Institution: The Institute of Cancer Research

Unit of Assessment: Clinical Medicine

Title of case study: Clinical development of immunotherapies in melanoma, renal, and head and neck cancers

Period when the underpinning research was undertaken: 2015 to 2019

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 Kevin Harrington	ICR Team Leader	28/03/2001–Present
Professor James Larkin	ICR Honorary Faculty	19/11/2001–28/02/2005; 28/04/2015–Present

Period when the claimed impact occurred: 2016 onwards

Is this case study continued from a case study submitted in 2014? No.

1. Summary of the impact

Immunotherapy is now an established pillar of cancer treatment, improving the outcomes of patients with a wide variety of cancers. Professors James Larkin and Kevin Harrington at The Institute of Cancer Research (ICR) have facilitated the international approval and use of a range of immunotherapies through their roles as investigators in clinical trials, and by providing expert clinical opinion at regulatory committee review meetings. These immunotherapies include:

- **Ipilimumab in combination with nivolumab** for the treatment of advanced melanoma;
- **Avelumab in combination with axitinib** for the treatment of renal cancer;
- **Nivolumab** as a second-line therapy in patients with recurrent or metastatic head and neck cancer;
- **Pembrolizumab** as a first-line treatment in head and neck cancer; and
- **Talimogene laherparepvec** (trade name T-VEC) for treating inoperable metastatic melanoma—the first approved oncolytic virus therapy.

2. Underpinning research

Background. Over the last 10 years, clinical development of immunotherapies has led to significant advances in cancer treatment:

1. Immune checkpoints are critical regulators of the immune system, preventing it from targeting cells indiscriminately. Cancers frequently exploit these checkpoints to subvert the immune system and evade detection. Inhibiting these immune checkpoints therefore helps restore immune function in cancer patients. This case study focuses on:
    - Ipilimumab—an inhibitor of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4);
    - Avelumab—which inhibits programmed death-ligand 1 (PD-L1);
    - Nivolumab and pembrolizumab—which inhibit the programmed death 1 (PD-1) receptor.
2. Oncolytic virus therapies use genetically modified viruses, designed to specifically target cancer cells. This case study focuses on Talimogene laherparepvec (T-VEC)—a modified form of herpes simplex virus type-1 which has been genetically engineered to stimulate the immune system to attack and destroy the tumour.

Immune checkpoint inhibitors in melanoma. CTLA-4 and PD-1 inhibit antitumour immunity through complementary and non-redundant mechanisms. Therefore, it was thought that there could be a clinical benefit in combining inhibitors that target these two checkpoints, which was further supported by preclinical and early phase studies. Professor James Larkin—ICR Honorary Faculty and Reader from 2015 (Professor from 2018)—working with Bristol-Myers Squibb, developed and led a randomised double-blind phase 3 study of nivolumab (a PD-1 inhibitor) plus

ipilimumab (a CTLA-4 inhibitor), compared to nivolumab or ipilimumab alone, in patients with metastatic melanoma. The trial involved 137 sites in Australia, Europe, Israel, New Zealand, and North America, and a total of 945 patients. The study found median progression-free survival for nivolumab plus ipilimumab was 11.5 months, compared to 6.9 months for nivolumab alone, and 2.9 months for ipilimumab alone **(Ref. 1)**. The five-year survival outcomes from this trial were published in 2019—overall survival at five years was 52% for nivolumab plus ipilimumab, 44% for nivolumab alone, and 26% for ipilimumab alone. For context, advanced melanoma has historically had a five-year survival rate of less than 10%.

In an effort to improve the outcomes of patients with stage 3 melanoma and patients with surgically resected stage 4 melanoma (who are generally excluded from phase 3 trials of adjuvant therapy), Professor Larkin also jointly led the phase 3 CheckMate 238 trial, and showed that treatment with nivolumab is superior to the standard of care in high-risk patients with resected stage 3B–C or 4 melanoma. Nivolumab also had a lower rate of grade 3 or 4 adverse events, compared to adjuvant therapy with ipilimumab. This trial was designed, overseen, and analysed through collaboration between Professor Larkin, other senior academic authors, and Bristol-Myers Squibb **(Ref. 2)**.

Immune checkpoint inhibitors in renal cancer. Following previous studies that showed activity of avelumab (a PD-L1 inhibitor) in renal-cell carcinoma, it was hypothesised that the combination of avelumab and axitinib (a VEGF-targeted antiangiogenic therapy) might have clinical benefit, as the drugs have complementary mechanisms of action. The JAVELIN Renal 101 phase 3 trial—sponsored by Pfizer—was developed to test this hypothesis. Professor Larkin and other investigators worked with Pfizer on the trial design, the collection and analysis of data, and interpretation of results. The trial **(Ref. 3)** demonstrated that:

- Patients with PD-L1-positive tumours had a median progression-free survival of 13.8 months with avelumab plus axitinib, compared to 7.2 months with the standard of care.
- In the overall population, patients had a median progression-free survival of 13.8 months with avelumab plus axitinib, compared to 8.4 months with the standard of care, and a higher objective response rate.

