapy, without any increase in adverse effects, and indeed the combination reduced the incidence of a number of skin toxicities associated with BRAF inhibitor therapy **[D]**. Based on the figures from drug sales in 2018, the combination of trametinib and dabrafenib continues to be a widely used treatment option for *BRAF*-mutant melanoma (see '*Economic impact for the pharmaceutical industry*').

Impact in non-small cell lung cancer (NSCLC). The ICR's work (**Ref. 1**) and research by others has shown that around 7% of NSCLCs harbour *BRAF* mutations—there is also some evidence that the presence of mutant *BRAF* in NSCLC is associated with reduced platinum doublet efficacy (the standard therapy for these cancers), and poorer patient outcomes. Building on this research, clinical trials explored the option of using BRAF inhibitors to treat *BRAF*-mutant NSCLC. BRF113928, a phase 2 trial of dabrafenib plus trametinib in stage 4 NSCLC, showed an average overall response rate of 64%, and median progression-free survival of 10 months. The American Society of Clinical Oncology and the US National Comprehensive Cancer Network (NCCN) recommend the use of dabrafenib plus trametinib in NSCLC patients with V600E-mutant *BRAF*; in 2017, the FDA granted approval to the combination for the same indication **[E]**.

Impact in colorectal cancer. The ICR's research showed that 10% of colorectal cancers contain *BRAF* mutations (**Ref. 1**), and patients with a *BRAF* V600E mutation have a poor prognosis. The NCCN guidelines specifically recommend that genomic testing at the time of diagnosis of metastatic colorectal cancer includes *BRAF* testing. The phase 3 trial BEACON combines a BRAF inhibitor (encorafenib) with an EGFR inhibitor (cetuximab) in colorectal cancer, and showed a significant improvement in both overall response rate and overall survival. There was a median overall survival of 8.4 months with the combination compared to 5.4 months with the control arm. Based on results from the BEACON trial, in April 2020, the FDA approved the encorafenib-cetuximab combination for the treatment of adult patients with metastatic colorectal cancer and a *BRAF* V600E mutation (as detected by an FDA-approved test), after prior therapy **[F].** This is the first-and-only targeted regimen for people with *BRAF* V600E mutant metastatic colorectal cancers who have received prior therapy, and therefore is a much-needed new treatment option for these patients. In November 2020, this combination therapy was also approved for use in the NHS in England.

Economic impact for the pharmaceutical industry. Many international pharmaceutical companies have created considerable shareholder value by adding BRAF inhibitor products to their cancer therapeutic pipeline—a commercial benefit derived from the ICR's underpinning research. In 2019, Pfizer acquired Array BioPharma Inc. for approximately USD11,400,000,000—Pfizer's press release stated it would strengthen their

"… leadership in Oncology with the addition of a breakthrough combination of BRAF/MEK inhibitors under investigation for a potential first-in-class therapy for patients with BRAF-mutant metastatic colorectal cancer." **[G]**

In 2020, Novellus Ltd. acquired from Plexxikon the exclusive worldwide rights to research, develop, manufacture, and commercialise PLX8394, a BRAF inhibitor that selectively binds to and inhibits the activity of wild-type and mutated forms of *BRAF* (including V600) **[H]**. PLX8394 is a next-generation BRAF inhibitor that does not induce paradoxical activation of the MAPK pathway in cells with stimulated RAS signalling. Novellus subsequently raised USD57,000,000 in a Series C financing round to fund the phase 2 clinical development of PLX8394. Michael Vidne, Chief Executive Officer of Novellus, stated that

"…PLX-8394 has the potential to address a major unmet need by targeting patient populations that are bereft of effective treatment options. The financing from this group of leading life science investors will enable us to realize the potential of PLX-8394 as a unique BRAF inhibitor." **[I]**

In 2020, the combination of dabrafenib with trametinib (Tafinlar + Mekinist) reached USD1,542,000,000 in global sales. This made it one of the top 20 'Innovative Medicines' products for Novartis **[J]**.

Stratification tests. The discovery by the ICR that mutant *BRAF* is an oncogene has led to the clinical stratification of certain cancers such as melanoma. The development of inhibitors that specifically target mutant *BRAF*-driven tumours means that patients must now be genetically screened for those who have mutant *BRAF*-tumours and to exclude those who also carry an activating *RAS* mutation to stratify patients suitable for the targeted therapies. A number of diagnostic companies have developed tests for mutant *BRAF* and have had these tests approved by the FDA and other regulatory authorities—examples include bioMerieux's THxID®-*BRAF* in vitro diagnostic and Roche's cobas 4800 *BRAF* V600 Mutation Test **[K]**. The marketing of these tests has added commercial value to the companies—all a direct result of the ICR's underpinning research.

5. Sources to corroborate the impact

A. BRAF patent: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2003056036

B. NICEimpact cancer report: https://www.nice.org.uk/Media/Default/About/what-we-do/Into-practice/measuring-uptake/nice-impact-cancer.pdf

C. Approvals of trametinib plus dabrafenib: https://www.novartis.com/news/media-releases/european-commission-approves-novartis-combination-therapy-tafinlar-mekinist-adjuvant-treatment-braf-v600-mutation-positive-melanoma

D. NICE recommendation of the combination of trametinib with dabrafenib: https://www.nice.org.uk/guidance/ta396/chapter/4-Committee-discussion

E. BRAF targeted therapy in NSCLC: http://dx.doi.org/10.21037/jtd.2018.01.129

F. Approval in colorectal cancer: https://investors.pfizer.com/investor-news/press-release-details/2020/US-FDA-Approves-BRAFTOVI-Encorafenib-in-Combination-with-Cetuximab-for-the-Treatment-of-BRAFV600E-Mutant-Metastatic-Colorectal-Cancer-CRC-After-Prior-Therapy/default.aspx

G. Pfizer acquisition of Array BioPharma Inc: https://www.pfizer.com/news/press-release/press-release-detail/pfizer_to_acquire_array_biopharma

H. Novellus acquisition of PLX8394 from Plexxikon: https://www.businesswire.com/news/home/20200603005355/en/Novellus-Executes-Exclusive-Worldwide-License-Agreement-Plexxikon

I. Novellus Series C funding for PLX8394: https://www.businesswire.com/news/home/20200921005290/en/

J. Novartis sales of the combination 2020: https://www.novartis.com/investors/financial-data/product-sales

K. Roche cobas® Test: https://diagnostics.roche.com/global/en/products/params/cobas-4800-braf-v600-mutation-test.html