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Translational Development and Clinical Implementation of Pd-1 Inhibitor Pembrolizumab in the Republic of Ireland

Yun Hui Liau [1], Nikhil Vasandani *[1], Ke En Oh [1], Tiong Ming Chia [2], Jing Er Low [1]

1. Department of General Surgery, Galway University Hospital, Galway, Republic of Ireland.

2. Department of General Internal Medicine, Portiuncula University Hospital, Ballinasloe, Republic of Ireland.

Corresponding Author: Nikhil Vasandani, Department of General Surgery, Galway University Hospital, Galway, Republic of Ireland.

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Introduction and Target Discovery

Pembrolizumab also known as Keytruda, is an immunotherapeutic agent used for a variety of cancers such as melanoma, non-small cell lung carcinoma (NSCLC), classical Hodgkin's Lymphoma (cHL), urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), renal cell carcinoma (RCC), esophageal carcinoma, triple negative breast cancer, endometrial cancer, cervical cancer, hepatocellular carcinoma (HCC) and microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers in colorectal, endometrial and unresectable or metastatic gastric, small intestine, or biliary cancer. **[**1**]**

Surprisingly, this drug was discovered by serendipity. Greg Carven, a biotech scientist working in Organon was trying to discover a drug that would suppress the overactive immune responses of patients with autoimmune diseases. To do so, they needed an agonist that would activate PD-1 to silence T-cells. However, what they identified instead was a potent inhibitor. Research on this was slow as there was uncertainty about the application of a PD-1 antagonist at a time where immunotherapy did not exist. However, this came to a turning point in 2010 when Bristol-Myers Squibb (BMS) published a successful phase 3 study on refractory metastatic melanoma involving ipilimumab which targeted T-cell inhibitor molecule CTLA4. This signified a potential efficacy of a checkpoint inhibitor in the management of cancer. **[**2**]** This kickstarted their research into pembrolizumab as a possible form of immunotherapy.

In normal physiology, programmed death receptor-1 (PD-1) on lymphocytes provides a checkpoint to ensure the immune system does not attack itself. Inhibition of T-cell function occurs when programmed death receptor ligand (PD-L1) engages with PD-1. Some tumors have increased expression of PD-L1 whereas others adapt the normal physiology of PD-L1 induction to inhibit active T cell immune surveillance of tumors. Pembrolizumab is a humanized monoclonal IgG4 kappa antibody that binds to PD-1 receptors and this inhibits the formation of PD-1 and PD-L1 complexes. (see Figure 1) **[**3**]** This allows for enhanced tumor immunosurveillance and antitumor immune responses. **[**4**]**

Pre-Clinical Studies:

In preclinical studies, pembrolizumab had comparable pharmacological potency as well as binding affinities to PD-1 that was derived from human or cynomolgus monkeys whereas it did not bind to PD-1 that was derived from rodent or dog. Cynomolgus monkey PD-1 was the most toxicologically relevant and thereby used in most studies. Pembrolizumab was shown to be able to inhibit both PD-

L1 and PD-L2 and increase antigen-stimulated IL-2 in vitro assays for human and cynomolgus monkey proteins. As expected, there were changes in histology consistent with an increased immune surveillance. In mice implanted with syngeneic tumor cell lines, when murine anti-PD-1 antibody was given either alone or with another chemotherapeutic agent, there was a decrease in tumor growth and increased survival. **[**4**]** Toxicology studies were done on cynomolgus monkeys and no severe toxicities or histopathological changes that would signify target organ toxicity was identified. Immune-related autoimmune diseases such as thyroid disorders, pneumonitis and colitis are the most common reported adverse events of pembrolizumab. This is likely secondary to the pharmacological action of the drug. Deficiency in PD-1 or its ligands are associated with autoimmune diseases such as Hashimoto's thyroiditis.