Immune checkpoint inhibitors in head and neck cancer. Patients with relapsed squamous cell carcinoma of the head and neck (HNSCC) that progress within six months of first-line chemotherapy have a poor prognosis—and previously had limited therapeutic options to prolong survival. It was known that the recurrence of HNSCC is facilitated by immune evasion and, therefore, it was hypothesised that immune checkpoint inhibitors could be effective in these cancers. The ICR's Professor Harrington was involved in the CheckMate 141 clinical trial, which found that nivolumab increased survival of patients with recurrent or metastatic HNSCC cancer **(Ref. 4)**. The trial was designed and overseen by the academic authors, including Professor Harrington, in collaboration with Bristol-Myers Squibb. Professor Harrington also led a study into the effect of nivolumab on patient-reported outcomes from the CheckMate 141 trial, which showed that patients on nivolumab gave consistently better patient-reported outcomes ratings throughout. Due to the importance of improving quality of life for these patients, these data support nivolumab as a new standard of care in this setting **(Ref. 5)**.

Professor Harrington co-led the KEYNOTE-040 study which showed that pembrolizumab provides a clinically meaningful survival benefit in patients with recurrent or metastatic HNSCC that progressed during or after platinum-based therapy. This therapy was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) based on the results of this trial. The indication was not pursued by NICE due to results from KEYNOTE-048 (see below). With the activity of immune checkpoint inhibitors in HNSCC demonstrated, it was hypothesised a combination of immune checkpoint inhibitors and chemotherapy in the first-line setting would be synergistic, as chemotherapy leads to immunogenic cell death and antigen shedding. Professor Harrington led the UK arm of the KEYNOTE-048 phase 3 trial—funded by Merck—which found that, in previously untreated recurrent or metastatic HNSCC, the pembrolizumab with chemotherapy combination improved overall survival compared to cetuximab with chemotherapy (13.0 months compared to 10.7 months) **(Ref. 6)**. Professor

Harrington played a leading role in conceiving, designing, and planning the study alongside Professor Barbara Burtness (Yale), Dr Jonathan D Cheng (Merck), and Dr Fan Jin (Merck).

Talimogene laherparepvec (T-VEC) in melanoma. Professor Harrington treated melanoma patients with T-VEC in the initial phase 1 trial (Hu Clin. Cancer Res. 2006), which then led to a phase 2 clinical trial in patients with melanoma, in which Professor Harrington was the UK Principal Investigator (Senzer et al. J. Clin. Oncol. 2009). Professor Harrington then led the UK arm of a landmark phase 3 trial—the first to show the benefit of viral immunotherapy for patients with unresected stage 3B to 4 melanoma **(Ref. 7)**. In this trial, patients treated with T-VEC had a 21% reduced risk of death and, 4.4-month longer median overall survival compared to the control group. This culminated in global approval of the treatment.

3. References to the research

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

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2. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, Dalle S, Schenker M, Chiarion-Sileni V, Marquez-Rodas I, Grob JJ, Butler MO, Middleton MR, Maio M, Atkinson V, Queirolo P, Gonzalez R, Kudchadkar RR, Smylie M, Meyer N, Mortier L, Atkins MB, Long GV, Bhatia S, Lebbé C, Rutkowski P, Yokota K, Yamazaki N, Kim TM, de Pril V, Sabater J, Qureshi A, **Larkin J***, Ascierto PA*; CheckMate 238 Collaborators. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017 Nov 9;377(19):1824-1835. *Contributed equally to this work. (http://dx.doi.org/10.1056/NEJMoa1709030). *Times cited: 821 (WOS).*
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4. Details of the impact

Impact of immune checkpoint inhibitors in melanoma. Melanoma is the fifth most common cancer in the UK, accounting for 4% of all new cancer cases and approximately 2,300 deaths annually **[A]**. Until 2012, the standard therapy for advanced melanoma in the UK was dacarbazine chemotherapy when the National Institute for Health and Care Excellence (NICE) recommended two new therapies—ipilimumab and vemurafenib for BRAF-mutant melanoma (a focus of one of our UOA5 impact case studies). In 2016, NICE approved nivolumab for the treatment of advanced melanoma (TA384)—this approval was based on data from the CheckMate 066, CheckMate 067 **(Ref. 1)**, and CheckMate 03 trials:

> *"The Committee agreed that the low toxicity and the favourable adverse effects profile of nivolumab compared with other treatments represent a promising new advance in immunotherapy for the treatment of metastatic melanoma."* **[B]**

In July 2016, NICE recommended nivolumab in combination with ipilimumab (TA400)—based on data from CheckMate 067 **(Ref. 1)**—as the combination is more effective than ipilimumab alone. Professor Larkin was nominated (by the charity Melanoma Focus) to be one of two clinical experts that attended the NICE Committee Appraisal meeting that resulted in this decision. In this meeting, Professor Larkin made the case that the combination represented a step-change in the management of melanoma, due to its unprecedented clinical benefit **[C]**. The NICE recommendation led to a rapid increase in the prescribing rates of ipilimumab **[D]**.