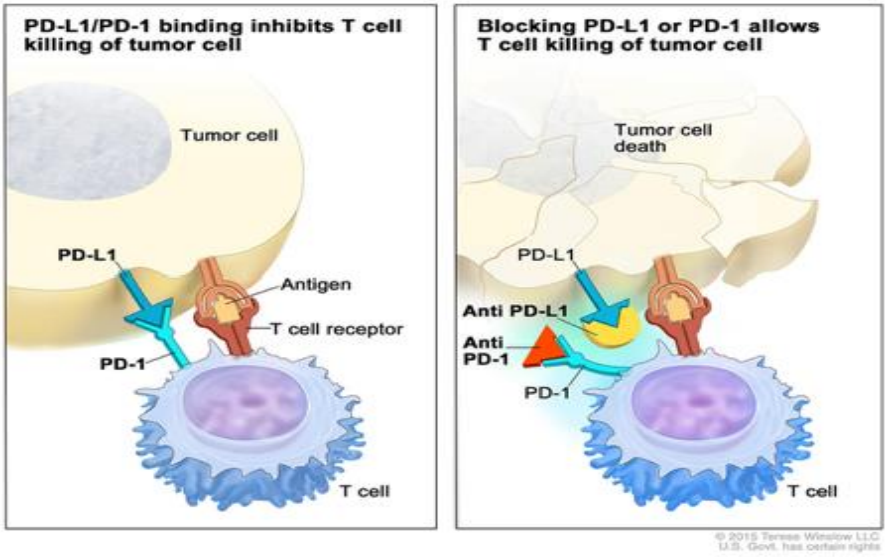

Figure 1: PD-1 receptor antagonist mechanism of action

Drug Development

In terms of Pembrolizumab's drug development, it did not follow the classical drug development pathway.

Keynote-001 was a phase 1 and phase 2 nested clinical trial which included NSCLC specific and melanoma expansion cohorts. In 2010, an application for an investigational new drug was submitted to the FDA. Keynote-001 was started thereafter in patients with advanced solid tumors. In 2012, orphan drug designation for the treatment of advanced melanoma was granted to pembrolizumab, this is granted for drugs that are used to treat rare diseases. In 2013, breakthrough therapy designation was

granted. This is specifically for drugs that are designed to treat serious conditions which have demonstrated remarkable results in preliminary clinical trials. This enables expedited clinical development, which allowed for pembrolizumab's accelerated approval in the USA in 2014. **[**5**]**

Due to the finding of PD-L1 expression in both melanoma and NSCLC tumors, it was hypothesized that pembrolizumab might be of benefit. In 2011, phase 1 Keynote-001 was initiated with the primary goal of investigating safety, tolerability, dose-limiting toxicities (DLT), maximum tolerated dose (MTD) and antitumor activity in patients with advanced solid tumors. Based on this study, it was found that pembrolizumab was well tolerated with no DLTs. There was also no MTD and maximum administered dose (MAD) was 10mg/kg. Commencement of engagement of peripheral target began at 1 mg/kg and it was predicted with translational modeling that there would be robust responses with a >2 mg/kg dose. With this, it was decided that a dose range of 2-10mg/kg be used in subsequent studies. It was also found that there was substantial antitumor activity, however, these cohorts were not powered for efficacy. **[**5**]**

Pooled analysis from the entire melanoma expansion cohort, showed an ORR of 33%, 12-month progression-free survival (PFS) of 35%, median overall survival (OS) of 23 months and response lasted >1 year in 44% of responders. A durable objective response was achieved in a substantial proportion of patients, and this supported the accelerated approval of 2 mg/kg thrice weekly. **[**5**]** Dose finding and efficacy was assessed and thus this was considered to be akin to a phase 2 trial.

Keynote-006 was a phase 3 study including 834 patients with advanced melanoma. Primary endpoints were PFS and OS. It was found that in advanced melanoma, pembrolizumab increased PFS and OS and had less high-grade toxicity compared to ipilimumab. The study revealed a 55% 2-year OS rate with pembrolizumab versus 43% with ipilimumab. The study revealed a continued improved OS rate of 37% at 5 years with pembrolizumab relative to 31% with ipilimumab. Most common side effects found were fatigue, rash and pruritus. **[**6**] [**7**]**

Clinical implementation

In September 4, 2014, the FDA approved pembrolizumab for use in patients with unresectable or metastatic melanoma under the accelerated approval program. This was the first PD-1 blocking antibody approved for use in the USA at the time. **[**8**][**9**]** In the subsequent years following that, after more clinical trials assessing pembrolizumab's therapeutic efficacy in management of common oncological pathologies, pembrolizumab slowly started to get FDA approval for use in other cancers. (see Table 1)