Just 10 years ago, less than 10% of patients with advanced melanoma would survive for five years. The impact of CheckMate 067 has been remarkable—the five-year follow-up was published in 2019 and showed sustained long-term survival in approximately 50% of patients who received nivolumab plus ipilimumab. Pamela Smith, 67, joined the Checkmate 067 trial in January 2014 soon after finding out that her melanoma had spread. Pamela said:

> *"It was inoperable, so the trial was my only option. I'd been having treatment every two weeks for about four months when I developed diarrhoea that was so bad I had to come off treatment. Amazingly, the first scan and every scan since has shown that in that relatively short time, it worked. My tumour shrank to less than half its original size and it hasn't changed in five years. I've not had any treatment since and I feel brilliant."* **[E]**

The impact from these treatments has not been confined to the UK. In January 2016, the FDA approved nivolumab in combination with ipilimumab in unresectable or metastatic melanoma, again on the basis of data from the CheckMate 067 trial **(Ref. 1)**—the first FDA-approved combination of immune checkpoint inhibitors. As of 2019, the combination is approved in more than 50 countries **[F]**. Professor Larkin contributed to the approval of the combination in Europe by attending the EMA CHMP Oral Explanation in January 2016. In 2017, the FDA and EMA approved adjuvant treatment with nivolumab based on the CheckMate 238 trial **(Ref. 2)**—the first PD-1 therapy to receive EMA approval in the adjuvant setting. In the European Union, the therapy now has eight indications, across six distinct tumour types **[F]**.

Impact of immune checkpoint inhibitors in renal cancer. In 2018, an estimated 136,500 new cases of renal cancer were diagnosed in Europe, and approximately 54,700 people died from the disease—there is a significant need for additional treatment options, particularly for advanced disease where the five-year survival rate is 12%. In May 2019, the FDA approved the combination of avelumab with axitinib based on the JAVELIN Renal 101 results **(Ref. 3)** and

EMA approval followed in October 2019 **[G]**. Avelumab with axitinib is now also recommended for use within the Cancer Drugs Fund for untreated advanced renal cell carcinoma (TA645).

Impact of immune checkpoint inhibitors in head and neck cancer. In 2018, there were approximately 705,000 cases of HNSCC diagnosed worldwide, with over 358,000 deaths from the disease **[H]**. In December 2016, the FDA approved nivolumab in recurrent or metastatic HNSCC, on the basis of the CheckMate 141 trial data **(Ref. 4** and **Ref. 5)**. In April 2017, EMA approval followed. In October 2017, nivolumab was recommended for use within the Cancer Drugs Fund for some HNSCC patients—in the NICE review process, Professor Harrington provided expert clinical opinion, and it was highlighted that nivolumab is better tolerated than docetaxel and that most patients report a higher quality of life with nivolumab **[I]**.

In June 2019, the FDA approved pembrolizumab as a first-line treatment in combination with chemotherapy in HNSCC **[H]**, based on the KEYNOTE-048 trial **(Ref. 6)**. In October 2019, EMA approval followed. Pembrolizumab was the first anti-PD-1 treatment option in the first-line setting for metastatic or unresectable recurrent HNSCC—the first new therapies approved in the EU for more than a decade. Since October 2020, pembrolizumab monotherapy is recommended on the NHS as an option for untreated metastatic or unresectable recurrent HNSCC expressing PD-L1 (TA661) based on the results from the KEYNOTE-048 trial.

Impact of Talimogene laherparepvec (T-VEC) as a treatment for melanoma. In 2015, the FDA and EMA approved T-VEC as a treatment for advanced melanoma as a direct result of the phase 3 trial **(Ref. 7)**—this was the first FDA- and EMA-approved oncolytic virus therapy. In 2016, NICE approved the use of T-VEC for treating inoperable metastatic melanoma in adults, when systemically administered immunotherapies are not suitable. The committee concluded that the availability of a new treatment option with a novel mechanism of action and improved tolerability would be valuable for people with metastatic melanoma **[J]**. As part of the review process, Professor Harrington was nominated to attend the initial committee discussion and provide a written statement, giving clinical evidence to support the committee's decision making. In clinical practice, treatment with T-VEC is suitable for approximately 10% to 15% of people with unresectable metastatic melanoma. The committee considered T-VEC to be cost effective compared with dacarbazine (GBP23,900 per quality-adjusted life year (QALY) gained) and best supportive care (GBP24,100 per QALY gained) in people whose disease was not suitable for treatment with systemically administered immunotherapies **[J]**.

5. Sources to corroborate the impact

A. Melanoma incidence and survival statistics: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer .
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C. Nivolumab in combination with ipilimumab for treating advanced melanoma: https://www.nice.org.uk/guidance/ta400/documents/committee-papers-2
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