Year of FDA approval	Cancer Pathology Approved
2014	Unresectable or metastatic melanoma
2015	Advanced NSCLC expressing PD-L1
2016	Recurrent or metastatic HNSCC
2017	cHL, metastatic solid tumors expressing MSI-H or dMMR and recurrent locally advanced or metastatic gastric cancers.
2018	metastatic cervical cancer, refractory or relapsed primary mediastinalB-cell lymphoma, hepatocellular and merkel cell carcinoma.
2019	advanced renal cell carcinoma, metastatic small cell lung cancer,metastatic esophageal SCC and advanced endometrial carcinoma
2020	BCG unresponsive, high risk, non-muscle invasive bladder cancer, metastatic cutaneous SCCs, colorectal cancer and metastatic triple negative breast cancer
2023	Metastatic urothelial cancer

Table 1: Table highlighting different clinical applications of Pembrolizumab as approved by the United States Food and Drug Administration (FDA)

Currently, in Ireland, the wholesale price of Pembrolizumab (100 mg) is €3,286.81 excluding VAT. **[**11**]** In 2022, Pembrolizumab was the second highest selling drug worldwide, only second to COVID-19 vaccines, with reported sales of €16.7 billion. **[**12**]** Thankfully, in 2016, after evaluation by the NCPE, Pembrolizumab has been deemed cost-effective for the first line treatment of unresectable or advanced metastatic melanoma since it was approved for reimbursement. **[**13**]**

In conclusion, pembrolizumab has revolutionized the treatment of malignant melanoma and many other malignancies. It is the first PD-1 receptor antagonist approved by the FDA for clinical implementation. The drug has demonstrated significant improvements in all aspects of survival and disease free status with only minor limitations to include resistance and side effects in many of the cancers listed within its arsenal. The discovery and success of pembrolizumab portrays an evolution in targeted cancer therapy and will continue to serve as a platform for future translational drug development.

Reference

1. EMA Europe SPC) - Ema (2022) Keytruda, European Medicines Agency.

2. Shaywitz, D. (2017) The startling history behind Merck's new Cancer blockbuster, Forbes. Forbes Magazine.

3. Flynn, J.P. and Gerriets, V. (no date) Pembrolizumab, StatPearls. StatPearls Publishing.

4. Weis, S.L. (no date) Pembrolizumab (Keytruda), U.S. Food and Drug Administration - Center for Drug Evaluation and Research. FDA.

5. Kang, S.P. et al. (2017) "Pembrolizumab keynote-001: An adaptive study leading to accelerated approval for two indications and a companion diagnostic," Annals of Oncology, 28(6), pp. 1388–1398.

6. Robert, C. et al. (2015) "Pembrolizumab versus Ipilimumab in advanced melanoma," New England Journal of Medicine, 372(26), pp. 2521–2532.

7. Puzanov, I. et al. (2020) "Association of braf V600E/K mutation status and prior BRAF/MEK inhibition with pembrolizumab outcomes in advanced melanoma," JAMA Oncology, 6(8), p. 1256.

8. Raedler LA. Keytruda (Pembrolizumab): First PD-1 Inhibitor Approved for Previously Treated Unresectable or Metastatic Melanoma. Am Health Drug Benefits. 2015 Mar;8(Spec Feature):96-100. PMID: 26629272; PMCID: PMC4665064.

9. Ema (2022) Keytruda, European Medicines Agency.

10. Stewart, J. (no date) Keytruda (pembrolizumab) FDA approval history, Drugs.com.

11. NCPE, N.C.P.E. (2023) NCPE pembrolizumab (Keytruda®) assessment: National Centre for Pharmacoeconomics, National Centre for Pharmacoeconomics | NCPE Ireland.

12. Coyle, D. (2022) Ireland to the fore in delivering powerhouse Cancer Drug, The Irish Times. The Irish Times.

13. Rahway, N.J. and Nutley, N.J. (2023) Merck and Eisai provide update on phase 3 trials of Keytruda® (PEMBROLIZUMAB) plus LENVIMA® (lenvatinib) in certain patients with advanced melanoma (LEAP-003) and metastatic colorectal cancer (LEAP-017), Merck.com.